CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 019297/S014

TRADE NAME: Novantrone

GENERIC NAME: Mixtoxantrone for injection concentrate

SPONSOR: Immunex Corporation

APPROVAL DATE: 11/13/96

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

L. Vaccari

Food and Drug Administration
Rockville MD 20857

NDA 19-297/S-014

Immunex Corporation
51 University Street
Seattle, Washington 98101-2936

NOV 13 1996

Attention: Mark W. Gauthier
Senior Regulatory Affairs Manager

Dear Mr. Gauthier:

Please refer to your May 10, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Novantrone (mitoxantrone for injection concentrate).

We acknowledge receipt of your amendments dated July 10; August 16; September 6 and 19; October 1,3,11,18 and 31; and November 11, 1996.

This new drug application provides for the use of Novantrone in combination with corticosteroids as initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer.

We have completed the review of this supplemental application, 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 enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling.

Please submit sixteen 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 NDA 19-297/S-014. 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.

In addition, please submit three copies of the introductory promotional material 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 this Division 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

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 Leslie Vaccari, Project Manager, (301) 594-5778.

Sincerely yours,

Robert J. DeLap 11-13-96

Robert J. DeLap, M.D., Ph.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE: Labeling

cc:
Original NDA 19-297
HFD-150/Div. files
HFD-2/M.Lumpkin
HFD-101/L.Carter
HFD-810/C.Hoiberg
DISTRICT OFFICE
HFD-80 (with labeling)
HFD-35/ PVaccari (with labeling)
HFD-40/DDMAC/TAcker (with labeling)
HFD-613 (with labeling)
HFD-021/J.Treacy (with labeling)
HFD-150/LVaccari (with labeling)
HFD-150/ JBeitz (with labeling)
HFD-150/GeWilliams (with labeling)
HFD-150/RBarron (with labeling)
HFD-150/TKoutouskos (with labeling)
HFD-150/DPease (with labeling)

Drafted by: LVaccari/11-9-96/FT:11-13-96
R/D Init.by: DPease/11-12-96 LAV 11-13-96
JBeitz/11-13-96
RJustice/11-13-96
RBarron/11-13-96
RWood/11-13-96
GeWilliams/11-12-96
ARahman/11-13-96
JDeGeorge/11-13-96
TKoutsoukos/11-12-96
CGnecco/11-12-96
final:

APPROVAL (Efficacy Supplement/S-014)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development(HF-35)
Food and Drug Administration 5600 Fishers Lane
Rockville, MD 20857

August 21, 1996

Immunex Corporation
Attention: Mr. Mark W. Gauthier
Senior Manager, Regulatory Affairs
51 University Street
Seattle, WA 98101

Dear Mr. Gauthier:

Reference is made to your orphan drug application of April 3, 1996 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of Novantrone® (mitoxantrone), as an orphan drug (application #96-966). We also refer to your amendment dated July 8, 1996.

We have completed the review of this application, as amended, and have determined that mitoxantrone qualifies for orphan designation for the treatment of hormone refractory prostate cancer. Please note that it is mitoxantrone and not its formulation that has received orphan designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity. Also please be advised that if mitoxantrone were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

In addition, please inform this office annually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of mitoxantrone as designated. If you need further assistance in the development of your product for marketing, please feel free to contact Dr. C. Carnot Evans at (301) 827-0987.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

cc:
HFD-85/M.A.Holovac
HFD-150/L.Vaccari ✓
HF-35/OP File #96-966
HF-35/C.Evans
HF-35/chron
HF-35/P.Vaccari 8/21/96 dsg.966


mor

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 19-297 Supplement # S-014 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HFD-150 Trade (generic) name/dosage form: Novantrone (mitoxantrone, for injection) Action: (AP) AE NA

Applicant Immunex Therapeutic Class _____

Indication(s) previously approved Acute nonlymphocytic leukemia in adults Pediatric labeling of approved indication(s) is adequate ✓ inadequate ___

Indication in this application Advanced hormone-refractory Prostate Cancer (For supplements, answer the following questions in relation to the proposed indication.)

✓ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Leslie Vaccari, PM — November 12, 1996

Signature of Preparer and Title (PM, CSO, MO, other) — Date

cc: Orig NDA/PLA # 19-297/S-014
HFD-150 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

3/96

DEBARMENT CERTIFICATION

I hereby certify, as of May 10, 1996, that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) in connection with this supplemental application.

Nancy L Kercher 5/10/96

Nancy L. Kercher
Director, Regulatory Affairs
Immunex Corporation

MEMORANDUM

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

DATE: June 17, 1996

Robert J DeLap 6/17/96

FROM: Robert J. DeLap, MD, PhD, Director
Division of Oncology Drug Products, HFD-150

TO: Director, Division of Scientific
Investigations, HFD-340

SUBJECT: Request for Study-Oriented Audits for sNDA 19-297/S-014
Novantrone (mitoxantrone HCL) Injection

We have identified the following studies as being pivotal to the approval of this supplemental application. We recommend that sites be audited. Refer to attached information on the pivotal study (CCI-NOV22) and the suppportive study 9182).

The reviewing medical officer for this application is Julie Beitz at 594-5745.

The responsible project manager is Leslie Vaccari at 594-5778.

The Sponsor is Immunex.

Contact: Mark Gauthier, Regulatory Affairs at (206) 389-4066.

The user fee goal date is 13 May 1997.

The division's action goal date is 13 November 1996.

This will be presented to the September '96 ODAC Meeting.

Attachments: Immunex letter dated May 10, 1996
Information on Pivotol Study CCI-NOV22 (3 pages)
Information on Supportive Study 9182 (1 page)

cc: ORIG. NDA 19-297
HFD-150/Div. File
HFD-150/JBeitz
[redacted]
HFD-150/outgoing consult file

Attachments : 6 pages

IMMUNEX

May 10, 1996

Robert L. Justice, M.D.
Acting Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Office Building
1451 Rockville Pike - 2nd Floor (HFD-150)
Rockville, MD 20852-1448

NOVANTRONE® mitoxantrone for injection concentrate
NDA 19-297/S-014
Efficacy supplement

Dear Dr. Justice:

Pursuant to 21 CFR 314.70, Immunex Corporation is submitting a supplemental application to request approval of a new indication for the product, NOVANTRONE mitoxantrone concentrate for injection. The additional indication being sought is:

Results are presented from a randomized phase III clinical trial (CCI-NOV22) which demonstrates that Novantrone provides a significant benefit for relief of pain in symptomatic hormone resistant prostate cancer patients and suggests that overall quality of life (QOL) also improves as a result of Novantrone treatment. Also included are results from a second phase III trial (9182) which confirm the activity of Novantrone in Hormonal Resistant Prostate Cancer and the QOL improvement. Final clinical trial reports for the pivotal study (CCI-NOV22) and the supportive study 9182), including all data tabulations and listings, are located in Item 8, Volumes 2-4 and 5-7, respectively, and in Item 10, Volumes 10-12 and 13-15, respectively. Please refer to the table of contents for a detailed listing.

The safety update (Item 9) will be filed 4 months from the date of submission of this supplement.

As discussed at the meeting between Immunex and the Agency on December 20, 1995, we anticipate that the supplement will receive priority review status under the Prescription Drug User Fee Act of 1992, because there is no currently approved chemotherapy for palliative treatment in this patient population.

Prostate cancer is a disease which is receiving much attention in the media of late. Rapid approval of this new indication may be viewed by patients and the press as a positive result of the "Reinventing the Regulation of Cancer Drugs..." initiative recently announced by the FDA and President Clinton, at least in spirit if not literally. Therefore, we would appreciate

51 University Street, Seattle, Washington 98101-2936
206.587.0430, Fax 206.587.0606

the opportunity to work closely with the Division to facilitate review of this submission and to prepare for a September 1996 presentation to the Oncologic Drugs Advisory Committee, should that be required. The goal of our collaboration being to accelerate availability of this promising new treatment for patients with hormone resistant prostate cancer. Novantrone has a proven safety record based on nine years of post marketing surveillance.

I will follow up by phone within two weeks to discuss how we can help to facilitate review of this submission.

Electronic SAS datasets for the NOV22 and 9182 studies as requested by the Statistician are provided with this submission. Refer to Volume 17 for the key to the data set documentation, diskettes provided and directory of files.

If you have any comments or questions regarding the contents of this submission, please contact me at (206) 389-4066.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

MG:nm

File: 31100, 31543

SYNOPSIS

Title: Phase III Trial of Mitoxantrone Plus Low-Dose Prednisone Versus Low-Dose Prednisone for Symptomatic Hormone-Resistant Prostate Cancer

Study Chairman: Ian Tannock, M.D.
Professor of Medicine, University of Toronto
Chairman, Department of Medicine
Princess Margaret Hospital
Toronto, Ontario
Canada

Aim: To compare the effectiveness of mitoxantrone plus low-dose prednisone to that of low-dose prednisone in providing symptom relief for subjects with hormone-resistant prostate cancer (HRPC).

Objectives

Primary:
To assess improvement in pain as defined by a six-point pain scale, the present pain intensity (PPI) scale, without an increase in analgesic score and no evidence of disease progression.

Secondary:
To compare the two randomized groups in terms of duration of response and survival, improvement in quality of life (QOL), and disease response by National Prostate Cancer Project (NPCP) criteria.

Design: This was a multicenter, prospective, open-label, randomized Phase III study with stratification according to baseline Eastern Cooperative Oncology Group (ECOG) performance status. Subjects were to be randomized to receive mitoxantrone plus prednisone (M+P) or prednisone alone (P). All subjects were to receive prednisone 5 mg orally (po) twice daily (BID). Subjects randomized to the M+P arm were to receive mitoxantrone 12 mg/m^2 by intravenous (IV) push every 3 weeks. Subjects randomized to

INVESTIGATOR AND SITE IDENTIFICATION

CAL	Tom Baker Cancer Centre Calgary, Alberta	Scott Ernst, M.D. Douglas A. Stewart, M.D. (8/94)
CCI	Cross Cancer Center Edmonton, Alberta	Peter Venner, M.D.
SHD	Hôtel Dieu Hospital St. Catherine's, Ontario	Brian Findlay, M.D.
PMH	Princess Margaret Hospital Toronto, Ontario	Ian Tannock, M.D. Malcolm J. Moore, M.D.
HMH	Humber Memorial Hospital Weston, Ontario	Jonathan Wilson, M.D.
HCC	Hamilton Regional Cancer Centre Hamilton, Ontario	Alan Neville, M.D.
NSC	Cancer Treatment & Research Foundation of Nova Scotia Halifax, Nova Scotia	Richard Gregg, M.D.
SCC	Saskatoon Cancer Clinic Saskatoon, Saskatchewan	George Armitage, M.D.
BCC	British Columbia Cancer Agency Vancouver, British Columbia	Chris Coppin, M.D.
MH-	The Mississauga Hospital Mississauga, Ontario	Michael King, M.D.
TBC	Toronto Bayview Regional Cancer Centre Toronto, Ontario	Neil Iscoe, M.D.

profile and with which investigators are considered to have clinical experience. It is therefore not surprising that given this setting, some observations were noted in the Immunex audits (Appendix III). However, Immunex has concluded that the audit findings do not affect the salient data for this study nor alter the statistical conclusions of this report.

4.0 RESULTS

4.1 SUBJECT DISPOSITION AND TREATMENT SUMMARY

One hundred and sixty-one subjects were enrolled at 11 participating sites in this study; 80 subjects were randomized to the M+P arm and 81 subjects were randomized to the P arm (Table 1). Forty-eight subjects (59%) in the P arm subsequently crossed over to receive mitoxantrone. Thus, a total of 128 subjects were treated with mitoxantrone. The table that follows lists the 11 participating sites by site-code, shows the number of subjects randomized to each of the treatment assignments at each site, and provides the number of subjects in the P arm at each site who crossed over to receive mitoxantrone.

Treatments Assignments and No. of Crossovers

Site*	M+P	P	Total	Crossovers
CAL	25	29	54	15/29
PMH	19	14	33	8/14
HCC	17	10	27	4/10
SCC	4	8	12	4/8
HMH	6	4	10	3/4
CCI	3	5	8	4/5
SHD	3	5	8	5/5
BCC	0	4	4	3/4
NSC	1	2	3	2/2
MH-	1	0	1	N/A
TBC	1	0	1	N/A

*Site codes are provided in Appendix VI

Subject No. [redacted] randomized to the P group received one dose of mitoxantrone after progressing on prednisone but was not reported as a crossover subject in the database. All 161 subjects enrolled were evaluable for response and safety. Reasons for early withdrawal are reviewed in Section 4.7.4 and in Appendix III.

CALGB 9182

Sites:

Dana Farber - 22

U. of Chicago - 20

Wash Univ - Barnes Hosp - 26
(St. Louis)

NOV 13 1996

MEDICAL OFFICER REVIEW OF NDA # 19-297, Supplement S-014

NOVANTRONE® (Mitoxantrone for Injection Concentrate)

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1. General Information and Timeline

Drug Name:	NOVANTRONE® (Mitoxantrone for Injection Concentrate)
Applicant:	Immunex Corporation
NDA Supplement Date:	May 13, 1996
Pharmacologic Category:	Synthetic anthracenedione
Proposed Indication:	Hormone-resistant prostate cancer
FDA Request for Information:	June 24, 1996
45-Day Meeting:	June 27, 1996
Sponsor's Response to FDA:	July 12, 1996
90-Day Meeting:	August 12, 1996
4-Month Safety Update	September 9, 1996
ODAC Meeting:	September 11, 1996
Post-ODAC Meeting (in-house)	September 18, 1996
FDA Requests for Information	September 18, October 9, and October 16, 1996
Sponsor's Responses	October 4, 11, and 28, 1996

2. Description of Clinical Data Sources

This supplemental NDA contains 9 volumes. Volume 32.1 contains the index to the application, the proposed text of the labeling for mitoxantrone, summaries of the pivotal phase 3 trial, CCI-NOV22, and of the supportive phase 3 trial, 9182, the integrated summaries of efficacy and safety, and a discussion of the benefit/risk relationship for mitoxantrone therapy of hormone-resistant prostate cancer.

The study report for CCI-NOV22 is contained in volumes 32.2-4 and that for 9182 in volumes 32.5-7. Three additional supportive phase 2 trials, CCI-NOV6, CCI-NOV14, and CCI-NOV16 are summarized in volume 32.8. Volume 32.19 contains twenty relevant publications. The study reports for the phase 3 trials contained the protocol and amendments, a list of investigators and sites, sample case report forms, and individual patient listings. Summary reports were provided for the phase 2 trials. No electronic data were submitted.

Case report forms were requested on June 24, 1996, to validate palliative responses for patients in the CCI-NOV22 trial for whom data was either missing or inconsistent from listing to listing. Case report forms were also requested to assess safety concerns for all patients withdrawn for toxicity on both the CCI-NOV22 and 9182 trials. These documents were received on July 12, 1996.

A four-month safety update was submitted on September 9, 1996.

At the September 11, 1996 ODAC Meeting, committee members raised questions regarding the duration of treatment received on the control arm prior to crossover to active treatment on the CCI-NOV22 trial. Additional analyses were requested on pain intensity and analgesic use for patients enrolled on the trial and the sponsor was urged to submit information regarding on study performance status for this trial. These concerns generated three requests for information by FDA to which the sponsor responded. In addition, the sponsor was requested to submit a revised analysis of TTP for all patients on the CCI-NOV22 trial, after it was learned that TTP in the sponsor's original submission had been calculated using different assumptions for responders and non-responders on this trial. Responses to all outstanding concerns were received by October 28, 1996.

3. Introduction

Immunex Corporation proposes an additional indication for NOVANTRONE® (Mitoxantrone for Injection Concentrate) be approved, namely that:

> "NOVANTRONE® in combination with corticosteroids is indicated as initial chemotherapy for treatment of patients with prostate cancer, after failure of primary hormonal therapy."

Mitoxantrone, also known as dihydroxyanthracenedione dihydrochloride (DHAD), is a synthetic anthracenedione cytotoxic agent derived from the anthraquinone dye ametandrone. It is structurally similar to anthracyclines, and acts by intercalating DNA resulting in DNA-protein crosslinks and DNA-protein double- and single-stranded breaks. In 1987, mitoxantrone in combination with cytarabine was approved for induction therapy of adults with acute non-lymphocytic leukemia.

- **Efficacy**

The rationale for investigating mitoxantrone for the palliative treatment of hormone-resistant prostate cancer (HRPC) is based on its cytotoxicity and its favorable safety profile compared to other agents, such as doxorubicin. In the 1980s, phase 1 and 2 trials evaluating mitoxantrone at various doses and schedules alone or in combination with other agents were conducted in approximately 300 patients with HRPC. Overall, a palliative response rate ranging from 25-50% was reported in patients with symptomatic disease.

A Canadian randomized open-label trial, CCI-NOV22, was conducted between 1990-1994 in 161 symptomatic HRPC patients. Patients were randomized to receive either mitoxantrone 12 mg/m² IVP every 21 days plus low-dose prednisone 5 mg bid daily (M+P) or low-dose prednisone alone (P). Palliative response, defined as a 2-point improvement in a 6-point pain intensity scale, accompanied by a stable analgesic score, and lasting at least 6 weeks was observed in 29% of patients on M+P as compared to 12% on P ($p = 0.011$). Patients on M+P had a longer median duration of palliative response (229 days vs 53 days, $p = 0.0001$), and a longer median time to disease progression (301 days vs 133 days, $p = 0.0001$). A decrease of $\geq$ 75% in PSA levels was observed in 27% of patients on M+P vs 5% on P prior to cross-over ($p = 0.011$). Median survival was similar for both treatment arms (11.3 vs 10.8 months, $p = 0.23$). Patients on M+P had greater improvement in mean LASA scores for the pain, physical activity, fatigue, appetite, mood, and overall well-being scales. They also had better scores on all five domains of the EORTC-Q30C core quality of life instrument and the disease-specific Prostate Module.

A second randomized open-label trial in HRPC was completed by (Trial 9182) in September 1995. A total of 242 patients were randomized to receive either mitoxantrone 14 mg/m² IVP every 21 days plus daily hydrocortisone (30 mg qAM, 10 mg q PM, M+H) or

hydrocortisone alone (H). There was no difference in the primary endpoint, median survival, between the two arms (11.1 vs 12 months, p= 0.33). A decrease of $\geq$ 80% in PSA levels was observed in 13% of patients on M+H vs 5% on H (p= 0.051). There was a trend toward greater improvement in pain-related QOL measures in the M+H arm compared to the H arm.

- **Safety**

Common mitoxantrone-related toxicities are myelosuppression, nausea, anorexia, constipation, and fatigue. Congestive heart failure, tachycardia, EKG changes including arrhythmias, chest pain, and asymptomatic decreases in left ventricular ejection fraction have been noted. In the CCI-NOV22 trial, 7 of 128 HRPC patients (5.5%) who received mitoxantrone had cardiac events, including congestive heart failure in three cases. Injection site reactions (phlebitis) and hypersensitivity reactions have been reported infrequently. Cumulative doses above 140-160 mg/m^2 are not recommended.

- **Sponsor's Conclusions Regarding Controlled Trials**

Results of the two randomized trials, CCI-NOV22 and 9182, support the use of mitoxantrone plus corticosteroids in the treatment of HRPC. The recommended dose of mitoxantrone is 12-14 mg/m^2 given as a short intravenous infusion every 21 days.

- **Proposed Studies**

Immunex Corporation does not plan to conduct additional studies in this indication.

4. Controlled Trials

4.1 CCI-NOV22

4.11 Protocol Review

Title: Phase III Trial of Mitoxantrone Plus Low-Dose Prednisone Versus Low-Dose Prednisone for Symptomatic Hormone-Resistant Prostate Cancer

Principal Investigator: Ian Tannock, MD, Princess Margaret Hospital, Toronto, Ontario
Study Dates: 9/90 - 4/94 **Data Cut-off Date:** Not given

- **Review of Protocol Amendments**

Three amendments to the original protocol are summarized below:

6/25/90: Baseline MUGA scans are required for patients with a prior history of cardiac disease.

9/17/90: 1) Patients who have received previous treatment with systemic chemotherapy (with the exception of Estramustine Sodium Phosphate) or glucocorticoids for malignant disease for $>$ 2 weeks are excluded. 2) The Present Pain Intensity score must be $\geq$ 1 at baseline. Patient's pain must be stable for at least 1 week prior to study entry. 3) If a patient on P progresses and requires radiation therapy, cross-over to the M+P arm must be delayed for $\geq$ 4 weeks from the time of radiation therapy. 4) With regard to the planned interim analysis, the study would be discontinued if a difference in response of $\geq$ 20% for the M+P arm can be concluded, based on a one-tailed test with $\alpha = 0.16$, $1-\beta = 0.95$.

11/26/91: Patients who are randomized to P may be crossed over to M+P if their disease remains stable on P for 6 weeks.

- **Study Design**

This was a phase 3, parallel-group, open-label, multicenter trial in symptomatic patients with HRPC. Patients were randomized to receive either mitoxantrone 12 mg/m^2 IVP every 21 days plus low-dose prednisone 5 mg bid daily (M+P) or low-dose prednisone alone (P). Patients were stratified according to baseline ECOG performance status (0,1 or 2,3). Crossover from the P to the M+P arm was permitted at the time of progression or if disease stabilization was observed for 6 weeks.

- **Objectives**

The primary objective was to compare the two treatment arms with respect to improvement in

pain, defined by the Present Pain Intensity scale. Secondary endpoints were response duration, survival, improvement in quality of life (QOL), and response by standard NPCP criteria.

- **Patient Population**

Eligible patients were symptomatic patients with hormone-resistant metastatic or locally advanced (T4) prostate cancer. Hormone-resistance was defined as disease that had progressed or recurred on standard hormonal therapy (orchiectomy, DES $\geq$ 3 mg/day, etc.) and a castrate serum testosterone level ($<$3.5 nmol/L). Patients must have a baseline pain intensity (PI) score of 1 or higher (i.e., at least mild pain). ECOG performance status of 3 or better and a life expectancy of 3 months were required. Patients with a previous history of cardiac disease were required to have a baseline LVEF $\geq$ "Institutional Normal" $\pm$ 5%. Patients were required to have normal hematopoietic and hepatic function.

Patients were excluded if they had received previous systemic chemotherapy (except for Estramustine) or treatment with glucocorticoids for malignant disease for more than 2 weeks. Patients previously treated with radiotherapy to a field $>$ 25 cm involving the spine or pelvis, or with more than one Strontium-89 chloride administration were excluded. Four weeks must have elapsed after the completion of radiotherapy or 8 weeks after Strontium-89 chloride administration. Patients with uncontrolled cardiac failure, active infection, or active peptic ulcer were excluded.

- **Procedure**

Patients randomized to the M+P arm received mitoxantrone 12 mg/m^2 IVP every 21 days plus low-dose prednisone 5 mg bid daily. If on day 22, WBCs $\leq$ 3000, granulocytes $\leq$ 1500, or platelets $\leq$ 100,000, mitoxantrone therapy was to be delayed by weekly intervals until these values were exceeded. If nadir counts showed granulocytes $<$ 500 or platelets $<$ 50,000, the mitoxantrone dose was to be decreased by 2 mg/m^2 on the next cycle. If nadir counts showed granulocytes $>$ 1000 and platelets $>$ 100,000 and non-hematologic toxicity was acceptable, then the mitoxantrone dose was to be increased by 2 mg/m^2 on the next cycle.

The maximum cumulative dose of mitoxantrone was specified as 140 mg/m^2. Responding patients who achieved this dose were recommended to switch to prednisone. However, in the event of disease progression after stopping mitoxantrone, patients with a normal LVEF could receive additional mitoxantrone doses (off study).

Patients randomized to the P arm received prednisone 5 mg bid daily; they were permitted to cross over to the M+P arm at the time of disease progression (per original protocol) or if their disease remained stable for 6 weeks (amendment dated 11/26/91).

Concurrent anti-emetic medications and anti-ulcer therapy was permitted. Patients without prior orchiectomy were permitted to receive one androgen antagonist (e.g., DES, LHRH

agonist). Treatment with flutamide or like drug alone was not considered to provide adequate androgen suppression. **Reviewer Comment:** In the publication that reported the results of this trial, Tannock et al. stated that "Most patients had discontinued additional antiandrogen treatment. Midway through this study, withdrawal responses to flutamide were recognized, and patients were then evaluated for at least 4 weeks after stopping flutamide before entry onto the study" (JCO 14: 1756-1764). This paper is included in the sponsor's ODAC briefing document.

- **Efficacy Assessments**

All subjects had the following assessments performed every 3 weeks: physical examination, QOL and pain questionnaires, analgesic records, CBC and differential, alkaline phosphatase, PAP, and any biochemical tests that were abnormal at baseline (e.g., PSA). Every 12 weeks, all pretreatment evaluations were repeated until disease progression or death.

The pain scale was derived from the PPI Index of the McGill Pain Questionnaire. Subjects were asked to determine how much pain they experienced during the 24 hours preceding their clinic visit using the following 6-point scale: 0=no pain, 1=mild pain, 2=discomforting pain, 3=distressing pain, 4=horrible pain, and 5=excruciating pain.

Subjects kept a daily diary of their analgesics, noting the name, strength, and number of pills/doses taken. The daily analgesic score was calculated as follows: each dose of a non-narcotic analgesic was given a score of 1; each dose of oral narcotic a 2; each dose of IV narcotic a 4. Scores were averaged for the last 7 days of each 21 day cycle and then entered on the CRF.

Palliative response was prospectively defined as a 2-point improvement in pain intensity, not accompanied by an increase in analgesic score and maintained for 2 successive visits 3 weeks apart (the so-called primary criterion of response). Subjects who had mild pain (PI score of 1) at baseline were to have complete pain relief to qualify as responders. If PI or analgesic scores were missing for a particular visit, that visit was not considered in the calculation. Subjects randomized to the P arm were classified as responders prior to crossover. Duration of palliative response was calculated from the cycle of response to the cycle of progression.

Time to disease progression (for the primary responders) was the time from the date of first treatment until the date of the second of two consecutive cycles in which progression was noted. Disease progression was defined as the occurrence of any one of the following events following documentation of response: 1) an increase in PI score of at least 1 point recorded for 2 consecutive visits in comparison to the lowest PI score; 2) an increase in analgesic score of $\geq$ 25% compared to the lowest score for 2 consecutive visits; or 3) evidence of new lesions, progression of existing lesions, or a requirement for radiotherapy.

Time to disease progression for all patients who were not primary responders was calculated

on the basis of an increase in PI score or analgesic use **only**.

Time to death was calculated from the date of first treatment until the date of death.

- **QOL Assessments**

QOL assessments were self-administered by subjects during clinic visits. These consisted of:

1. EORTC-Q30C: 30 items grouped into 5 subscales addressing symptoms/physical activity, functional activity, psychosocial interaction, overall physical assessment, and global QOL;

2. Specific Prostate Module: 11 items addressing pain and side effects of analgesics;

3. LASA scales: 9 scales evaluating various aspects of QOL.

QOL scores were analyzed by totaling the numerical responses for each EORTC subscale. When a response was missing, the value was prorated by multiplying the sum by the total number of possible responses, divided by the total number of actual responses in that subscale.

- **Safety Assessments**

Adverse events were graded using WHO criteria on a scale from 1 to 4. Nausea, vomiting and alopecia were collected prospectively in the CRFs. Laboratory toxicities were graded using NCI Common Toxicity Criteria.

- **Statistical Plan**

The palliative response endpoint was analyzed by comparing the M+P arm to the P arm using Fisher's exact test and by additional Cochran-Mantel-Haenszel general association tests controlling for baseline strata.

Time to progression and time to death endpoints were compared between groups using Kaplan-Meier estimation methods and log-rank tests.

QOL instruments were compared for "best change" and "best percent change" from baseline using Cochran-Mantel-Haenszel row means tests. Simple t-tests and Wilcoxon rank sum tests confirmed the Cochran-Mantel-Haenszel row means tests.

- **Study Conduct**

CCI-NOV22 was conducted under the sponsorship of and filed with the Health Protection Branch (INDS, File No. 9427-A45-357C). Eleven sites across Canada participated

in this trial. **Reviewer Comment:** Details regarding patient randomization were not specified in the protocol or the study report.

developed the CRFs, monitored investigator sites, compiled the database, and performed a preliminary analysis of the data in October 1995. At that time, the study database was transferred to Immunex Corporation who contracted with to perform site audits to assess compliance with the Declaration of Helsinki, Canadian regulations and GCP guidelines. Between November 1995 and February 1996, data for 30% of subjects at each site were audited. **Sites which had under-reported serious adverse events were to submit these to the sponsor. Immunex will then review these and report them in its 4-month safety update to this supplemental NDA (per Appendix III, Volume 32.2).**

A planned interim analysis for the primary endpoint was conducted by a contract statistician in February 1993. Palliative response rates were 11% (4/37) for the M+P arm and 4% (1/27) for the P arm. A Pearson Chi-square test resulted in a p value (0.2954) that was not small enough to warrant study discontinuation.

4.12 Baseline Patient Demographics

A total of 161 patients were enrolled in 11 participating sites across Canada, 80 patients on the M+P arm and 81 patients on the P arm. Since forty-eight patients on the P arm crossed over to the M+P arm, a total of 128 patients on this trial received mitoxantrone therapy. Three sites accrued 70% of the patients: Tom Baker Cancer Centre (Calgary), Princess Margaret Hospital (Toronto), and Hamilton Regional Cancer Centre (Hamilton). **Reviewer Comment:** No information has been provided regarding the rate of accrual at each site over the four year period.

The median age of patients enrolled on this trial was 67 years (range 43-86 years). The median time from original diagnosis was 36 months (range 2-194 months). Median serum testosterone level at baseline was 0.6 nmol/L (range 0-12 nmol/L). Five patients had baseline testosterone levels that exceeded the 3.5 nmol/L requirement, however, only one of these (patient [redacted] on the M+P arm) responded. Bone was the most common site of metastases, occurring in 96% of all patients. Other sites included lymph node metastases in 21%, and visceral metastases in 4%. The median PAP level at baseline was 14 U/L (range 0.1-2200 U/L) and the median PSA level at baseline was 170 μg/L (range 0.2-6290 μg/L). Treatment arms were balanced in all parameters.

Baseline performance status was 0 or 1 in 63%, 2 or 3 in 37%. Baseline PI score was 1 in 33%, 2 in 42%, 3 or 4 in 24%. One patient in each arm had a baseline PI of 0 (these were considered to be non-responders). The median analgesic score was 15 (range 0-182) at baseline. Treatment arms were well balanced in these parameters, as well as in all baseline QOL measures (i.e., EORTC-Q30C, Prostate Module, and LASA scales).

Previous therapy consisted of orchiectomy in 60%, estrogen in 12%, LHRH agonist in 17%, cyproterone acetate in 26%, and flutamide in 21%. Treatment arms were balanced except for prior flutamide use (30% for the M+P arm vs 12% for the P arm, p= 0.006).

Reviewer Comments:

1. The study **protocol** defined patients with hormone-resistant prostate cancer as those with symptomatic progression of disease despite castrate levels of testosterone. More specific criteria, such as consecutive increases in PSA levels over time, were not specified.

2. The study **report** did not specify the duration, the timing or sequence of prior hormonal manipulations, or the quality of patients' response to these treatments.

3. Although the protocol permitted continuation of androgen suppression while on study, only two patients apparently did so (according to Listing 3, patient [redacted] on the M+P arm continued to receive cyproterone acetate, and [redacted], an orchiectomy patient, received flutamide while on the P arm). Thus, prior to study entry, there were 21 patients on the M+ P arm and 8 patients on the P arm who had received flutamide, potentially as part of total androgen blockade, who apparently discontinued therapy at study entry. See discussion below on the possible impact of flutamide withdrawal responses on palliative responses noted on this study.

- **Comparison of Baseline Patient Characteristics Among Centers**

Three of the eleven centers, Calgary, Princess Margaret Hospital, and Hamilton entered 70% of the patients enrolled on this trial. The table below, adapted from Listing 1 of the study report, compares baseline characteristics for all patients by treatment arm, for patients enrolled at the three highest accruing centers, and for patients enrolled at the remaining centers. Patients were balanced with respect to median age, performance status, median testosterone level at baseline, and incidence of bone only disease.

Patients generally received one or two prior hormonal manipulations, including orchiectomy alone, orchiectomy and medical therapy, or medical therapy alone. The number and types of medical therapies received likely reflects standard medical practice within Canada in the early 1990's (note cyproterone acetate was marketed in Canada at that time). For patients who received two or more therapies, it is not known whether these were given sequentially or concurrently. Listing 1 also did not specify the duration or response to prior therapies.

At the higher accruing centers, relatively more patients were enrolled who had received 2 or more prior hormonal therapies compared to patients enrolled at the other centers. This resulted in a relatively higher number of patients enrolled with presumed prior total androgen blockade at the three highest accruing centers. Note that an imbalance exists between

treatment arms, in that 46% of patients on the M+P arm received two prior hormonal therapies compared to 23% of patients on the P arm at these centers. The majority of patients accrued at the other centers had received only one prior hormonal therapy.

Table 1. Patient Baseline Characteristics

Characteristic	All Patients		3 Highest Accruing Centers		All Other Centers	
	M+P N=80	P N=81	M+P N=61	P N=53	M+P N=19	P N=28
Age (yrs) range	67	67	70	69	64	65
ECOG PS range	1	1	1	1	1	1
% Patients with Bone Only Disease	65%	70%	69%	74%	53%	64%
Testosterone Level (nmol/L)	0.5 (0-7.4)	0.7 (0.2-12.0)	0.5 (0.0-7.4)	0.7 (0.3-12.0)	0.6 (0.2-3.3)	0.7 (0.2-2.5)
Prior Hormonal Tx*						
-O, alone	31%	46%	21%	36%	63%	64%
-O + (F±C)	24%	14%	30%	17%	5%	7%
-F±C	15%	12%	16%	15%	11%	7%
-F, alone	4%	1%	5%	2%	0	0
-C, alone	9%	9%	8%	11%	11%	4%
-E, alone	5%	14%	5%	15%	5%	11%
-L, alone	10%	9%	8%	9%	16%	7%
-L + (F±C)	10%	2%	13%	4%	0	0
-Other	4%	4%	5%	4%	0	4%
% Pts with Prior Total Androgen Blockade**	26%	10%	33%	15%	5%	4%
# Prior Hormonal Tx's						
-1	59%	78%	48%	74%	95%	86%
-2	36%	20%	46%	23%	5%	14%
-3 or more	5%	2%	6%	4%	0	0

* O = orchiectomy; F=flutamide; C=cyproterone acetate; E=estrogen; L=LHRH agonist
** Assumes orchiectomy, LHRH agonist, estrogen or cyproterone acetate were given concurrently with flutamide

Tables 2 and 3 below allow side-by-side comparisons of individual centers with respect to baseline patient characteristics. All centers were balanced with respect to median age, median performance status and median testosterone level at baseline. The majority of patients had bone only disease, except for those randomized on the M+P arm at Hamilton and Humber.

Centers varied markedly from each other with respect to the number and types of prior hormonal therapies given to patients prior to enrollment on study. For example, the proportion of patients who had prior orchiectomy alone was much lower at Princess Margaret Hospital and Hamilton than at the other centers. These two centers enrolled more patients who had received 2 or more therapies, and account for 19 of the 21 patients on the M+P arm and 7 of the 9 patients on the P arm who are presumed to have had total androgen blockade prior to study entry.

Table 2. Baseline Characteristics of Patients at the Three Highest Accruing Centers

Characteristic	Calgary		Princess Margaret		Hamilton	
	M+P N=25	P N=29	M+P N=19	P N=14	M+P N=17	P N=10
Age (yrs) range	75	70	70	67	68	69
ECOG PS range	1	1	1	2	1	1
% Patients with Bone Only Disease	76%	79%	79%	71%	47%	60%
Testosterone Level (nmol/L)	0.7 (0-4.0)	0.7 (0.3-5.0)	0.5 (0.2-7.4)	0.8 (0.3-1.9)	1.0 (0.5-2.0)	1.0 (0.5-12.0)
Prior Hormonal Tx*						
-O, alone	36%	52%	5%	21%	18%	10%
-O + (F±C)	8%	3%	42%	36%	47%	30%
-F+C	0	0	5%	0	6%	10%
-F, alone	8%	0	0	0	6%	10%
-C, alone	16%	14%	0	0	6%	20%
-E, alone	12%	28%	0	0	0	0
-L, alone	8%	3%	11%	29%	6%	0
-L + (F±C)	0	0	37%	7%	6%	10%
-Other	12%	0	0	7%	6%	10%
% Pts with Prior Total Androgen Blockade**	4%	3%	74%	36%	29%	20%
# Prior Hormonal Tx's						
-1	80%	97%	16%	50%	35%	40%
-2	16%	3%	74%	36%	59%	60%
-3 or more	4%	0	10%	14%	6%	0

* O = orchiectomy; F=flutamide; C=cyproterone acetate; E=estrogen; L=LHRH agonist
** Assumes orchiectomy, LHRH agonist, estrogen or cyproterone acetate were given concurrently with flutamide

Table 3. Baseline Characteristics of Patients at the Remaining Centers

Characteristic	Saskatoon		Humber		All Others	
	M+P N=4	P N=8	M+P N=6	P N=4	M+P N=9	P N=16
Age (yrs) range	62	64	66	66	63	65
ECOG PS range	1	1	1	1	2	1
% Patients with Bone Only Disease	75%	63%	33%	50%	56%	69%
Testosterone Level (nmol/L)	1.0 (0.6-3.3)	0.8 (0.3-2.5)	0.5 (0.2-0.7)	0.7 (0.2-1.2)	0.5 (0.4-1.3)	0.7 (0.3-1.6)
Prior Hormonal Tx*						
-O, alone	75%	88%	83%	75%	44%	50%
-O + (F±C)	0	0	0	0	11%	12%
-F±C	0	12%	0	0	0	0
-F, alone	0	0	0	0	0	0
-C, alone	25%	0	0	0	11%	6%
-E, alone	0	0	0	0	11%	18%
-L, alone	0	0	17%	25%	22%	6%
-L + (F±C)	0	0	0	0	0	0
-Other	0	0	0	0	0	6%
% Pts with Prior Total Androgen Blockade**	0	12%	0	0	11%	0
# Prior Hormonal Tx's						
-1	100%	88%	100%	100%	88%	81%
-2	0	12%	0	0	11%	19%
-3 or more	0	0	0	0	0	0

* O = orchiectomy; F=flutamide; C=cyproterone acetate; E=estrogen; L=LHRH agonist

** Assumes orchiectomy, LHRH agonist, estrogen or cyproterone acetate were given concurrently with flutamide

Centers varied markedly from each other with respect to the number and types of prior hormonal therapies given to patients prior to enrollment on study. For example, the proportion of patients who had prior orchiectomy alone was much lower at Princess Margaret Hospital and Hamilton than at the other centers. These two centers enrolled more patients who had received 2 or more therapies, and account for 19 of the 21 patients on the M+P arm and 7 of the 9 patients on the P arm who are presumed to have had total androgen blockade prior to study entry.

Table 2. Baseline Characteristics of Patients at the Three Highest Accruing Centers

Characteristic	Calgary		Princess Margaret		Hamilton	
	M+P N=25	P N=29	M+P N=19	P N=14	M+P N=17	P N=10
Age (yrs) range	75	70	70	67	68	69
ECOG PS range	1	1	1	2	1	1
% Patients with Bone Only Disease	76%	79%	79%	71%	47%	60%
Testosterone Level (nmol/L)	0.7 (0-4.0)	0.7 (0.3-5.0)	0.5 (0.2-7.4)	0.8 (0.3-1.9)	1.0 (0.5-2.0)	1.0 (0.5-12.0)
Prior Hormonal Tx*						
-O, alone	36%	52%	5%	21%	18%	10%
-O + (F±C)	8%	3%	42%	36%	47%	30%
-F+C	0	0	5%	0	6%	10%
-F, alone	8%	0	0	0	6%	10%
-C, alone	16%	14%	0	0	6%	20%
-E, alone	12%	28%	0	0	0	0
-L, alone	8%	3%	11%	29%	6%	0
-L + (F±C)	0	0	37%	7%	6%	10%
-Other	12%	0	0	7%	6%	10%
% Pts with Prior Total Androgen Blockade**	4%	3%	74%	36%	29%	20%
# Prior Hormonal Tx's						
-1	80%	97%	16%	50%	35%	40%
-2	16%	3%	74%	36%	59%	60%
-3 or more	4%	0	10%	14%	6%	0

* O = orchiectomy; F=flutamide; C=cyproterone acetate; E=estrogen; L=LHRH agonist
** Assumes orchiectomy, LHRH agonist, estrogen or cyproterone acetate were given concurrently with flutamide

Table 3. Baseline Characteristics of Patients at the Remaining Centers

Characteristic	Saskatoon		Humber		All Others	
	M+P N=4	P N=8	M+P N=6	P N=4	M+P N=9	P N=16
Age (yrs) range	62	64	66	66	63	65
ECOG PS range	1	1	1	1	2	1
% Patients with Bone Only Disease	75%	63%	33%	50%	56%	69%
Testosterone Level (nmol/L)	1.0 (0.6-3.3)	0.8 (0.3-2.5)	0.5 (0.2-0.7)	0.7 (0.2-1.2)	0.5 (0.1-1.3)	0.7 (0.3-1.6)
Prior Hormonal Tx*						
-O, alone	75%	88%	83%	75%	44%	50%
-O + (F±C)	0	0	0	0	11%	12%
-F±C	0	12%	0	0	0	0
-F, alone	0	0	0	0	0	0
-C, alone	25%	0	0	0	11%	6%
-E, alone	0	0	0	0	11%	18%
-L, alone	0	0	17%	25%	22%	6%
-L + (F±C)	0	0	0	0	0	0
-Other	0	0	0	0	0	6%
% Pts with Prior Total Androgen Blockade**	0	12%	0	0	11%	0
# Prior Hormonal Tx's						
-1	100%	88%	100%	100%	88%	81%
-2	0	12%	0	0	11%	19%
-3 or more	0	0	0	0	0	0

* O = orchiectomy; F=flutamide; C=cyproterone acetate; E=estrogen; L=LHRH agonist

** Assumes orchiectomy, LHRH agonist, estrogen or cyproterone acetate were given concurrently with flutamide

4.13 Efficacy Results

- **Mitoxantrone Administration**

On the M+P arm, the median cumulative dose of mitoxantrone delivered was 73 mg/m² (range 12-212 mg/m²). The median number of cycles given was 6.5 (range 1-18). The median mitoxantrone dose per cycle was 12 mg/m² (range 5.1-16.5 mg/m²). Eighteen patients received relatively high cumulative doses, ranging from 130-212 mg/m². Mitoxantrone therapy was delayed for one or more cycles in 9% (7/80) of patients on the M+P arm and in 10% (5/48) of patients on the P arm who crossed over to M+P. Myelosuppression was the most common reason for treatment delay.

Reviewer Comments: Patients enrolled on the M+P arm at Calgary, Princess Margaret Hospital, and Hamilton tended to receive higher cumulative doses and increased numbers of doses of mitoxantrone than patients enrolled at other centers (see Tables 4 and 5 below). Centers exhibited varying success with delivery of mitoxantrone in patients who crossed over from the P arm. In particular, patients who crossed over to the M+P arm at 4 centers

Table 4. Mitoxantrone Administration in Patients at the Three Highest Accruing Centers

Characteristic	Calgary		Princess Margaret		Hamilton	
	M+P N=25	P* N=15	M+P N=19	P* N=8	M+P N=17	P* N=4
Cumulative Dose (mg/m²) range	74	29	96	44	84	89
# of Doses Delivered range	7	3	8	3.5	7	6.5

*Patients crossed over

Table 5. Mitoxantrone Administration in Patients at the Remaining Centers

Characteristic	Saskatoon		Humber		All Others	
	M+P N=4	P* N=4	M+P N=6	P* N=3	M+P N=9	P* N=14
Cumulative Dose (mg/m²) range	47	54	60	48	62	68
# of Doses Delivered range	4.5	4.5	5	4	6	7

*Patients crossed over

(Calgary, Princess Margaret Hospital, Saskatoon, and Humber) received a median of 3-4 doses of M+P after crossover.

- **Palliative Response**

Twenty-three patients on the M+P arm (29%) and 10 patients on the P arm (12%) prior to crossover qualified as responders as defined by a 2-point improvement in pain intensity score that was associated with a stable analgesic score and was maintained for two consecutive visits (i.e., at least six weeks). The p value for this comparison was 0.011 (Fisher's exact test). The median time to response was 65 days for the M+P arm and 74 days for the P arm. **Reviewer Comment:** FDA confirmed responses in 21 patients and disagreed on the evaluability for response for two patients who had response durations of 0 days. If these patients are excluded, the response rate on the M+P arm declines to 26% (21/80). See details below.

In subset analyses, patients with a PI score > 1 had a superior palliative response rate on M+P than P alone (27% vs 9%). Similarly, patients with a baseline ECOG PS of > 1 had a higher response rate on M+P (24% vs 7%). Responses were seen at all mitoxantrone doses administered (i.e., $\leq$ 10, > 10 but < 14, and $\geq$ 14 mg/m^2/cycle).

The duration of palliative response for the 23 responders was 229 days for the M+P arm vs 53 days for the P arm (p= 0.0001, log-rank test). The treatment difference remains in favor of the M+P arm when patients randomized to each arm are compared while controlling for performance status and PI score at baseline.

A second criterion for palliative response was also evaluated retrospectively: a decrease in analgesic score of at least 50% from baseline, without an increase in PI at any time. If this criterion is used **in addition to** the one defined above, seven additional responses are achieved in each arm. Thus, using **both** criteria, 30 patients on M+P (38%) vs 17 patients on P (21%) experienced a palliative response (p= 0.025, Fisher's exact test). **Reviewer Comment:** If patients are excluded, the response rate using both criteria for the M+P arm declines slightly to 35% (28/80). The response rate for the P arm is unchanged (21%). See details below.

- **Reviewer's Characterization of Palliative Responders**

Using both criteria for palliative response and assuming 28 responders on the M+P arm, there were 22 patients (79%) who had at least one pain-free cycle (defined as a pain intensity score of 0, with or without analgesics). Twelve patients had a pain intensity score of 1 (mild pain) at study entry. The median number of pain-free cycles for these 22 responders was 5 (range 1-16 cycles). Mean analgesic use scores recorded for these pain-free cycles ranged from 0 to 34. Although analgesics were continued in many of these patients, analgesic use scores were reduced by $\geq$ 50% in 68% (15/22) of responding patients. Nine patients had at least one cycle for which pain intensity was 0 and no analgesics were required.

Using both criteria for palliative response, there were a total of 17 responders on the P arm. Of these, 13 (76%) were noted to have at least one pain-free cycle (defined as a pain intensity score of 0, with or without analgesics). Eight patients had a pain intensity score of 1 at study entry. The median number of pain-free cycles for these 13 responders was 5 (range 1-14 cycles). Mean analgesic use scores recorded for these pain-free cycles ranged from 0 to 22. Although analgesics were continued in many of these patients, analgesic use scores were reduced by $\geq$ 50% in 54% (7/13) of responding patients. Six patients had at least one cycle for which pain intensity was 0 and no analgesics were required.

In addition, there were a total of 9 patients who responded to M+P after crossover from the P arm. Of these, five patients had at least one pain-free cycle (defined as a pain intensity score of 0, with or without analgesics). Pain intensity scores at the cycle of crossover ranged from 1-3. The median number of pain-free cycles for these 5 patients was 3 (range 1-5 cycles). Mean analgesic use scores recorded for these pain-free cycles ranged from 0 to 48. Analgesic use scores were reduced by $\geq$ 50% in 3 patients. One patient ([redacted]) had a pain intensity score of 1 (mild pain) at the cycle of crossover, and 5 subsequent cycles for which pain intensity was 0 and no analgesics were required.

To summarize, the number of responding patients and the duration of palliative response was greater for the M+P arm compared to the P arm. Analgesic use also appeared to be reduced on the M+P arm (ten patients receiving M+P vs 6 patients receiving P had at least one cycle with a pain intensity of 0 on no analgesics). One can presume that potential side effects of analgesics, such as sedation, nausea, and constipation, were also reduced.

- **Flutamide Withdrawal**

A flutamide withdrawal response has been described that may be associated with disease regression, reduction in PSA levels and decrease in pain in nearly 30% of patients treated with total androgen blockade (Scher and Kelly, JCO 11:1566-1572, 1993; Herrada et al., J Urol, 155:620-633, 1996). Patients most likely to experience withdrawal responses received simultaneous androgen blockade (orchiectomy + flutamide or GnRH analog + flutamide). Patients who received sequential androgen blockade did not experience withdrawal responses.

Table 6. Impact of Flutamide Withdrawal Response on Palliative Response

Treatment Arm	# Pts with Total Androgen Blockade*	# Estimated WD Responses**	Observed # Palliative Responses
M+P (N=80)	21	6	8
P (N=81)	9	3	2

***Assumes that orchiectomy, LHRH agonist, estrogen, or cyproterone were given concurrently with flutamide**
****Assumes a 30% withdrawal response rate**

Although the timing and sequence of prior hormonal treatments received are not known, the

number of patients on study "at risk" for a flutamide withdrawal response may be estimated from the number of patients who may have received prior total androgen blockade therapy.

If all patients who could have had total androgen blockade are excluded, the palliative response rate for the remaining patients on the M+P arm still exceeds that for the remaining patients on the P arm (i.e., 34% [20/59] vs 21% [15/72]; assuming a total of 28 responders on the M+P arm and 17 responders on the P arm). These response rates are identical to those reported above for all patients enrolled on each of the two treatment arms. In addition, Kaplan-Meier plots of response duration for all patients vs patients not at risk for flutamide withdrawal responses were superimposable for each of the treatment arms (see Appendix). These findings support a treatment effect attributable to M+P over and above a putative flutamide withdrawal response.

- **Time to Progression**

Median time to progression was calculated separately for responders and non-responders in the study report. For 33 responders (primary criterion for response only), median TTP was 301 days for the M+P arm vs 133 days for the P arm (p= 0.0001, log-rank test). The treatment difference remained in favor of the M+P arm when patients randomized to each arm were compared while controlling for performance status and PI score at baseline.

Among the 128 non-responders, follow-up data were available for 114 patients (54 on M+P, 60 on P). Median TTP was 70 days for the M+P arm vs 54 days for the P arm (p= 0.0116).

Reviewer Comment: TTP was recalculated for all patients with available dates of progression, regardless of response to therapy. Progression for the majority of patients was defined as worsened pain intensity or analgesic requirement. See pp. 78-80 for a re-calculation of TTP based on worsening pain, analgesic use, and clinical criteria.

Table 7. Median Time to Progression (All Patients)

Treatment Arm	Treatment Failures	Median (days)	Log-rank P-value
M+P (N=77)	43	148	0.0001
P (N=70)	60	62	

- **Survival**

Median survival for the two treatment arms was similar: 339 days for the M+P arm vs 324 days for the P arm (p= 0.2324). Survival times ranged from 159-881 days for the M+P arm, and from 201-569 days for the P arm.

- **Quality of Life Assessments**

Completion of QOL scales (9 LASA scales, 5 EORTC-Q30C domains, and Prostate Module) was comparable among patients on the two treatment arms and compliance was considered to be high. A median of 7 records of each scale type was completed per patient. Four patients (5%) on the M+P arm and 11 patients (14%) on the P arm had only one completed LASA record. No differences were noted in baseline scores among patients on the M+P or P arms.

Mean scores over time for the LASA scales and mean values for the sum of patients' scores on the 5 EORTC-Q30C domains and the Prostate Module were presented graphically (see sponsor's Figures 6-20 in Appendix). Comparable findings were noted over time in the two arms, with a consistently better, though slight, advantage for the M+P arm in most scales.

In addition, tabulations were provided for 1) the best QOL scores achieved at any time on study, 2) the best change from baseline achieved on study, and 3) the best per cent change from baseline achieved (sponsor's Tables 15-17). There were no statistical differences in mean best scores for any scale among patients on the two arms. Differences between arms in best change from baseline were significant for the LASA constipation scale ($p = 0.016$), and borderline for the LASA mood scale ($p = 0.058$) and the Prostate Module ($p = 0.052$). Differences between arms in the best per cent change from baseline were borderline significant for the LASA passing urine scale ($p = 0.059$) only. For these analyses, p values were calculated using the Cochran-Mantel-Haenszel row means test.

- **Change in PSA Levels**

Serial (≥ 2) PSA measurements were available for 134 patients (71 on the M+P arm, 63 on P). The difference between the two arms with respect to decrease in PSA levels from baseline was not statistically significant. The proportion of patients on the M+P arm with a $\geq 75\%$ decrease from baseline PSA was 27% vs 5% for patients on the P arm prior to crossover ($p = 0.011$, Cochran-Mantel-Haenszel general association test). **Reviewer Comment:** A palliative response did not predict for a PSA response (defined as a decline in PSA level of $\geq 75\%$ from baseline). Nine of 45 (20%) patients on the M+P arm and 5 of 43 (12%) patients on the P arm did not have palliative responses, but did have PSA responses.

- **Efficacy After Crossover**

Forty-eight patients on the P arm crossed over to receive M+P. The median number of days from entry on study to crossover was 84 days (range 11-324 days). Nine patients had a palliative response (19%). Median survival for the 48 crossover patients was > 381 days.

- **Reviewer Analysis of Patients by Prior Hormonal Therapy**

In 1994, SWOG published a retrospective review of prognostic factors on response and

survival for hormone-resistant prostate cancer patients enrolled on five phase 2 chemotherapy trials (JCO, 12:1868-1875, 1994). A variety of chemotherapy agents were evaluated in these studies: menogaril, iproplatin, amonafide, ifosphamide/mesna and didenim B, and fluorouracil plus interferon alfa-2a. These studies required that all exogenous androgen deprivation therapy cease 1 month prior to study entry. Standard response criteria were utilized. This review failed to show any survival advantage for patients with continued gonadal suppression (i.e., orchiectomy) over patients who had discontinued androgen suppression therapy (i.e., non-orchiectomy). Orchiectomy patients had a slightly lower, but nonsignificant, likelihood of response to chemo-therapy when compared to non-orchiectomy patients (6% [11/172] vs 15% [5/33], p= 0.09).

On CCI-NOV22, all but two patients enrolled that had been receiving medical therapies for advanced prostate cancer discontinued such therapy prior to study entry according to Listing 3, "Concomitant Medications". (In contrast, Tannock et al., 1996, state that patients continued their primary androgen ablation therapy on study with either LHRH agonist, estrogen or cyproterone acetate.) Palliative response rates for M+P (using both primary and secondary criteria for response) were lower for orchiectomy patients than for non-orchiectomy patients (30% [14/46] vs 47% [16/34]). This difference was not observed for orchiectomy or non-orchiectomy patients on P alone (20% [10/50] vs 23% [7/31]).

Further breakdown of orchiectomy patients according to whether they received any additional medical therapy or not reveals no response advantage for M+P over P among patients whose only prior androgen deprivation therapy had been orchiectomy (20% vs 19%). Thus, the advantage of M+P appears among patients who had received medical therapies.

Table 8. Palliative Response Rates by Prior Hormonal Therapy (Prior to Cross-Over)

Treatment Arm	Orchiectomy Alone	Orchiectomy + Medical	Medical Therapy Alone
M+P	20% (5/25)	38% (8/21)	44% (15/34)
P	19% (7/37)	23% (3/13)	23% (7/31)
P value*	1	0.465	0.114

*Fisher's exact test

The median time to progression and time to death for each patient subset are shown below. Time to disease progression was calculated for both responders and non-responders to the first treatment randomized to (i.e., prior to crossover). Survival times may be confounded by the receipt of antineoplastic therapies after cessation of the first randomized treatment.

Table 9. Time to Event Endpoints by Prior Hormonal Therapy

Median Time to Progression	Orchiectomy Alone		Orchiectomy + Medical		Medical Therapy Alone	
	M+P (N=23)	P (N=33)	M+P (N=20)	P (N=10)	M+P (N=34)	P (N=27)
Treatment Failures	13	30	11	8	19	22
Median (days)	84	64	168	70	224	54
Log-rank P-value	0.18		0.009		0.0001	

Median Time to Death	Orchiectomy Alone		Orchiectomy + Medical		Medical Therapy Alone	
	M+P (N=25)	P (N=37)	M+P (N=21)	P (N=13)	M+P (N=34)	P (N=31)
Treatment Failures	23	32	20	13	32	30
Median (days)	220	388	434	321	319	199
Log-rank P-value	0.3654		0.0025		0.0304	

For patients who had previously received medical therapy, the median time to progression and time to death were longer on the M+P arm than on the P arm. No statistical difference in TTP or survival was noted between treatment arms for orchiectomy patients. Although the median survival on the P arm is longer for this group than on the M+P arm (388 vs 220 days), the two survival curves come together and cross.

The table below demonstrates that there were no major differences noted among patient subsets in age, baseline ECOG performance status and testosterone level, baseline pain intensity (PI) or analgesic use, proportion of patients with bone only disease or number of prior hormonal therapies (orchiectomy counted as one therapy). More patients on M+P had potentially received total androgen blockade (orchiectomy or GnRH or estrogen or cyproterone acetate + flutamide) prior to study entry, and subsequently discontinued flutamide on study. If patients who could have had prior total androgen blockade are excluded, the palliative response rates for the remaining patients on the M+P arm are higher than those for the P arm for the subset of patients who received orchiectomy + medical therapy (71% [5/7] vs 29% [2/7]) and for the subset of patients who received medical therapy only (37% [10/27] vs 21% [6/28]).

Patients in the orchiectomy alone subset received much less mitoxantrone (both in terms of cumulative dose and number of doses administered). Since there is no reason to believe that these patients experienced excessive toxicity, the lower median doses delivered are likely the result of the poor responses observed. (No information was provided on prior courses of radiotherapy which may have affected bone marrow reserve in some patients. However, the

protocol required that patients receiving > 1 course of radiotherapy or strontium chloride be excluded from study.

Table 10. Patient Characteristics by Prior Hormonal Therapy (Prior to Cross-Over)

Characteristic at Baseline	Orchiectomy, Alone		Orchiectomy + Medication		Medication, Alone	
	M+P N=25	P N=37	M+P N=21	P N=13	M+P N=34	P N=31
Age (yrs) range	65	67	71	68	68	66
ECOG PS	1	1	1	1	1	1
Median PI	2	2	2	2	2	2
Median Analgesic Score	12	18	19	12	20	12
% Patients with Bone Only Disease	60%	65%	62%	54%	68%	77%
Testosterone Level (nmol/L)	0.6 (0.0-1.4)	0.6 (0.2-1.5)	0.5 (0.2-1.0)	0.8 (0.3-1.4)	0.7 (0.2-7.4)	0.9 (0.3-12.0)
# Patients w/ Total Androgen Blockade*	0	0	14	6	7	3
# Prior Hormonal Txs** -1 -2 -3 or more	100% 0 0	100% 0 0	0 81% 19%	0 85% 15%	65% 35% 0	84% 16% 0
Total Mitoxantrone Dose (mg/m^2) range	46	NA	74	NA	83	NA
# of Doses Mitoxantrone Delivered range	4	NA	7	NA	8	NA

*Assumes that therapies in question were given concurrently with flutamide
**Orchiectomy = 1 treatment

These results are exploratory and retrospective, involving small numbers of patients, and hence, should be interpreted with caution. Possible conclusions from this analysis are:

1. Receipt of medical therapies (with or without orchiectomy) predicts for a superior palliative response, TTP, and survival on M+P over P alone. Orchiectomy patients experienced similar palliative responses, times to progression, and survival times on either treatment arm.

2. Unlike patients who underwent orchiectomy alone, those who received medical therapy may have had hormone-insensitive tumor subpopulations that could be depleted by the addition of chemotherapy to corticosteroids.

3. Definitive exploration of these findings would require a prospective randomized trial of continuous androgen suppression compared with cessation of such therapy in orchiectomy and non-orchiectomy patients with hormone-resistant prostate cancer.

- **Clarification of Selected Palliative Responses**

On June 24, 1996, FDA requested that Immunex Corporation justify the assignment of palliative response for seven patients identified with one of the following discrepancies. The patients in question and the sponsor's responses follow. Case report forms for these patients were submitted and reviewed.

1. Missing PI Scores

There were two patients with missing PI scores. Section 3.6.1 of the final clinical/statistical report stated that "If PPI or analgesic scores were missing for a particular visit, that visit was not considered in the calculations described [of response status]. This occurred for 2 subjects who were classified as responders." The corresponding PI scores for these two responding patients were:

Patient (on the P arm): response was noted to occur from cycle 5 to 8, but PI scores were missing for cycles 4 and 6 on Listing 4.

Patient (on the M+P arm): response was noted to occur from cycle 6 to 14, but PI scores were missing for cycles 3, 5, 7, 9, and 12 on Listing 4.

Sponsor responded with more specific guidance regarding the handling of missing PI scores. Although the PI scores were missing, the two PI scores that bracket the missing score(s) satisfied the primary response criterion, i.e., were 2 points lower than the score in the first (baseline) cycle. In addition, there was no increase in analgesic score for the three cycles, i.e., the cycle with the missing PI score(s) and the two cycles bracketing that missing cycle; and there was no objective evidence of disease progression at any time during these three cycles.

FDA accepts the sponsor's clarification with the assurance that there was no evidence of disease progression for patients 11 and 15 during the cycles in question.

2. **Response Noted After Withdrawal of Study Treatment**

Patient [redacted] (on the M+P arm): withdrawn for unknown reason after cycle 5, but response is noted to occur in "cycles" 6 through 9 (duration was 70 days).

Patient [redacted] (on the M+P): last course given was cycle 5; patient withdrawn for toxicity at "cycle" 6, and last follow-up date is "cycle" 7. Response is noted to occur in "cycles" 5 through 7 (duration was 77+ days).

Sponsor clarified that patient [redacted] discontinued therapy at the beginning of cycle 6 due to unspecified toxicity, but also satisfied the primary response criterion at the same time. There was no evidence of progression by PI or analgesic scores thereafter, "through cycle 9". Similarly, patient [redacted] was withdrawn for toxicity in cycle 6, but satisfied the secondary response criterion in cycle 5. "The duration of 77 days was derived using PI and analgesic scores and represents the time during which this subject's symptoms were improved even though he was off therapy."

FDA accepts the sponsor's clarification. Review of case report forms revealed that there was no evidence of disease progression and no administration of antineoplastic therapy for patient 21. **However, when patient [redacted] went off-study due to sepsis in cycle 6, he was noted to be "maintained on PO prednisone only with good symptom control". Thus, strictly speaking, the response duration for this patient is 55+ days (4/24 - 6/18/92) instead of 77+ days. TTP is 139+ days instead of 161+ days as reported in Listing 11.**

3. **Response Duration of Zero Days**

Patient [redacted] (on the M+P arm): completed treatment at cycle 11; follow-up 3 weeks later confirmed a response by PI score. However, since this is the last available score, the response duration was 0 days.

Patient [redacted] (on the M+P): refused treatment after cycle 3; follow-up 3 weeks later confirmed a response by PI score. However, since this is the last available score, the response duration was 0 days.

Sponsor agreed that the response duration for these patients was, in fact, 0 days. These patients were censored in the sponsor's analyses of response duration and time to progression.

FDA does not accept the sponsor's assignment of palliative response for patients [redacted] and [redacted] These patients are unevaluable for palliative response as it was defined in this study. If these patients are included among the non-responders, then the overall palliative response rate for the M+P arm declines slightly to 35% (28/80) from 38% (30/80).

4. **Response by Primary Criterion but Progression by Secondary Criterion**

Patient [redacted] (on the M+P arm): response was noted to occur from cycle 5 to 15 using PI scores (Listing 4), however, using analgesic scores, this patient would have progressed at cycle 3 (Listing 5) without ever achieving a response.

Sponsor stated that the patient's analgesic requirement increased by 25% at cycle 3. "However, the patient was continued on the study by the Investigator (possible protocol deviation) because the PI scores were stable/improving and there was no objective evidence to tumor growth. In cycle 5, the patient met the primary response criteria and his response was maintained for 10 cycles. Thus, he was included in the analysis as a responder." **Sponsor acknowledges that patient had disease progression at cycle 15 (2/11/94) rather than cycle 16. Thus, TTP is reduced from 336+ days to 315 days, and response duration from 252+ days to 231 days.**

FDA notes that this patient's analgesic requirement increased by > 75% in cycle 2. A baseline analgesic score of 139 rose to 245 at cycle 2, to 194 at cycle 3, and declined thereafter to 50 or less. The CRF offers no explanation for the abrupt increase in dilaudid use in cycles 2 and 3. This patient's corresponding PI scores were 2, 2, 1, and 0 for these timepoints. The patient's case report form documents an initial increase followed by a decrease in alkaline phosphatase levels (118, 554, 862, and 420, respectively) for this period, with normalization thereafter. In addition, there were declines in PSA (2650, 418, 79, and 35 μg/L, respectively) and no evidence of disease progression out to cycle 15. The bone scan at cycle 15 revealed disease progression.

FDA accepts this patient as a responder to M+P, with changes in alkaline phosphatase levels consistent with a "healing response". Note, that "healing response" had been observed in three patients experiencing antiandrogen withdrawal response as reported by Scher and Kelly. (This patient had received orchiectomy and cyproterone acetate prior to study entry; if he had discontinued the antiandrogen, he would have been "at risk" for a withdrawal response.)

- **Clarification of Duration of Palliative Response and/or TTP in Selected Patients**

On June 24, 1996, FDA requested that Immunex Corporation justify the calculation of palliative response duration and/or TTP for six patients identified with one of the following discrepancies. The patients in question and the sponsor's responses follow. Case report forms for these patients were submitted and reviewed.

Patient [redacted] (on the P arm): progressed at cycle 6 (8/21/92, Listing 11) or at cycle 18 (11/26/93, Listing 20); evidence of progression at cycle 12 using analgesic score. TTP was 113 days; response duration was 0 days.

Sponsor stated that the patient was erroneously declared progressed at cycle 6 on Listing 11.

Patient did, in fact, progress by analgesic score at cycle 12, however, he continued treatment until objective evidence of tumor progression was noted in cycle 18.

FDA review of the patient's case report form revealed progression by analgesic score at cycle 11. Thus, by protocol criteria, the patient's TTP was 232 days (4/30-12/18/92) and response duration was 119 days (8/21-12/18/92).

Patient [redacted] (on the P arm): patient is reported as not progressed on prednisone at cycle 11 (3/24/93, Listing 11) or as progressed at cycle 11 (5/5/93, Listing 20). TTP was 210+ days; response duration was 126+ days.

Sponsor stated that both listings are correct. This patient was a responder using secondary criteria (analgesic use). At the time of the last assessment for PI and analgesic score (3/24/93) he had not progressed (response duration 210+ days). However, shortly thereafter, this patient did have objective evidence of tumor progression (optic nerve compression by bony metastases) and was taken off-study on 5/5/93, 4 weeks after receiving radiotherapy.

FDA accepts the TTP of 210+ days and response duration of 126+ days for this patient based upon protocol criteria for progression noted on 3/24/93. **The protocol did not take into account objective evidence for progression in the definition of progression for patients who were not primary responders.**

Patient [redacted] (on the M+P arm): received 10 cycles of treatment; patient is reported to have progressed at cycle 18 dated as 1/26/94 (Listing 7) or as 6/1/94 (Listing 20). TTP was 420 days; response duration was 378 days.

Sponsor stated that the patient did progress on 1/26/94 (cycle 20, not 18) on the basis of PI score. However, patient progressed on the basis of objective response on 6/1/94.

FDA accepts the TTP of 420 days and response duration of 378 days for this patient based upon protocol criteria for progression noted on 1/26/94.

Patient [redacted] (on the M+P arm): received 12 cycles of treatment; patient is reported to have progressed at cycle 7 on 9/10/93 (Listing 11) or at cycle 12 on 12/23/93 (Listing 20). TTP was 126 days, response duration 63 days.

Sponsor stated that the patient did progress on 9/10/93 on the basis of PI score. However, patient progressed on the basis of objective response on 12/23/93.

Upon review of the case report form, progression on the basis of PI score occurred at cycle 6 (8/20/93). FDA calculates the TTP as 105 days and response duration as 42 days for this patient based upon protocol criteria for progression noted on 8/20/93.

Patient (on the M+P arm): received 9 cycles of treatment; withdrawn immediately (2/4/94) for surgical procedure but patient is reported to have progressed at "cycle" 9 dated 10/31/94 (Listing 7). No PI scores were given after cycle 9 to document progression. TTP was 451 days; response duration 409 days.

Sponsor stated that the patient did stop treatment on 2/4/94 (cycle 9) due to a UTI and urinary/rectal fistula that required surgical repair. At that time, there was no evidence of progression based on PI or analgesic scores. Objective evidence of progression occurred several months later on 10/31/94.

FDA accepts the TTP of 451 days and response duration of 409 days for this patient based upon objective disease progression noted on 10/31/94.

Patient (on the P arm): reported to have progressed at cycle 4 (5/18/94, Listing 20) or at cycle 6 (6/29/94, Listing 7). Using PI scores, progression occurred at cycle 6, however, using analgesic scores, progression occurred at cycle 5. TTP was 119 days; response duration 77 days.

Sponsor agreed that progression of PI scores occurred at cycle 6, while progression by analgesic scores occurred at cycle 5. In reality, patient stopped treatment at cycle 4 (5/18/94) due to increased pain. Cycle 6 was used in the analysis of TTP.

FDA accepts the date of progression by analgesic scores (6/8/94, cycle 5). Thus, TTP was 98 days, and response duration 57 days.

- **Clarification of Additional Discrepancies**

Patient (M+P arm): withdrawn from treatment due to myelosuppression (Table 25) or due to disease progression (Listing 11)?

Sponsor stated that the patient progressed by PI scores at cycle 8 (6/28/91) but remained on study until 8/9/91. He was taken off study due to myelosuppression and was switched to prednisone.

Review of the case report form confirmed these findings; myelosuppression was in the form of "persistent thrombocytopenia" ranging from 89,000-106,000. FDA agrees with the calculation of
TTP and response duration using the 6/28/91 date as the date of progression.

Patient (on the P arm): reported to have disease progression at cycle 6 (Listing 7) but PI score missing; how was progression determined?

Sponsor stated that the patient was crossed over from the P arm to the M+P arm at cycle 6.

The patient was considered progressing at that time, although the PI score was missing in cycle 6, because of 1) worsening bone scan findings in cycle 5, 2) increase in PSA from 572 at baseline to 2250 at cycle 6, and 3) increase in analgesic score from 0 to 5 in cycle 6.

Review of the case report form confirmed the worsened bone scan, with new lesions noted in cycle 5. PSA was 94 at baseline and 186 at cycle 6. Analgesic score rose to 4 at cycle 6, up from 0 in cycles 2-5. FDA concurs that these changes constitute disease progression on the P arm.

Patient [redacted] (on the M+P arm): received 7 cycles of treatment; 3 weeks later, patient is reported as not progressed (Listing 11) or progressed (Listing 20); response affects whether patient is censored for TTP.

Sponsor stated that the patient had objective evidence of tumor progression by bone scan and PSA in cycle 8, but did not progress on the basis of PI or analgesic score. This accounts for the different designations in the two listings. Since this patient had responded by secondary criteria, and no analysis of TTP for secondary responders was presented in the study report, this patient was not "censored" in any analysis.

Case report form review confirmed the changes in bone scan and PSA, as well as an increase in the size of a pelvic side wall mass on CT scan. **However, since objective evidence of progression is not a criterion for progression for secondary responders, the TTP is "correctly" listed as 154+ days.**

Patient [redacted] (on the M+P arm): received 8 cycles of treatment; 3 weeks later, patient is reported as not progressed (Listing 7) or progressed (Listing 20); response affects whether patient is censored for TTP.

Sponsor stated that the patient, a primary responder, had objective evidence of tumor progression by chest xray in cycle 9, but did not progress on the basis of PI or analgesic score. This accounts for the different designations in the two listings. **Sponsor has revised this patient's status to progressed at cycle 9 (3/18/94). FDA concurs. Thus, TTP should be 179 days rather than 179+ days as reported in Listing 7.**

- **Summary**

The sponsor and FDA analyses differ in the following respects:

Overall Palliative Response Rate: 38% for the M+P arm vs 35% if patients are excluded (unevaluable for response due to response duration of 0 days).

Table 11. Palliative Response Rates: Sponsor vs FDA

Palliative Response Rate	Sponsor's Analysis			FDA's Analysis		
	M+P N=80	P N=81	P-value*	M+P N=80	P N=81	P-value*
Primary Responders	29% (N=23)	12% (N=10)	0.011	26% (N=21)	12% (N=10)	0.029
Primary + Secondary Responders	38% (N=30)	21% (N=17)	0.025	35% (N=28)	21% (N=17)	0.055

*Fisher's two-tailed exact test

The palliative response rate, based on the primary criterion, for patients on the M+P arm remains significantly higher than that for patients on the P arm if patients are excluded. The difference between treatment arms in overall palliative response rate is borderline significant, favoring the M+P arm.

Time to Event Endpoints: The table below summarizes the differences in response duration and time to progression for six responding patients noted following the sponsor's clarifications described above and FDA's review of relevant case report forms. **The sponsor has agreed with revisions in time to event endpoints for patients**

Table 12. Time to Event Endpoints: Sponsor vs FDA

	Sponsor's Analysis		FDA's Analysis	
Primary Responders	Resp Duration (days)	TTP (days)	Resp Duration (days)	TTP (days)
[redacted] (M+P)	252+	336+	231	315
[redacted] (M+P)	98+	179+	98	179
[redacted] (P)	77	119	57	98
Secondary Responders	Resp Duration (days)	TTP (days)	Resp Duration (days)	TTP (days)
[redacted] (M+P)	77+	161+	55+	139+
[redacted] (M+P)	63	126	42	105
[redacted] (P)	0	113	119	232

When response duration was recalculated using FDA's assessments, the median duration was 207 days for the M+P arm vs 57 days for the P arm (p=0.0007; assumes 28 and 17

responders, respectively). When TTP was recalculated using FDA's assessments, the result remained significantly higher for the patients treated on the M+P arm. See Appendix for a graphical representation of TTP.

Table 13. Time to Progression: Sponsor vs FDA

Treatment Arm	Sponsor's Analysis			FDA's Analysis		
	Treatment Failures	Median (days)	Log-rank P value	Treatment Failures	Median (days)	Log-rank P value
M+P (N=77)	43	148	0.0001	44	168	0.0001
P (N=70)	60	62		60	62	

Subset Analysis of Patients by Prior Hormonal Therapy: TTP was recalculated using FDA's assessments for the patient subsets of orchiectomy alone, orchiectomy + medical therapy, and medical therapy alone described above. There were no appreciable differences noted in TTP when FDA's assessments were used instead of sponsor's assessments (compare to Table 8). The median TTP on the two treatment arms (M+P vs P) for orchiectomy patients was 86 vs 64 days (log-rank p = 0.12); for orchiectomy + medical therapy, TTP was 168 vs 70 days (p = 0.007); and, for medical therapy alone, TTP was 224 vs 54 days (p = 0.0001).

4.14 Safety Results

- **Deaths**

There were five deaths on the M+P arm (patient on study or within 30 days of the last dose of mitoxantrone. Patient was removed from study after requiring hospitalization for an acute confusional state and died of pneumonia 13 days after the last dose of mitoxantrone. Patients died of malignant disease 11, 27, 20, and 28 days after the last dose of mitoxantrone. In addition, two patients died within 30 days of removal from study, both due to malignant disease.

There were six deaths on the P arm (patient , all due to malignant disease. These deaths occurred 12, 7, 17, 14, 27, and 12 days respectively, after the last dose of mitoxantrone. In addition, two patients died within 30 days of removal from study, both due to malignant disease.

- **Cardiotoxicity**

The following seven patients treated on the M+P arm experienced mitoxantrone-related cardiotoxicity ranging from asymptomatic reductions in LVEF to life-threatening congestive heart failure. Case report forms for these patients were submitted and reviewed.

Patient [redacted]: 65 year old male with metastatic disease involving bone and lymph nodes who received a cumulative mitoxantrone dose of 48 mg/m^2. He was removed from study due to worsening of PI score, however, mitoxantrone was continued off study for an additional three months. The total cumulative dose received was not reported. Twenty days after the final dose of mitoxantrone, the patient was hospitalized with a suspected inferior wall MI and CHF. LVEF was reduced to 18-20% from a baseline of 51-53%. The patient died ten days later; **death was considered possibly related to study drug**. No autopsy was performed.

Patient [redacted]: 60 year old male with metastatic disease involving bone and lymph nodes who received a cumulative mitoxantrone dose of 136 mg/m^2. He experienced grade 2 dyspnea throughout the study, however, one day after the last dose of mitoxantrone, he developed severe dyspnea. Atrial fibrillation and severe cardiomyopathy were noted, as well as a reduced LVEF of 20.5% (baseline unknown). Dyspnea resolved two days later after treatment with furosemide and digoxin. These events (dyspnea, cardiomyopathy, and atrial fibrillation) were considered probably related to study drug.

Patient [redacted]: 65 year old male with metastatic disease involving bone and lymph nodes who received a cumulative mitoxantrone dose of 130 mg/m^2. The patient was withdrawn from study 21 days after the last mitoxantrone dose due to disease progression and a reduced LVEF of 42% (baseline unknown). The patient had no symptoms of CHF. The patient's decrease in LVEF was considered related to study drug.

Patient [redacted]: 86 year old male with metastatic prostate cancer and a history of CHF who received a cumulative mitoxantrone dose of 72 mg/m². The patient developed CHF 21 days after the last dose of mitoxantrone and was removed from study. Prior LVEFs were reported to be normal or difficult to assess but not markedly reduced. This case of "potential" cardiotoxicity was considered related to study drug.

Patient [redacted]: 65 year old male with metastatic disease involving bone and lymph nodes who received a cumulative mitoxantrone dose of 136 mg/m². The patient had two episodes of rheumatic fever as a child but an LVEF of 67% prior to study entry. The patient achieved a palliative response to therapy. Nine months after study completion, he was found to have a reduced LVEF, as low as 22%, with a borderline dilated LV, grade III LV dysfunction and diffuse hypokinesis, and severe MR. The patient had mild dyspnea on exertion.

Patient [redacted]: 64 year old male with metastatic disease involving bone who received a cumulative mitoxantrone dose of either 228 or 264 mg/m². The patient had a palliative response to therapy and was asymptomatic, however, a decline in LVEF to 36% from 52% prompted cessation of therapy. The decrease in LVEF was considered probably related to study drug.

Patient [redacted]: 60 year old male with metastatic prostate cancer and a history of angina and prior MI who received a cumulative mitoxantrone dose of 120 mg/m². The patient developed severe cervical spine pain and was removed from study to receive radiotherapy. At the time of study discontinuation, LVEF declined to 40% from 54%, however, the patient had no symptoms of CHF. The decrease in LVEF was considered probably related to study drug.

- **Serious Adverse Events**

Thirty-six patients experienced 43 serious adverse events (SAEs) on study. These included events that were related or unrelated to study drugs. Twenty-one SAEs were reported on the M+P arm and 22 on the P arm with 15 occurring prior to crossover and 7 after crossover. The most common SAE was death due to disease progression.

In descending order of frequency, the SAEs were: death due to disease progression (7 patients), deep venous thrombosis (4 patients), UTI (4 patients), infection (4 patients), thrombocytopenia (3 patients), gastrointestinal symptoms, pain, pneumonia, or cardiomyopathy (2 patients each), and sepsis, angina, atrial fibrillation, balance problems, cardiotoxicity, confusion, dyspnea, dysuria, fever, pleural effusion, pulmonary embolism, seizure or spinal cord compression (one patient each).

All four serious infections and 3 of 4 serious UTIs occurred in patients on the M+P arm, whereas both cases of pneumonia occurred on the P arm. Other than infection, no SAE was predominant in either treatment arm.

- **Treatment Withdrawals**

The reasons for treatment withdrawal on the two treatment arms are listed below. Twelve patients withdrew for toxicities occurring on M+P therapy. One patient [redacted] was originally randomized to the P arm, then crossed over to the M+P arm. He discontinued therapy due to nausea/diarrhea that developed following the crossover.

Table 14. Reasons for Treatment Withdrawal

Reason	M+P (N=80)	P (N=81)
Disease Progression	50	58
Toxicity	11	1 (after crossover to M+P)
Death	4	6
Patient Refusal	2	3
Completed Therapy	9	1
Protocol Violation	0	3
Other	4	8

Case report forms for the twelve patients withdrawn for toxicity were submitted and reviewed:

Table 15. Patients Withdrawn for Toxicity

Patient #	Cumulative M's (mg/m²)	Days on Study	Reason Off Study	Outcome Off Study/ Additional Tx's
[redacted]	112	149	Low WBC nadirs, anemia	Alive at 1701+ days; Prednisone, RT
[redacted]	77	203	Thrombocytopenia	Died on day 299; Prednisone
[redacted]	86	209	Severe nausea/diarrhea; hospitalization	Died on day 465; Prednisone
[redacted]	72	104	Sepsis; obstructive uropathy; hosp	Died on day 150; TURP
[redacted]	74	139	Urosepsis; hospitalization	Died on day 619; Prednisone

Patient #82	Cumulative M# (mg/m²)	Days on Study	Reason Off Study	Outcome Off Study/ Additional Txs
	42	83	Acute confusional state; hospitalization	Died on day 86
	12	21	Febrile neutropenia; hematemesis	Died on day 218
	96	238	Thrombocytopenia	Died on day 277; Prednisone
	130	210	Decreased LVEF (42%)	Died on day 295; Prednisone
	104	233	Increased fatigue, anorexia	Alive at 931+ days; Prednisone, RT
	72	198	CHF, pulmonary edema	Died on day 459
	228 or 264	374	Decreased LVEF (36%)	Alive at 729+ days

- **Adverse Events**

Selected adverse events occurring on the M+P and P arms are listed below (adapted from sponsor's Tables 20-24 included in Appendix). The final column includes toxicities occurring among the 48 patients on the P arm who subsequently crossed over to M+P.

Table 16. Hematologic Adverse Events

Hematologic Adverse Event	M+P (N=80)	P (toxicities prior to crossover) (N=81)	P (all toxicities) (N=81)
Leukopenia -grade 4	96% 15%	9% 0	58% 14%
Neutropenia -grade 4	94% 54%	5% 1%	56% 24%
Thrombocytopenia -grade 4	55% 1%	10% 0	33% 3%
Anemia -grade 4	3% 1%	- -	2% 1%

Table 17. Non-Hematologic Adverse Events

Non-Hematologic Adverse Event	M+P (N=80)	P (toxicities prior to crossover) (N=81)	P (all toxicities) (N=81)
Nausea	61%	35%	61%
Fatigue	31%	10%	20%
Alopecia	29%	0	10%
Anorexia	25%	6%	14%
Constipation	16%	14%	16%
Dyspnea	10%	4%	6%
UTI	9%	4%	4%
Edema	8%	3%	7%
Mucositis	6%	0	5%
Vomiting	5%	3%	10%
Systemic Infection	5%	6%	7%
Pneumonia	4%	3%	5
Decrease in LVEF	8%*	0	0
CHF	4%	0	1%
Hyperglycemia	80%	75%	81%
Elevated SGOT	34%	36%	42%
Elevated Alk Phos	79%	94%	96%
Elevated LDH	32%	30%	34%

*includes two cases of CHF

Grade 4 toxicities occurring in $\geq$ 5% of patients on the M+P arm were: leukopenia, neutropenia, and elevations of LDH (in 7%). Grade 4 toxicities occurring in $\geq$ 5% of patients on the P arm prior to crossover were: elevations of LDH (in 8%) and alkaline phosphatase (in 8%). One case of hypercalcemia (grade 4) was noted in a patient on M+P. **Reviewer Comment:** Since there was no specification to the contrary, it is assumed that these adverse events include both those related and unrelated to study drugs.

4.15 Sponsor's Conclusions

This study was designed to mimic typical oncology practice and involved both academic and community hospitals in Canada. Only patients with symptomatic HRPC were enrolled, with no limitation on age or prior medical history. Crossover was permitted so that patients on the corticosteroid arm would not be denied the opportunity to receive chemotherapy.

Compliance with study procedures was very high. Patients completed daily diaries of analgesic use and answered an average of eight serial assessments of pain and QOL measures on an every 3-week basis.

The primary endpoint of palliative response was achieved in significantly more patients on the M+P arm compared to the P arm. This was true if the primary criterion for response was used ($\geq$ 2-point decrease in PI score without an increase in analgesic score observed in two consecutive cycles) or if primary and secondary criteria were combined (secondary criterion defined as a $\geq$ 50% decrease in analgesic score without an increase in PI score). Duration of palliative response and median time to disease progression for responders was significantly longer on the M+P arm.

Median survival was similar in both arms, an expected finding in a study with a crossover design.

A statistically significant difference favoring the M+P arm was noted for PSA declines of $\geq$ 75% from baseline.

Of the patients who were randomized to the P arm, 59% crossed over to M+P. Nine of these or 19% achieved a palliative response (primary criterion).

Patients on both arms had similar baseline scores on QOL measures. On study, there was a trend favoring the M+P arm, particularly in selected disease-related symptoms.

This study did not reveal previously unreported adverse events. There were seven cases of mitoxantrone-related cardiotoxicity, including 3 cases of congestive heart failure, the most serious cardiac complication of mitoxantrone.

The combination of mitoxantrone + prednisone was effective for the treatment of patients with advanced or metastatic prostate cancer who have failed hormonal therapy. The combination did not produce significant toxicity.

4.2 9182

4.21 Protocol Review

Title: Randomized Comparison of Low-Dose Steroids and Mitoxantrone Versus Low-Dose Steroids in Patients with Hormone-Refractory Stage D_2 Carcinoma of the Prostate: A Phase III Study

Principal Investigator: Philip W. Kantoff, MD, Dana-Farber Cancer Institute, Boston, MA
Study Dates: 10/92 - 9/15/95
Data Cut-off Date: 12/96

- **Review of Protocol Amendments**

There were seven protocol amendments:

Update #1 (10/15/92) provided information on drug availability and shipment, clarified the requirement for participation in the QOL portion of the study, and amended the title to reflect that this was a "limited access" protocol.

Update #2 (12/3/92) revised the eligibility criteria to permit more than one prior hormonal therapy and provided for stratification by number of prior hormonal therapies. Patients could continue on testosterone suppression with either orchiectomy, LHRH analogue or DES; all other forms of hormone therapy, including flutamide must be discontinued. The study was now open group-wide.

Update #3 (5/15/93) added toxicity as an additional reason for discontinuation for patients on the H alone arm.

Updates #4 (8/15/93) - #7(11/15/94) made minor editorial, eligibility, and enrollment changes.

- **Study Design**

This was a phase 3, parallel-group, open-label, multicenter trial in patients with HRPC. Patients were randomized to receive either mitoxantrone 14 mg/m^2 IVP every 21 days plus hydrocortisone 40 mg daily (M+H) or daily hydrocortisone alone (H). Hydrocortisone was administered in doses of 30 mg at 8 AM and 10 mg at 8 PM. Patients were stratified according to baseline performance status (0-1 vs 2), disease status (measurable vs evaluable), and number of prior endocrine manipulations (1 vs $\geq$ 2). Crossover was not permitted at the time of disease progression, however, hydrocortisone could be continued until death or serious toxicity.

- **Objectives**

The primary objective was to compare the two treatment arms with respect to improvement in survival. The secondary endpoint was quality of life as assessed by questionnaires measuring physical function and cancer-related symptoms.

- **Patient Population**

Eligible patients must have Stage D_2 prostate cancer with disease that has progressed despite at least one endocrine manipulation. One of the manipulations must have included either orchiectomy, an LHRH analogue or DES. Progressive disease was defined as: 1) progressive symptoms in a patient with lesions on bone scan, plain radiographs/CT scan or physical exam; and/or 2) a $>$ 25% increase in the sum of the perpendicular diameters of all measurable masses or the appearance of $>$ 25% new lesions on bone scan; and/or 3) a $\geq$ 2-fold increase in PSA level confirmed by at least two values two or more weeks apart. Patients must have measurable or evaluable nonosseous disease or bone-only disease with an abnormal PSA. Patients must have a performance status of 0, 1, or 2 and a normal LVEF.

Patients were excluded if they had serious intercurrent illness, significant cardiac disease (NYHA Class III or IV), angina or MI within 6 months, brain metastases, prior chemotherapy or immunotherapy or if they were receiving exogenous corticosteroids. At least 3 weeks must have elapsed since any major surgery and at least 4 weeks since any radiotherapy.

- **Procedure**

Patients randomized to the M+H arm received mitoxantrone 14 mg/m^2 IVP every 21 days plus hydrocortisone 40 mg daily. If on day 22, granulocytes $\leq$ 1500, or platelets $\leq$ 100,000, mitoxantrone therapy was to be delayed by weekly intervals until these values were exceeded. If the next cycle was delayed more than 6 weeks, the patient was removed from study. If nadir counts showed granulocytes $\geq$ 1000 or platelets $<$ 25,000, the mitoxantrone dose was to be decreased by 50% on the next cycle. If nadir counts showed granulocytes $\geq$ 1000 and platelets 25,000-49,000, the mitoxantrone dose was to be decreased by 25% on the next cycle. If nadir counts showed granulocytes $\geq$ 1000 and platelets $\geq$ 50,000 there was no reduction in mitoxantrone dose.

The maximum cumulative dose of mitoxantrone is 160 mg/m^2. Patients who achieved this dose were recommended to switch to hydrocortisone alone.

Patients randomized to the H arm received hydrocortisone 30 mg at 8 AM and 10 mg at 8 PM daily. For intercurrent illness, hydrocortisone doses were increased 2-fold or higher.

Patients without prior orchiectomy were permitted to receive one androgen suppressive therapy (e.g., DES, LHRH agonist or flutamide). Total androgen deprivation was not required to

continue. If the serum testosterone level was not in the castrate range on medical therapy, orchiectomy was to be considered.

Palliative whole brain radiotherapy may be given for documented CNS metastases; protocol chemotherapy was to continue during CNS irradiation.

- **Efficacy Assessments**

All subjects had the following assessments performed every 3 weeks: medical history, physical examination with tumor assessments, performance status, and PSA levels. CBCs and differentials were checked weekly during the first two cycles of M+H, then every 3 weeks x 2, then every 3 months. Every 6 weeks, CXRs, skeletal surveys or xrays of bony involvement, and any other scans required to assess tumor response were performed. EKGs and LVEFs were performed every 3 months on the M+H arm. Changes in analgesic requirements and pain relief were recorded in the medical records.

The National Prostate Cancer Project (NPCP) criteria for tumor response were used (see Appendix for a detailed description). Briefly, response criteria for each disease category are:

For the measurable disease category, standard tumor response criteria for CR, PR, SD and PD were used. In addition, a PR could be defined as a reduction of $\geq$ 80% in PSA level confirmed twice over a 6 week period; a stable or improved performance status on two occasions more than 2 weeks apart was also required.

For the evaluable disease category, standard tumor response criteria for CR and PD were used. A PR was defined as a reduction of $\geq$ 80% in PSA confirmed twice over a 6 week period; a stable or improved performance status was also required. Response must last at least 28 days. Stable disease was defined as meeting neither criteria for CR, PR or SD.

For the bone-only disease category, response was assessed by bone scan, PSA (which must be elevated at baseline) and performance status. These responses were defined as:

CR: normalization of bone scan, tumor markers on two consecutive 3 week evaluations;
PR: a reduction of $\geq$ 80% in PSA confirmed twice over a 6 week period; a stable or improved performance status was also required;
SD: neither a CR, PR or PD; and
PD: either a PSA increase of > 100% of baseline at week 6 confirmed by repeat determination, and/or worsening of performance status by > 1 level, and/or worsening of bone scan. A decrease in performance status of > 1 level as sole evidence of PD was to be discussed with the study chair.

Reviewer Comment: Although not explicitly stated for every category of response, it is assumed that a response duration of at least 28 days was required.

Time to death was calculated from the on-study date to date of death or last date known alive. Time to progression was calculated from the on-study date to date of progression or date of death or date last known alive. TTP data were analyzed in two ways- deaths censored and deaths not censored. Duration of response was calculated from the time complete or partial response is noted until progression. Follow-up after disease progression or treatment failure was for survival only. No information on subsequent therapy given after progression was collected.

- **QOL Assessments**

Following the baseline assessment, QOL was measured by mailed self-administered questionnaires at 6 and 12 weeks, every 12 weeks thereafter, and at end of study. Data was collected by follow-up telephone interviews; completed questionnaires were mailed to Dr. Eric P. Winer, Duke University Medical Center. The assessments consisted of:

1. Functional Living Index - Cancer (FLIC): 22 items presented in linear analog fashion to provide a global assessment of QOL (includes 3 items on pain);

2. Symptom Distress Scale (SDS): 13 items addressing symptoms common to oncology patients (pain - 2 items, nausea, fatigue, etc.);

3. Sexual and Urologic Functioning: 7 items taken from the EORTC Prostate Cancer Patients' QOL Questionnaire;

4. Functional Limitations Scale: 8 items evaluating self-care, mobility, physical activity, and role limitations; and

5. Impact of Pain on Daily Activities: 7 items adapted from the Wisconsin Brief Pain Questionnaire evaluating the impact of pain on mood, relations with other people, walking ability, sleep, work, and enjoyment of life.

If a patient did not speak English, he could enroll on the study but did not need to complete the QOL assessment. If a patient spoke but was unable to read English, the data manager was to complete the QOL assessment with the patient.

- **Safety Assessments**

Adverse events were graded using Use of hematopoietic growth factors was strongly discouraged but these could be used to treat established myelosuppression or to prophylax to prevent recurrent myelosuppression only if dose modifications were also followed.

- **Statistical Plan**

The sample size was computed to have 80% power for detecting a 50% increase in the median survival of patients receiving M+H over those receiving H (survival of patients on H was estimated to be 9-12 months). It is assumed that approximately 100 patients per year would be accrued, with 2/3 having had one prior endocrine manipulation and 1/3 having had more than one endocrine manipulation. Using a 2-sided test at a significance level of .05, and an ineligibility rate of 5%, the accrual goal for this trial was calculated to be 232 patients.

According to the protocol, interim monitoring for survival was planned after 20%, 40%, 60%, 80%, and 100% of the expected number of failures had occurred. Overall survival curves were calculated using the Kaplan-Meier life-table method. Cox proportional hazards model was to be used to examine the joint effect of performance status and treatment on survival. **Reviewer Comment:** The study report does not mention whether interim analyses were performed.

Scores for each of the five QOL instruments were summed to obtain scores for each visit. For each instrument, missing answers resulted in the score for that visit to be mathematically prorated. QOL-derived measures (day 42 best value, change from baseline, and percent change from baseline) were averaged over subject and compared using both analysis of variance and Wilcoxon rank-sum tests.

Rates for disease response categories were compared using chi-square and Fisher's exact tests.

- **Study Conduct**

This study was conducted under a IND (under an agreement with the sponsoring company, and Immunex Corporation, Immunex agreed to sponsor so that the trial could be completed.

Monitoring Committee was responsible for monitoring the study. The study database was maintained by the Data Management Center. Ten of the highest enrolling sites were audited by Immunex in 1995 and records were found to be in good order.

On 12/20/95, FDA requested information on this trial at a meeting with Immunex. released the study database and all data collected to Immunex on 2/29/96. The study report submitted in this supplemental NDA summarizes the data.

Reviewer Comments: Details regarding patient randomization and rate of accrual at each participating site were not provided.

4.22 Baseline Patient Demographics

A total of 242 patients were enrolled in 62 participating sites, 119 patients on the M+H arm and 123 patients on the H arm. Follow-up data were available for 209 (86%) patients (15 patients on the M+H arm and 18 on the H arm had no follow-up data other than last alive dates). Adverse event data were available for 206 (85%) patients. Disease response data were available for 181 (75%) patients. Baseline QOL data were available for 198 (82%) patients, but follow-up assessments at weeks 6 and 12 were available for fewer patients. Information was not provided in this report regarding study drug administration and use of concomitant medications. **Reviewer Comment:** As per sponsor's faxed communication (9/25/96), the final study report for ___ 9182 will be submitted to the NDA when available in mid-to-late 1997.

Table 18. Baseline Characteristics by Treatment Arm*

Characteristic	M+H (N=119)	H (N=123)
Age (yrs) range	72	72
PS 0-1	86%	89%
% Patients w/ Evaluable Disease	70%	69%
Analgesic Use at Entry -None -Non-narcotics -Narcotics	 37% 22% 41%	 39% 21% 40%
Median PSA at Entry (μg/L)	167	167
Prior Hormonal Therapies -O, alone -O + AA -AA, alone -E, alone -L, alone -L + AA -Other	N=116 16% 22% 3% 2% 5% 22% 30%	N=116 6% 28% 3% 1% 3% 22% 38%
# Prior Hormonal Therapies -1 -2 -3 or more	 61% 36% 3%	 58% 37% 5%

*Adapted from sponsor's Tables 3,4, 5 and 7, and Listing 6

The median age of patients enrolled on this trial was 72 years (range 38-85 years). Ninety percent of patients were white. Bone was the most common site of metastases, occurring in 90% of all patients. Other sites were lymph nodes in 28%, lung in 9%, and liver in 6%. As

shown in the table below, treatment arms were well balanced with respect to several baseline characteristics, including number and types of prior hormonal therapies, baseline performance status scores, analgesic requirements, and PSA levels.

Reviewer Comments: Patients enrolled on the two pivotal trials, CCI-NOV22 and 9182 appear to be comparable in several parameters (e.g., sites of disease, baseline PSA level, proportion of orchiectomy patients, etc.). However, compared to the CCI-NOV22 trial, patients on this trial:

1. were slightly older (median age of 72 vs 67 years);
2. had a better performance status at entry (87% vs 63% of patients had a score of 0 or 1);
3. received a greater number of endocrine manipulations (41% vs 32% of patients had 2 or more manipulations);
4. had a greater prior exposure to antiandrogens (72% vs 42%) and to LHRH analogues (43% vs 17%); and,
5. included 38% with no analgesic requirement at baseline; such patients were ineligible for the CCI-NOV22 trial.

Note that since listings of concomitant medications were not provided, it is not possible to document which androgen suppressive therapies, in fact, were continued on study.

- **Comparison of Baseline Patient Characteristics Among Centers**

Table 11 below was adapted from Listings 2, 3, 4, and 6 of the study report to allow side-by-side comparison of the three highest accruing centers. The Dana-Farber Cancer Institute, Barnes Hospital, and University of Chicago enrolled a total of 67 (28%) patients. All centers were balanced with respect to median age and performance status at baseline. Most patients had evaluable disease at entry; it was not possible to ascertain the true number of patients with bone-only disease due to missing data in Listing 3 on specific site involvement.

Patients received at least one prior hormonal manipulation. Unlike patients on CCI-NOV22, very few patients entered this trial with orchiectomy as the sole prior therapy. Most patients had received prior antiandrogen therapy at Dana-Farber and University of Chicago, roughly half had done so at Barnes Hospital. Use of LHRH analogues, however, varied widely. At least one-half to three quarters of patients at these sites had received two prior hormonal manipulations.

Table 19. Baseline Characteristics of Patients at the Three Highest Accruing Centers

Characteristic	Dana-Farber		Barnes		U of Chicago	
	M+H N=7	H N=14	M+H N=13	H N=13	M+H N=8	H N=12
Age (yrs) range	74	72	68	73	73	70
CALGB PS 0-1	86%	100%	100%	92%	100%	83%
% Patients with Evaluable Disease	86%	86%	62%	58%	100%	58%
Prior Hormonal Tx*						
-O, alone	0	0	8%	0	12%	0
-O + AA	0	7%	25%	33%	12%	33%
-AA, alone	14%	21%	0	0	12%	0
-E, alone	0	7%	0	0	0	0
-L, alone	0	0	33%	8%	0	0
-L + AA	71%	43%	17%	17%	38%	8%
-Other	14%	21%	17%	42%	25%	58%
% Pts with Prior AA	100%	93%	42%	58%	88%	92%
# Prior Hormonal Tx's						
-1	14%	28%	42%	8%	25%	0
-2	71%	50%	58%	75%	50%	50%
-3 or more	14%	21%	0	17%	25%	50%

* O = orchiectomy; AA=antiandrogen; E=estrogen; L=LHRH analogue

4.23 Efficacy Results

- **Mitoxantrone Administration**

The study report provided no information on mitoxantrone administration for patients entered on the M+H arm.

- **Survival**

At the time of database transfer to Immunex Corporation, there were 58 (49%) patients alive on the M+H arm, and 68 (55%) patients alive on the H arm. The median time to death was similar on both arms (334 vs 359 days, p= 0.3298).

- **Tumor Response**

Response evaluations were complete for 75% of patients enrolled on this study. Using National Prostate Cancer Project criteria for tumor response, there were 65 (54%) patients who achieved partial response or disease stabilization on the M=H arm, and 57 (47%) patients on the H arm (p=0.20 per FDA).

Reviewer Comment: According to Listing 11, the majority of responses were, in fact, disease stabilization. On the M+H arm, there were 10 PRs for an objective response rate of 8.4%, whereas on the H arm, there were 2 PRs for an objective response rate of 1.6% (p=0.018). These responses were reported in summary form only and could not be independently confirmed. The sponsor's descriptions of these responses are shown in the table below (additional details provided in the Appendix).

The response duration for PRs was calculated using the date of partial response to the date of progression or the date of last follow-up. For the PRs on the M+H arm, the median response duration was 195 days (range 22-410+ days), whereas for the two PRs on the H arm, the response duration was 315+ and 381 days. **Given the small numbers of PRs in either arm, and the incomplete documentation of tumor response and progression in the data listings, one possible conclusion that can be drawn is that durable PRs did occur, but infrequently.**

- **Time to Disease Progression**

The median time to progression for patients on the M+H arm was 218 days versus 122 days for patients on the H arm (p= 0.0654). The median time to progression or death for patients on the M+H arm was 159 days versus 118 days for patients on the H arm (p= 0.0723). **Reviewer Comment:** While these TTP calculations favor the M+H arm, the differences seen are of borderline significance statistically.

Table 20. Disease Status of Partial Responders in 9182

Patient	Disease Site(s)	Site(s) of Response	Site(s) of Progression	Response Duration (days)
	Bone, marrow, lymph node	Lymph node	Bone	22
	Bone	Bone, PSA	Evaluable disease	216
	Bone, lymph node	Bone, PSA	Evaluable disease, PSA	142
	Bone, pleura	Bone, PSA	Evaluable disease, bone, PSA	318
	Marrow	PSA by 32%	Continues with stable disease	410+
	NA	PSA	Evaluable disease	122
	Bone	Bone, PSA	Evaluable disease	322
	Bone, lymph node	Lymph node, PSA	Bone	175
	Marrow	Bone, PSA	Still Responding	101+
	Bone, lymph node	PSA	Still Responding	143+
	Bone	PSA	Continues with stable disease	315+
	Bone	PSA	Evaluable disease, PSA	381

- **Reviewer Analysis of Time to Event Endpoints by Baseline Analgesic Use**

Although both pivotal trials enrolled a majority ($\geq$ 90%) of HRPC patients with bony involvement, over a third of patients on the 9182 trial were relatively asymptomatic in that they required no analgesics at study entry. Since such patients were ineligible for enrollment on the CCI-NOV22 trial, this constitutes a potential major difference in the patient populations being evaluated on these two trials.

Although response rates (by NPCP criteria) were similar for patients regardless of analgesic requirement at baseline, the median time to progression for patients who did not require analgesics at baseline was significantly longer on the M+H arm compared to the H arm (218 vs 108 days). The median TTP for patients who required analgesics at baseline was also longer on the M+H arm but the difference was not significant (310 vs 132 days; TTP curves separated but later came together). Graphical representations of TTP for these two patient subsets are included in the Appendix.

Table 21. Median Time to Progression by Analgesic Requirement at Baseline

Outcome	Analgesics at Baseline		No Analgesics at Baseline	
	M+H (N=73)	H (N=69)	M+H (N=42)	H (N=45)
Treatment Failures	33	41	21	27
Median (days)	310	132	218	108
Log-rank P value	0.4275		0.0243	

No survival differences between treatment arms were noted for the two patient subsets. Survival times may be confounded by the receipt of antineoplastic therapies after cessation of the first randomized treatment.

Table 22. Median Time to Death by Analgesic Requirement at Baseline

Outcome	Analgesics at Baseline		No Analgesics at Baseline	
	M+H (N=73)	H (N=69)	M+H (N=42)	H (N=45)
Treatment Failures	42	39	17	12
Median (days)	276	312	531	Not reached
Log-rank P value	0.1228		0.9188	

These results are exploratory and retrospective, and hence, should be interpreted with caution. Possible conclusions regarding NPCP and palliative response criteria are:

1. NPCP criteria may allow the detection of a positive treatment effect (in terms of TTP, not with respect to tumor response) in patients treated with mitoxantrone + corticosteroids who were relatively asymptomatic (i.e., did not require analgesics at baseline); whereas,

2. Palliative response criteria may allow the detection of a positive treatment effect (in terms of changes in pain intensity and analgesic use) in symptomatic patients treated with mitoxantrone + corticosteroids who require analgesics.

- **Effects on Analgesic Use**

Analgesic usage on study was scored on a scale of 0 - 4, with 0 = no analgesics, 1 = nonnarcotic analgesics taken occasionally, 2 = nonnarcotic analgesics taken regularly, 3 = narcotic analgesics taken occasionally, and 4 = narcotic analgesics taken regularly. Sponsor's

Figures 4 and 5 show the mean analgesic score and the number of analgesic observations for each treatment arm out to day 148. Baseline values were similar for patients on the M+H and H arms, however, a trend toward a reduction in analgesic use over time was noted favoring the M+H arm. **Reviewer Comment:** See sponsor's figures in Appendix. The analgesic use scale in this study did not take into account the number of doses taken of each analgesic as did the scale used in CCI-NOV22.

- **Change in PSA Levels**

Baseline PSA levels were available for most patients enrolled on the study (missing for 3 patients on the M+H arm and for 7 patients on the H arm). Median baseline PSA levels were similar for both treatment arms. When the lowest PSA levels noted are taken into account, more patients on the M+H arm had a reduction in PSA from baseline of $\geq$ 50% than patients on the H arm (31% vs 17%, p= 0.023). PSA reductions of $\geq$ 80% were noted in 13% of patients on the M+H arm vs 5% of patients on the H arm (p= 0.051). **Reviewer Comment:** Defining PSA response as an 80% or greater reduction from baseline is consistent with NPCP response criteria which assign a PR to a patient with evaluable disease or bone-only disease if the PSA level decreases by $\geq$ 80% of the pretreatment value confirmed on two occasions.

- **Quality of Life Assessments**

Five measures were identified prospectively as important endpoints in the assessment of pain and its effects: FLIC questions 11 and 13, SDS pain items 1 and 2, and the Impact of Pain on Daily Activities questionnaire (7 items). Briefly, these measures were:

1. FLIC Question 11: "How uncomfortable do you feel today", rated on a scale of 1 to 7 with 1 being the best score;
2. FLIC Question 13: "How much is pain or discomfort interfering with your daily activities?", rated on a scale of 1 to 7 with 1 being the best score;
3. SDS Pain Item 1: The frequency of pain rated on a scale of 1 ("I almost never have pain" to 5 ("I am in some degree of pain almost constantly");
4. SDS Pain Item 2: The intensity of pain rated on a scale of 1 ("When I do have pain, it is very mild") to 5 ("The pain I have is almost unbearable"); and
5. Impact of Pain on Daily Activities: rated the following seven topics on a scale of 1 ("Does not interfere") to 11 "(Completely interferes"): general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. A sum of all seven questions was used in the analyses.

Baseline vs day 42: Scores on these items were obtained on day 42 ($\pm$ 7 days) and compared to baseline scores for patients on the two treatment arms. Change in actual scores from baseline and the percent change from baseline were evaluated for all patients and for the subset of patients on analgesics at baseline. No statistically significant differences between the two treatment arms were noted for these five measures when evaluated by these methods.

Reviewer Comment: Baseline QOL data were available for 198 of the 242 patients on this trial. The number of patients evaluable both at baseline and at day 42 (± 7 days) for these analyses is relatively small. The sponsor stated that QOL data were incomplete either because evaluations were not obtained, or possibly not entered into the database.

Table 23. Number of Patients Evaluable for QOL Analyses

QOL Measure	All Patients		All Patients on Analgesics at Baseline	
	M+H	H	M+H	H
FLIC Ques 11	43	34	25	19
FLIC Ques 13	45	38	26	23
SDS Pain Item 1	42	35	24	20
SDS Pain Item 2	38	34	22	20
Impact of Pain	40	33	23	19

Baseline vs best score: The same five measures were analyzed for best assessment achieved at **any time** after study entry and for percent change from baseline to best assessment. There were no statistically significant differences between the two treatment arms noted for these measures, with the exception of SDS Pain Item 2 - pain intensity rated on a 5-point scale. For 37 patients on analgesics at study entry treated on the M+H arm, mean pain intensity scores declined from 2.4 to 1.9; for 38 patients on analgesics at study entry treated on the H arm, mean scores declined from 2.3 to 2.2, a borderline significant difference ($p = 0.0630$). The percent change from baseline to best assessment also favored the M+H arm ($p = 0.0560$). On the SDS Pain Item 2, a score of 2 was "When I do have pain, it is mildly distressing", while a score of 3 was "The pain I do have is usually fairly intense".

Reviewer Comments:

1. Missing QOL data has resulted in small numbers of patients being evaluated, and only a single best score is counted rather than consecutive improved scores over time as was done in the CCI-NOV22 trial. Despite these shortcomings, the results here with the SDS Pain Item 2 hint at the utility of a pain intensity scale in detecting treatment differences among symptomatic patients with HRPC.

2. At the recommendation of ODAC (see minutes of the 9/11/96 meeting, Section 9), time trend analyses of analgesic use and pain intensity (as measured by the SDS Pain Item 2) for individual patients on the two treatment arms will be carried out.

4.24 Safety Results

- **Deaths**

Causes of death were available for 86% of the 116 patients reported dead: 52 on the M+H arm and 48 patients on the H arm. The timing of deaths with respect to study drugs was not provided. The most common cause of death was disease progression (28 and 29 patients dying of prostate cancer on each treatment arm). On the M+H arm, there were 8 deaths due to cardiopulmonary arrest and 1 due to congestive heart failure. On the H arm, there were 12 deaths due to cardiopulmonary arrest and 1 due to congestive heart failure. Other causes were infrequent, but did include one death due to sepsis on M+H and one due to pneumonia on H.

- **Serious Adverse Events**

Eight patients on each treatment arm experienced serious adverse events. Only one of these, a case of cerebral hemorrhage occurring on day 36 of therapy with M+H (patient was considered to be possibly related to study drug.

Other than disease progression, on the M+H arm there was a single patient each with: cerebral hemorrhage with subdural hematoma; DIC; endocarditis with fever and hypercalcemia with nausea and dehydration; and interstitial pulmonary fibrosis/hemorrhage.

Other than disease progression, on the H arm there was a single patient each with: GI hemorrhage; duodenal/esophageal ulcers; and pneumonia.

- **Treatment Withdrawals**

Reasons for treatment withdrawals were available for 72% of the 242 patients enrolled on the trial. Withdrawal due to excessive toxicity occurred primarily on the M+H arm.

Table 24. Reasons for Treatment Withdrawal

Reason	M+H (N=85)	H (N=89)
Disease Progression	58	79
Toxicity	13	1
Death	3	2
Patient Refusal	2	3
Completed Study/Max dose	4	0
Other	5	4

Case report forms for the fourteen patients withdrawn for toxicity were submitted and reviewed. Of these, seven patients were removed from study for decreases in LVEF (listed variously as a >15% decrease from baseline or a grade 2 abnormality in cardiac function). These patients were: These documents did not state the cumulative mitoxantrone dose given. "Early CHF" was noted for one patient

- **Adverse Events**

Toxicities were graded on a scale of 1 to 5 according to Expanded Common Toxicity Criteria. Selected adverse events occurring on the M+H and H arms are listed below (adapted from sponsor's Table 11). These events include both those related and unrelated to study drugs.

Table 25. Hematologic Adverse Events

Hematologic Adverse Event	M+H (N=103)	H (N=103)
Leukopenia	88%	4%
-grades 3,4,5	55%	1%
Neutropenia	79%	3%
-grades 3,4,5	57%	1%
Thrombocytopenia	37%	9%
-grades 3,4,5	4%	0
Anemia	72%	40%
-grades 3,4,5	5%	2%

Reviewer Comments: According to Expanded Common Toxicity Criteria, leukopenia grades 3-4 is defined as WBC < 2000; neutropenia grades 3-4 is a granulocyte count < 1000; thrombocytopenia grades 3-4 is a platelet count < 50,000; anemia grades 3-4 is a Hgb < 8. (While grade 5 toxicities were not defined, the sponsor combined grades 3-5 in its adverse event tables.) Thus, the incidence of grades 3-5 toxicities as reported here are not strictly comparable to the grade 4 toxicities reported for the CCI-NOV22 trial.

Grades 3-5 toxicities occurring in $\geq$ 5% of patients on the M+H arm were: leukopenia, neutropenia, anemia, sterility (6%), and elevations of alkaline phosphatase (11%). Grades 3-5 elevations of alkaline phosphatase occurred on the H arm with a frequency of 9%. Hypercalcemia grade 1 or 2 was reported in 5 patients, two on the M+H arm, and three on the H arm.

Compared to the adverse events reported in the CCI-NOV22 trial, the following events were

reported with **greater** frequency on this trial: anemia and edema (both arms); cardiac dysfunction (M+H arm only). Compared to the adverse events reported in the CCI-NOV22 trial, the following events were reported with **lower** frequency on this trial: nausea, hyperglycemia, and elevations of alkaline phosphatase (both arms).

Table 26. Non-Hematologic Adverse Events

Non-Hematologic Adverse Event	M+H (N=103)	H (N=103)
Nausea	24%	10%
Fatigue	34%	17%
Alopecia	20%	2%
Anorexia	24%	15%
Constipation	8%	3%
Dyspnea	12%	8%
Edema	29%	17%
Stomatitis	8%	2%
Vomiting	11%	6%
Infection	18%	4%
Decreased Cardiac Function	16%	0
Congestive Heart Failure	2%	1%
Impotence/Libido	8%	4%
Sterility	6%	4%
Hyperglycemia	30%	31%
Elevated Transaminase	19%	17%
Elevated Alk Phos	39%	41%

4.25 Sponsor's Conclusions

This study involved institutions throughout the United States and was designed to mimic typical oncology practice. Patients were eligible if they had disease progression demonstrated by clinical signs and symptoms, imaging studies and/or isolated PSA elevations. Patients were not required to have symptomatic HRPC at study entry. No crossover was permitted.

The primary endpoint of survival was similar for patients on both treatment arms. These results were possibly confounded by therapies given after the failure of primary treatment.

Using NPCP tumor response criteria, responses (partial responses + disease stabilization) were comparable in both treatment arms. However, when only partial responses are evaluated, a significantly improved response rate was noted for the M+H arm (8.4% vs 1.6%, $p=0.018$). Median time to progression was longer for patients on M+H as compared to patients H, with $p= 0.0654$.

A trend toward a reduction in analgesic use over time was noted favoring the M+H arm.

A statistically significant difference favoring the M+H arm was noted for PSA declines of $\geq$ 80% from baseline, and for PSA declines of $\geq$ 50% from baseline.

Patients on both arms had similar baseline scores on QOL measures. There was a trend favoring the subset of patients on analgesics on the M+H arm with regard to best post-baseline scores and percent change from baseline for the SDS Pain Item 2 (a 5-point pain intensity scale).

This study did not reveal previously unreported adverse events. The rate of cardiotoxic events was not higher than the rates reported in other studies of mitoxantrone.

The combination of mitoxantrone + hydrocortisone was effective for the treatment of patients with hormone-resistant prostate cancer who have failed hormonal therapy. The combination did not produce significant toxicity.

5. Supportive Studies

5.1 CCI-NOV16: Mitoxantrone + Prednisone

- **Study Design**

Report of this phase 2 study of mitoxantrone plus low-dose prednisone as first line therapy for HRPC was provided in Volume 8 of the NDA. The study, conducted at seven Canadian centers between July 1989 and June 1990, was undertaken to define the palliative response endpoint for subsequent use in the CCI-NOV22 trial (i.e., the phase 3 study of mitoxantrone plus prednisone vs prednisone alone).

Eligible patients had a history of locally advanced (T4) or metastatic prostate cancer which was hormone-resistant (defined as progression or recurrence in the face of a standard hormonal maneuver) and a documented castrate serum testosterone concentration (< 30 ng/mL). All patients were required to have disease-related pain not controlled by analgesics or radiotherapy, and an ECOG performance status of 3 or better.

Palliative response was defined as at least a 50% decrease in analgesic use score from baseline OR a 2-point decrease from baseline in a 6-point pain intensity scale and no increase in analgesic use. A palliative response must be maintained for two consecutive treatment courses (approximately 6 weeks). **Reviewer Comments:** This definition encompasses both primary and secondary response criteria used in the analysis of the CCI-NOV22 trial. Analgesic use was computed for the week prior to the study visit date as follows: each dose of a non-narcotic analgesic taken was assigned a 1; and each dose of oral narcotic was a 2. This was the same scoring system used in CCI-NOV22, except that the latter trial also assigned each dose of IV narcotic a score of 4.

Disease response was also defined in this study. A PR required a 50% reduction in measurable tumor mass from baseline OR a 75% improvement from baseline in one the of the markers for evaluable disease (PAP, PSA or CEA). Responses of this type were also to be maintained for two consecutive treatment courses (approximately 6 weeks).

Patients kept daily analgesic diaries and completed the EORTC Core questionnaire and disease-specific Prostate Module. Data from these two instruments, however, were not provided to the sponsor and were not included in their final report.

The mitoxantrone starting dose was 12 mg/m^2 every 21 days. Dose modifications (either 2 mg/m^2 up or down) were similar to those in the CCI-NOV22 trial. The maximum cumulative dose was 152 mg/m^2. All patients received prednisone 10 mg PO daily as a single dose.

Orchiectomy patients were to have their hormone therapy withdrawn unless a documented second line response had been observed. Non-orchiectomy patients continued on standard

hormonal therapies, and were required to have a castrate testosterone level for a minimum of one month.

- **Baseline Patient Demographics**

Twenty-seven patients were entered on this trial; ten of these (37%) were enrolled at Princess Margaret Hospital. The median age was 70 years (range 54-87 years). The median time from first diagnosis of prostate cancer was 2 years (range 1 to 15 years). Seven patients (26%) had measurable disease. Bone was the most common site of metastases, occurring in 81% of patients. Previous therapy consisted of orchiectomy alone 26%, orchiectomy plus medical therapy in 19%, and medical therapy alone in 56%. The median PSA level at baseline was 173 μg/L (range 6-1970 μg/L).

Baseline PI score was 1 in 22%, 2 in 41%, 3 or 4 in 34%. The median analgesic use score was 13 (range 0-76). Additionally, the study report notes that the "palliative status of this patient population was far from homogeneous, and the baseline analgesic use scores are not normally distributed".

- **Mitoxantrone Administration**

The 27 patients completed a total of 126 courses of mitoxantrone and low-dose prednisone (median of 4 courses). The median cumulative dose of mitoxantrone delivered was 48 mg/m^2 (range 12-136 mg/m^2). **Reviewer Comment:** Patients on this trial received less mitoxantrone than the 80 patients on the M+P arm of CCI-NOV22: a median of 4 courses vs 6.5, and a median cumulative dose of 48 mg/m^2 vs 73 mg/m^2. No information was provided on the receipt of prior radiotherapy which may have hampered delivery of mitoxantrone.

- **Palliative Response**

Nine patients achieved either a complete (4 patients) or partial (5 patients) palliative response. Thus, the overall palliative response rate was 33% (95% CI: 13-53%). Five responses were achieved after the first treatment course; the remainder were documented after the second treatment course. Response was maintained for a median of 4 treatment courses or 12 weeks (range 6-27 weeks).

The study report cautions that analysis of pain intensity revealed that one cannot account for any corresponding change in analgesic use. By increasing analgesic use, a patient's pain level may decrease, independent of any effect of the study medication. For this reason, the sponsor expects the analgesic score to be the more unbiased measure of pain relief. In this study, no significant reduction in analgesic use was detected after any treatment course. Thus, it was concluded that pain intensity should not be used alone in the assessment of pain relief.

In addition, the study report states, "The non-sensitivity of the analgesic score to detect pain relief seems to contradict the overall palliative response. However, the failure of the analgesic use score to detect a significant response in the early treatment courses may be due to the non-homogeneous nature of the patient population with respect to this score". "Small sample sizes, especially in the later treatment courses, may account for the failure to detect a significant change from baseline. Finally, this analgesic use score had not been validated prior to this study, and perhaps a further review of the scoring system is required."

Reviewer Comments:

1. The statements quoted above lend insight to the choice of criteria for defining palliative response in the pivotal phase 3 trial, CCI-NOV22. Recall that the primary endpoint prospectively defined in that trial was an improvement in pain intensity without an increase in analgesic use score. The second criterion for response, defined as an improvement in analgesic score without an increase in pain intensity, was also assessed and described in the study report. However, the sponsor's analyses of palliative response duration and time to progression were based on those patients with a response based on the primary criterion only.

2. The published report of this trial by MJ Moore et al. (JCO 12:689-694, 1994) states that of 9 patients who had received total androgen blockade, 5 withdrew antiandrogen therapy prior to starting mitoxantrone. Only one of these patients achieved a palliative response. Antiandrogen withdrawal syndrome was not well recognized at the time the study was performed. This publication is included in the sponsor's ODAC briefing document.

- **Disease Response**

Three patients achieved either a partial disease response for an overall disease response rate of 11% (95% CI: 3-30%). One patient had a > 50% reduction in a measurable cervical lymph node mass that was maintained for 8 treatment courses. The other two patients had a > 75% reduction in PAP that was maintained for 6 courses in 1 patient and for two courses in the other. **Reviewer Comment:** The published report of this trial states that using NPCP criteria, there would be only one partial responder, and 12 patients with stable disease for more than 2 months.

- **Other Efficacy Endpoints**

The median time to disease progression (measured from the date of study entry) was 51 days (range 20-545 days). The median survival was 172 days (range 50-810 days). Among evaluable patients with adequate follow-up levels, a > 75% reduction in tumor markers was noted for PSA in 4% of patients (1/23 patients) and for PAP in 31% (5/16 patients).

Reviewer Comments:

1. Patients in the CCI-NOV16 and CCI-NOV22 trials experienced similar palliative response rates (33% vs 38%) and rates of disease progression (56% vs 63%). However, TTP and survival endpoints in this trial were surprisingly shorter than those observed on the M+P arm of CCI-NOV22 (TTP: 51 vs 148 days; survival: 172 vs 339 days).

2. The published report of this trial included quality of life analyses. All 27 patients completed baseline EORTC core QOL questionnaires and the Prostate Module. Seventeen patients did not complete three on-study questionnaires, 16 due to disease progression and one due to withdrawal from the study for other reasons. Social functioning and pain scores, in particular, improved throughout the on-study period. No demonstrable changes were noted in physical functioning or in global QOL scores. These QOL instruments were later used in the pivotal CCI-NOV22 trial.

- **Safety Results**

WHO Grade 4 hematologic toxicities were noted as follows: ANC < 500, 44%; ANC < 100, 7%; and anemia 4%. There were no reports of grade 4 thrombocytopenia.

Nausea or vomiting was reported by 48% of patients; no case was grade 2 or higher. Mild alopecia was reported by 37%. Infections developed in 3 patients: one case each of shingles, UTI and thrush.

- **Treatment Withdrawals**

Nine patients (33%) completed the required treatment period of at least 8 courses. Fifteen patients (56%) experienced disease progression prior to completing 8 courses. Two patients developed concurrent illness (DVT or hypercalcemia) requiring protocol-violating therapy and one patient developed claustrophobia after 1 week on prednisone which he attributed to therapy.
No patient on this trial withdrew for toxicity (compared to 11 of 80 (14%) patients on the M+P arm of CCI-NOV22 who withdrew for this reason).

5.2 Princess Margaret Hospital Study: Prednisone Alone

Tannock et al. published the Princess Margaret Hospital experience with prednisone alone as therapy for patients with metastatic prostate cancer (JCO 7:590-597, 1989; see sponsor's ODAC briefing document). A retrospective chart review of 28 patients treated with prednisone between 1976 and 1980 revealed that 25% had improvement in pain with a reduced requirement for analgesics for a median of 5 months (range 2-11 months).

This observation lead to the development of a prospective trial in thirty-seven HRPC patients with progressive symptomatic bone metastases despite estrogen therapy or previous orchiectomy. Patients received either 5 mg prednisone qAM and 2.5 mg qPM or 5 mg bid. Patients on estrogen therapy were allowed to continue it on study.

Pain was assessed using the 6-point pain intensity scale, and a more complex pain rating index. Analgesic use was scored as in the CCI-NOV16 study, and patients were required to complete 17 linear analog self-assessment (LASA) scales.

The median age was 62 years (range 46-76 years); the median interval from diagnosis of prostate cancer was 27 mos (range 6-119 mos). Patients had received a median of 2 prior endocrine therapies (including orchiectomy and different estrogens). The mean pain intensity score was 2 and the mean analgesic use score was 10.

Of the 37 patients, 14 or 38% had improvement in pain and a decreased or stable requirement for analgesics for a minimum of 1 month. Five patients became free of pain and required no analgesics while seven patients experienced improvement for 3 to 30 months (median of 4 months). There was little evidence for consistent improvement in serum PAP or alkaline phosphatase levels, or in xrays or bone scans. However, symptomatic response was associated with a decrease in serum levels of adrenal androgens.

Reviewer Comments:

1. This pilot study demonstrated the use of pain intensity scores and analgesic use scores in the evaluation of treatments for symptomatic patients with HRPC. The publication does not state whether a predetermined decrease in pain intensity (e.g., 2 points) was required to define response, as was the case in CCI-NOV16 and CCI-NOV22. Thus, if any magnitude decrease was permitted, the palliative response rate could have been inflated (compare the 38% response rate here vs the 12% response rate for patients on the P arm in CCI-NOV22 using the primary criterion of response only).

2. As in the previous studies described in this review, the palliative response appears to have greater sensitivity for assessing treatment effects in symptomatic HRPC patients as compared to "objective" radiographic or biochemical methods of determining response. No time to event parameters for the study population as a whole were provided.

5.3 Single Agent Mitoxantrone Therapy

Single agent mitoxantrone therapy, administered every 21 days was evaluated in three phase 2 studies enrolling 104 patients. The CCI-NOV14 trial, with 38 HRPC patients, is reviewed in detail below. Two additional published studies in this patient population were conducted by SWOG (CK Osborne et al., Cancer Treat Rep, 67:1133-1135, 1983) and by Raghavan et al. (Proc ASCO, 5:395, 1986). In the SWOG study poor-risk patients (n=20, age > 70 years,

heavy prior chemotherapy or poor tolerance to chemotherapy, prior radiotherapy to > 25% of bone marrow) received mitoxantrone 10 mg/m² every 21 days. Good-risk patients (n=17) received mitoxantrone 12 mg/m² every 21 days. Patients received a median of five treatment courses. Of 35 evaluable patients for response, two (6%) had an objective partial response lasting 7 and 17+ months. In the study conducted by Raghavan et al., mitoxantrone 12-14 mg/m² every 21 days was administered to 29 patients, none of whom had received prior chemotherapy. The median cumulative mitoxantrone dose was 36 mg/m². One patient achieved a PR, while eight patients had improvement in pain, performance status and in QOL measures.

Results of single agent mitoxantrone therapy given by other schedules have been published for 39 patients. Dosing schedules investigated were: escalating-dose continuous infusions (PW Kantoff, et al., Am J Clin Oncol, 16:489-491, 1993); 3-4 mg/m² IV bolus weekly (TP Rearden et al., Proc ASCO, 11:688, 1992); and, 10 mg IV bolus weekly (R Knop et al., Proc ASCO, 12:250, 1993). All studies showed modest objective response rates with improvement noted in pain, performance status, or QOL measures.

5.31 CCI-NOV14

- **Study Design**

Report of this phase 2 study of mitoxantrone as first line therapy for hormone-resistant metastatic or locally advanced prostate cancer was provided in Volume 8 of the NDA. The study was conducted by the
between February 1984 and March 1988. As it was widely known that objective response by NPCP criteria was not common, this study attempted to incorporate pain relief, performance status and disease markers into the efficacy criteria.

Eligible patients had a history of prostate cancer which was hormone-resistant (defined as progression or recurrence in the face of a standard hormonal maneuver) and a documented castrate serum testosterone concentration (< 30 ng/mL). All patients were required to have an ECOG performance status of 3 or better.

In addition to standard NPCP criteria for response, a palliative response was defined using a 5-point scale (0=no analgesics; 1=ASA/Tylenol; 2=codeine; 3=oral narcotics; and, 4=parenteral narcotics). A CR required a decrease in pain score from 3 to 0 or from 2 to 0 maintained for at least 6 weeks. A PR required a 2-point decrease (e.g., from 3 to 1) for at least 6 weeks. A patient was not evaluable for a palliative response if the baseline pain score was 0 or 1, or if the pain was not evaluated at or after 6 weeks. **Reviewer Comments:** This definition of palliative response is essentially based on the type of analgesic used (at two specific timepoints only?) and does not take into account the dose of analgesics consumed over time. This scale was not used in the response evaluation of later trials.

The mitoxantrone starting dose was 12 mg/m² every 21 days. The maximum cumulative dose was 160 mg/m².

- **Baseline Patient Characteristics**

Thirty-eight patients were enrolled with a mean age of 68 years (range 39-87 years). Twenty patients were stage D_2, 6 were stage D_1, 8 were stage C, 3 were stage B_2 and 1 was stage B. The mean time from diagnosis of prostate cancer to study treatment was 3.6 years (range 0.3-12.1). Previous therapy consisted of orchiectomy alone in 37%, orchiectomy + medical therapy in 18%, and medical therapy alone in 45%. The median ECOG performance status at baseline was 2, and the median pain score at baseline was 2 (=codeine). Four patients had baseline pain scores of 0 or 1 and were unevaluable for a palliative response.

- **Efficacy Results**

A total of 182 treatment courses were administered with a mean of 4.8 courses (range 1-8). The median cumulative mitoxantrone dose delivered was 60 mg/m² (range 10-154 mg/m²).

There were no objective responses based on NPCP criteria. However, 11 of 34 evaluable patients achieved a complete palliative response and 1 additional patient achieved a partial palliative response, for an overall palliative response rate of 35%. A partial PAP response was observed in 17% (5/29) of patients (defined as a $\geq$ 75% decrease in PAP from an elevated baseline of $\geq$ 12 µg/L which was maintained for at least 6 weeks).

The median TTP (all patients, NPCP criteria) was 81 days (range 21-252 days). Median survival was 238 days (range 40-570 days).

Reviewer Comments: Compared to patients on the M+H arm of the trial, the median TTP (81 vs 218 days) and survival (238 vs 334 days) results in this trial are shorter (both trials defined progression using NPCP criteria). This is surprising given that nearly a third of the study population had stage B or C prostate cancer. On the other hand, most patients had a performance status of $\geq$ 2. The omission of corticosteroids in the CCI-NOV14 trial also may have resulted in a less satisfactory outcome.

- **Safety Results**

There were no unexpected toxicities observed. There were no withdrawals for toxicity. Primary cause of death was reported as prostate cancer in 28 patients, as marantic endocarditis, congestive heart failure or CVA in 1 patient each, or as missing in 6 patients.

5.4 Mitoxantrone plus Other Cytotoxics

Additional phase 2 studies of mitoxantrone in combination with other cytotoxic agents have

been conducted in HRPC patients. CCI-NOV6 evaluated mitoxantrone/5FU/mitomycin C. Two studies evaluated mitoxantrone/cisplatin (CK Osborne et al., Eur J Cancer, 28:477-478, 1992; and J Kuhbock et al., Rec Adv Chemother, 1031-1033, 1994) and one study evaluated mitoxantrone/5FU/high-dose folinic acid (R Magarotto et al., Ann Oncol, 5(Suppl 8):73, 1994). Efficacy results in these trials are consistent with those cited above for mitoxantrone alone or mitoxantrone plus corticosteroids.

6. Integrated Summary of Efficacy

Phase 1/2 trials of single agent mitoxantrone conducted in HRPC patients in the early 1980s showed modest cytotoxic activity in this patient population using standard disease response criteria. Studies conducted in the mid to late 1980s also demonstrated effects of mitoxantrone on cancer-related symptoms, particularly pain. In general, mitoxantrone was reasonably well tolerated.

Two phase 3 studies comparing mitoxantrone plus corticosteroids vs corticosteroids alone have been conducted and serve as the pivotal trials for this supplemental NDA. The studies were both multicenter and open-label in design and evaluated similar dosing regimens. The studies differed in their requirement for symptomatic patients, in the crossover design, in the choice of primary efficacy endpoints and QOL instruments.

The tables below summarize important features of these phase 3 trials and two earlier pilot phase 2 studies, the CCI-NOV16 trial (mitoxantrone plus prednisone) and the CCI-NOV14 trial (mitoxantrone alone).

Table 27. Comparison of Phase 2 and 3 Trials of Mitoxantrone +/- Corticosteroids

Feature	CCI-NOV22	9182	CCI-NOV16	CCI-NOV14
Design	Randomized	Randomized	Phase 2	Phase 2
Crossover?	Yes	No	NA	NA
Treatment Arms	M+P vs P	M+H vs H	M+P	M
# Patients	80 vs 81	119 vs 123	27	38
Prior Chemo?	No	No	No	No
Pain at Entry	Yes	Not mandatory	Yes	Yes
Antiandrogen Continued?	Probably not	Probably	Yes, in 4/9 patients	NA
Primary Endpoint	Palliative Response	Survival	Palliative Response	NPCP Response
QOL Assessed?	Yes	Yes	Yes	No

Table 28. Characteristics of Patients Receiving Mitoxantrone + Corticosteroids

Characteristic	CCI-NOV22 M+P	9182 M+H	CCI-NOV16 M+P	CCI-NOV14 M
Median Age (years)	67	72	70	68
% w/ Bone Mets	98%	91%	81%	NA
Performance Status ≥ 2	37%	14%	NA	74%
Mean PI Score at Entry	2	NA	2	NA
Mean Analgesic Score at Entry	26	2 (0-4 scale)	23	2 (=codeine)
Median Baseline PSA (μg/L)	180	167	173	150

Table 29. Efficacy Results for Patients Receiving Mitoxantrone + Corticosteroids

Endpoint	CCI-NOV22 M+P	9182 M+H	CCI-NOV16 M+P	CCI-NOV14 M
Median Cumulative Dose (mg/m^2)	73	NA	48	60
Overall Palliative Response	35%[1] (PI/analgesic use)	NA	33% (PI/analgesic use)	35% (analgesic use)
NPCP Response	NA	8.4%[2] (NPCP, PRs only)	4% (PRs only)	0
PSA Reduction	27%[3] (PSA dec $\geq$ 75%)	13%[4] (PSA dec $\geq$ 80%)	4% (PSA dec $\geq$ 75%)	NA
Response Duration (days)	169[5] (1° + 2° palliative response)	195 (NPCP, PRs only)	84 (palliative response)	NA
Median TTP (all patients, days)	131[6]	218[7]	51	81
Median Survival (all patients, days)	339	334	172	238

[1] p=0.055 [2] p=0.011 [3]p=0.0004 [4]p=0.0001 [5]p=0.018 [6]p=0.051
[7]p=0.0654

The shaded areas refer to efficacy endpoints in the pivotal phase 3 trials that approached or achieved statistical significance for the mitoxantrone + corticosteroid arm over the corresponding corticosteroid arm. The corrected response duration and TTP results for the CCI-NOV22 trial are given here.

The next two tables summarize important features of patients receiving corticosteroids alone on the two pivotal phase 3 trials.

Table 30. Characteristics of Patients Receiving Low-dose Corticosteroids

Characteristic	CCI-NOV22 Prednisone	9182 Hydrocortisone
Median Age (years)	67	72
% w/ Bone Mets	95%	90%
Performance Status $\geq$ 2	38%	11%
Mean PI Score at Entry	2	NA
Mean Analgesic Score at Entry	19	2 (0-4 scale)
Median Baseline PSA (µg/L)	156	167

Table 31. Efficacy Results for Patients Receiving Low-dose Corticosteroids

Endpoint	CCI-NOV22 Prednisone	9182 Hydrocortisone
Overall Palliative Response	21%	NA
Disease Response	NA	1.6% (NPCP, PRs only)
PSA Reduction	5% (PSA decrease $\geq$ 75%)	5% (PSA decrease $\geq$ 80%)
Response Duration (days)	57 (1° + 2° palliative response)	315+, 381 (NPCP, 2 PRs only)
Median TTP (all patients)	69	122
Median Survival (days)	324	359

Interpretation of QOL results is made difficult by missing values and by the use of multiple comparisons. In general, patients in both arms of the two phase 3 trials had comparable QOL findings at baseline. On the CCI-NOV22 trial, there was a trend favoring better results in patients treated on the M+P arm when measures evaluating disease-related symptoms were assessed. On the trial, there was a trend favoring better results in patients on the M+H arm for pain-related measures, particularly for the subset of patients who required analgesics at baseline. In the Princess Margaret Hospital pilot study of prednisone alone, reduction in pain was also associated with improved overall well-being.

The sponsor's major conclusion is that the combination of mitoxantrone + corticosteroids results in a nearly double palliative response rate and in a nearly double duration of response over corticosteroids alone.

Reviewer Comments:

1. The sponsor's conclusion is based primarily on the findings of the CCI-NOV22 trial, as the trial did not assess palliative response.

2. The CCI-NOV16 pilot trial (mitoxantrone + prednisone) supports the idea that palliative response can be achieved in a third of patients, however, time to event endpoints are shorter than those noted in the phase 3 CCI-NOV22 trial.

3. The CCI-NOV14 trial (mitoxantrone alone) supports the contention that NPCP criteria are less sensitive than measures of palliative response in discerning treatment effects that primarily impact on disease-related symptoms. However, time to event endpoints on this trial are shorter than those noted in the phase 3 trial that utilized NPCP criteria.

7. Integrated Summary of Safety

Detailed safety information is available for a total of 353 patients treated with mitoxantrone, including 274 patients who received mitoxantrone in combination with corticosteroids. Section 4 of this review summarizes the major findings for the two pivotal trials. The adverse events reported in these two trials were not different from that reported for mitoxantrone's labeled indication (acute non-lymphocytic leukemia). When mitoxantrone is administered at doses of 12 to 14 mg/m^2 every 21 days, the principal toxicity is myelosuppression, particularly neutropenia.

Decreases in LVEF and congestive heart failure occur. Product labeling states that for patients who receive a cumulative dose of 140 mg/m^2, the cumulative probability of developing moderate or serious decreases in LVEF is 13%, and of congestive heart failure, 2.6%. Cardiotoxicity may be more common in patients with pre-existing cardiac disease or in those who previously received anthracyclines or mediastinal radiotherapy. Labeling recommends that such patients should have regular monitoring of LVEF from the start of therapy.

There was no evidence of clinically apparent drug-drug interactions when mitoxantrone was administered with corticosteroids. In particular, there was no evidence for increased nausea, vomiting, alopecia, marrow suppression or cardiotoxicity for the combination compared to single agent mitoxantrone administered to patients with HRPC or other solid tumors.

The only known long-term adverse event resulting from mitoxantrone administration is the development of rare cases of secondary leukemia one to five years later. This observation is consistent with events following administration of other topoisomerase II inhibitors. The leukemias are characterized by non-random cytogenetic abnormalities, low response rates to standard chemotherapy regimens, and poor outcomes. No cases of secondary leukemia have been reported among HRPC patients who received mitoxantrone.

- **Post-Marketing Surveillance**

In addition to the safety results reported for individual trials, the entire mitoxantrone post-marketing database at Immunex Corporation was searched for COSTART terms reported five or more times since mitoxantrone's approval in the US in 1987. The only unlabeled events reported five or more times are: death (19 events), dehydration (5 events), subdural hematoma (5 events), and skin discoloration (10 events).

Dehydration may be a complication of vomiting and diarrhea, both of which are expected adverse events with mitoxantrone. Skin discoloration is associated with the blue color of mitoxantrone which may extravasate from an injection site (blue sclera and urine are labeled). The five reports of subdural hematoma were contained in one publication involving intensive chemotherapy for acute myeloid leukemia (E Jourdan et al., Brit J Haematol, 89:527-530, 1995). The authors did not single out mitoxantrone as the cause. Rather, the etiology of these

events was believed to be related to meningeal leukemic infiltration and hyperleukocytosis.

In addition to one death due to disease progression, the causes of death reported were:

Table 32. Post-Marketing Deaths in Patients Receiving Mitoxantrone

Cause of Death	Frequency	Labeled?
Acute tumor lysis syndrome	2	Yes
Arrhythmia	1	Yes
Cardiac arrest due to intrapleural injection	2	No
Cerebral infarct due to thrombocytopenia	1	No
Congestive heart failure	3	Yes
Secondary leukemia	3	Yes
Sepsis	3	Yes
Multisystem organ failure	1	No
Neurologic toxicity due to high dose Ara-C	2	No

Reviewer Comment: The sponsor has proposed additional statements in product labeling regarding dehydration, injection site reactions, and skin discoloration.

The sponsor's conclusions are that mitoxantrone 12 to 14 mg/m^2 every 21 days is well tolerated by the somewhat older patient with HRPC. No differences were noted in the safety profile of the two starting doses evaluated. No unexpected adverse events occurred in the HRPC patients studied thus far.

8. Four-Month Safety Update

A 4-month safety update was submitted on 9/9/96 that provides updated safety information for the two phase 3 trials available as of June 3, 1996 (for the CCI-NOV22 trial) or July 3, 1996 (for the [redacted] 9182 trial).

- **CCI-NOV22 Trial**

Since the original filing of this supplemental NDA in May 1996, there have been four additional deaths among patients enrolled on this study. One patient treated on the M+P arm and three patients on the P arm who later crossed over to the M+P arm have died as of their last follow-up. At least one year had elapsed between the date of last mitoxantrone administration and date of death. Reasons for death were not provided. In summary, there have been a total of 154 deaths (76 on the M+P arm, 78 on the P arm) on this study.

There have been no additional reports of treatment withdrawals due to toxicity.

Twenty-two previously unreported SAEs were recorded for 22 patients at 7 sites. On the M+P arm these were: back pain/spinal cord compression (2 patients), GI symptoms (3 patients), pain (2 patients), pneumonia (1 patient), cardiorespiratory failure (1 patient), and general wasting (1 patient). On the P arm SAEs were: back pain/spinal cord compression (3 patients), GI symptoms (2 patients), pain (1 patient), pneumonia (1 patient), GU symptoms (1 patient), hip fracture (1 patient), hyperglycemia (1 patient), and disease progression (1 patient). One patient on the P arm developed a blood clot after crossover. In summary, a total of 65 SAEs were reported, with 31 on the M+P arm and 34 on the P arm (26 prior to crossover). **There have been no new reports of cardiotoxicity.**

No additional information on clinical laboratory results has been reported, thus an updated tabulation of hematologic adverse events could not be created.

The table below lists selected non-hematologic adverse events included in the original filing or in this update that occurred in patients on the M+P arm or on the P arm prior to crossover. A complete listing of adverse events is provided in sponsor's Table 1 of the safety update. The information provided by investigators did not permit the assignment of intensity grading.

Table 33. Non-Hematologic Adverse Events (Any Intensity)

Non-Hematologic Adverse Event	M+P (N=80)	P (toxicities prior to crossover) (N=81)
Nausea	61%	35%
Fatigue	39%	14%
Alopecia	29%	0
Anorexia	25%	6%
Constipation	16%	14%
Dyspnea	11%	5%
UTI	9%	4%
Edema	10%	4%
Mucositis	10%	0
Vomiting	5%	3%
Systemic Infection	10%	7%
Pneumonia	4%	3%
Decrease in LVEF	8%*	0
CHF	4%	0
Hyperglycemia	80%	75%
Elevated SGOT	34%	36%
Elevated Alk Phos	79%	94%
Elevated LDH	32%	30%

*includes two cases of CHF

- 9182

Twenty-six additional deaths occurred since the filing of this supplemental NDA: 12 deaths on the M+H arm and 14 deaths on the H arm. Reasons for death were not provided. The total number of deaths for patients on this study is 142 (73 on the M+H arm, 69 on the H arm).

Seventy-six new adverse events graded as 3/4 were reported (66 on the M+H arm, 10 on the H arm). The majority of these events were hematologic or laboratory abnormalities. The tables below show adverse hematologic and non-hematologic events of any severity, and are derived from sponsor's Table 2. **Reviewer Comment:** At the ODAC Meeting (9/11/96),

the sponsor indicated that 54% of patients on the M+H arm had an ANC < 500, 11% had neutropenic fever (no specific definition provided), and 4% had a platelet count < 50,000.

Table 34. Hematologic Adverse Events (Any Severity)

Hematologic Adverse Event	M+H (N=112)	H (N=113)
Leukopenia	87%	4%
Neutropenia	79%	3%
Thrombocytopenia	39%	7%
Anemia	75%	39%

Table 33. Non-Hematologic Adverse Events (Any Severity)

Non-Hematologic Adverse Event	M+H (N=112)	H (N=113)
Nausea	26%	8%
Fatigue	34%	14%
Alopecia	20%	1%
Anorexia	22%	14%
Constipation	7%	2%
Dyspnea	15%	8%
Edema	30%	14%
Stomatitis	8%	1%
Vomiting	11%	5%
Infection	17%	4%
Decreased Cardiac Function	18%	0
Congestive Heart Failure	2%	1%
Impotence/Libido	7%	3%
Sterility	5%	3%
Hyperglycemia	31%	30%
Elevated Transaminase	20%	14%
Elevated Alk Phos	37%	38%

- **Additional Information**

There is no new safety information related to dose, no new information on drug-drug interactions or long-term adverse events. A spontaneous post-marketing report from Japan (15-day report to FDA, 96-05-0071) stated that a 36 year old female with acute lymphocytic leukemia had received an accidental intrathecal injection of 15 mg of mitoxantrone and developed lower extremity paralysis.

- **Summary and Conclusions**

The additional safety information presented in this update is consistent with the safety profile of mitoxantrone previously reported in the original filing of this supplemental NDA. Survival remains similar for hormone-resistant prostate cancer patients treated on the pivotal phase 3 trials, CCI-NOV22 and 9182, regardless of treatment assignment.

9. ODAC Meeting (9/11/96)

Efficacy results for hormone-resistant prostate cancer patients enrolled on the two open-label controlled trials comparing mitoxantrone plus corticosteroids versus corticosteroids alone are shown below. P values are given for those comparisons that approached or achieved statistical significance. Selected disease-specific quality of life measures showed consistent trends in favor of the combination, but differences between treatment arms were not statistically significant.

Efficacy Endpoint	CCI-NOV22		9182	
	Mitoxantrone/ Prednisone N=80	Prednisone N=81	Mitoxantrone/ Hydrocortisone N=119	Hydrocortisone N=123
Palliative Response Rate (1° Criterion)	21 (26%)	10 (12%) p=0.029	NA	NA
Palliative Response Rate (1° + 2° Criteria)	28 (35%)	17 (21%) p=0.055	NA	NA
NPCP Response (PRs + stable disease)	NA	NA	54%	47%
Response Duration (1° + 2° responders, days)	207	57 p=0.0007	NA	NA
PSA Reduction	27%	5% p=0.011 (PSA decrease ≥ 75%)	13%	5% p=0.051 (PSA decrease ≥ 80%)
Time to Progression (all patients, days)	168	62 p=0.0001 (pain intensity/analgesic use)	218	122 p=0.0654 (NPCP criteria)
Survival (median, days)	339	324	334	359

(**Reviewer Comment:** For the CCI-NOV22 trial, the response duration and TTP have been re-calculated; Tables 29 and 31 of this review list the corrected results.)

Question 1. Usually pain assessments are blinded since pain scales are sensitive to small changes that may or may not be due to the treatment of interest. In the CCI-NOV22 trial, palliative response was defined as a 2-point decline on a 6-point pain intensity scale with stable analgesic use lasting ≥ 6 weeks. Do you agree that this 2-point improvement in pain intensity in patients with hormone-resistant prostate cancer is clinically meaningful when measured in an unblinded setting?

The primary reviewers, Dr. James Krook and Dr. Howard Scher, stated that the lack of blinding in this trial did not adversely affect the findings and that a 2-point improvement in pain intensity

measured on a 6-point scale was clinically meaningful in the study population.

Dr. Richard Simon asked for clarification with respect to the patients on the P arm who later crossed over. A total of 48 patients crossed over to M+P. Thirty of these patients had progressed on P prior to crossover, while 18 patients had stable disease prior to crossover. The median cycle of crossover was 5 cycles for both progressed and stable disease patients.

Dr. Simon also suggested that the 18 stable disease patients should be censored at the time of crossover for the TTP analysis. The FDA analysis had considered these patients as treatment failures if they ultimately progressed after crossover, a more conservative approach. Dr. Simon was not certain his suggested method would change the TTP analysis much.

Dr. Simon also suggested that time trends analyses for pain intensity and analgesic use for individual patients on the P arm be performed, comparing patients who crossed over to M+P with those who remained on the P arm.

The vote on Question 1 was 9 Yes, 0 No.

Question 2. In the two trials, progression was measured using different criteria. Do you agree that the TTP results based on NPCP criteria trial) support the TTP results in the CCI-NOV22 trial which were based on worsening pain and increasing analgesic requirement?

Concerns were voiced regarding the incomplete nature of the study report. Over 75% of the QOL data was available for submission, but the remaining data was missing due to difficulties in reaching patients by phone to obtain follow-up.

Dr. Krook asked about performance status on study. Drs. Nicholas Vogelzang and Philip Kantoff, representing stated that performance status scores were collected for each cycle but that only baseline data were submitted to the NDA. They stated that on study performance status scores could be provided to the FDA, but they could not comment on how complete this dataset was.

Dr. Simon stated that the sponsor's presentation of mean analgesic use scores was "inadequate" and suggested that time trends analysis of analgesic use and pain intensity scores for individual patients on the two treatment arms be performed.

The consensus of opinion was that the trial was supportive of the CCI-NOV22 in that it confirmed the acceptable safety profile of the mitoxantrone + corticosteroid combination in hormone-resistant prostate cancer patients. However, the study was sufficiently different from the CCI-NOV22 trial in terms of primary endpoints and their definition, so that it could not be considered supportive in terms of efficacy. However, it was pointed out by several members that none of the findings of the study went against the CCI-NOV22 trial, and that there were trends favoring the mitoxantrone + corticosteroid combination over corticosteroids alone.

Dr. Justice asked if the phase 2 trial of mitoxantrone + prednisone (CCI-NOV16), that was conducted prior to the CCI-NOV22 trial and which piloted many of the QOL scales used in the latter trial, could be considered supportive. ODAC members responded in the negative, viewing this trial as exploratory, unblinded, and uncontrolled.

The vote on Question 2 was 0 Yes, 9 No.

Question 3. Given the known toxicities of mitoxantrone (especially myelosuppression and cardiotoxicity), does the combination of mitoxantrone plus corticosteroids offer net clinical benefit to patients with hormone-resistant prostate cancer?

ODAC recommended that FDA perform additional analyses suggested by Dr. Simon with regard to crossover patients on the CCI-NOV22 to confirm that they had, in fact, received an adequate course of treatment with corticosteroids alone. It was recommended that the sponsor submit to the FDA any additional data from the study that was available, particularly analgesic use and performance status scores on study. FDA was to perform additional time trends analyses on analgesic use and pain intensity scores for individual patients on this study.

Assuming that the findings of the CCI-NOV22 trial held up and that the QOL data from the study did not negate the first study, the committee recommended approval of the mitoxantrone + corticosteroid combination for hormone-resistant prostate cancer.

The vote on Question 3 was 6 Yes, 2 No, 1 Abstaining.

10. FDA Requests for Information (9/18/96)

In order to address the clinical and statistical concerns of ODAC members raised at the September 11, 1996 meeting, FDA made the following written requests of Immunex Corporation.

- **Fax Transmittal of 9/18/96**

A. CCI-NOV22

1. Time to progression: We appreciate Dr. Rubin's efforts thus far to show that the statistical difference between the two treatment arms is highly significant despite "worse case" assumptions. However, the TTP analysis that is to be written in product labeling must accurately reflect protocol-specified definitions of progression (as outlined in Section 10.5 of the protocol). Thus, for patients who do not progress by pain intensity or analgesic use, radiologic progression or requirement for radiotherapy were to have been used by investigators as criteria for progression. As per our conversation with Dr. Rubin on 9/17/96, a TTP analysis based on protocol specifications of progression was forthcoming.

B. 9182 Trial

1. Please provide an update on the status of the study: what data are now available that were not at the time of the original filing, what data will be forthcoming in the near future, etc. Please submit any additional data that may have become available with regard to a) response evaluations, b) times to progression, c) analgesic use (Listing 13), or d) pain intensity (SDS Pain Item 2, Listing 20). Please submit baseline and on-study performance status scores for all patients. A complete, final study report for 9182 should be submitted to the NDA when it is available.

2. In the interest of time our statistical reviewer, Dr. Tony Koutsoukos, will be performing the time trend analyses for analgesic use and pain intensity for individual patients on the two treatment arms, as suggested by Dr. Richard Simon. We invite Dr. Rubin to join him collaboratively in this effort.

Reviewer Comments: In order to address Dr. Simon's concern about the length of treatment received on the two arms of the CCI-NOV22 trial, Dr. Koutsoukos plans to further assess the time to response for patients on each of the two treatment arms using Kaplan-Meier plots, evaluating primary responders only, as well as all responders. In addition, he will assess times to crossover for patients on the P arm, comparing those who progressed prior to crossover with those who had stable disease prior to crossover. The primary data required for these analyses was submitted in the original filing and did not have to be requested at this time.

- **Fax Transmittal of 10/9/96**

We are requesting clarification of your response (on 10/4/96) to FDA's Question A (faxed 9/18/96) regarding the calculation of TTP for patients enrolled on the CCI-NOV22 trial.

Comparison of the TTP for non-responders listed in the original report (Listing 10) with TTP data listed in Listing 1 (10/4/96) revealed changes in an additional 8 patients. These patients are:

Subject No.	Treatment Group	Original Report	Current Analysis
	P	41	69+
	P	75	11+
	P	41	84+
	P	128	86+
	P	42	196
	P	149	149+
	P	70	70+
	P	108	108+

For each patient whose TTP has changed from that originally reported in the NDA, please provide a brief explanation for the change. In particular, please address:

a) why a patient who had progressed according to Listing 10 in the original report is now listed as censored (M+P arm: ; P arm: ; and

b) the disparate TTP data for progressed patients (M+P arm: , P arm: , and

Reviewer Comments: In order to address Dr. Simon's concern about the length of treatment received on the two arms of the CCI-NOV22 trial, Dr. Koutsoukos plans to further assess the time to response for patients on each of the two treatment arms using Kaplan-Meier plots, evaluating primary responders only, as well as all responders. In addition, he will assess times to crossover for patients on the P arm, comparing those who progressed prior to crossover with those who had stable disease prior to crossover. The primary data required for these analyses was submitted in the original filing and did not have to be requested at this time.

- **Fax Transmittal of 10/16/96**

We are requesting clarification of your response (on 10/11/96) to FDA's question (faxed 10/9/96) regarding the calculation of TTP for patients enrolled on the CCI-NOV22 trial.

1. For patient [redacted], please provide the reason code for original and current TTP calculations.

2. For patient [redacted], using reason code A, should the date of progression be 9/22/94 rather than 7/13/94?

3. Patient [redacted] a responder by secondary criteria, progressed by CT scan in cycle 5 (per CRF) but did not progress by PPI or analgesic score. According to protocol section 10.5.2, evidence for progression of existing lesions at any time was to be considered progression. Why is radiologic information not being utilized in this case, or for any other patient who is not a primary responder? Please identify any additional patients that may have been censored for TTP in the current analysis who also had radiographic evidence of progression prior to assessment of progression. Please provide the dates of radiographic progression, and a calculation of TTP based on these dates for comparison to your current TTP analysis.

11. Additional Analyses

The following analyses were performed to address ODAC's concerns raised at the September 11, 1996 meeting. Most analyses were performed by the FDA or the sponsor independently, with the exception of the re-calculation of the TTP endpoint for the CCI-NOV22 trial which required a joint effort.

- **Were patients on the P arm given adequate treatment prior to crossover?**

This analysis was carried out by the FDA medical reviewer. The median cycle of response for patients on each treatment arm (prior to crossover) was similar:

Patient Group	No. of Patients	Median Cycle of Response (range)
M+P: 1° Responders	21*	4 (3 -10)
M+P: 2° Responders	7	4 (3 - 8)
P: 1° Responders	10	4 (3 - 6)
P: 2° Responders	7	3 (3 - 6)

*excludes patients #68 and 75 with response durations of 0 days

A total of 48 patients on the P arm crossed over to the M+P arm. Of these, 30 patients progressed on P prior to the crossover; the median cycle of crossover for this group was 5 (range 3 - 16 cycles). Five patients (17%) subsequently achieved responses on M+P after a median of 4 cycles (range 2-5 cycles).

Eighteen patients crossed over who had stable disease on P. The median cycle of crossover for this group was also 5 (range 2 - 12 cycles). Four patients (22%) achieved responses on M+P, all at 3 cycles. (Note: these responses were not included in the calculation of response rate for the M+P arm since they occurred after crossover.)

The FDA statistical reviewer performed time trend analyses for pain intensity (prior to crossover) for the 48 crossover patients compared to 22 patients who remained on the P arm. The two-sided t test p value (0.012) was in favor of the patients who did not crossover. Time trends for pain intensity for the 18 patients with stable disease prior to crossover were compared to the 22 patients who did not crossover. Again, the two-sided t test p value (0.05) was in favor of the patients who did not crossover. These findings are consistent with the idea that worsening pain was the primary reason for crossover. (See Dr. Koutsoukos' review for details.)

Reviewer's Conclusions: Patients who progressed on P and those with stable disease on P had similar median treatment durations prior to crossover, and similar response rates to M+P after crossover. Patients who had stable disease on P appeared to have worse pain intensity

scores over time compared with patients who did not crossover. Note that response rates after crossover appear to be lower than the 35% response rate for patients on M+P as initial treatment. This lower response rate correlates with the lower number of mitoxantrone doses delivered after crossover (see Section 4.13 of this review). Despite this, overall survival for crossover patients (12.7 months) was similar to that for patients initially treated with M+P (11.3 months).

- **Re-calculation of Time-to-Event Endpoints**

At FDA's recommendation, the definition of progression as outlined in Section 10.5 of the CCI-NOV22 trial would be utilized to calculate response duration and TTP, rather than the sponsor's "worst case" assumptions. **A tabulation of TTP in days for all patients was provided by the sponsor, confirmed by FDA, and included in the Appendix.** It compares the TTP as reported in the original submission, in the sponsor's submission of 10/9/96 (faxed 10/11/96), and in the current analysis. Explanations regarding how and which criteria were used to determine progression are provided for each patient. The following rules have been applied in the current and final analysis.

1. Primary responders were declared progressed using pain intensity or analgesic use criteria or clinical evidence of worsening disease if the latter was noted before meeting pain intensity/ analgesic criteria. Subjects with no evidence of progression by pain intensity, analgesic criteria, or other clinical criteria were censored at the date of last follow-up. This rule was generally followed in all analyses.

2. The remaining patients (including secondary responders, patients with stable disease or progression as the best response) were declared progressed using pain intensity and analgesic use criteria **only** in the original submission. In the current analysis, **clinical criteria are also used.** Again, patients with no evidence of progression by pain intensity, analgesic use or clinical criteria were censored at the date of last follow-up, regardless of the reason for study discontinuation.

3. In the protocol, progression by pain intensity was defined as an increase of one unit on the pain intensity scale relative to the "best" previous value maintained for two consecutive visits. In the original submission, a "best" score could occur at **any time**, including times following the cycle at which the pain intensity criterion is being assessed. In the current analysis, the "best" score is restricted to **any time prior to** assessment of the pain intensity criterion.

4. In the protocol, progression by analgesic score was defined as an increase of $> 25\%$ in analgesic score relative to the "best" previous value maintained for two consecutive visits. In the original submission, analgesic scores were compared to baseline rather than best score. In the current analysis, analgesic scores are compared to the best score at any time prior the assessment of the analgesic score criterion.

5. Fourteen patients had only one pain intensity cycle reported in the database. In the original analysis, these patients were assessed as missing, i.e., not evaluable for TTP. In the current analysis, four of these patients are censored at day 20 (end of cycle 1) for the calculation of TTP (patient [redacted] on the M+P arm and patients on the P arm). The remaining ten patients are progressed on clinical criteria.

6. In the original submission, all patients on the P arm without evidence of pain intensity or analgesic score progression prior to or after crossover who crossed over were treated as **progressed** at the time of crossover. In the current analysis, patients who did not progress prior to crossover using pain intensity or analgesic score criteria were **censored.**

7. In the original submission, if a patient progressed after crossover, then the progression dates after crossover were used to determine TTP. In the current analysis, patients who crossed over were declared progressed prior to or at the time of crossover, or censored at the time of crossover.

The table below lists the final outcomes for each patient enrolled on the CCI-NOV22 based on

Treatment Arm	Criterion for Progression			Censored*
	Pain Intensity	Analgesic Use	Clinical/RTReq'd	
M+P 1° Responders	15, 22, 40, 41, 63, 102, 103, 107, 111, 114	-	4, 122, 126, 135,142	21, 51, 92, 95, 98, 150
P 1° Responders	11, 19, 127, 158	129, 159	55, 69	121(8), 156(6)
M+P 2° Responders	10, 128	74	104, 151	44, 54
P 2° Responders	78	91	48, 73, 86, 93	85
M+P All Others	8, 16, 18, 23, 37, 46, 49, 97, 113, 119, 125, 143, 152, 157	5, 26, 35, 38, 88, 108, 116, 124, 137, 139, 145	2, 20, 31, 52, 57, 61, 66, 67, 72, 83, 84, 89, 99, 120, 138, 146, 155, 161	9, 32, 50, 68, 70, 75, 77, 79, 82,
P All Others	1, 6, 7, 12, 24, 29, 34, 39, 53, 56, 80, 96, 109, 118, 123, 131, 133, 136, 148, 149, 153	14, 42, 59, 62, 71, 76, 87, 90, 106, 144, 154	3, 17, 25, 27, 30, 33, 36, 43, 45, 47, 58, 60, 64, 65, 100, 101, 110, 112, 115, 117, 130, 132, 134, 160	13(5), 28, 81(3), 94, 105(3), 140, 141(2), 147

***At last pain intensity determination or at crossover**

the current analysis. Patients are grouped as 1) primary responders, 2) secondary responders,

or 3) all others. **Patients shown in boldface type had a change in TTP from the original submission.** For patients on the P arm who were censored at the time of crossover, the cycle of crossover is shown in parentheses. Clearly, inclusion of clinical criteria has a major impact on the calculation of TTP. Reasons for progression (i.e., pain intensity, analgesic use, or clinical criteria) were similarly distributed across treatment arms, however the number of censored patients was higher on the M+P arm than on the P arm (17 or 21% vs 11 or 14%).

Four serious disease-related outcomes as described in the sponsor's table (submitted 10/18/96) are summarized below. For spinal cord compression and fracture, patients are included from the original study report and from the 4-month safety update. Taken together, this preliminary information suggests that spinal cord compression and fractures occurred less frequently on the M+P arm.

Disease-Related Adverse Outcome	M+P (N=80)	P (N=81)
Spinal Cord Compression	84, 89, 99	12, 17, 43, 59, 65, 101, 110, 117
Fracture	2	3, 25, 30, 109
Radiation Required	4, 20, 52, 67, 84, 99, 126, 135	3, 17, 30, 101, 110, 134

Thus, the revised time to event endpoints for patients enrolled on CCI-NOV22 are:

Median Time to Progression (All Patients)

Treatment Arm	Treatment Failures	Median (days)	Log-rank P-value
M+P (N=80)	63	131	0.0001
P (N=81)	70	69	

Median Response Duration (Primary Responders Only)

Treatment Arm	Treatment Failures	Median (days)	Log-rank P-value
M+P (N=21)*	15	229	0.0009
P (N=10)	8	63	

*excludes patients #68 and 75 with response durations of 0 days

Median Response Duration (Primary and Secondary Responders)

Treatment Arm	Treatment Failures	Median (days)	Log-rank P-value
M+P (N=28)*	20	169	0.0004
P (N=17)	14	57	

*excludes patients #68 and 75 with response durations of 0 days

- **TTP by Baseline Analgesic Use on the 9182 Trial**

The sponsor calculated the median TTP for patients grouped by baseline analgesic use, confirming the reviewer's calculations as shown in Table 19 in Section 4.23 of this review. In addition, the median TTP was reported for the subset of patients on non-narcotics at baseline vs. those on narcotics at baseline. No statistically significant differences between arms were noted.

Median Time to Progression by Analgesic Requirement at Baseline

Outcome	Non-narcotics at Baseline		Narcotics at Baseline	
	M+H (N=26)	H (N=24)	M+H (N=47)	H (N=45)
Treatment Failures	11	15	22	26
Median (days)	491	109	189	156
Log-rank P value	0.6636		0.3078	

- **Quality of Life Assessments on the 9182 Trial**

After the ODAC Meeting, the sponsor contacted the Central Office to inquire about updating the database for the 9182 study. stated that the most recent update of the database was provided in February 1996, that the next update will not be prepared until mid-1997, and that the Final Study Report would not be ready until 1998. The sponsor agrees to submit the Final Study Report to the sNDA when it becomes available.

The database provided to Immunex in February 1996 served as the basis for the original sNDA submission. However, information on performance status and weight contained in the database were not analyzed by the sponsor or submitted to FDA since that data was not viewed as relevant to confirm the endpoints of the pivotal CCI-NOV22 trial. At the suggestion of ODAC, FDA requested and received this additional data on 10/4/96. These findings are summarized below. **The sample size of this trial was based solely on survival differences between the two treatment arms. The sponsor does not believe this trial is**

adequately powered to show significant treatment differences in performance status, weight change, analgesic use, and/or pain intensity.

In the . database, follow-up values for analgesic use, weight, and performance status are reported by "time periods" rather than cycles, with a period corresponding to a variable number of cycles. **Reviewer Comment:** Comparison was made with available CRFs and data listings for analgesic use, performance status and weight. For a given time period, the intervening cycles were determined and the single relevant score/value recorded for the period was listed for each cycle. For example, a 3-month time period would translate into 4 cycles, say cycles 3-6. If analgesic use for the period was recorded as a "4" (regular use of narcotics), then this was recorded as the analgesic use for cycles 3-6.

The database used for the original sNDA submission contained baseline and at least one follow-up value for weight and performance status for 83% of patients, and baseline and at least 2 follow-up values for 43% of patients. According to the sponsor, missing data appear to be due to dropouts, so that future updates are not expected to provide much new information.

Performance Status: Baseline performance status was 0-1 in 85% of patients enrolled on this study. Thus, analyses of PS were conducted to assure that chemotherapy with mitoxantrone did not negatively impact the performance status of patients while on study.

For analysis of "best improvement in PS", only patients with a baseline PS > 0 were included (N=55 for the M+H arm, N=65 for the H arm). For patients on the M+H arm, the mean baseline PS was 1.25 and the mean best PS was 0.89. For patients on the H arm, the mean baseline PS was 1.23 and the mean best PS was 0.74. Similar findings were reported for patient subsets on any analgesics or on narcotics at baseline. There was no statistically significant difference between the treatment groups in mean best change from baseline PS or mean best percent change from baseline PS.

For analysis of "maximal worsening in PS", all patients with available data were included (N=98 for the M+H arm, N=102 for the H arm). For patients on the M+H arm, the mean baseline PS was 0.70 and the mean worst PS was 1.56. For patients on the H arm, the mean baseline PS was 0.78 and the mean worst PS was 1.57. Similar findings were reported for patient subsets on any analgesics or on narcotics at baseline. There was no statistically significant difference between the treatment groups in mean worst change from baseline PS or mean worst percent change from baseline PS.

Weight: For analysis of maximum weight gain or maximum weight loss, there were 100 evaluable patients on the M+H arm and 101 on the H arm. For patients on the M+H arm, the mean weight gain on study was 2.6 kg while on the H arm the mean weight gain was 2.2 kg. Similar findings were reported for patient subsets with or without analgesic requirements at baseline. There was no statistically significant difference between the treatment groups in mean best weight gain from baseline, or mean best percent weight gain from baseline.

For patients on the M+H and H arms, the mean weight loss on study was -2.5 kg. Similar findings were reported for patient subsets with or without analgesic requirements at baseline. There was no statistically significant difference between the treatment groups in mean worst weight loss from baseline, or mean worst percent change from baseline.

Analgesic Use: The following analyses were conducted using those patients who required analgesics at baseline (N=61 for each arm). For all 61 patients on the M+H arm, the mean best percent change in analgesic level was -17% compared with +17% for patients on the H arm (p= 0.014). For the patient subsets on non-narcotics (N=21 for the M+H arm, N=23 for the H arm), the mean best percent change in analgesic level was -21% vs. +72% (p= 0.006). No significant difference between treatment arms was noted for the patient subsets on narcotics. **Reviewer Comments:** This information adds to that which the sponsor presented previously in the sNDA and at the ODAC meeting, i.e., mean analgesic use scores for the two treatment arms over time (see sponsor's Figures 4 and 5 in the Appendix). **The FDA statistical reviewer has performed time trend analyses for analgesic use for individual patients and has shown a trend in favor of the mitoxantrone + corticosteroid arm that was not statistically significant. See statistical review for further details.**

Pain Intensity and Frequency: In the trial, two 5-point scales were used to evaluate pain intensity and frequency (SDS Pain Items 1 and 2) at baseline, at 6-week intervals, and at the end of study. The mean best per cent change in pain frequency for patients on analgesics on the M+H arm was -24% (N=38) vs -10% on the H arm (N=39, p= 0.093). There was no statistical difference in mean best per cent change in pain frequency for the subset of patients on non-narcotics at baseline or for the subset on narcotics at baseline.

The mean best per cent change in pain intensity for patients on analgesics on the M+H arm was -14% (N=37) vs +8% on the H arm (N=38, p= 0.057). There was no statistical difference in mean best per cent change in pain intensity for the subset of patients on non-narcotics at baseline. For the subset of patients on narcotics at baseline, the mean best per cent change in pain intensity was -20% on the M+H arm (N=24) vs +10% on the H arm (N=25, p= 0.024), a significant result.

The percent of patients with a 1-point fall in pain intensity was 36% for patients enrolled on the M+H arm (N=36) compared with 15% for patients on the H arm (N=39, p= 0.041). For the subset of patients on analgesics at baseline, 48% of patients on the M+H arm (N=25) had a 1-point fall in pain intensity compared with 23% on the H arm (N=26, p= 0.065). There was no statistical difference in this endpoint for the subset of patients on non-narcotics at baseline or for the subset on narcotics at baseline.

Reviewer Comment: The FDA statistical reviewer has performed time trend analyses for pain intensity for individual patients and has shown no significant differences between treatment arms. See statistical review for further details.

12. Reviewer's Conclusions and Recommended Regulatory Action

A major challenge facing the treatment of advanced prostate cancer following an initial positive response to androgen suppressive therapy is the development of hormone-resistant progressive disease. Development of new therapies has been hampered, in part, by the inherent difficulties that arise in the assessment of objective response in patients with disease progression. Most patients develop progressive bone metastases for which radiographic assessment is often unreliable. The rate of disease progression is generally slow, with new lesions or symptoms occurring only intermittently. Changes in tumor markers may not always correlate with disease response. If a new agent is myelosuppressive, it may be poorly tolerated due to the patient's advanced age, bone marrow involvement by tumor, or receipt of prior radiotherapy to bone-marrow containing areas. These factors, taken together, may limit drug delivery.

Extensive evaluation of antineoplastic agents in the 1970s and 1980s provided insufficient evidence that these agents could produce significant objective regressions or prolong survival. However, reduction in bone pain was observed although the impact of chemotherapy on patients' quality of life had not been adequately addressed. Moreover, chemotherapy added toxicity. These considerations lead to the initiation of a Canadian multicenter phase 2 pilot study (CCI-NOV16) evaluating pain intensity and analgesic use in patients with pain related to advanced hormone-resistant prostate cancer. A 33% palliative response rate was observed in 27 patients receiving the mitoxantrone + prednisone combination despite scant objective evidence of disease regression. This finding lead to the development of a randomized controlled trial in Canada (CCI-NOV22) comparing treatment with mitoxantrone + prednisone to prednisone alone in this patient population. Palliative response rate was the primary endpoint.

A second randomized controlled trial comparing mitoxantrone + hydrocortisone with hydrocortisone alone was conducted in the US by the This trial was designed with survival as the primary endpoint. While the two randomized trials are inherently different in the manner in which critical efficacy endpoints were defined, each contributes important efficacy and safety information for patients with hormone-resistant prostate cancer receiving the combination of mitoxantrone + corticosteroids.

Both trials required and documented castrate testosterone levels in all patients at study entry. The CCI-NOV22 trial required that eligible patients have symptomatic progression, and assessed these patients for response based on reduction in pain intensity and analgesic use. Progression on this trial was based on worsening pain intensity, analgesic use, clinical criteria, or requirement for radiotherapy. In contrast, the trial did not mandate that patients have disease-related symptoms to be eligible. Standard National Prostate Cancer Project (NPCP) criteria were used to assess disease response and progression.

Several questions remain regarding patient eligibility on these trials. Specific criteria defining

hormone-resistance were not delineated. Details of prior hormonal therapies were not provided, including the duration of administration of each agent, response to prior therapies, and the sequence with which agents were administered. The latter is particularly important when assessing the impact of antiandrogen withdrawal responses, since these occur following total androgen blockade, not sequential androgen blockade. If and when antiandrogen withdrawal responses were monitored, the specifics of how this was accomplished were not provided (i.e., was progression documented by serial PSA levels over time, etc.).

In the evaluation of treatment success in hormone-resistant prostate cancer, reductions in pain intensity and analgesic requirement, and improvements in daily functioning and quality of life are important goals. The magnitude and duration of the palliative response as defined in the CCI-NOV22 trial are certainly promising findings. However, we have little information regarding other bone-related complications which may have been positively affected by treatment, for example, a reduced need for or delayed timing of palliative radiotherapy for pain control, or a reduced incidence of spinal cord compression or pathologic fracture. Taken together, the sponsor's most recent safety update and TTP analysis (listing reasons for progression) suggest that spinal cord compression occurred in 4% of patients on the mitoxantrone + prednisone arm compared with 10% of patients on the prednisone alone arm. However, there were no reports of spinal cord compression on the study. Reports in the literature suggest that up to 10% of patients with advanced prostate carcinoma develop cord compression due to extradural metastasis, more commonly with higher-grade and later stage disease. Is the lower incidence of spinal cord compression on the mitoxantrone + prednisone arm of the CCI-NOV22 trial due to treatment success, patient selection, or under-reporting?

With regard to patient selection, additional evidence suggests that patients enrolled on the two randomized trials were better prognosis patients at the time of study entry. Contrast the favorable baseline performance status scores, median times to disease progression, and overall median survival times approaching one year in these studies with the corresponding findings in earlier phase 2 trials (CCI-NOV16 and CCI-NOV14).

Finally, information is also lacking on the potential mechanism(s) by which the combination of mitoxantrone + corticosteroids relieves pain in patients with hormone-resistant prostate cancer. No biochemical evaluation of adrenal androgens was undertaken nor was investigation of androgen-receptor gene mutations feasible in these studies. No references in MEDLINE could be found linking mitoxantrone to markers of new bone formation, to cytokines associated with bone resorption, or to histologic changes within bone consistent with healing.

- **Recommended Regulatory Action**

Approval is recommended for an additional indication for NOVANTRONE® (Mitoxantrone for Injection Concentrate) in combination with corticosteroids **for the palliative treatment of pain related to advanced hormone-refractory prostate cancer.** Approval is based upon

significantly higher palliative response rates, response duration and time to disease progression among patients who received mitoxantrone + prednisone compared to those treated with prednisone alone in a randomized controlled trial, CCI-NOV22. Pilot phase 2 data from a multicenter trial (CCI-NOV16) are deemed supportive. A second randomized controlled trial conducted by the (9182) defined efficacy endpoints differently, but nevertheless demonstrated an improvement in TTP and reduction in analgesic use that favored mitoxantrone + hydrocortisone over hydrocortisone alone. Taken together, the totality of evidence supports approval for the indicated population. The recommended dose of mitoxantrone in this combination is 12-14 mg/m² every 21 days. Low-dose corticosteroid regimens that have been given concurrently with mitoxantrone are prednisone 5 mg bid orally, and hydrocortisone 30 mg q AM and 10 mg q PM orally.

In the CCI-NOV22 trial, a primary palliative response was prospectively defined as a 2-point decrease in a 6-point pain intensity scale that was associated with a stable analgesic use score and was maintained for at least six weeks. Patients on the mitoxantrone + prednisone arm had a 26% primary palliative response rate (vs 12% for patients on prednisone alone, p=0.029) lasting a median of 229 days (vs 63 days, p=0.0009). A secondary palliative response was defined as a 50% or greater decrease in analgesic use associated with stable pain intensity, and lasting a minimum of six weeks. An overall palliative response rate (defined as primary plus secondary responses) was achieved in 35% of patients randomized to mitoxantrone + prednisone compared to 21% of patients randomized to prednisone alone (p=0.055). The median duration of overall palliative response for patients randomized to mitoxantrone + prednisone was 169 days compared to 57 days for patients randomized to prednisone alone (p=0.0004). (Calculations are based on FDA's assessment of palliative response which excluded patients as primary responders on the mitoxantrone + prednisone arm since the response duration for these patients was zero days.)

Time to progression was defined as a 1-point increase in pain intensity, or a >25% increase in analgesic use, or evidence of disease progression on radiographic studies, or requirement for radiotherapy. The median time to progression (for all patients) was 131 days on the mitoxantrone + prednisone arm (vs 69 days on the prednisone alone arm, p=0.0001). No survival difference was noted between the two treatment arms.

A second randomized clinical trial, 9182, compared mitoxantrone + hydrocortisone with hydrocortisone alone in hormone-resistant prostate cancer. There was no difference between the two treatment arms with respect to the primary endpoint, survival. Disease response and progression were evaluated using standard NPCP criteria. There were 10 partial responders on the M+H arm compared to 2 partial responders on the H arm (response rate 8.4% vs 1.6%, p=0.018). The median time to disease progression (defined using NPCP criteria) favored the combination (218 vs 122 days, log-rank p=0.0654). This finding may have been driven by the favorable time to progression noted for the subset of asymptomatic patients (no analgesic requirement at study entry) who received the combination.

Approximately 60% of patients on each arm required analgesics at baseline. Analgesic use was measured in this study using a 5-point scale. The best per cent change from baseline in mean analgesic use was -17% for 61 patients with available data on the mitoxantrone + hydrocortisone arm, compared with +17% for 61 patients on hydrocortisone alone ($p=0.014$). A time trend analysis for analgesic use in individual patients also showed a trend favoring the mitoxantrone + hydrocortisone arm over hydrocortisone alone, but was not statistically significant.

Pain intensity was measured using the Symptom Distress Scale (SDS) Pain Item 2 (a 5-point scale). The best per cent change from baseline in mean pain intensity was -14% for 37 patients with available data on the mitoxantrone + hydrocortisone arm, compared with +8% for 38 patients on hydrocortisone alone ($p=0.057$). A time trend analysis for pain intensity in individual patients showed no difference between treatment arms.

There was no difference between treatment arms in baseline performance status, in best performance status achieved on study, or in best per cent change from baseline.

In clinical practice, assessment of pain intensity on a 6-point scale was simple, did not require use of lengthy questionnaires, and could be repeated frequently. However, pain intensity should not be used alone. Reduction in pain intensity is only meaningful when analgesic use has remained stable (or decreased) during the assessment period.

There were no unexpected toxicities reported for the hormone-resistant prostate cancer population or in the sponsor's post-marketing database since mitoxantrone's approval in 1987. The principal toxicity was myelosuppression (neutropenia). Decreases in LVEF and cases of congestive heart failure occur. Patients with pre-existing cardiac disease, or who have previously received anthracyclines or mediastinal radiotherapy should have regular monitoring of LVEF. The recommended maximum cumulative dose of mitoxantrone is 140-160 mg/m^2, although patients have tolerated higher doses with careful monitoring.

The relief in disease-related pain observed with the mitoxantrone + corticosteroids combination outweighs the potential toxicities and results in meaningful palliation of patients with advanced hormone-resistant prostate cancer.

Julie Beitz 11/7/96
Julie Beitz, MD Date

Robert C. Justice, M.D. 11/13/96
Robert Justice, MD Date

cc:
NDA #19-297
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ R. Justice
HFD-150/ A. Koutsoukos
HFD-150/ L. Vaccari

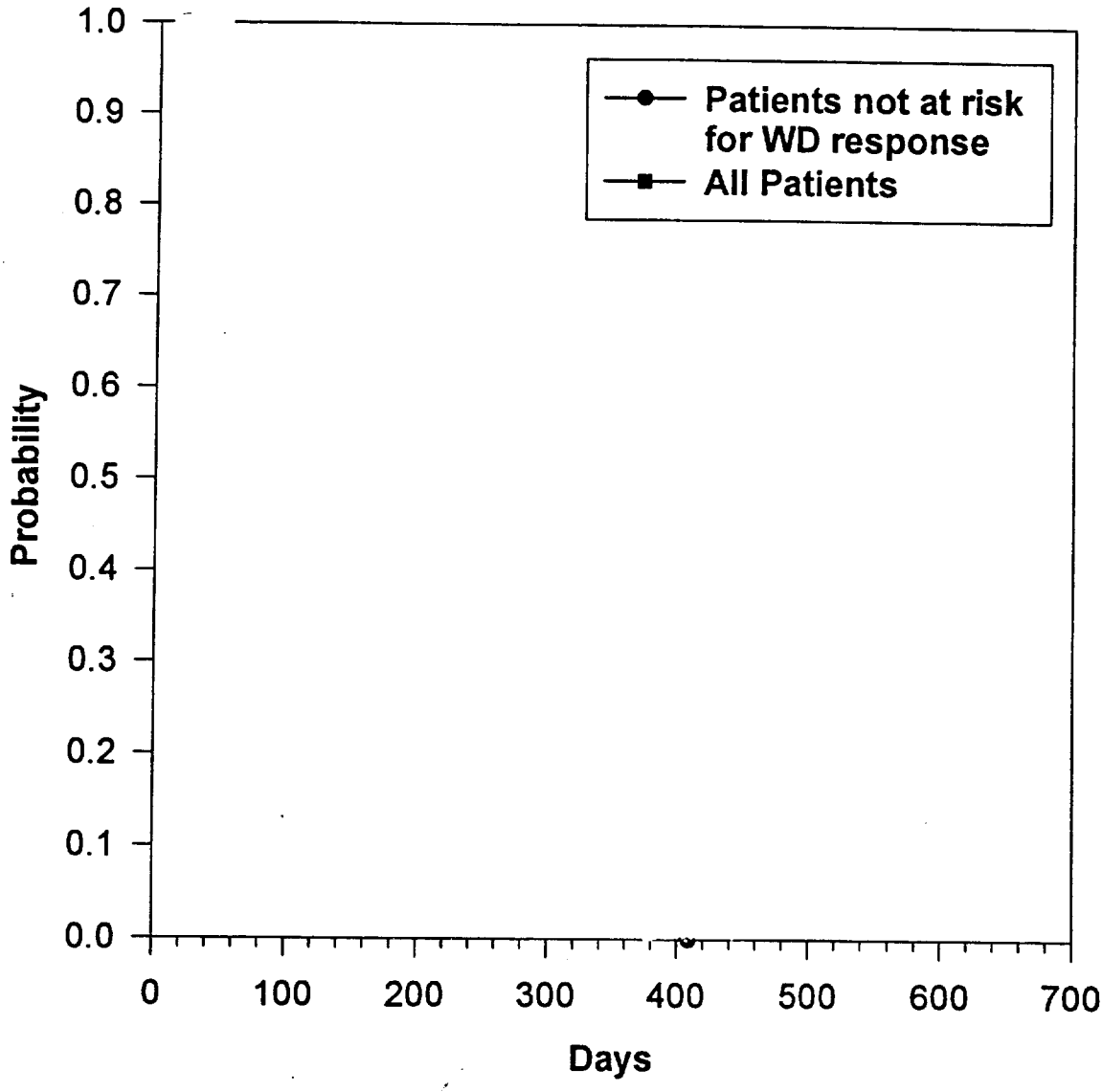
APPENDIX

NOVANTRONE[R] (Mitoxantrone for Injection Concentrate)

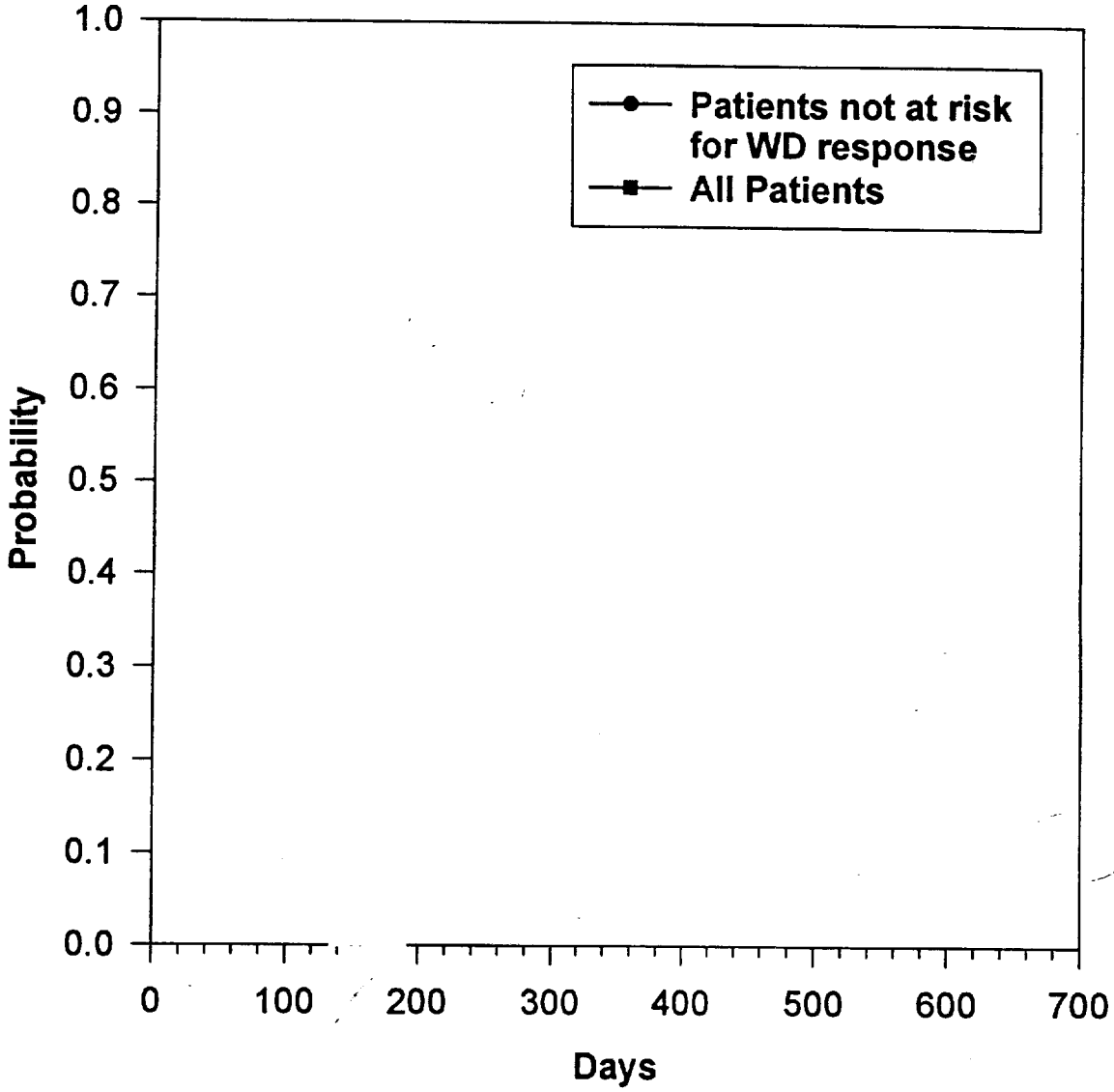
NDA # 19-297, Supplement S-014

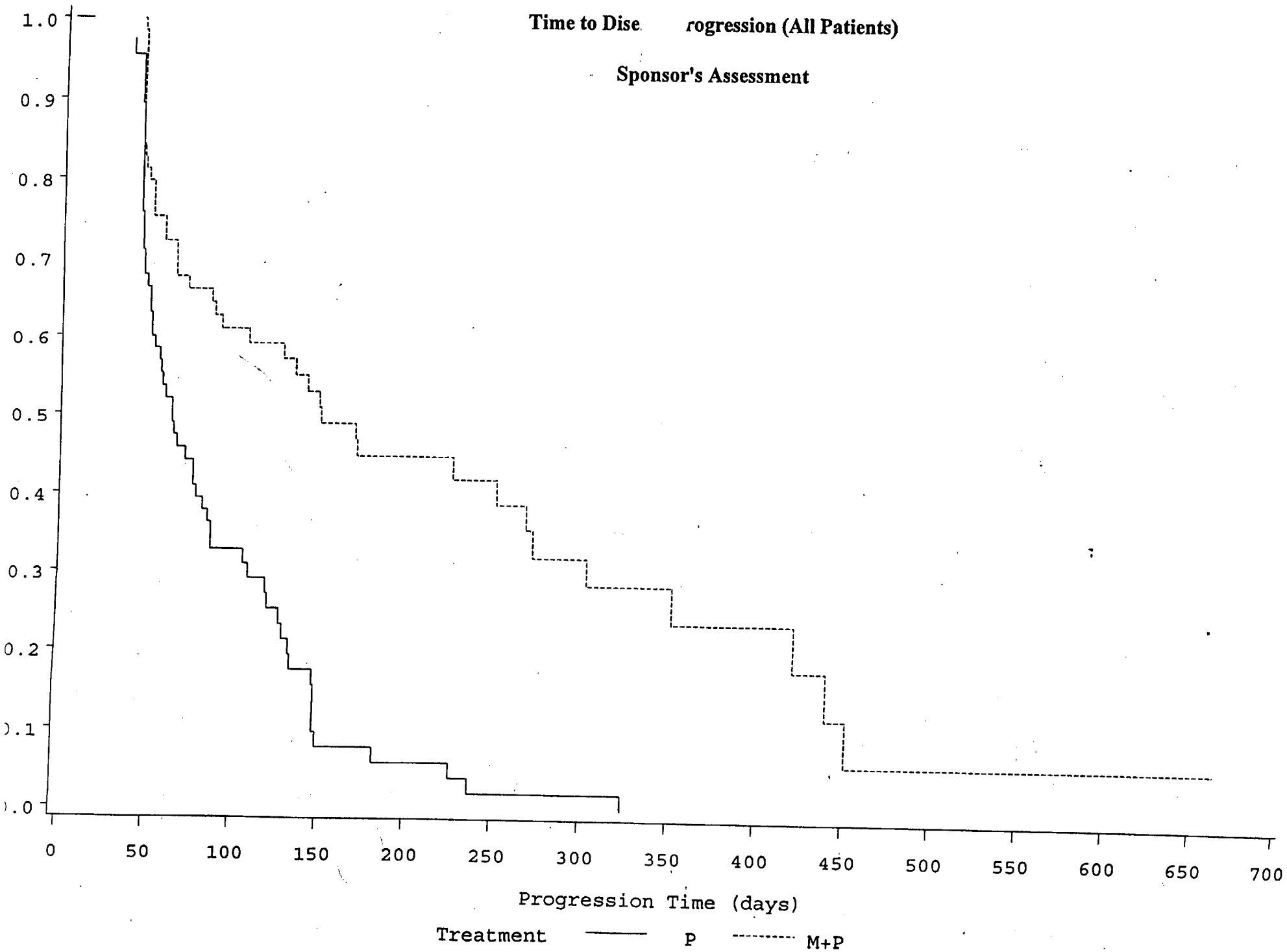
CCI-NOV22 Trial

Duration of Response for M+P Arm:
All Patients vs
Patients Not At Risk for Flutamide Withdrawal Response



Duration of Response for P Arm:
All Patients vs
Patients Not At Risk for Flutamide Withdrawal Response




Time to Dise rogression (All Patients)
Sponsor's Assessment
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
.1
.0
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
Progression Time (days)
Treatment
P
M+P

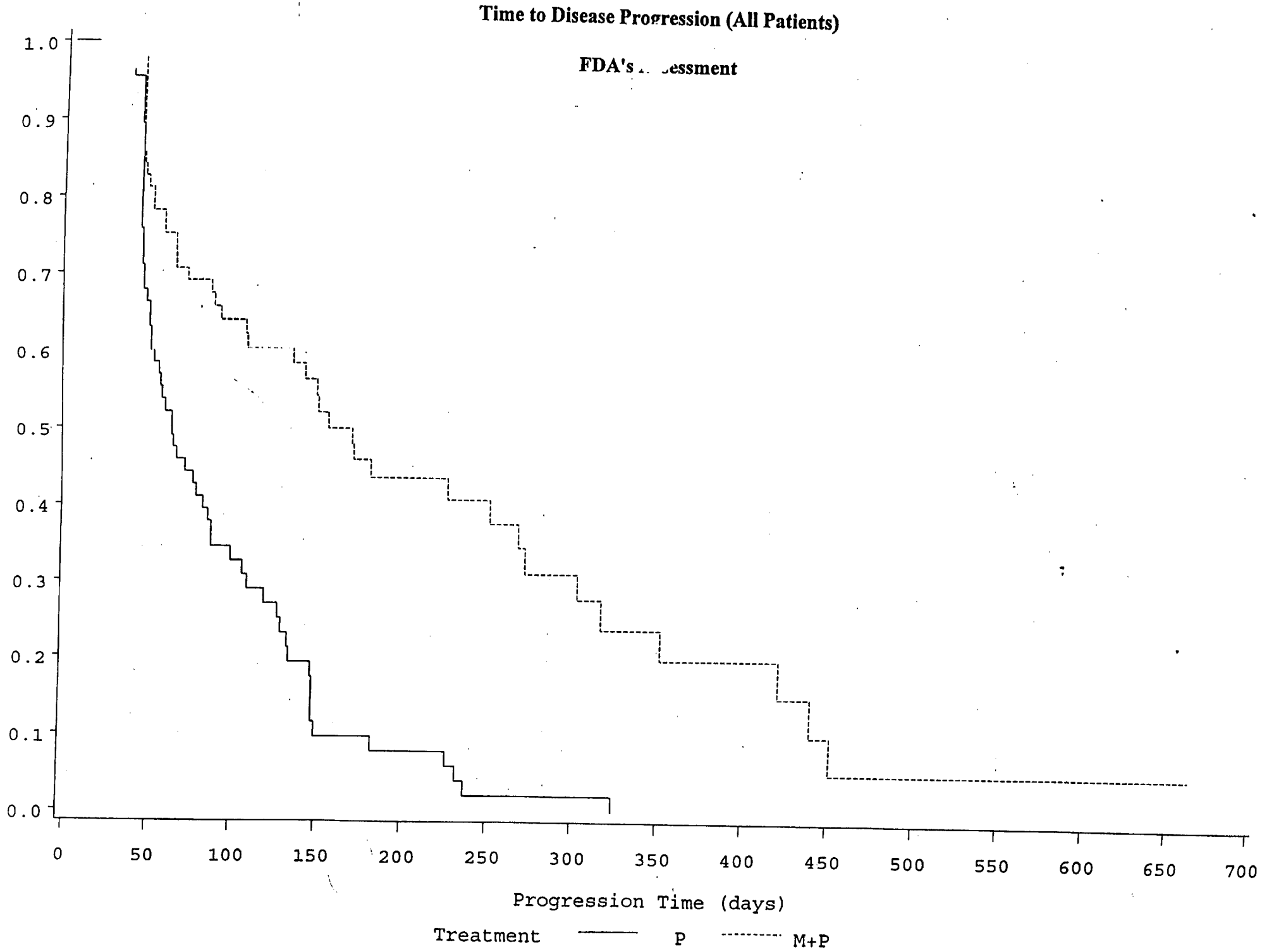
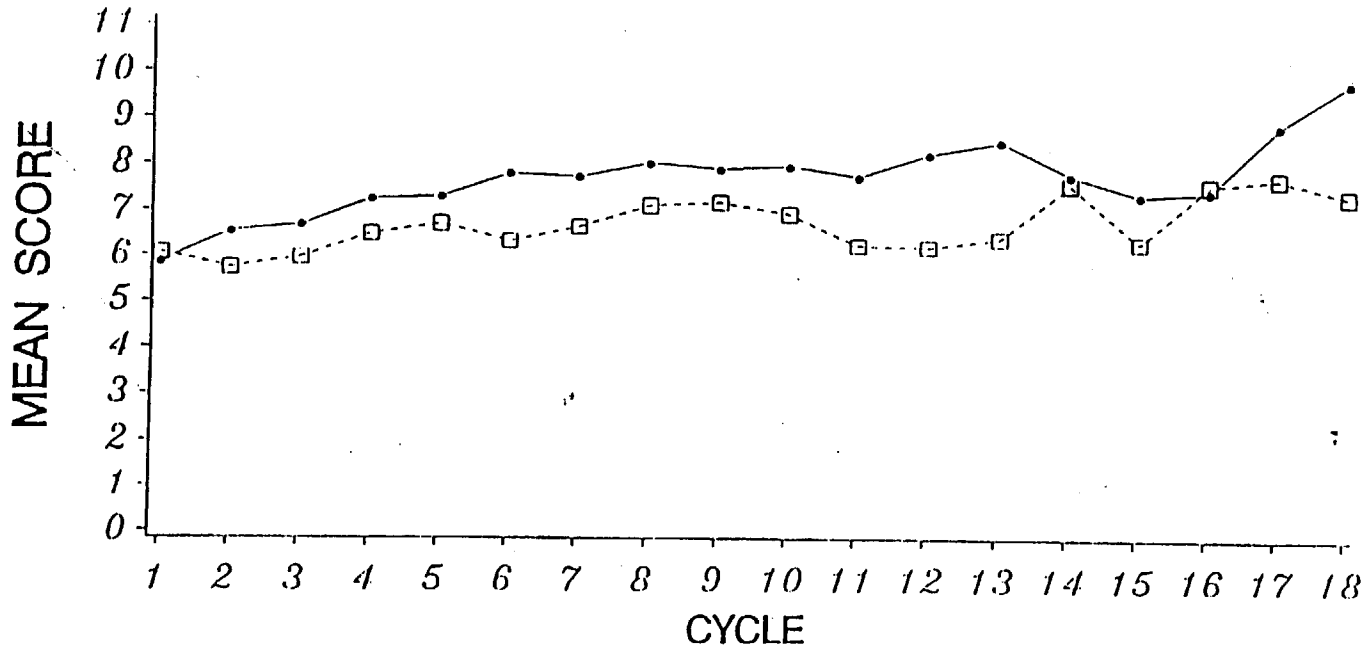

Time to Disease Progression (All Patients)
FDA's Assessment
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
Progression Time (days)
Treatment
P
M+P

Figure 6 – LASA – PAIN
(MEAN OF SUBJECTS OVER TIME)



STUDY CCI-NOV22

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Figure 7 – LASA – PHYSICAL ACTIVITY (MEAN OF SUBJECTS OVER TIME)

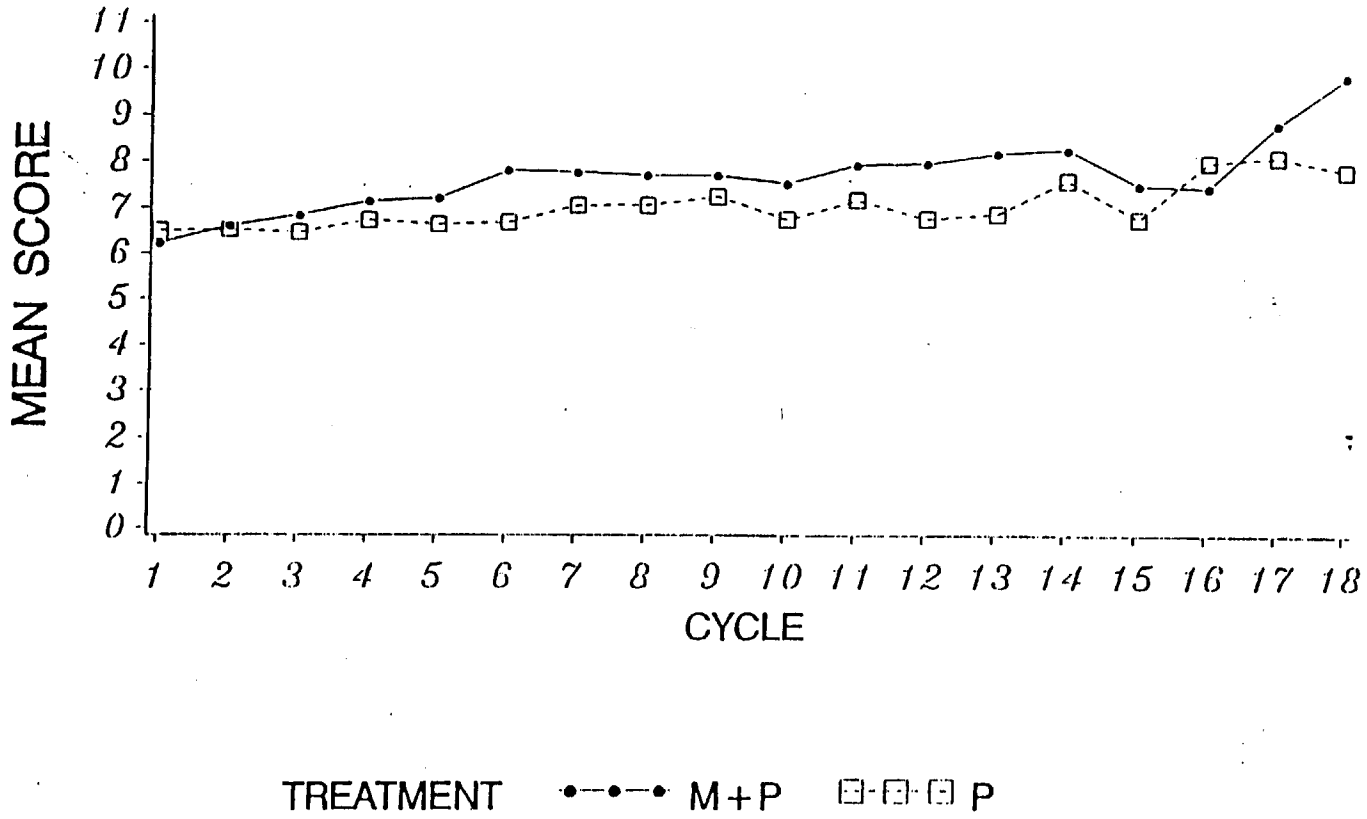

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Figure 8 – LASA – FATIGUE
(MEAN OF SUBJECTS OVER TIME)

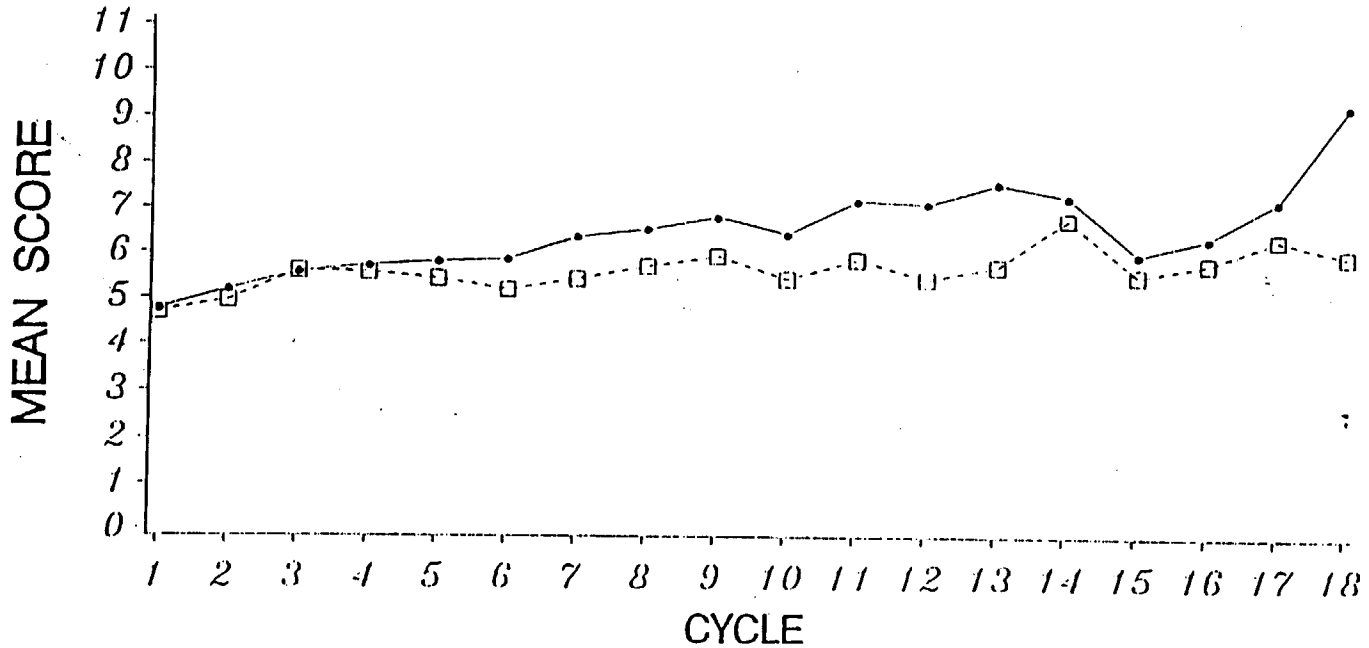

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Figure 9 – LASA – APPETITE
(MEAN OF SUBJECTS OVER TIME)

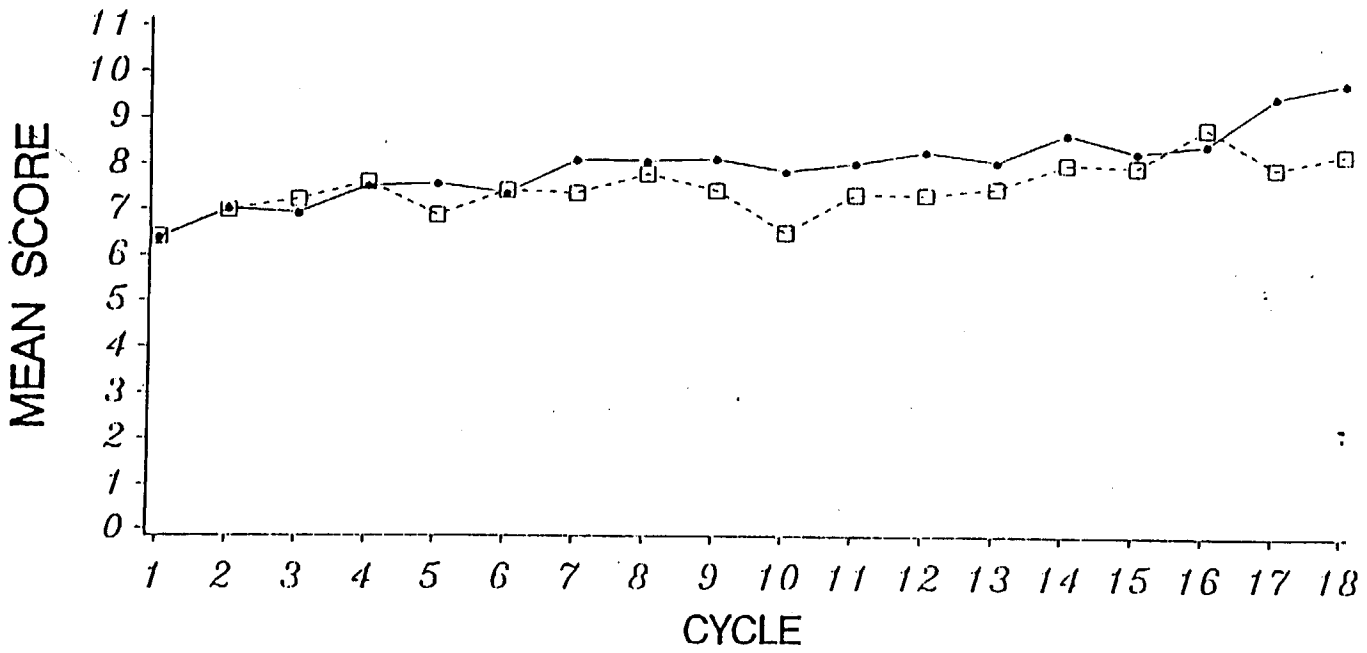

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Figure 10 – LASA – CONSTIPATION
(MEAN OF SUBJECTS OVER TIME)

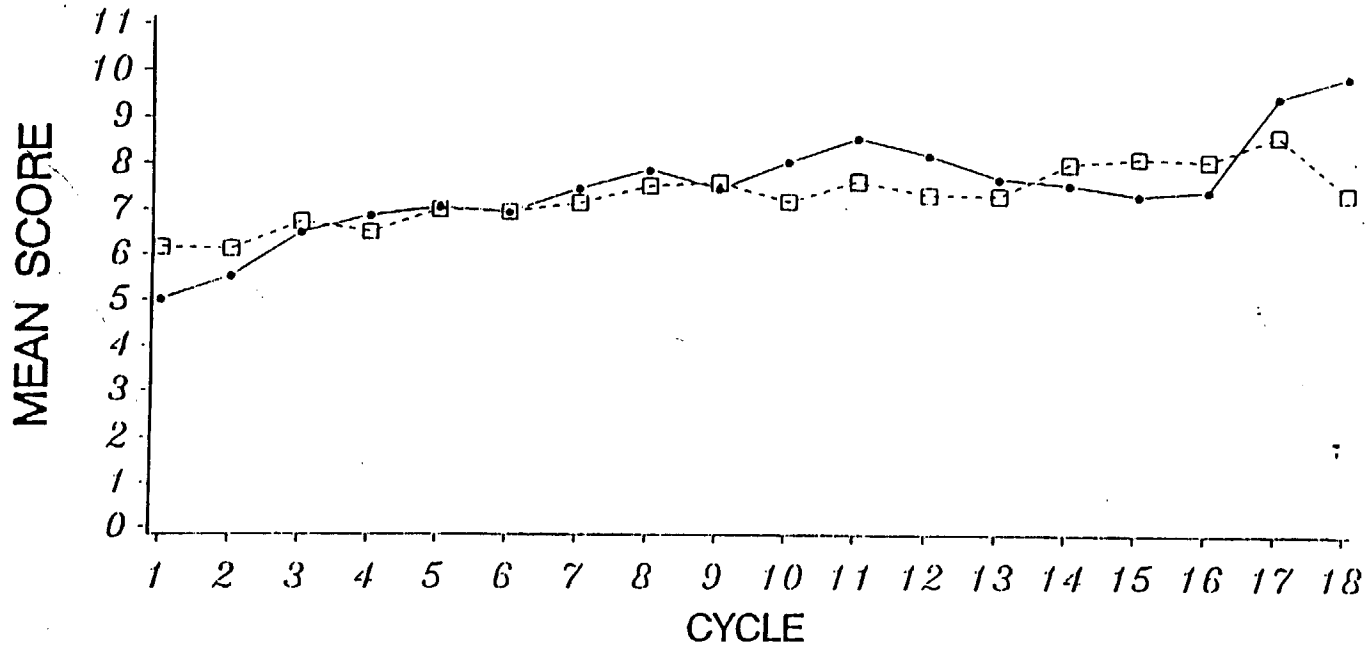

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Figure 11 – LASA – FAMILY/MARRIAGE RELATIONSHIPS (MEAN OF SUBJECTS OVER TIME)

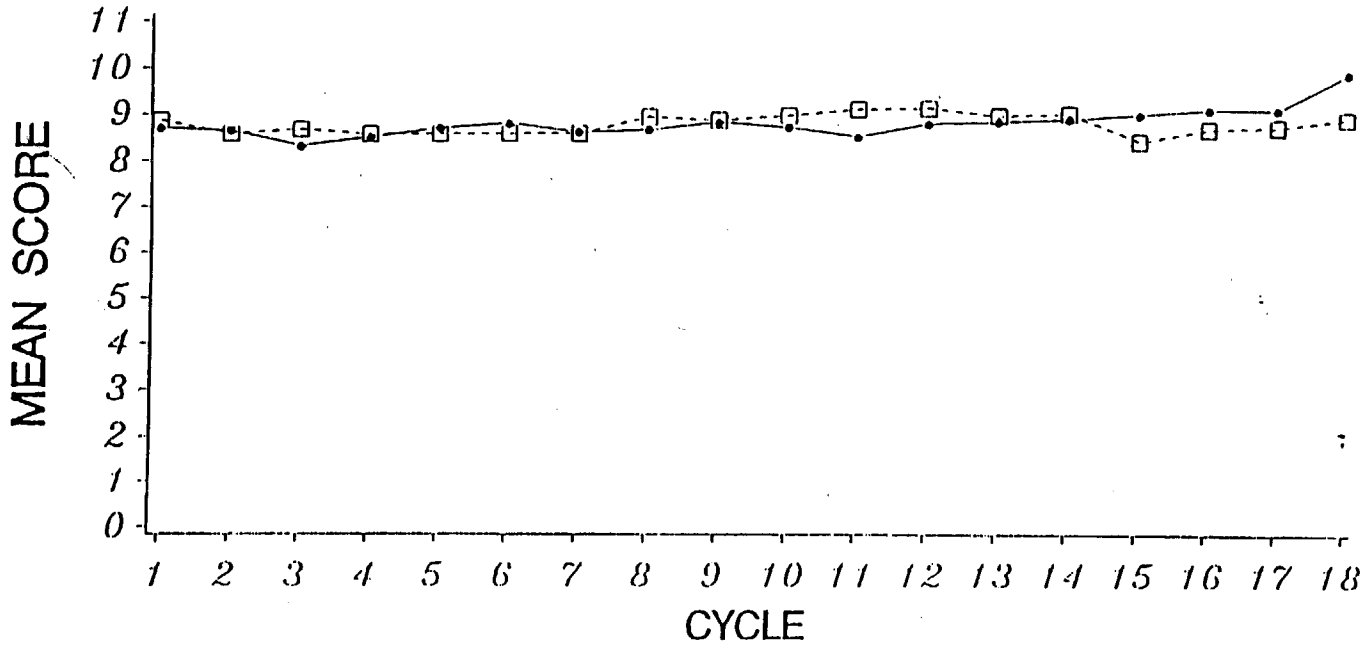

Figure 12 – LASA – MOOD
(MEAN OF SUBJECTS OVER TIME)

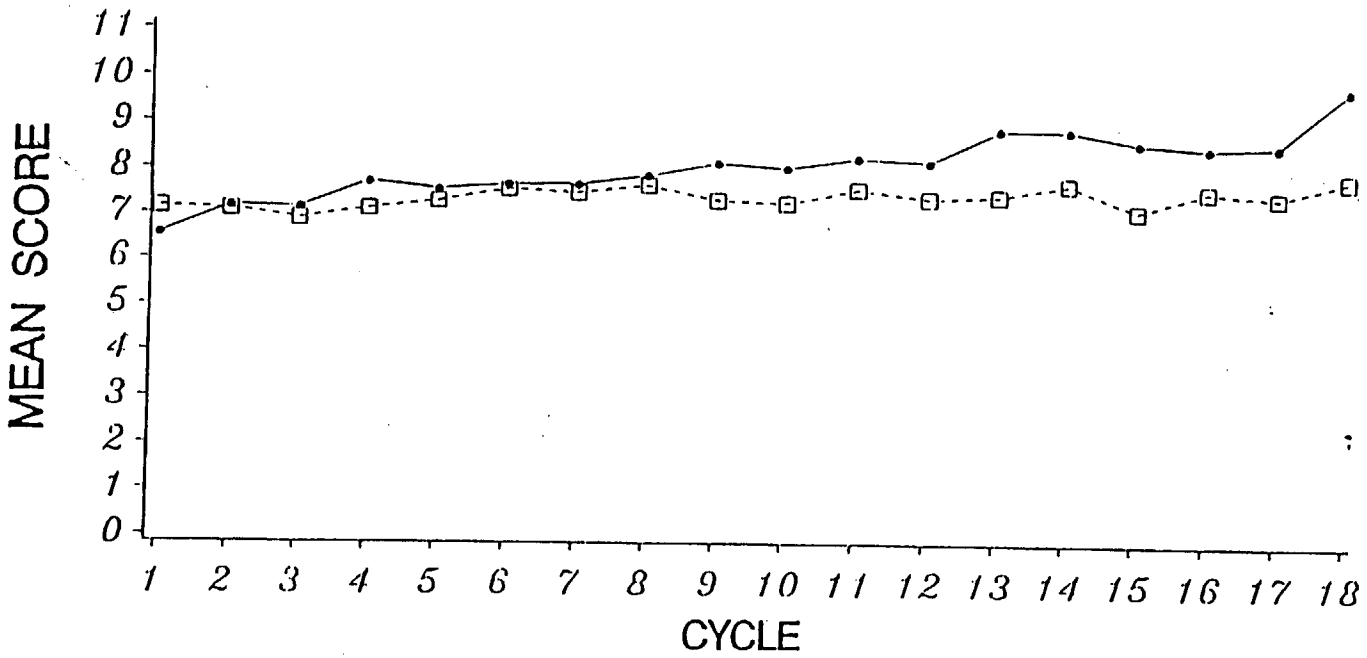

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Figure 13 – LASA – PASSING URINE
(MEAN OF SUBJECTS OVER TIME)

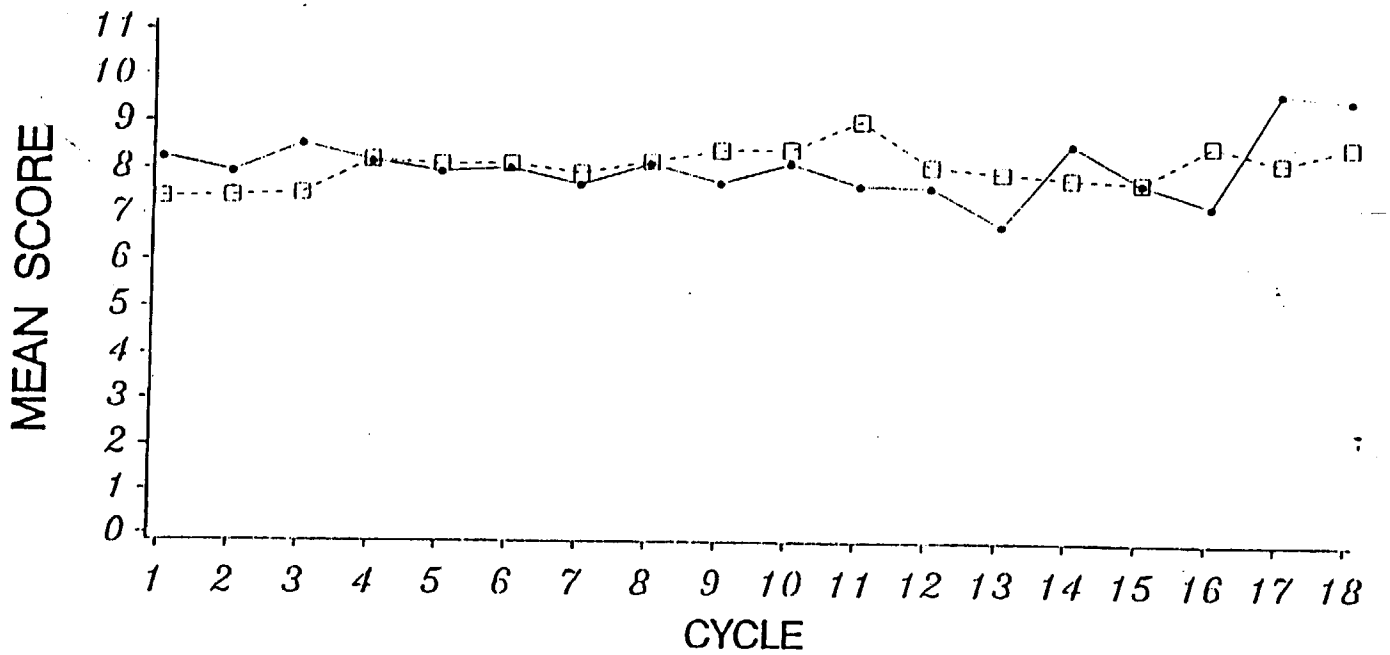

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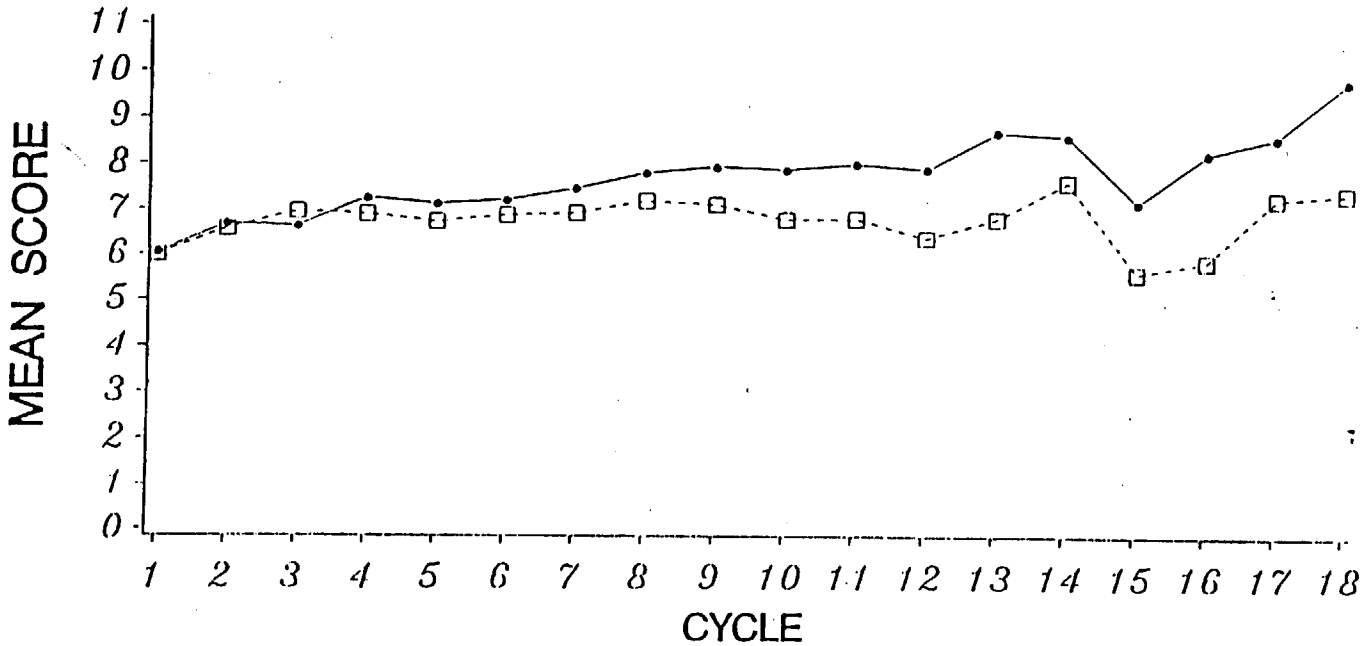
Figure 14 – LASA – OVERALL WELL-BEING (MEAN OF SUBJECTS OVER TIME)



STUDY CCI-NOV22

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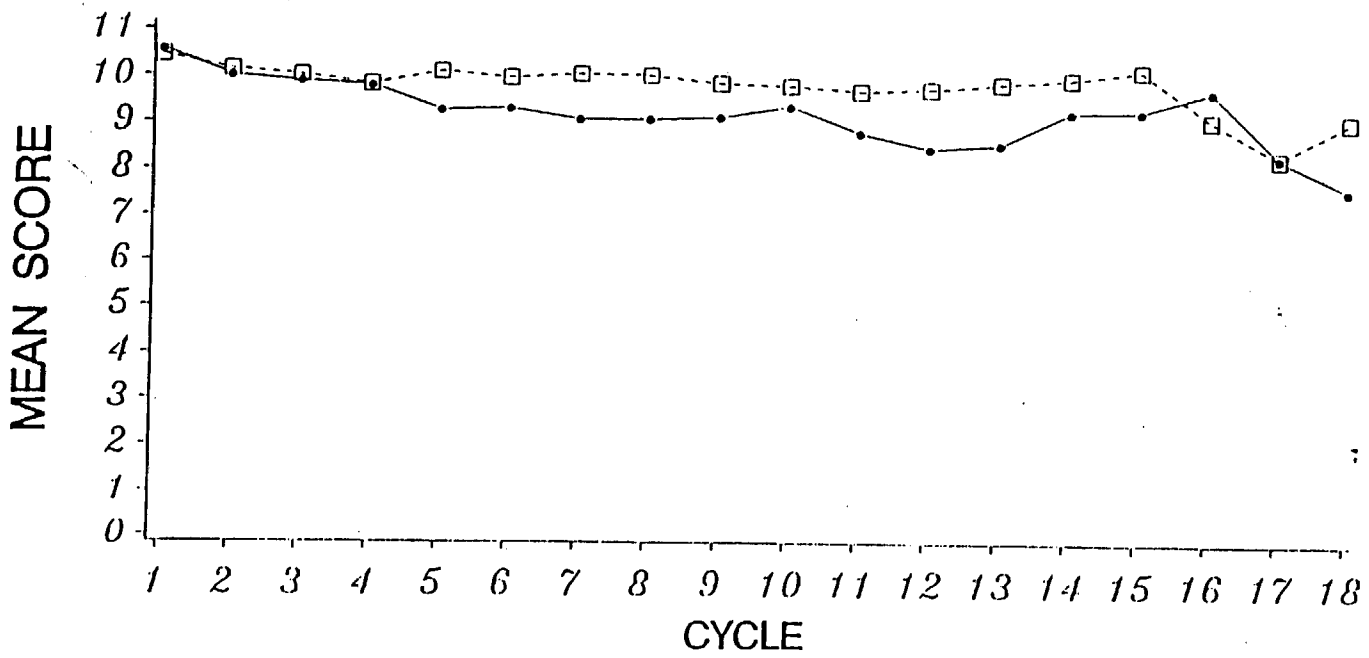
Figure 15 – QOL – SYMPTOMS AND PHYSICAL ACTIVITY
(MEAN OF SUBJECTS' SUMS OVER TIME)



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STUDY CCI-NOV22

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Figure 16 – QOL – FUNCTIONAL ACTIVITY
(MEAN OF SUBJECTS' SUMS OVER TIME)

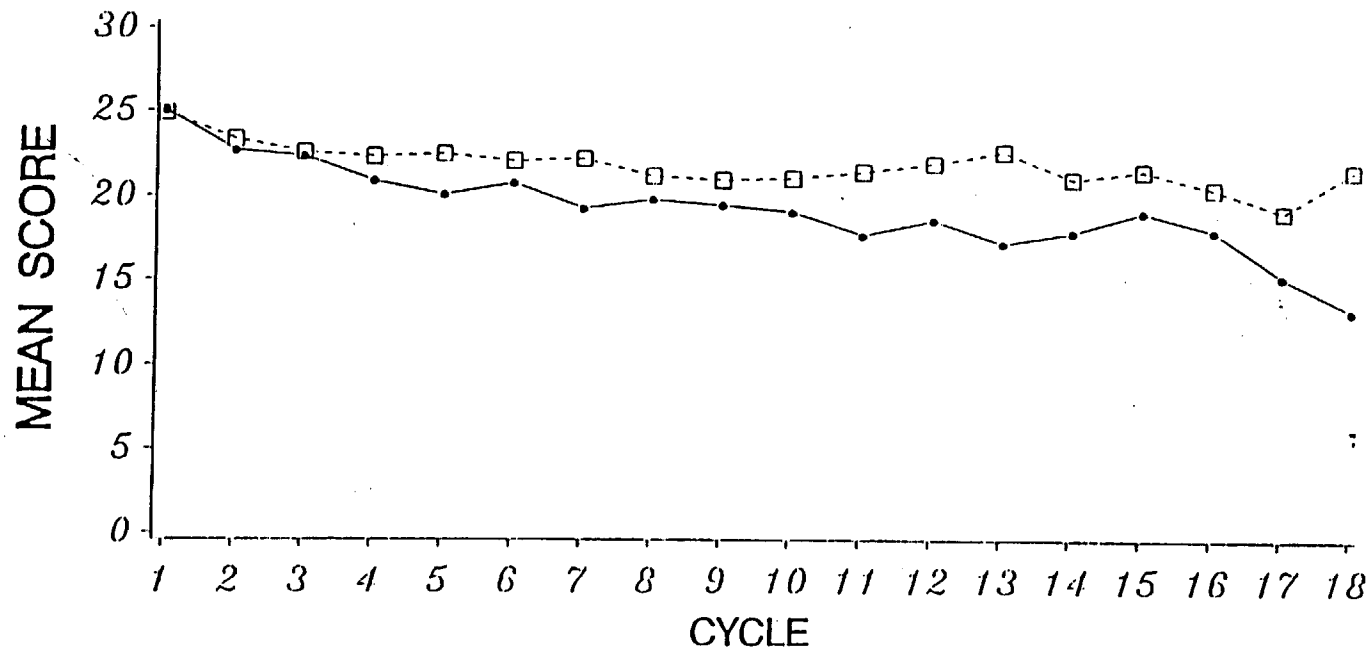

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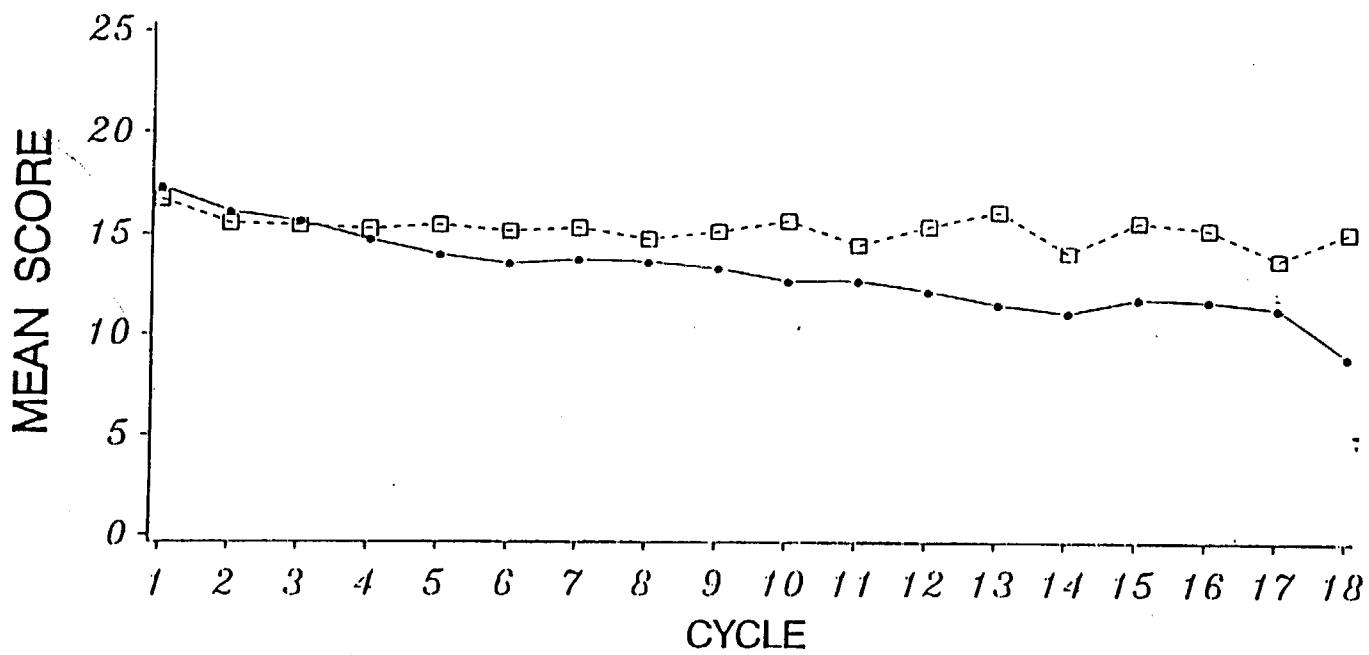
Figure 17 – QOL – PSYCHOSOCIAL
(MEAN OF SUBJECTS' SUMS OVER TIME)



STUDY CCI-NOV22

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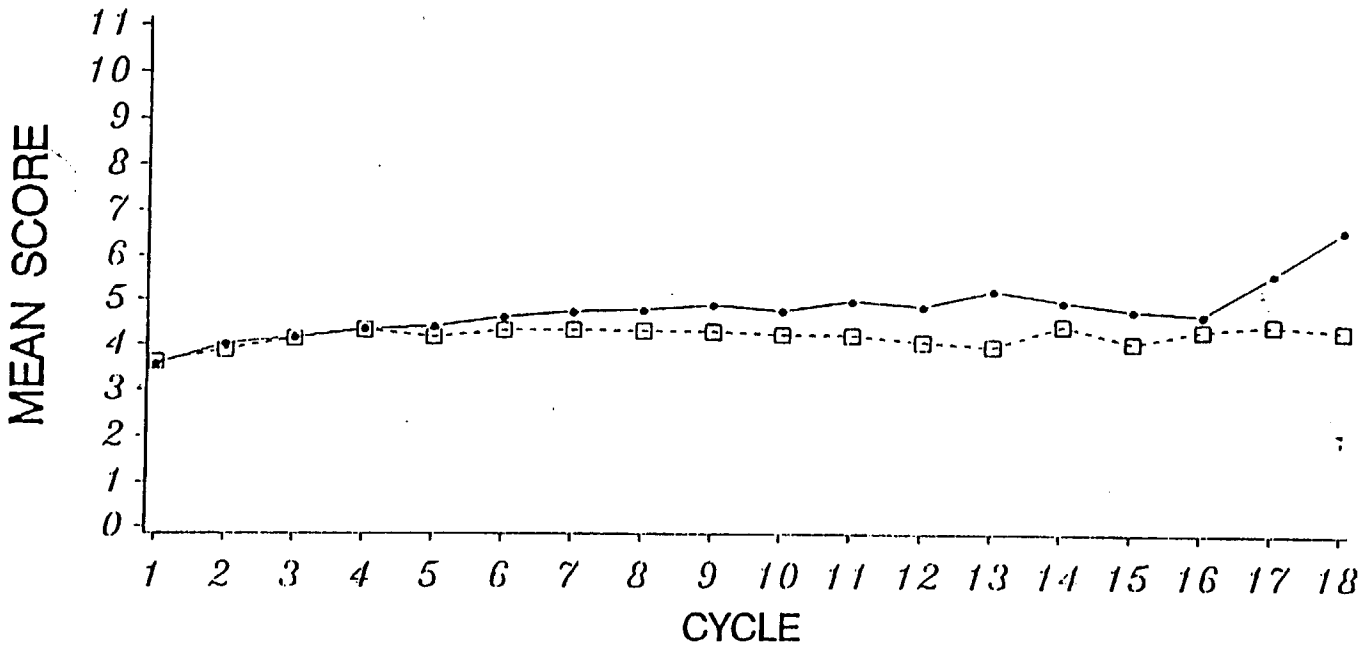
Figure 18 – QOL – OVERALL PHYSICAL (MEAN OF SUBJECTS OVER TIME)



STUDY CCI-NOV22

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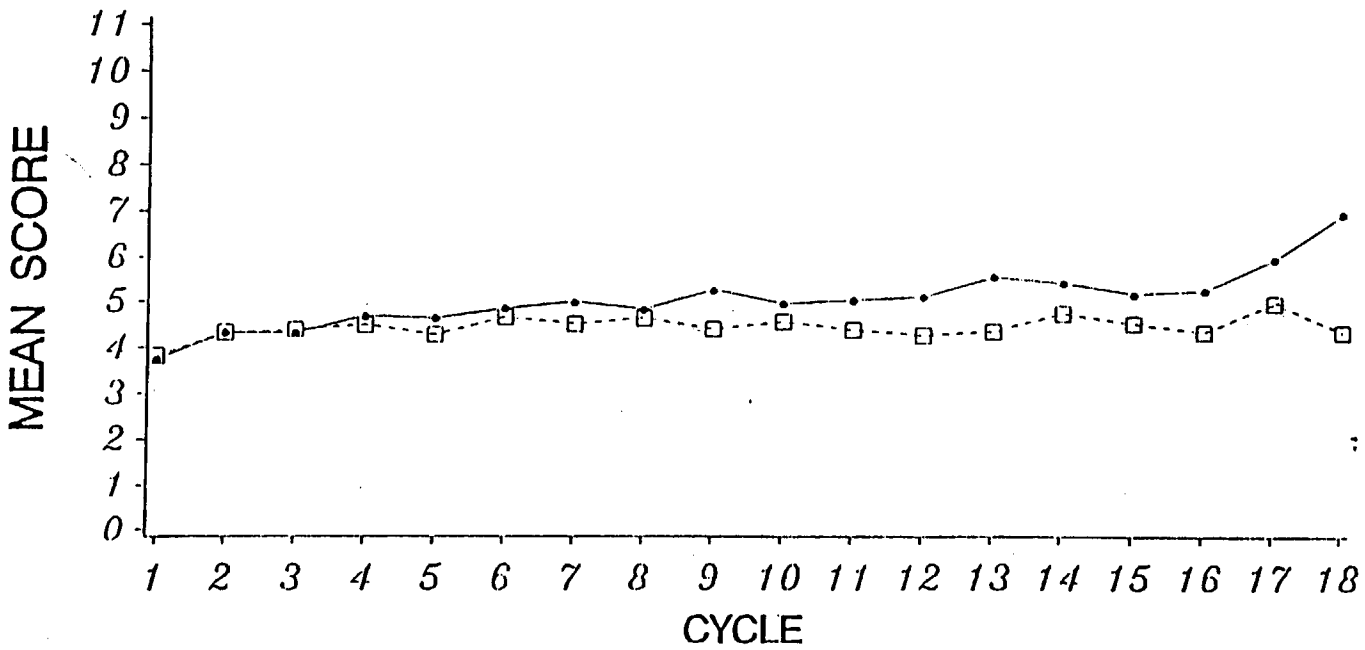
Figure 19 – QOL – OVERALL QUALITY OF LIFE (MEAN OF SUBJECTS' OVER TIME)



STUDY CCI-NOV22

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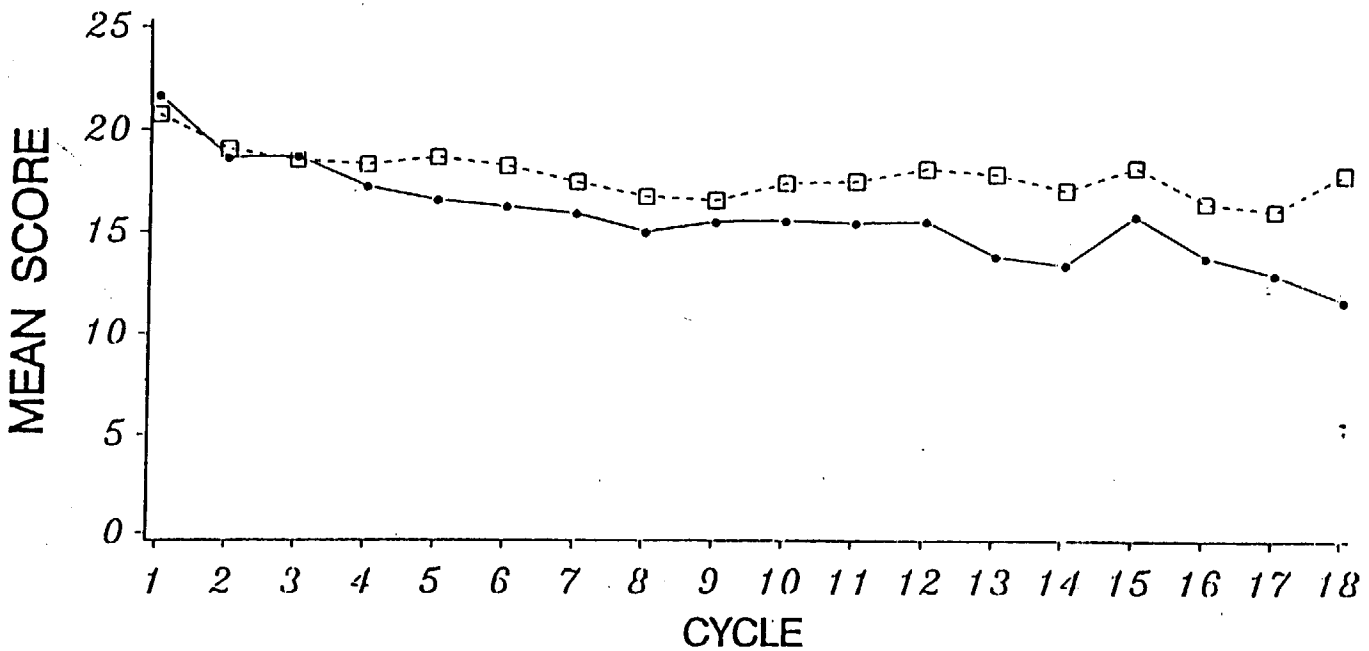
Figure 20 – QOL – PROSTATE MODULE (MEAN OF SUBJECTS' SUMS OVER TIME)



STUDY CCI-NOV22

04APR96

IMMUNEX CORPORATION

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REGULATORY AFFAIRS/QUALITY ASSURANCE
FACSIMILE COVER SHEET

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Division of Oncology Drug Products, FDA

Date: October 28, 1996
Fax: (301) 594-0498

From: Mark Gauthier
Sr. Regulatory Affairs Manager

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Fax: (206) 223-0468

Number of Pages (including cover sheet) - 11 -

MESSAGE:

Leslie,

Attached please find a copy of the final table for TTP for all patients in trial NOV22 as requested by Dr. Koutsoukos from Abbe Rubin by telephone on 10/23/96. The table combines the answers of the response to the 10/9/96 FDA request (analysis conducted 10/3/96; submitted to FDA on 10/11/96) and the 10/18/96 analyses and documents all of the changes from the original filing to the analyses submitted on 10/11/96 and on 10/18/96.

We intend to submit the attached material formally to our unapproved supplement within the next 1 week. Please provide the table to Dr. Koutsoukos and Dr. Beitz for their information.

If you have any comments or concerns regarding this response, please contact me at your convenience.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier

Treatment Group	Subject Number	Original* Report Days Reason Code	Analysis* 10/9/96[1] Days Reason Code	Analysis* 10/18/96 Days	Explanation (Date of Response given to FDA)
P		46	46	46	Progressed by PPI.
M+P		39+	39+	53	Originally censored at last available PPI score. Subject taken off study due to vertebral body fracture at C7 (10/18/96).
P		missing	20+	21	Originally missing since only 1 cycle. Bone fracture, required surgery and radiotherapy (10/18/96).
M+P		270	270	270	Progressed by radiotherapy requirement.
M+P		63	63	63	Progressed by analgesic score.
P		146	146	146	Progressed by PPI.
P		65	65	65	Progressed by PPI
M+P		63	63	63	Progressed by PPI
M+P		42 A	350+ A	350+	Censored since subject never satisfied criteria for progression (10/11/96).
M+P		42 A	161 A	161	Progressed by PPI (10/11/96).
P		147	147	147	Progressed by PPI.
P		62	62	62	Progressed by PPI.
P		77 D	56+ C	56+	Subject progressed using analgesic score in Cycle 6 but crossed over in Cycle 5 (10/11/96).
P		84	84	84	Progressed by analgesic score.
M+P		224	224	224	Progressed by PPI.
M+P		42	42	42	Progressed by PPI.
P		missing	20+	14	Originally missing since only 1 cycle. Cord compression, required radiotherapy (10/18/96).
M+P		42	42	42	Progressed by PPI.
P		132	132	132	Progressed by PPI.
M+P		70+	70+	58	Originally censored at last available PPI score. Progressive disease, increase in pain, subject to receive radiotherapy on sacrum (10/18/96).

+ means censored

[1] Provided in response to 10/9/96 FDA fax, analysis was actually run on 10/3/96.

Treatment Group	Subject Number	Original* Report Days Reason Code	Analysis* 10/9/96[1] Days Reason Code	Analysis* 10/18/96 Days	Explanation (Date of Response given to FDA)
M+P		175+	175+	175+	Censored at last PPI.
M+P		133	133	133	Progressed by PPI.
M+P		44	44	44	Progressed by PPI
P		51	51	51	Progressed by PPI.
P		43 A	66+ C	53	Censored at time of crossover in analysis (10/11/96). Pathologic fracture of 8th rib (10/18/96).
M+P		91+ B	70 B	70	Originally censored since analgesic score compared to missing Baseline (10/11/96).
P		41 A	69+ C	69	Censored at time of crossover in analysis (10/11/96). Worsening bone scan, new bone lesions (10/18/96).
P		42+	42+	42+	Originally censored at last available PPI score. Same as before (10/11/96).
P		126	126	126	Progressed by PPI.
P		missing	20+	14	Originally missing since only 1 cycle. Pathologic fracture, required surgery and radiotherapy to right humerus (10/18/96).
M+P		42+	42+	89	Originally censored at last available PPI. Increase in pain, subject died due to disease progression on 10/17/91 (10/18/96).
M+P		126+	126+	126+	Censored at last PPI.
P		75 D	11+ C	11	Subject progressed by PPI in Cycle 5 but crossed over in Cycle 2 (10/11/96). Increased hepatolmegaly by CT Scan (10/18/96).
P		62	62	62	Progressed by PPI.
M+P		140	140	140	Progressed by analgesic score.
P		missing	20+	22	Originally missing since only 1 cycle. Increased hepatomegaly, worsening pain, subject taken off study (10/18/96).
M+P		56	56	56	Progressed by PPI.
M+P		42	42	42	Progressed by analgesic score.

+ means censored

[1] Provided in response to 10/9/96 FDA fax, analysis was actually run on 10/3/96.

Treatment Group	Subject Number	Original* Report Days Reason Code	Analysis* 10/9/96[1] Days Reason Code	Analysis* 10/18/96 Days	Explanation (Date of Response given to FDA)
P		56	56	56	Progressed by PPI.
M+P		147	147	147	Progressed by PPI.
M+P		148	148	148	Progressed by PPI
P		147 B	105 B	105	Subject originally progressed after crossover using analgesic score relative to baseline; now progressed by analgesic score at Cycle 6 relative to best (10/11/96).
P		missing	20+	10	Originally missing since only 1 cycle. Spinal cord compression required surgery, taken off study (10/18/96).
M+P		266+	266+	266+	Censored at last PPI.
P		42 A	105+ C	105	Censored at time of crossover in analysis (10/11/96). Worsening pelvic x-ray (10/18/96).
M+P		63	63	63	Progressed by PPI.
P		missing	20+	14	Originally missing since only 1 cycle. Progression of pulmonary metastases (10/18/96).
P		48 A	99+ C	82	Censored at time of crossover in analysis (10/11/96). Worsening of bone scan and pelvic x-ray (10/18/96).
M+P		70	70	70	Progressed by PPI.
M+P		missing	20+	20+	Originally missing. Censored at Day 20 in analysis (10/11/96).
M+P		105+	105+	105+	Censored at last PPI.
M+P		36+	36+	36	Originally censored at last PPI. Progressive disease, cervical pain requiring radiotherapy (3/10/92-3/16/92) (10/18/96).
P		81	81	81	Progressed by PPI.
M+P		41 A	139+ A	139+	Censored at last PPI (10/11/96).
P		118	118	118	Originally progressed at crossover. Progressed by evidence of tumor progression (10/3/96).

+ means censored

[1] Provided in response to 10/9/96 FDA fax, analysis was actually run on 10/3/96.

Treatment Group	Subject Number	Original* Report Days Reason Code	Analysis* 10/9/96[1] Days Reason Code	Analysis* 10/18/96 Days	Explanation (Date of Response given to FDA)
P		41	41	41	Progressed by PPI.
M+P		84+	84+	96	Originally censored at last PPI. Progressive disease, increased pain, subject taken off study (10/18/96).
P		missing	20+	37	Originally missing since only 1 cycle. Progressive disease in liver and spine leading to death (10/18/96).
P		58	58	58	Progressed by analgesic score.
P		91+	91+	111	Originally censored at last PPI. Worsening pain, new metastases to ribs (10/18/96).
M+P		42+	42+	53	Originally censored at last PPI. Subject died due to disease progression (10/18/96).
P		55	55	55	Progressed by analgesic score.
M+P		90	90	90	Progressed by PPI.
P		41 A	84+ C	84	Censored at time of crossover in analysis (10/11/96). Worsening bone scan in spine (10/18/96).
P		21+	21+	21	Originally censored at last PPI. Spinal cord compression leading to death (10/18/96).
M+P		308+	308+	308	Originally censored at last PPI. Progressive disease, bone scan findings worse (10/18/96).
M+P		42+	42+	42	Originally censored at last PPI. Progressive disease, increase in pain, worsening x-ray findings, subject required radiotherapy (10/18/96).
M+P		231+	231+	231+	Censored at last PPI.
P		226	226	226	Originally progressed at crossover. Progressed by evidence of tumor progression (10/3/96).
M+P		73+	73+	73+	Censored at last PPI.
P		49	49	49	Progressed by analgesic score.
M+P		170+	170+	170	Originally censored at last PPI. Progressive disease, increase in pain, worsening x-ray findings, marrow metastases (10/18/96).

+ means censored

[1] Provided in response to 10/9/96 FDA fax, analysis was actually run on 10/3/96.

Treatment Group	Subject Number	Original* Report Days Reason Code	Analysis* 10/9/96[1] Days Reason Code	Analysis* 10/18/96 * Days	Explanation (Date of Response given to FDA)
P		128 A	86+ C	86	Subject progressed by PPI in Cycle 7 but crossed over in Cycle 5 (10/11/96). Worsening bone scan and pelvic x-ray (10/18/96)
M+P		106	106	106	Progressed by analgesic score.
M+P		63+	63+	63+	Censored at last PPI.
P		48	48	48	Progressed by analgesic score.
M+P		218+	218+	218+	Censored at last PPI.
P		75	232	232	Subject [redacted] was erroneously declared progressed at Cycle 6 in Listing 11 and declared progressed at Cycle 4 by PPI score prior to secondary response on Listing 10. Currently, Subject [redacted] is accurately progressed by PPI at Cycle 11 (10/3/96).
M+P		21+	21+	21+	Censored at last PPI.
P		35	35	35	Progressed by PPI
P		42 A	42+ C	42+	Censored at time of crossover in analysis (10/11/96).
M+P		21+	21+	21+	Censored at last PPI.
M+P		21+	21+	35	Originally censored at last PPI. Subject died due to disease progression (10/18/96).
M+P		105+	105+	112	Originally censored at last PPI. Progressive disease, increase in pain, spinal cord compression required radiotherapy on 10/23/92 (10/18/96).
P		105+	105+	105+	Censored at last PPI.
P		42 A	63+ C	84	Censored at Cycle 4 in current analysis (10/11/96). Worsening bone scan and lumbar spine x-ray (10/18/96).
P		182 B	84 B	84	Subject originally progressed after crossover using analgesic score relative to baseline; now progressed by analgesic score at Cycle 5 relative to best (10/11/96).

scans censored

[1] Provided in response to 10/9/96 FDA fax, analysis was actually run on 10/3/96.

Treatment Group	Subject Number	Original* Report Days Reason Code	Analysis* 10/9/96[1] Days Reason Code	Analysis* 10/18/96 Days	Explanation (Date of Response given to FDA)
M+P		105+ B	105 B	105	Progressed by analgesic score relative to best in analysis 10/11/96 (originally censored since relative to baseline in original analysis)
M+P		23+	23+	23	Originally censored at last PPI. Subject withdrew due to progressive disease documented by MRI (10/18/96).
P		63	63	63	Progressed by analgesic score.
P		42 A	196 A	196	Subject progressed using analgesic score in analysis (10/11/96).
M+P		663+	663+	663+	Censored at last PPI.
P		84+	84+	84	Originally censored at last PPI. Worsening bone scan, worsening x-ray of lumbar and thoracic spine (10/18/96).
P		missing	20+	20+	Originally missing since only 1 cycle. Now censored at Day 20 (10/3/96).
M+P		210+	210+	210+	Censored at last PPI.
P		43 A	106 A	106	Progressed by PPI score at Cycle 6 in analysis (10/11/96).
M+P		56 A	140 A	140	Progressed by PPI at Cycle 7 in analysis (10/11/96).
M+P		237+	237+	237+	Censored at last PPI.
M+P		91+	91+	131	Originally censored at last PPI. Progressive disease, subject required radiotherapy on right hip (10/18/96).
P		84+	84+	84	Originally censored at last PPI. Worsening pain, subject taken off study (10/18/96).
P		23+	23+	23	Originally censored at last PPI. Spinal cord compression at T6, required surgery and radiotherapy (10/18/96).
M+P		266	266	266	Progressed by PPI
M+P		301	301	301	Progressed by PPI

cans censored

[1] Provided in response to 10/9/96 FDA fax, analysis was actually run on 10/3/96.

Treatment Group	Subject Number	Original* Report Days Reason Code	Analysis* 10/9/96[1] Days Reason Code	Analysis* 10/18/96 Days	Explanation (Date of Response given to FDA)
M+P		49 A	154+ A	114	Censored since subject never satisfied criteria for progression (10/11/96). Progressive disease by bone scan on 2/25/93, increased pelvic mass (10/18/96).
P		42 A	42+ C	42+	Censored at time of crossover in analysis (10/11/96).
P		324	324	324	Progressed by analgesic score.
M+P		420	420	420	Progressed by PPI.
M+P		46	46	46	Progressed by analgesic score.
P		49	49	49	Progressed by PPI.
P		20+	20+	20	Originally censored at last PPI. Spinal cord compression required radiotherapy and surgery (10/18/96).
M+P		249	249	249	Progressed by PPI.
P		26+	26+	63	Originally censored at last PPI. Obstructive uropathy due to progressive disease, subject taken off study (10/18/96).
M+P		86	86	86	Progressed by PPI
M+P		350	350	350	Progressed by PPI.
P		missing	20+	15	Originally missing since only 1 cycle. Worsening pain and thrombocytopenia, subject taken off study (10/18/96).
M+P		49	49	49	Progressed by analgesic score.
P		42+	42+	42	Originally censored at last PPI. Spinal cord compression, subject taken off study (10/18/96).
P		43 A	127 A	127	Progressed by PPI at Cycle 7 in analysis (10/11/96).
M+P		42	42	42	Progressed by PPI.
M+P		49 A	133+ A	133	Censored since subject never satisfied criteria for progression (10/11/96). Worsening bone scan, subject taken off study due to progressive disease by bone scan findings (10/18/96).

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Provided in response to 10/9/96 FDA fax, analysis was actually run on 10/3/96.

Treatment Group	Subject Number	Original* Report Days Reason Code	Analysis* 10/9/96[1] Days Reason Code	Analysis* 10/18/96 Days	Explanation (Date of Response given to FDA)
P		149 C	149+ C	149+	Censored at time of crossover at Cycle 8 (10/11/96).
M+P		336+	315	315	Originally censored, now progressed by bone scan (10/11/96).
P		41	41	41	Progressed by PPI.
M+P		169	169	169	Progressed by analgesic score.
M+P		43	43	43	Progressed by PPI.
M+P		439	439	439	Progressed by radiotherapy requirement.
P		86	86	86	Progressed by PPI.
M+P		126	105	105	Originally progressed at Cycle 7 to be conservative regarding missing Cycle 5. Currently, per FDA reviewer, progressed by PPI at Cycle 6 (10/3/96).
P		147	147	147	Progressed by analgesic score.
P		21	21+	21	Originally progressed at crossover at Cycle 2. Worsening pain and analgesic score, subject crossed over (10/18/96).
P		35	35	35	Progressed by PPI.
P		70 C	70+ C	70	Censored at time of crossover in Cycle 5 (10/11/96). Worsening bone scan and x-ray in spine, ribs and pelvis (10/18/96).
P		44	44	44	Progressed by PPI.
P		42 A	63+ A	42	Censored at Cycle 4 in analysis (10/11/96). Required radiotherapy for progressive bone lesion, subject taken off study (10/18/96).
M+P		451	451	451	Progressed by radiotherapy requirement.
P		44 A	65 A	65	Progressed by PPI at Cycle 4 in analysis (10/11/96).
M+P		84	84	84	Progressed by analgesic score.
M+P		missing	20+	17	Originally missing since only 1 cycle. Progressive disease, brain metastases by CT scan (10/18/96).

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[1] Provided in response to 10/9/96 FDA fax, analysis was actually run on 10/3/96.

Treatment Group	Subject Number	Original* Report Days Reason Code	Analysis* 10/9/96[1] Days Reason Code	Analysis* 10/18/96 Days	Explanation (Date of Response given to FDA)
M+P		42	42	42	Progressed by analgesic score.
P		missing	20+	20+	Originally missing since only 1 cycle. Now censored at Day 20 (10/3/96).
P		42 A	21+ C	21+	Censored at time of crossover in analysis (10/11/96).
M+P		179+	179	179	Originally censored. Currently progressed by chest x-ray (10/3/96).
M+P		42 A	181 A	181	Progressed by PPI (10/11/96).
P		86	86	86	Progressed by analgesic score.
M+P		42	42	42	Progressed by analgesic score.
M+P		32+	32+	32	Originally censored at last PPI. Subject taken off study due to increase in pain (10/18/96).
P		missing	20+	20+	Originally missing since only 1 cycle. Now censored at Day 20 (10/3/96).
P		42	42	42	Progressed by PPI.
P		105	105	105	Progressed by PPI.
M+P		374+	374+	374+	Censored at last PPI.
M+P		219+	219+	184	Originally censored at last PPI. New lesion on bone scan, worsening x-rays, off study on 7/20/94 due to progressive disease (10/18/96).
M+P		168	168	168	Progressed by PPI.
P		54	54	54	Progressed by PPI.
P		237 B	216 B	216	Originally progressed by PPI when analgesic score compared to baseline; when compared to best, get Cycle 11 (10/11/96).
M+P		missing	20+	8	Originally missing since only 1 cycle. Subject taken off study due to brain metastases by scan (10/18/96).
P		108 C	108+ C	108+	Censored at time of crossover at Cycle 6 (10/11/96).
M+P		42 A	160 A	160	Progressed by PPI (10/11/96).

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[1] rrovided in response to 10/9/96 FDA fax, analysis was actually run on 10/3/96.

Treatment Group	Subject Number	Original* Report Days Reason Code	Analysis* 10/9/96[1] Days Reason Code	Analysis* 10/18/96 Days	Explanation (Date of Response given to FDA)
P		133	133	133	Progressed by PPI.
P		119 B	98 B	98	Originally analgesic score compared to baseline so progressed by PPI. Now score compared to best, so progressed by analgesic score (10/11/96).
P		42 A	110+ C	82	Censored at time of crossover in analysis (10/11/96). Progressive bone scan and x-ray in spine and shoulders (10/18/96).
M1P		84+	84+	84	Originally censored at last PPI. Subject taken off study due to worsening bone scan and x-ray findings (10/18/96).

+ Means censored

[1] Provided in response to 10/9/96 FDA fax, analysis was actually run on 10/3/96.

9182 Trial

9.411 Complete Response:

Complete normalization of bone scan and normalization of tumor markers. Tumor measurement will be performed on two consecutive three,week evaluations (at three weeks and six weeks). If at any time a CR is observed, two additional, consecutive evaluations must be performed and demonstrate CR status.

9.412 Partial Response:

As no uniformly accepted criteria for response in bone scans exists, bone scans will be serially assessed to evaluate progression, and tumor reduction in bone-only patients will be characterized by PSA. Response of PSA will be constituted by decrease of 80% or more of pretreatment value confirmed by repeat test at least twice over a 6 week period. Performance stable or improved. Tumor measurement will be performed on two consecutive three week evaluations (at three weeks and six weeks). If at any time a PR is observed, two additional, consecutive evaluations must be performed and demonstrate PR status.

9.413 Stable:

Neither response or progression and stable or improved performance status.

9.414 Progression:

Either a PSA increase at week 6 of >100% of the baseline PSA value, confirmed by repeat determination and/or deterioration of performance status of >1 level and/or worsening bone scan as evidenced either by increasing intensity of two or more lesions or the appearance of two or more new lesions. If there is discordance between the PSA and the tumor response (i.e. normalization or decrease of PSA and growth of evaluable or measurable disease) the patient will be considered to have progressed. A decreased performance status of >1 level as sole evidence of progressive disease should be discussed with the study chair.

9.5 Unevaluable Tumor Response: All evaluable except the following:

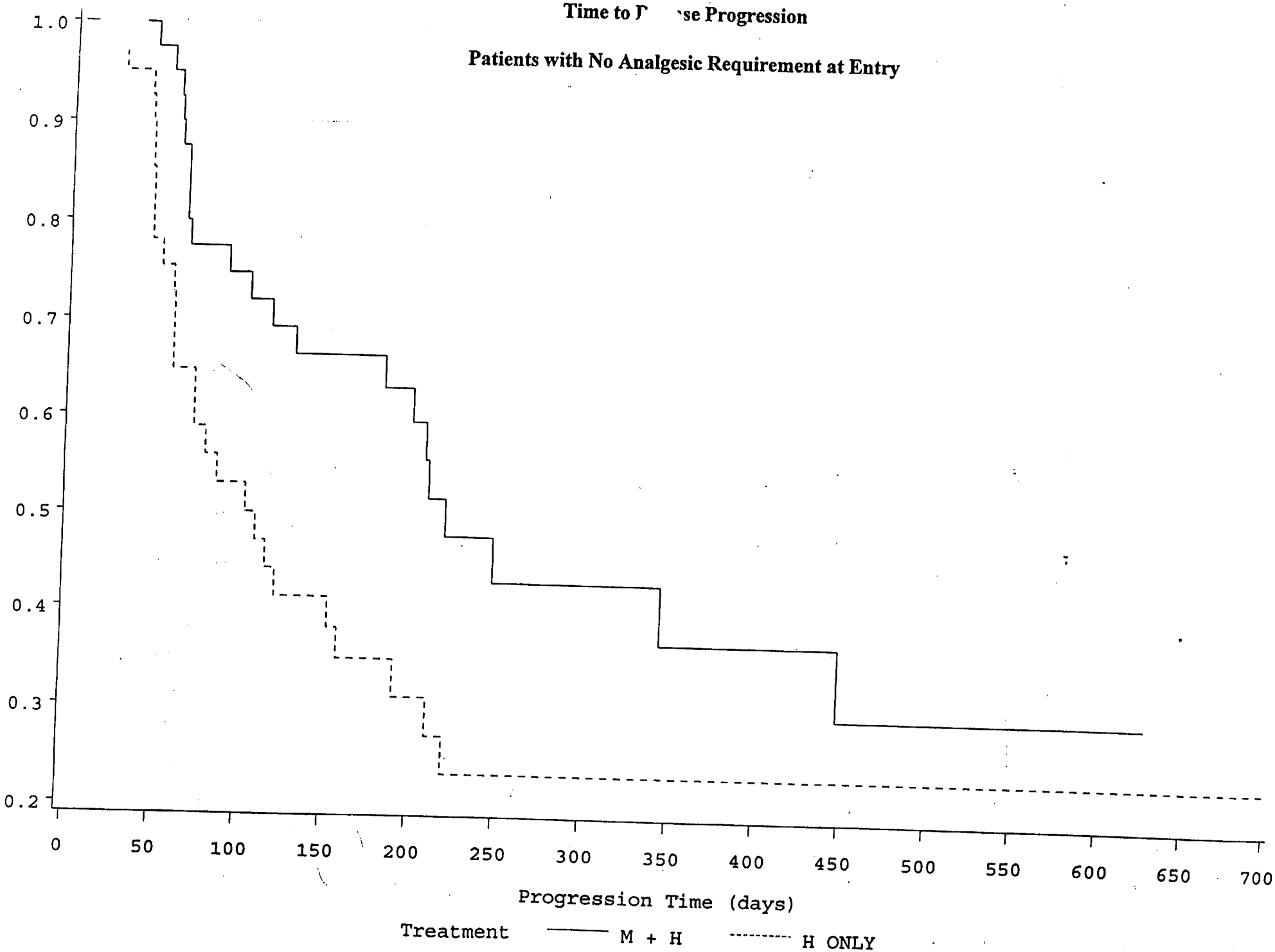
9.51 If follow-up disease assessment is not performed, tumor response is unevaluable.

9.52 If a patient who has received treatment has not experienced disease progression, early death, nor satisfied the criteria for complete response, partial response, regression, or stable disease, response is unevaluable.

9.6 Simultaneous progression and regression of measurable lesions or other indices of response will be called a mixed response and scored as disease progression for the purposes of this study.

9.7 Performance Status (PS):

PS will be assessed using the following criteria. Normal performance =0; Decreased performance but ambulatory=1; Increased time in bed, less than 50% of day=2; Increased time in bed, more than 50% of day=3; Totally bedridden=4.


Time to P se Progression
Patients with No Analgesic Requirement at Entry
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
Progression Time (days)
Treatment
M + H
H ONLY

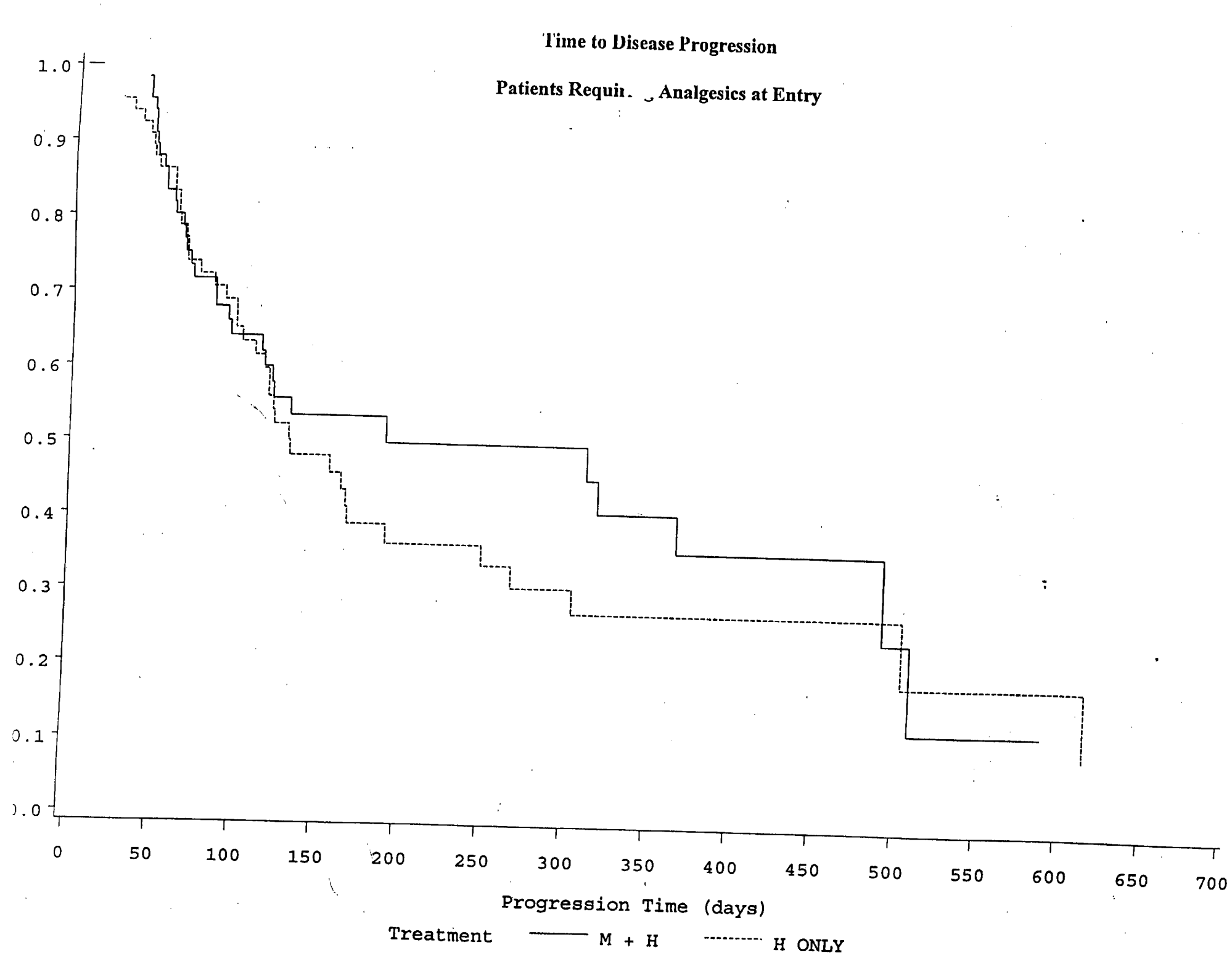

Time to Disease Progression
Patients Requi. Analgesics at Entry
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
Progression Time (days)
Treatment
M + H
H ONLY

Figure 4
STUDY 9182
MEAN ANALGESIC USAGE
BY TREATMENT

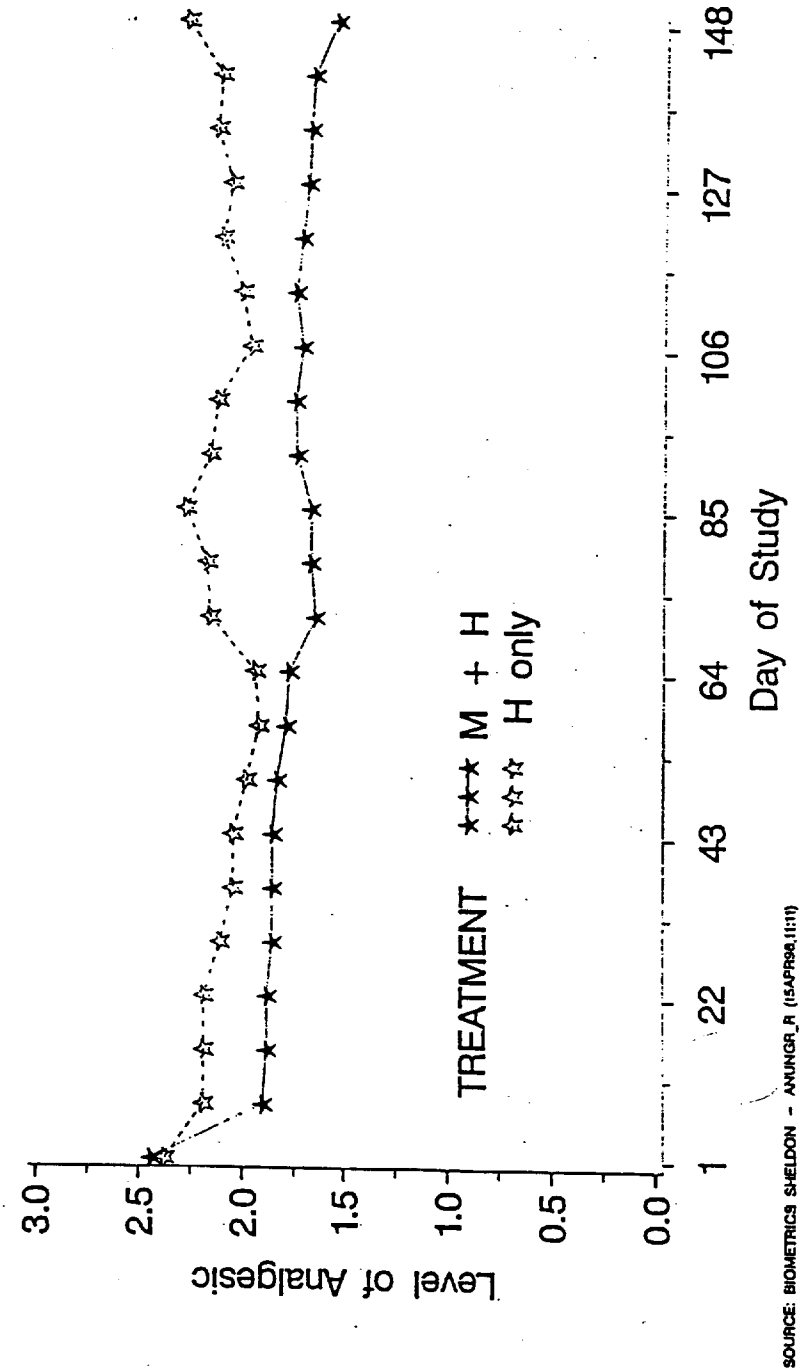
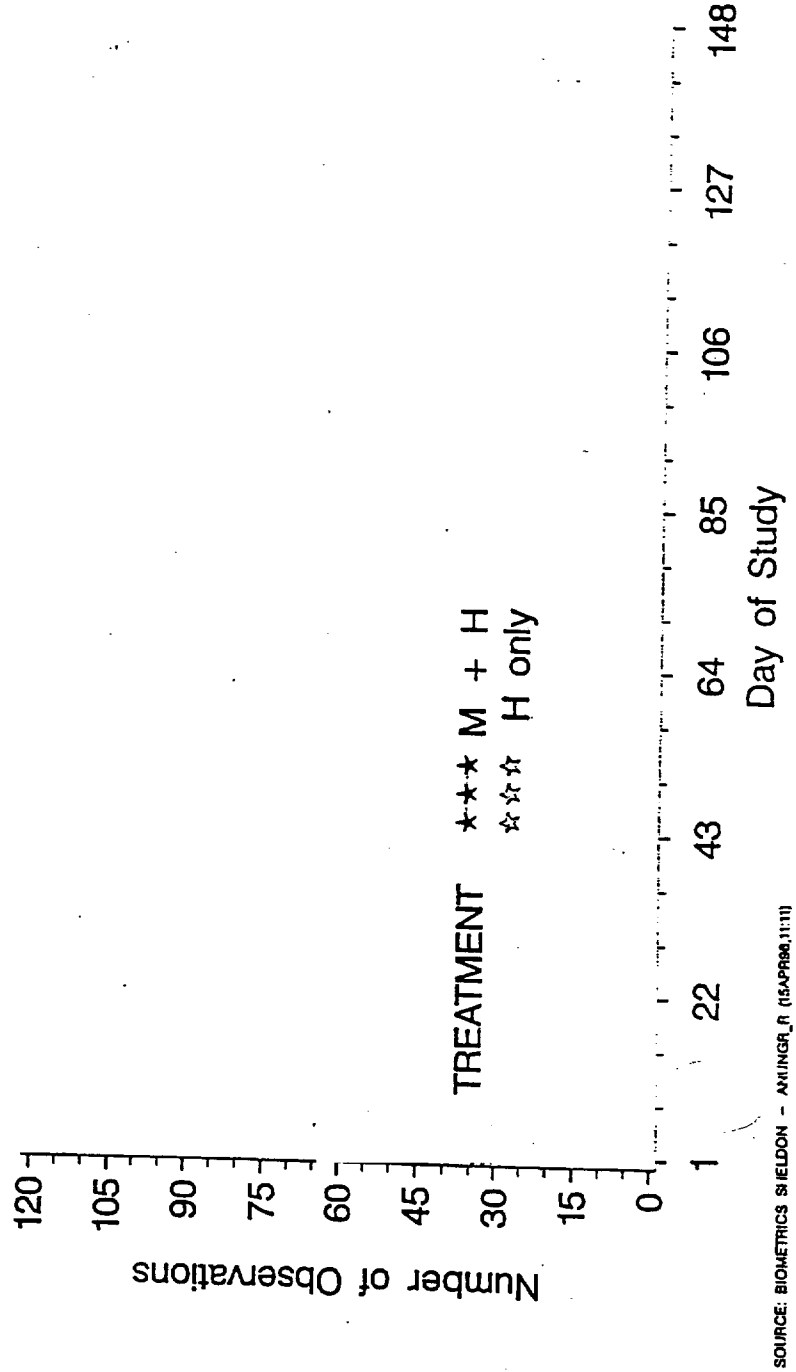


Figure 5
STUDY 9182
NUMBER OF ANALGESIC OBSERVATIONS
BY TREATMENT



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Clinical Pharmacology and Biopharmaceutics Review

NDA:	19297/SE1-014 19297/SE1-014(B2)	**Submission Date:**	May 10, 1996 October 31, 1996
Type of Submission:	supplemental NDA		
Generic Name:	mitoxantrone		
Formulation:	injection		
Sponsor:	Immunex Corp. 51 University Street Seattle, WA 98101-2936		
Reviewer:	Gene M. Williams, Ph.D.		

This supplemental NDA is for the use of NOVANTRONE® as palliative therapy in hormone-refractory prostate cancer.

No item 6 submission was made at the time of s-NDA filing. At our request the sponsor has provided literature information, and data from the original NOVANTRONE® NDA, that allows the NOVANTRONE® labeling to be updated. This review is the update of the labeling.

The Clinical Pharmacology section of our revised NOVANTRONE® package insert is provided on the following page of this review. Our request to the sponsor for information and the current NOVANTRONE® package insert are attached.

In addition to revision of the Clinical Pharmacology section, we recommended that a "hepatic impairment" section be added to the DOSAGE AND ADMINISTRATION portion of the label. Our recommendation was heeded and the below, authored by the medical officer and ourselves, has been added to the label:

> **Hepatic Impairment**: For patients with hepatic impairment, there is at present no laboratory measurement that allows for dose adjustment recommendations. (See **CLINICAL PHARMACOLOGY**, Special Populations: *Hepatic Impairment*)

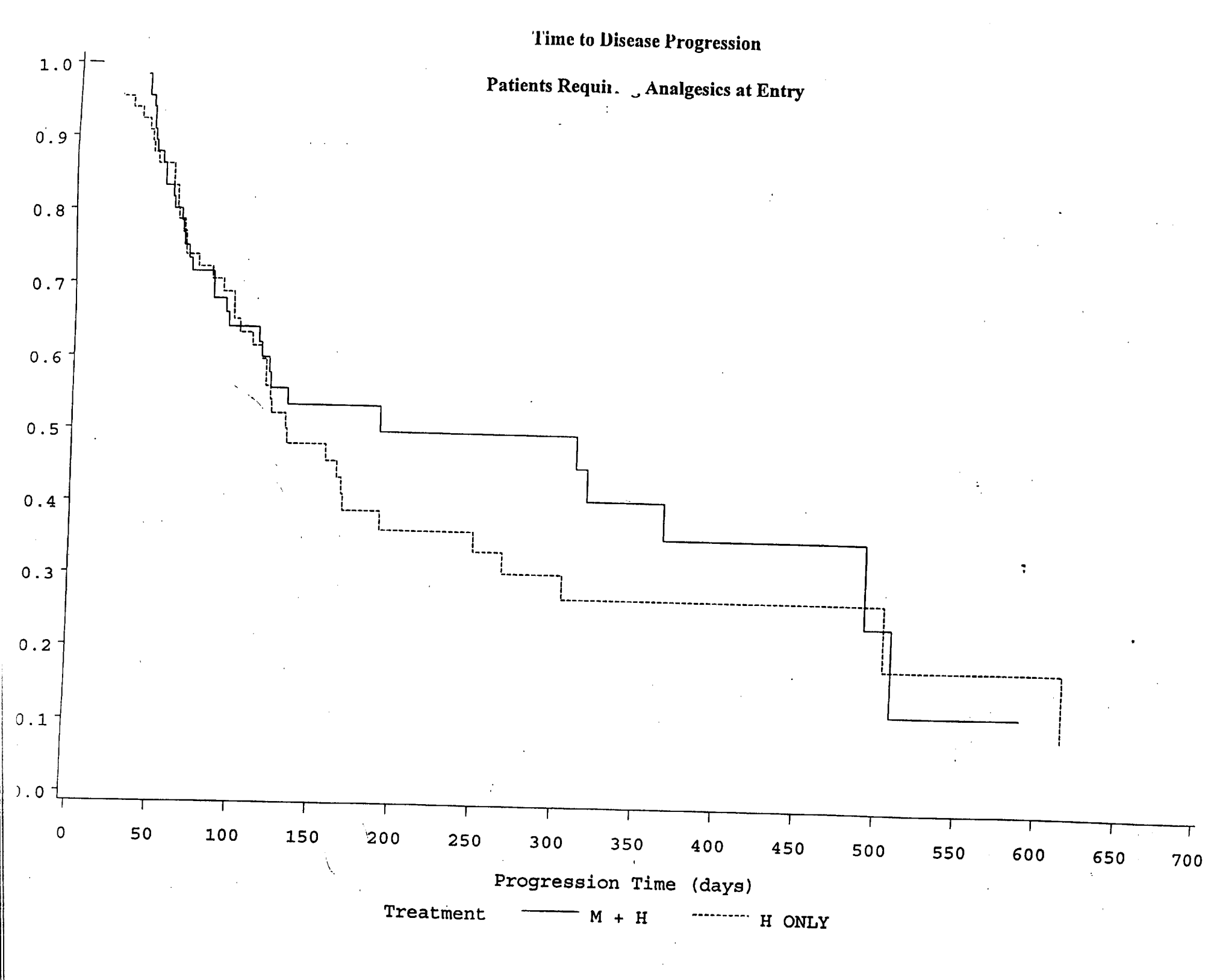

Time to Disease Progression
Patients Requi. Analgesics at Entry
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
Progression Time (days)
Treatment
M + H
H ONLY

Figure 4
STUDY 9182
MEAN ANALGESIC USAGE
BY TREATMENT

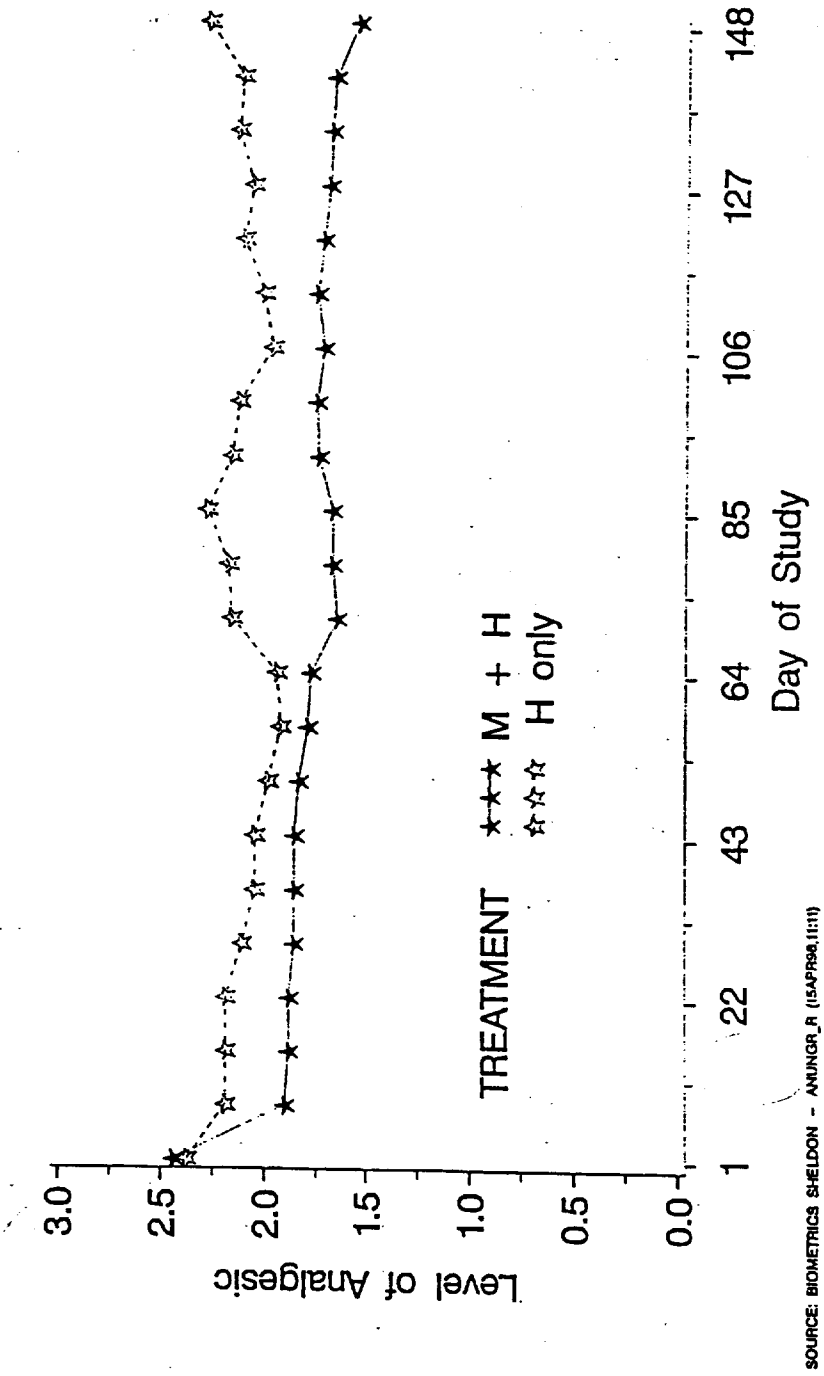
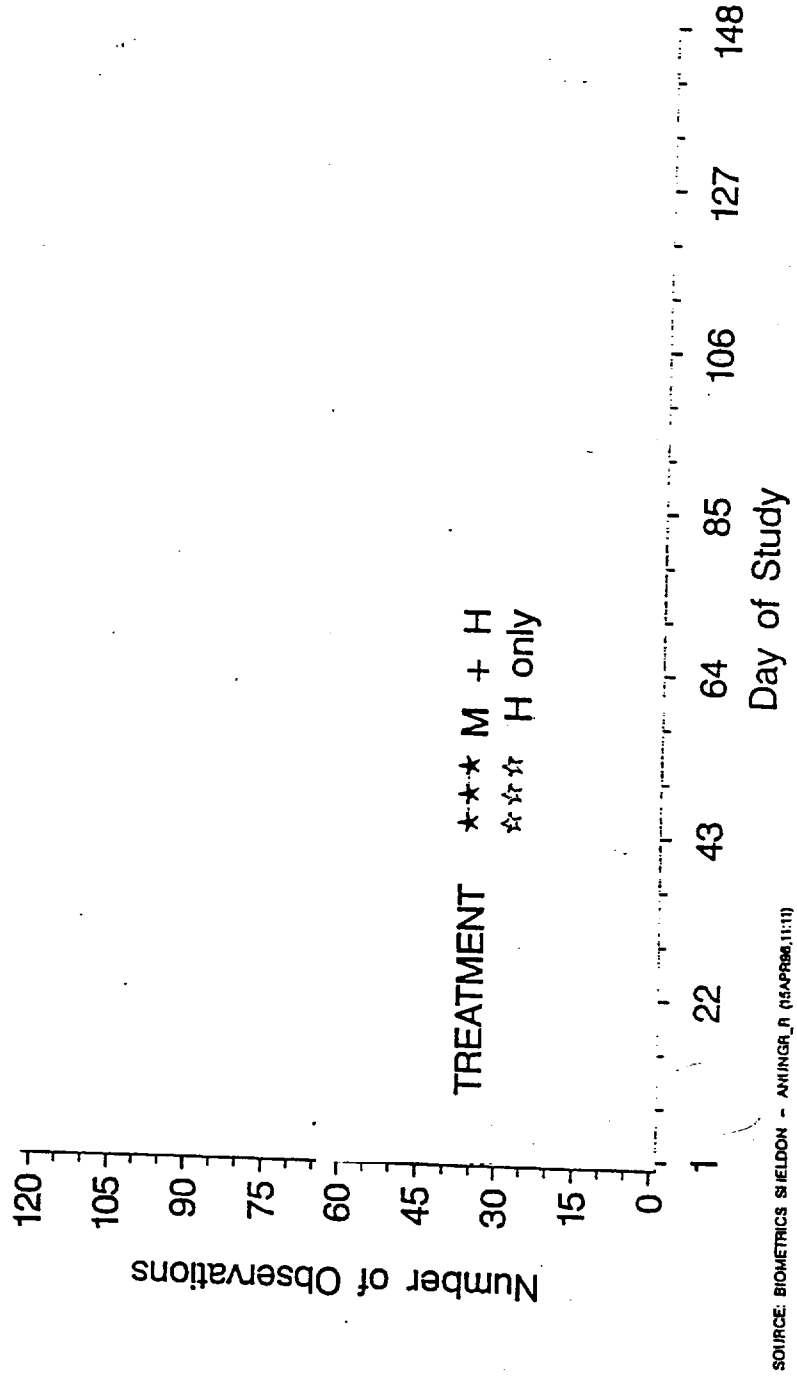


Figure 5
STUDY 9182
NUMBER OF ANALGESIC OBSERVATIONS
BY TREATMENT



Clin. Pharm.
& Bio

CLINICAL PHARMACOLOGY

Mechanism of Action

Although its mechanism of action is not fully elucidated, mitoxantrone is a DNA-reactive agent. It has a cytocidal effect on both proliferating and non proliferating cultured human cells, suggesting lack of cell cycle phase specificity.

Pharmacokinetics

Pharmacokinetic in patients following a single intravenous administration of NOVANTRONE® can be characterized by a three-compartment model. The mean alpha half-life of mitoxantrone is 6 to 12 minutes, the mean beta half-life is 1.1 to 3.1 hours and the mean gamma (terminal or elimination) half-life is 23 to 215 hours (median approximately 75 hours). Pharmacokinetic studies have not been performed in humans receiving multiple daily dosing. Distribution of mitoxantrone to tissues is extensive: steady-state volume of distribution exceeds 1,000 L/m2, and tissue concentrations of mitoxantrone appear to exceed those in the blood during the terminal elimination phase. In the monkey, distribution to the brain, spinal cord, eye, and spinal fluid is low. In patients administered 15 - 90 mg/m^2 of NOVANTRONE® intravenously, there is a linear relationship between dose and the area under the concentration-time curve. Mitoxantrone is 78% bound to plasma proteins in the observed concentration range of ng/mL. This binding is independent of concentration and is not affected by the presence of phenytoin, doxorubicin, methotrexate, prednisone, prednisolone, heparin, or aspirin.

Metabolism and elimination: Metabolism and elimination of mitoxantrone following NOVANTRONE® administration are not well characterized. 11% or less of the mitoxantrone is recovered in the urine, and 25% or less is recovered in the feces, within five days after drug administration. Of the material recovered in the urine, 65% is unchanged drug. The remaining 35% is comprised primarily of a mono- and a dicarboxylic acid derivative and their glucuronide conjugates. These carboxylic acid metabolites are not DNA-reactive/cytocidal, and their route of formation is unknown.

Special Populations

Gender: The effect of gender on mitoxantrone pharmacokinetics is unknown.

Geriatric: The effect of old age on mitoxantrone pharmacokinetics is unknown.

Pediatric: The effect of young age on mitoxantrone pharmacokinetics is unknown.

Race: The effect of race on mitoxantrone pharmacokinetics is unknown.

Renal Impairment: The effect of renal impairment on mitoxantrone pharmacokinetics is unknown.

Hepatic Impairment: Mitoxantrone clearance is reduced by hepatic impairment. Patients with severe hepatic dysfunction (bilirubin greater than 3.4 mg/dL) have an AUC more than 3-fold that of patients with normal hepatic function receiving the same dose. No laboratory measurement that allows for dose adjustment recommendations for patients with hepatic impairment is available.

Drug Interactions: Pharmacokinetic studies of the interaction of NOVANTRONE® with concomittantly admistered medications have not been performed. The interaction of mitoxantrone with the human P450 system has not been investigated.

FT

Atiqur Rahman, Ph.D. 11/13/96
Team Leader
Division of Pharmaceutical Evaluation I

Gene M. Williams 11/13/96
Gene M. Williams, Ph.D.
Reviewer
Division of Pharmaceutical Evaluation I

cc:

NDA 19297	original
HFD-150	division file
HFD-150	Vaccari, Beitz
HFD-340	Viswanathan
HFD-850	Lesko
HFD-860	Malinowski, Mehta, Rahman
HFD-870	Drug file (Clarence Bott, Pkln Rm 13B-31)
HFD-870	Chron file (Clarence Bott, Pkln Rm 13B-31)
HFD-870	Reviewer's file (Clarence Bott, Pkln Rm 13B-31)

Pharm/Tox

SEP 17 1996

L. Vassan

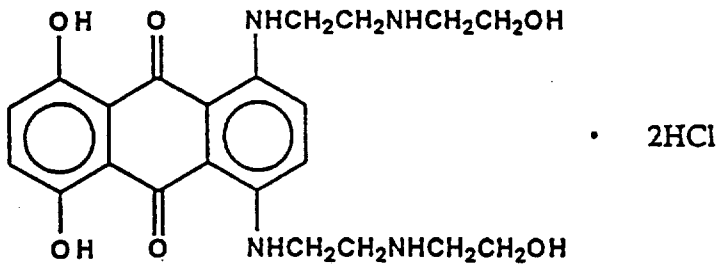
DIVISION OF ONCOLOGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original, Review (No. 1) of Supplement Submission

sNDA No.:	19,297
Supplement No.	S-014
Date(s) of Submission:	6/10/96

Information to be Conveyed to Sponsor: Yes (x), No ( )

Reviewer:	Diana Wroblewski Giorgio, Ph.D.
Date Review Completed:	8/9/96
Sponsor:	Immunex Corporation 51 University Street Seattle, Washington 98101-2936
Drug Name:	Novantrone® (Mitoxantrone hydrochloride for injection)
Chemical Name:	1,4-Dihydroxy-5, 8-bis[[2-[(2-hydroxyethyl]amino]ethyl] amino)]-9, 10-anthracenedine dihydrochloride

Structure:



• 2HCl

Molecular Formula:	$C_{22}H_{28}N_4O_6 \cdot 2HCl$
Molecular Weight:	517.4
Related INDs/NDAs/DMFs:	IND IND NDA 19,297 (Lederle)

Class:	Antineoplastic agent; topoisomerase II inhibitor
Indication:	In combination with corticosteroids, Novantrone is indicated as initial chemotherapy for treatment of patients with prostate cancer, after failure of primary hormonal therapy. In addition, in combination with other approved drug(s), Novantrone is indicated in the initial therapy of acute nonlymphocytic leukemia (ANLL) in adults, including myelogenous, promyelocytic, and erythroid acute leukemia.
Route of Administration:	Intravenous
Proposed Dose:	12 - 14 mg/m^2, administered as a short intravenous infusion every 21 days.
Previous Reviewer(s):	Ching-Long Joseph Sun, Ph.D. David Richman, Ph.D. Doo Y. Lee-Ham, Ph.D.
Studies Reviewed in this NDA:	None

Studies Previously Reviewed:

Antitumor Activity:

Mouse leukemia system.
Mouse solid-tumor system.
Mechanism of Action.

Pharmacokinetics: Both in animal and human.

Excretion.
Distribution.
Plasma level.
Metabolism.

Toxicology and Pathology:

Mouse, LD50.
Rat, LD50.
Rat, single dose I.V. toxicity and effect on rat myocardium.
Dog, single dose I.V. toxicity.
Monkey, single dose I.V. toxicity.
Rat, daily for one month toxicity.
Dog, X5, I.V. toxicity.
Dog, X14 I.V. toxicity.
Dog, X5, 9 day recovery, 3 cycles toxicity.
Monkey, X5, I.V.
Monkey, X14, I.V.
Monkey, once/21 days, 2 cycles I.V.
Rat, I.V., once/21 days for 12 months.
Dog, 30 weeks I.V. intermitten dosing.
Monkey, 44 weeks I.V. intermitten dosing.
Rabbit, 21 weeks I.V. intermitten dosing.
Dog, I.V. toxicity intermitten dosing after Doxorubicin.

Genetic toxicity:

Microbial mutogenicity.
Unscheduled DNA synthesis.
Sister chromatid exchange.
Mouse lymphoma test.
Cell transformation.
Rat Cytogenetics.
Dominant lethal test.

Reproductive Toxicology and Teratology.

Carcinogenicity:

Mouse.
Rat.

Miscellaneous Studies.

Topical toxicity, rat and rabbit.
Ocular irritation, rabbit.
Dermal sensitization, guniea pig.
Combination toxicity, dog.
Heparin activity in vitro.

COMMENTS ON PACKET INSERT:

RECOMMENDATIONS TO BE CONVEYED TO SPONSOR:

This NDA is approvable, provided that the packet insert is modified as indicated above.

Diana Wroblewski Giorgio, Ph.D.
Pharmacologist/Toxicologist

9/5/96

Original NDA 19-297
c.c. HFD-150/Division File
/J. DeGeorge/Pharmacology Team Leader
/J. Beitz/Medical Officer
/L. Vaccari/C.S.O.
/D. Giorgio/Reviewer

9/6/96

Stat

Statistical Review and Evaluation.

NOV 7 1996

NDA#: 19-297

Title: Phase III Trial of Mitoxantrone Plus Low-Dose Prednisone Versus Low-Dose Prednisone for Symptomatic Hormone-Resistant Prostate Cancer

Applicant: Immunex

Name of Drug: Novantrone (Mitoxantrone Hydrochloride Concentrate for injection)

Indication: Hormone Resistant Prostate Cancer (HRPC)

Documents Reviewed: Volumes 9-17, and 19 of submission dated May 13, 1996, Volume 1 of submission dated October 4, 1996, and Volume 1 of submission dated November 4, 1996.

Medical Reviewer: Julie Beitz, M.D.

RELEVANT STATISTICAL ISSUES:

CCI-NOV22 Study:

1) The sponsor has defined and analyzed a secondary criterion for response, Criterion 2: *"a 50% or more decrease in analgesic score without increase in pain intensity"*. This criterion was not prospectively defined in the protocol.

2) The interim analysis plan specified by the protocol is not clear to this reviewer. The sponsor did not provide details about the interim analysis plan (design, methods, nominal significance α-levels, etc.) No adjustments of the significance level have been made for interim look at the data.

3) Duration of response (pain relief) was measured from the start of therapy to progression (instead of from the beginning of relief to progression).

4) The sponsor did not provide any formal longitudinal analyses (i.e. GEE or Laird/Ware methods, etc.) that could be used to assess time trends on the primary endpoint and on the quality of life data. Even though these are somewhat exploratory, they provide important insights regarding the pattern of missing data and sources of potential bias. **This reviewer performed a longitudinal data analyses on PPI and analgesic scores. The results are included in an addendum to this review.**

Study 9182

1) The sponsor did not provide any details about the interim analyses results specified by the protocol. No adjustments of the significance level have been made for interim looks.

In Section 1 we give a brief background on Novantrone...Section 2 contains a description (Section 2.A.1), the efficacy results and analyses (Section 2.A.2), and the summary (Section 2.A.3) for the Canadian study (CCI-NOV22 study). In addition, Section 2 contains a description (Section 2.B.1), the efficacy results and analyses (Section 2.B.2), and the summary (Section 2.B.3) for the STUDY 9182. Section 3 contains the conclusions and recommendations regarding this application. Electronic data files were provided for all the pivotal studies by the Sponsor. Safety data analyses would be included only in the Medical Review.

There are 3 Attachments with tables and figures referenced at the end of this review. Attachment 1 contains Reviewer's Figures 1-10 for both studies. Attachment 2 contains Sponsor's Tables 2,3, and 15-17, and Sponsor's Figures 6-20 of the CCI-NOV22 study. Attachment 3 contains Sponsor's Tables 3-7, 9, 12-32, and Sponsor's Figures 1-3 of the study.

1) BACKGROUND: In this NDA the sponsor seeks approval of Novantrone for the treatment of patients with symptomatic Hormone-Resistant Prostate Cancer. Mitoxantrone is approved for the treatment of acute myelogenous leukemia, and has been studied extensively in the treatment of lymphoma, metastatic breast cancer, and other solid tumors in the United States.

This submission contains two reports of multicenter, prospective, open-label, randomized Phase III studies. The objective of the first study, CCI-NOV22 study, was to assess improvement in pain defined by a 6-point pain scale (PPI, for present pain intensity) with no increase in analgesic score and no evidence of disease progression in patients with hormone-resistant prostate cancer (HRPC) treated with Mitoxantrone+Prednisone versus Prednisone alone. The objective of the second study, STUDY 9182, was to compare the survival of HRPC patients with Mitoxantrone+Hydrocortisone (M+H) to a control group treated with Hydrocortisone (H) alone.

2) DESCRIPTION OF STUDIES:

2.A.1) CCI-NOV22 study in patients with Symptomatic Hormone-Resistant Prostate Cancer:

Study Design: This study was a multicenter (11 Canadian centers), prospective, open-label, randomized Phase III study with central randomization and stratification according to baseline ECOG performance status (0, 1 versus 2, 3). One hundred and sixty-one subjects were enrolled; 80 subjects were randomized to the M+P (Mitoxantrone+Prednisone) arm and 81

subjects were randomized to the P (Prednisone) arm. Forty-eight subjects (59%) on the P arm subsequently crossed over to receive Mitoxantrone.

Subjects with symptoms that could not be relieved by analgesic administration or locoregional radiation therapy were to be enrolled. Subjects were to be randomized to receive Mitoxantrone plus Prednisone or Prednisone alone. All subjects were to begin taking Prednisone 5 mg po BID. Subjects who had received Prednisone for no more than 2 weeks prior to study entry were eligible. Subjects randomized to the M+P arm were to receive Mitoxantrone 12 mg/m^2 by IV push every 3 weeks, to a maximum cumulative dose of 140 mg/m^2. Subjects achieving a subjective response were to continue on Prednisone alone if they had reached the maximum cumulative dose of Mitoxantrone. If disease progression occurred after stopping Mitoxantrone, treatment could be restarted if a multigated angiogram (MUGA) scan or echocardiogram showed a normal LVEF, and could continue as long as subsequent MUGA scans performed after every third cycle of treatment showed a normal LVEF.

Subjects randomized to the P arm were to be crossed over to receive Mitoxantrone at the time of symptom progression. Optional crossover was permitted for subjects randomized to the Prednisone arm who had SD for six weeks.

Concomitant Therapy: Prochlorperazine at a dose of 10 mg po was recommended as antiemetic therapy. Treatment with Metoclopramide and/or Lorazepam was permitted for more severe nausea. Use of Dexamethasone or similar steroids was not permitted.

Subjects with prior orchiectomy were to have discontinued any anti-androgen treatment prior to entry into the study. Subjects without prior orchiectomy were to continue therapy with one androgen antagonist. Treatment with Flutamide alone was not considered to provide adequate androgen suppression.

Use of analgesics for symptomatic relief was permitted. To provide an accurate estimate of baseline analgesic use, entry into the study for subjects who required an adjustment in analgesic dose was to be delayed for a minimum of one week following stabilization of analgesic requirements.

Radiation therapy was to be completed at least four weeks prior to study entry. A requirement for radiation therapy after entry into the study was considered as evidence of disease progression. Subjects randomized to the M+P arm who had disease progression and required radiation therapy were to be removed from study. Subjects randomized to the Prednisone treatment arm who had disease progression and required radiation therapy were to delay crossover to the chemotherapy treatment arm for a minimum of four weeks from the time of completion of radiation therapy.

Selection Criteria: Subjects with a diagnosis of prostatic adenocarcinoma documented either by biopsy or by a combination of clinical features consistent with the diagnosis of prostate

cancer and elevated prostatic acid phosphatase (PAP) or PSA were eligible for participation in the study as further defined by the criteria below.

Inclusion Criteria:

- Metastatic or locally advanced (T4) disease with symptoms that included pain.
- Hormone resistance defined by progression or recurrence of disease despite standard hormonal therapy (orchiectomy, diethylstilbestrol dosage of $\geq$ 3 mg/day, etc.), and a documented castrate serum testosterone concentration ($<$ 3.5 nmol/L).
- ECOG performance status $\leq$ 3.
- A baseline LVEF $\geq$ the institutional normal $\pm$ 5% in subjects with a history of cardiac disease.
- Completion of pain and QOL questionnaires with a PPI score $\geq$ 1 at baseline.
- Signed informed consent form indicating awareness of the investigational nature of the study.

Exclusion Criteria:

- Previous systemic chemotherapy (with the exception of estramustine sodium phosphate) or treatment of malignant disease with Prednisone or other glucocorticosteroids for longer than 2 weeks.
- Active malignancy except for non-melanotic skin cancers. Subjects with quiescent malignancy for 10 years following resection were considered eligible.
- Life expectancy $<$ 3 months.
- Radiation therapy to more than one large axial field (defined as having a maximum dimension $>$ 25 cm) to either the spine or pelvis for advanced disease, or more than one treatment with strontium chloride (Sr_{89}).
- WBC $< 3x10^3 mm^3$, granulocytes $< 1.5x10^3/mm^3$, platelets $< 150x10^3/mm^3$, and bilirubin $>$ 54 μmol/L.
- Uncontrolled cardiac failure, active infection, or other contraindications to treatment with Mitoxantrone. Subjects with diastolic pressure $>$ 100 mmHg were to be treated at the discretion of the Investigator before entry into the study.
- Contraindications to the use of Prednisone such as active peptic ulcer. Subjects with a history of peptic ulcer, hypertension or diabetes were eligible if, in the opinion of the investigator, they were able to receive low-dose Prednisone.
- Radiation therapy within the previous 4 weeks, or discontinuation of Sr_{89} within the previous 8 weeks.

Evaluations During Treatment:

For subjects randomized to receive Mitoxantrone:

- CBC and differential on Days 1, 10, and 14 of Cycle 1. CBC on Day 1 and between Days 10 to 14 of subsequent cycles.

For all subjects every 3 weeks:

- Physical examination, completion of QOL and pain questionnaires, and analgesic record.
- CBC and differential, alkaline phosphatase, PAP. Any biochemical tests (e.g. PSA, blood sugar) that showed abnormal results at study onset were to be repeated.

For all subjects every 12 weeks:

- All pretreatment evaluations were to be repeated every 12 weeks until there was evidence of disease progression, and during follow-up for duration of survival.

Endpoints: The primary efficacy variable was **response** to treatment. All subjects who were randomized and treated with Prednisone with or without Mitoxantrone were evaluated for response based on the following prospectively defined endpoints that were considered indicative of a meaningful clinical benefit: A 2-point improvement in the 6-point scale for PPI that was not accompanied by an increase in analgesic score and was maintained for 2 successive visits 3 weeks apart. Subjects who had mild pain (1+) at baseline were to have complete relief of pain.

A sample size of about 150 patients would allow detection of a 20% increase (from 20% to 40%) in response in the treatment group with 80% power and an one-sited $\alpha=0.05$ according to the protocol.

The secondary efficacy variables were:
1) Time to progression (defined for responders) was considered as the time from the date of first treatment with Prednisone alone or Prednisone plus Mitoxantrone until the date of the final assessment that satisfies response criteria.

Progression is defined if either of the following are sustained on 2 consecutive visits, compared with the best score:

1. An increase in PPI by $\geq$ 1 point
2. An increase in analgesic score by $\geq$ 25% or at anytime:
3. unequivocal evidence of new lesions, progression of existing lesions, or requirement for radiation therapy
4. evidence of progression based solely on a bone scan will require a second confirmation by bone scan at least one month

according to the protocol. There will be more details on how time to progression was applied by the sponsor to define events in Section 2.A.2, under "Statistical Methodology".

2) **Duration of survival** defined as the period from the date of administration of the treatments to the last date the patient was known to be alive.

3) **Quality of Life:** The QOL assessments were self-administered by subjects during clinic visits. The QOL assessments consisted of:

a) EORTC QOL Questionnaire (EORTC - Q30C), consisting of 30 items grouped into 5 subscales addressing symptoms and physical activity, functional activity, psychosocial interaction, overall physical assessment, and global QOL.
b) Specific Prostate Module, an 11-item module, including questions about pain and possible side effects from analgesic medication.
c) A series of nine LASA scales evaluating various aspects of QOL.

Pain Scale: The pain scale was derived from the PPI Index of the McGill Pain Questionnaire. Subjects were asked to determine how much pain they experienced during the 24 hours preceding their visit to the clinic using the following six terms:

Present Pain Intensity

PAIN	no pain	mild pain	discomforting	distressing	horrible	excruciating
SCALE	0	1	2	3	4	5

Analgesic Score: Subjects were asked to record in a subject diary the name, strength, and number of pills or doses taken for pain control for each day in the cycle. The daily analgesic score was calculated using a numerical scale. Each standard tablet/capsule of non-narcotic analgesic taken (acetaminophen, acetylsalicylic acid, indomethacin) was scored as 1. Each dose of oral narcotics (e.g., hydromorphone, codeine, morphine, anileridine, Percodan®, Percocet®, Tylenol III®) was scored as 2. Each dose of IV narcotics was scored as 4. Analgesic scores were averaged for the last 7 days of each cycle and were then transcribed to the CRF for entry into the database.

2.A.2) EFFICACY RESULTS:

Statistical methodology: The primary endpoint, response status, was calculated for each subject, according to the sponsor, as follows: Subjects with a baseline PPI $\geq$ 2 were classified as responders at the second of 2 consecutive visits if a 2-point improvement in PPI was maintained for those 2 consecutive visits, and was not accompanied by an increase in analgesic score. Subjects with a baseline PPI of 1 were classified as responders at the second of 2 consecutive visits if a PPI score of 0 was maintained for those 2 consecutive visits, and was not accompanied by an increase in analgesic score. If PPI or analgesic score values were missing for a particular visit, that visit was not considered in the calculations described above. This occurred for 2 subjects (patients 11 and 15) who were classified as responders. Two

subjects with a PPI of 0 at baseline (patients 12 and 18) were enrolled. These subjects were classified as non-responders.

If radiologic evidence of disease progression was observed, or delivery of radiation therapy was needed prior to achieving a response as defined earlier, the subject was classified as a non-responder.

Subjects randomized to the P group were classified as responders prior to crossover based on the criteria described above. We will refer to this criterion of response as **criterion 1.**

Subjects who responded based on the above definitions were considered as having evidence of disease progression if at least one of the following occurred for 2 consecutive cycles after the cycle in which they were defined as responders: 1) an increase in PPI score by at least 1 point recorded for 2 consecutive visits in comparison to the lowest PPI score; 2) an increase in analgesic score of ≥ 25% compared to the lowest score for 2 consecutive visits; or 3) confirmed evidence of new lesions, progression of existing lesions, or a requirement for radiation therapy.

The sponsor has defined and analyzed the time to disease progression for responders and non-responders separately. Time to disease progression for responders was calculated from the date of start of study to the date of the second of two consecutive cycles in which the criteria of progression were observed. Duration of palliative response was calculated from the date of cycle of response until the date of cycle of progression. Time to progression for non-responders was defined as an increase in PPI score by at least 1 point in comparison to the lowest PPI score recorded for 2 consecutive visits, or an increase in analgesic score of ≥ 25% compared to the lowest score for 2 consecutive visits. This reviewer has performed analyses of the time to disease progression on all patients (by combining both, responders and non-responders).

A secondary criterion for response was defined and analyzed retrospectively after the study was completed; subjects whose analgesic use decreased by 50% or more for 2 consecutive visits with no increase in PPI score at any time were classified as responders based on this secondary response criterion. Time to progression for subjects who satisfied this secondary criterion was defined by an increase in PPI score by at least 1 point in comparison to the lowest PPI score recorded for 2 consecutive visits, or by an increase in analgesic score of ≥ 25% compared to the lowest score for two consecutive visits. For subjects classified as responders based on the secondary criterion for response, progression was to have occurred following the cycle of response. We will refer to this criterion of response as **criterion 2.**

Quality of Life scores were analyzed by totaling the numerical responses for the separate EORTC subscales including symptoms and physical activity, functional activity, and psychosocial interaction. When a response was missing, the value was prorated by multiplying the sum by the total number of possible responses, divided by the total number of actual

responses in that particular QOL category. Linear analogue self assessment scores were analyzed separately and were not summed except at baseline, in which case the prorating described above was performed. Baseline variables that were categorical or discrete were compared using Cochran-Mantel-Haenszel general association tests. Baseline variables that were continuous were compared using Cochran-Mantel-Haenszel row means tests.

The primary endpoint of response status was analyzed by comparing the M+P arm to the P arm using Fisher's exact test and by additional Cochran-Mantel-Haenszel general association tests controlling for baseline strata.

Time to event endpoints were compared between groups using Kaplan-Meier methods and log-rank tests.

Quality of life instruments were compared for 'best change' and 'best percent change' from baseline using Cochran-Mantel-Haenszel row means tests. Simple t-tests and Wilcoxon rank sum tests were used to confirm the Cochran-Mantel-Haenszel row means tests.

Results of an Interim analysis: According to the sponsor, a planned interim analysis was conducted for this study to assess whether results for the primary endpoint were sufficiently strong to end the study. The contracted statistician performed a Chi-square test on 64 subjects in March of 1993. The resulting p-value was not sufficiently small to warrant stopping the study. According to the sponsor "no statements were made in the protocol or subsequently about the assessment of significance at the time of final analysis". No details of the results of the interim analysis were given to Lederle (the sponsor) or to the investigators. The interim analysis plan specified by the protocol is not clear to this reviewer. The following results of the interim analysis were provided on 8-14-96 to this reviewer by the sponsor:

Interim analysis of primary endpoint: (criterion 1)

	M+P (n=37)	P (n=27)
Responses	4 (11%)	1 (4%)
P-value*	0.5655	

*Chi-Square test with continuity correction

Summary of Baseline Assessments: There were no statistically significant differences between the two groups for any of the demographic and baseline assessments (Sponsor's Tables 2 and 3 respectively in the Appendix) with the exception of Flutamide therapy. 30% of patients in the M+P and 12.3% of patients in the P group had Flutamide therapy (Fisher's two-sided test p-value=0.006). It was not clear to this reviewer if patients (how many and for how long) continued to receive Flutamide therapy after entry to the study.

PAP and PSA: For the M+P and P group respectively, median PAP levels were 16.3 U/L

and 10.7 U/L, and median PSA levels were 179.9 μg/L and 156 μg/L.

PPI: One subject in each treatment group had a PPI score of 0 at baseline (Subject No. [redacted] in the M+P arm, and Subject No. 18 in the P arm). In the M+P group, the remaining scores at baseline were distributed as follows: 30 subjects had a PPI score of 1, 30 subjects had a PPI score of 2, 15 subjects had a PPI score of 3, and 4 subjects had a PPI score of 4.

In the P group, 23 subjects had a PPI score of 1, 37 subjects had a PPI score of 2, 15 subjects had a PPI score of 3, and 5 subjects had a PPI score of 4.

Analgesic Score: Median baseline analgesic score was 17.7 for the M+P group, and 14 for subjects in the Prednisone group (p-value=0.104). Baseline analgesic score was missing for 2 subjects in the M+P arm (Subject Nos.

QOL Scores: Subjects in both treatment groups had similar median baseline scores for all measures of QOL. For the 9 LASA scales, median sums of baseline scores were 57.2 for the M+P group, and 58.7 for the P group.

Baseline scores for the EORTC-Q30C QOL questionnaire were similar in the two groups for all subscales. For the M+P and P groups respectively, the median sum scores for symptoms and physical were 10.3 and 10; functional activity 25.5 and 25; psychosocial 17.5 and 16; overall physical 3.5 and 4; and overall quality of life was 4 for both groups.

Baseline sum scores for the Prostate Module were 21.5 for the M+P group and 19.8 for the P group.

Results:

Palliative Response (Primary Endpoint): According to the sponsor, twenty-three subjects in the M+P group (29%) and 10 subjects in the P group (12%), prior to crossover, qualified as responders as demonstrated by a 2-point improvement in PPI that was maintained for 2 consecutive visits and was not accompanied by an increase in analgesic score ($p = 0.011$, two-sided Fisher's exact test). This reviewer performed also a logistic regression analysis adjusting for the Flutamide therapy imbalances between the two groups. Flutamide therapy turned out not to be a statistically significant factor. The median time to response was 65 days for the M+P group, and 73.5 days for the P group. The following table describes the response parameters observed in the two treatment groups.

Sponsor's Table 1: Response Parameters

	Treatment Group M+P (n = 80)	P■ (n = 81)	p-value
Palliative response n (%)	23 (29)	10 (12)	0.011*
Median duration of response (days)***	229	53	0.0001**
Median time to progression (days)***	301	132.5	0.0001**

*Two-tailed Fisher's exact test
** Logrank test
*** Responders only
■ Prior to crossover

Two patients in the treatment group (patient numbers 68 and 75), who were classified as responders by the sponsor, were classified as non responders by the Medical Reviewer. Results on the time to event endpoints analyses (e.g. duration of response and time to progression) remain the same. The Medical review explains the changes made by the Medical Reviewer on response, duration of response, and time to progression for certain patients. The following table describes the palliative response based on the Medical Reviewer's assessment:

Reviewer's Table 1 : Palliative response based on the Medical Reviewer's assessment (Criterion 1)

Treatment	M+P (n=80)	P (n=81)	P-value*
Responders	21	10	0.029

* Fisher's two-tailed test

According to the sponsor, when subjects who responded are examined separately based on their baseline PPI score (> or ≤ 1), more subjects in the M+P group who had a baseline PPI score > 1 responded (26.5%) than did subjects in the P group who also had a baseline PPI score >1 (8.8%). Similarly, when baseline ECOG performance status is taken into account, in the M+P group, 30% of subjects with a baseline performance status of 0 or 1 and 24% with a baseline performance status of 2 or 3 were classified as responders versus 14% and 7% of subjects in the P group with respective baseline performance status. When tests are conducted stratifying for baseline ECOG performance status or baseline pain score, the resulting p-values comparing the two treatment groups are significant (p = 0.014 when controlling for baseline pain, and p = 0.009 when controlling for ECOG performance status).

Duration of Palliative Response: Duration of palliative response was evaluated for the 33 responders by the sponsor. For subjects in the M+P group, the median duration of response was 229 days, compared to 53 days for subjects in the P group (p = 0.0001, logrank test). According to the sponsor, the treatment difference remains in favor of the M+P group when

subjects randomized to each group are compared while controlling for performance status (p = 0.0007, logrank test) and PPI at baseline (p = 0.0005, logrank test).

It was determined after the ODAC meeting on 9/11/1996 that the algorithm used by the sponsor to calculate the duration of response did not include all the protocol criteria for assessing it. The sponsor provided the following analysis of duration of response using the protocol criteria, on October 18, 1996:

Sponsor's Table 2 gives the duration of response analysis. Patient numbers (M+P group) were excluded from the total number of responders by this reviewer. The Medical Reviewer assessed that these patients had 0 duration of response and the sponsor agreed on that. Kaplan-Meier curves of the duration of palliative response are given in Figures 1-2 (Attachment 1).

Sponsor's Table 2: Duration of response based on the Sponsor's assessments:

	Treatment (size)	Events	Median (days)	P-value*
Criterion 1	M+P (n=21)	15	229	0.0009
	P (n=10)	8	63	
Criterion 2	M+P (n=28)	20	169	0.0004
	P (n=17)	14	57	

*Logrank test

Time to Disease Progression: Time to disease progression was evaluated for only the 33 responders by the sponsor. From sponsor's Table 1, which is included in the beginning of this section, subjects in the M+P group had a median time to progression of 301 days, compared to 132.5 days for subjects in the P group (p = 0.0001, logrank test). According to the sponsor, when subjects randomized to the M+P group and subjects randomized to the P group are compared while controlling for performance status and PPI at baseline, the treatment difference remains in favor of the M+P group (p = 0.0001, logrank test).

It was determined after the ODAC meeting on 9/11/1996 that the algorithm used by the sponsor to calculate the TTP did not include all the protocol criteria for assessing the time to progression. The sponsor provided the following analysis of TTP using the protocol criteria, on October 18, 1996. This reviewer and the Medical Reviewer agreed on the sponsor's assessment of TTP:

Sponsor's Table 3: Analysis of TTP based on the sponsor's assessments

	Treatment (size)	Treatment Failures	Median (days)	P-value*
All patients	**M+P (n=80)**	**63**	**131**	**0.0001**
	P (n=81)	**70**	**69**	

***Logrank test**

Kaplan-Meier curves of time to progression are given in Figures 3 (Attachment 1).

An exploratory analysis of time to progression was performed for certain groups of patients suggested by the Medical Reviewer. Results are included in Reviewer's Table 4, for patients who had Orchiectomy only, Medication only, or Orchiectomy and Medication. Patients who had one or more of the following were classified as having Medication: Fyproterone acetate, Flutamide, Luteinizing hormone-releasing hormone agonist, and Estrogen. It was not clear to this reviewer how, when, and for how long, these medications were given. The results of this retrospective analysis should be interpreted with caution due to the small size of these subgroups. Kaplan-Meier curves of time to progression are given in Figures 4-6 (Attachment 1).

Reviewer's Table 4: Analysis of Time to Progression based on the sponsor's assessments by Orchiectomy only, Orchiectomy and Medication, or Medication only.

	Treatment (size)	Treatment Failures	Median (days)	P-value*
Orchiectomy	M+P (n=25)	19	70	0.38
	P (n=37)	34	65	
Orchi+Medic	M+P (n=21)	17	168	0.001
	P (n=13)	11	70	
Medication	M+P (n=34)	27	140	0.0003
	P (n=31)	25	63	

*Logrank test

Overall Palliative Benefit: To assess overall palliative benefit from therapy, a second criterion of response was evaluated retrospectively. This was defined as a decrease in analgesic score of at least 50% from baseline, without an increase in PPI at any time. Seven more subjects in each group responded based on this criterion according to the sponsor.

In total, 30 subjects (37.5%) in the M+P group, and 17 subjects (21%) in the P group satisfied either primary or secondary criteria for response, demonstrating almost a doubling of the response rate in the M+P arm (p = 0.025, Fisher's two-sided test) according to the sponsor.

Reviewer's Table 5 gives the results for this secondary criterion of response based on the Medical Reviewer's assessment:

Reviewer's Table 5 : Palliative response based on the Medical Reviewer's assessment (Criterion 2)

Treatment	M+P (n=80)	P (n=81)	P-value*
Responders	28	17	0.055

* Fisher's two-tailed test

A Kaplan-Meier curve of the duration of palliative response for this criterion is given in Figure 8 (Attachment 1).

Reviewer's Table 6 gives the results for this secondary criterion of response based on the Medical Reviewer's assessment by prior therapy:

Reviewer's Table 6: Palliative response based on the Medical Reviewer's assessment by prior therapy (Criterion 2).

	M+P	P	P-value*
Orchiectomy	20% (5/20)	19% (7/27)	1
Orchi+Medic	38% (8/21)	23% (3/13)	0.465
Medication	44% (15/34)	23% (7/31)	0.114

* Fisher's two-tailed test

Quality of Life: The sponsor's Baseline QOL evaluations for the nine individual LASA scales, the sum of all nine LASA scales, the five EORTC-Q30C questionnaire subgroups, and the Prostate Module questionnaire show that there was no a statistically significant difference in baseline QOL characteristics between the two groups.

The sponsor presents changes in the means of the 9 individual LASA scales actual values over time in Figures 6 to 14 (Attachment 2). Higher scores represent an improvement in QOL measures for the LASA instrument. The figures describe the QOL assessments obtained up to Cycle 18 which is the last cycle for which PPI measurements were available in the database. The figures representing data for the P group include QOL assessments obtained prior to and

after crossover. Subjects randomized to the M+P arm had consistently better scores than subjects randomized to the P arm for the following LASA scales: pain, physical activity, fatigue, appetite, mood, and overall well-being. The LASA figures were comparable in the two groups for the following scales: constipation, family relationships, and passing urine. Subjects randomized to the M+P arm had statistically significantly better "best changes from baseline" scores than subjects randomized to the P arm for the following QOL scales: LASA constipation, LASA mood, and QOL prostate module. There were not any statistically significant improvements in the M+P arm over the P arm in the QOL scales when "best score" or "best % change from baseline" scores are analyzed.

Sponsor's Figures 15 to 20 (Attachment 2) represent changes in the actual mean values for the sum of the 5 EORTC-Q30C subgroups and the Prostate Module questionnaires. Only the first 18 cycles are represented and subjects who crossed over are also included. Subjects randomized to the M+P arm had consistently better scores (but not statistically significant) than subjects randomized to the P arm for all 6 questionnaires: symptoms and physical assessment, functional activity, psychosocial effect, and the Prostate Module (in all of which lower scores are better), and overall physical activity and overall QOL (in all of which higher scores are better).

Sponsor's Tables 15-17 (Attachment 2) describe the best QOL scores and best change from baseline achieved at any time following the initial QOL assessments in the two groups. Table 16 provides the actual differences between the best QOL Figures 6 to 14 (Attachment 2) scores achieved and baseline scores, and Table 17 presents these differences as a percentage of baseline values. The three tables include information from the nine individual LASA scales, the five EORTC-Q30C subgroups, and the Prostate Module questionnaire.

Potential bias could arise by analyzing measures such as "best changes from baseline", "best score", or "best % change from baseline" , because they do not take into account all data collected (sample size), and the pattern of missing data. The sponsor did not provide any formal longitudinal analyses (i.e. GEE or Laird/Ware methods, etc.) that could be used to assess time trends on the quality of life data. Even though these are somewhat exploratory, they provide important insights regarding the pattern of missing data and sources of potential bias.

All sponsor's tables and figures mentioned above are included in Attachment 2.

Survival: Survival was similar for the two treatment groups. However, the survival comparison is subject to the confounding effects of crossover. The median time to death was 338.5 days for the 80 subjects in the M+P group, compared to 324 days for the 81 subjects randomized to receive Prednisone alone ($p = 0.2324$). The median time to death for the 23 responders in the M+P group was 476 days, versus 476.5 days for the 10 responders in the P arm ($p = 0.3713$). Median time to death was significantly longer for subjects in the M+P group compared to subjects in the P group (338.5 days versus 145 days respectively, p =

0.0086) when subjects randomized to the P group, who subsequently crossed over, are excluded, representing a 6-month increase in median survival.

Change in PSA Levels: The sponsor has presented the following results: Serial (≥ 2) measurements of PSA were available for 134 subjects (71 and 63 in the M+P and P groups respectively). There was not a statistically significant difference between the two treatment groups with respect to decrease in PSA concentrations from baseline. Compared to the P group, there were more subjects in the M+P group who had a decrease ≥ 75% from baseline PSA; 27% versus 14%, respectively (p = 0.077, Cochran-Mantel-Haenszel general association test).

When data for subjects who responded were evaluated separately, significantly more responders in the M+P group demonstrated a ≥ 75% decrease from baseline compared to the P group responders; 52% versus 10%, respectively (p = 0.026, Cochran-Mantel-Haenszel general association test, two-sided), suggesting that palliative response in the M+P group was also accompanied by substantial decrease in PSA concentrations .

Efficacy After Crossover: Forty-eight subjects in the P arm subsequently crossed over to receive Mitoxantrone. The median number of days from entry on study to crossover for these 48 subjects was 84 days, and ranged from 11 to 324 days. Nine of these 48 subjects (19%) demonstrated a response after crossover. Time to death (median number of days to death) for the 48 subjects who crossed over was 380.5 days.

2.A.3) SUMMARY:

Twenty-one patients in the M+P group (26%) and 10 patients in the P group (21%), prior to crossover, qualified as responders by demonstrating a 2-point improvement in PPI that was maintained for 2 consecutive visits and was not accompanied by an increase in analgesic score (p = 0.029, two-sided Fisher's exact test). This is criterion 1 for response. Flutamide therapy did not change the statistically significant treatment effect.

Twenty-eight patients in the M+P group (35%) and 17 patients in the P group (12%), prior to crossover, responded using criterion 2 for response with a p-value = 0.055 (two-sided Fisher's exact test). Criterion 2 for response was defined as a decrease in analgesic score of at least 50% from baseline, without an increase in PPI at any time.

Duration of palliative response was evaluated for the 31 responders (criterion 1). For patients in the M+P group, the median duration of response was 229 days, compared to 63 days for patients in the P group (p = 0.0009, logrank test).

If we use criterion 2, the duration of palliative response was evaluated for 45 responders. For patients in the M+P group, the median duration of response was 169 days, compared to 57 days for patients in the P group (p = 0.0004, logrank test).

Time to disease progression was evaluated for all patients. Patients in the M+P group had a median time to progression of 131 days, compared to 69 days for patients in the P group ($p = 0.0001$, logrank test).

There is some indication from exploratory analysis of time to progression that patients who took medication only (one or more of cyproterone acetate, flutamide, luteinizing hormone-releasing hormone agonist, and estrogen), or who had orchiectomy and took medication, had statistically significantly longer time to progression in the M+P arm than those in the P arm. The results of this retrospective analysis should be interpreted with caution due to the small size of these subgroups.

Survival was similar for the two treatment groups. However, the survival comparison is subject to the confounding effects of crossover. The median time to death was 338.5 days for the 80 subjects in the M+P group, compared to 324 days for the 81 subjects randomized to receive Prednisone alone (logrank p-value = 0.2324).

There was not a statistically significant difference between the two treatment groups with respect to decrease in PSA concentrations from baseline. According to the sponsor, compared to the P group, there were more subjects in the M+P group who had a decrease of $\geq 75\%$ from baseline PSA; 27% versus 14%, respectively ($p = 0.077$, Cochran-Mantel-Haenszel general association test, two-sided).

There was not any statistically significant improvement in the M+P arm over the P arm in the various QOL instrument measures used in this study. Moreover, this was an open label study and any claims about improvement in the QOL measures for either group should be interpreted cautiously.

2.B.1) STUDY 19182 in patients with Hormone-Refractory Stage D_2 Prostate Cancer:

Study design: This was a two-arm, randomized, open-label Phase III study with central randomization and stratification, comparing the survival of patients with metastatic hormone resistant prostate cancer treated with Mitoxantrone+Hydrocortisone (M+H) versus Hydrocortisone (H) alone. Three stratification factors were used: performance status (0-1 vs. 2), disease status (measurable vs. evaluable), and number of prior endocrine manipulations (one vs two or more). A total of 242 patients were enrolled: 119 patients in the M+P group and 123 in the H group. These patients were enrolled at 62 participating sites and their affiliates.

The secondary objective was to compare the impact of M+H and H on QOL as assessed by questionnaires that measured physical functioning and cancer-related symptoms in subjects with metastatic hormone-resistant prostate cancer.

Patients in the M+H arm were to receive Mitoxantrone 14 mg/m^2 as an IV infusion over 10-30 minutes plus oral Hydrocortisone 40 mg (30 mg at 8 a.m. and 10 mg at 8 p.m.) daily. Mitoxantrone was to be repeated every 21 days as tolerated. Hydrocortisone was to be continued until death or serious toxicity.

Patients in the H arm were to receive Hydrocortisone 40 mg (30 mg at 8 a.m. and 10 mg at 8 p.m.) daily until death or serious toxicity. One cycle was defined as three weeks of therapy. Dose modification for nadir counts was also done.

Selection criteria:

Inclusion Criteria:

Subjects who met the following criteria were eligible for this study:

- Histologically documented adenocarcinoma of the prostate (Stage D_2) with progressive systemic disease despite at least one or more endocrine manipulations. One of the manipulations must have included either orchiectomy, $LHRH_a$, or DES. Progressive disease was defined as 1) progressive symptoms in a patient with lesions on bone scan, plain radiographs/CT scan, or physical examination; and/or 2) progression of objective evidence of disease either by > 25% increase in the sum of the perpendicular diameters of all measurable masses or the appearance of > 25 % new lesions on bone scan, and/or (3) rising PSA. PSA must have doubled compared to values before progression, with ≥ two-fold increase confirmed by at least two values ≥2 weeks apart in order to use PSA as the sole marker of progression. Pathology review of each subject's slides was to be carried out by the institution enrolling the subject and documented in the subject's chart.
-

Performance status of 0, 1, or 2 on the scale.

- AL least 3 weeks since any major surgery and fully recovered.
- At least 4 weeks since any radiation treatment and fully recovered.
- At least one prior endocrine therapy (orchiectomy with or without flutamide. $LHRH_a$ with or without flutamide, DES)
- Normal multigated angiogram (MUGA) scan or ultrasound assessment of ventricular ejection fraction.
- Either measurable or evaluable nonosseous disease or bone-only disease with an abnormal PSA.
- Willing consent after being informed of the neoplastic nature of disease, the procedure to be followed, the experimental nature of the therapy alternatives, potential benefits, side-effect risks, and discomforts.
- Willingness and ability to complete the serial QOL questionnaires. If a subject did not speak English, he could still be enrolled in the study but did not need to complete the QOL instrument. If a subject spoke but was unable to read English, the data manager was to complete the questionnaire with the subject.

Exclusion Criteria:

Subjects with any of the following conditions were not eligible to enter the study:

- Serious intercurrent medical illnesses, which in the judgement of the investigator would compromise the subject.
- Significant cardiac disease (New York Heart Association Class III or IV), angina pectoris or myocardial infarction within 6 months.
- Presence of an active acute infection requiring antibiotics. Subjects on suppressive therapy for chronic urinary tract infection (UTI) were not excluded.
- Presence of parenchymal brain metastases.
- History of another malignancy, active or initially diagnosed, within 2 years other than curatively treated nonmelanoma carcinoma of the skin.
- Prior chemotherapy or immunotherapy.

•

Subjects receiving exogenous corticosteroids.

Clinical Evaluations: Prior to treatment, subjects were required to have completed the following, tests and evaluations: medical history, physical examination, performance status, weight, tumor measurement and assessment, QOL assessment, bone scan, skeletal survey as required to evaluate disease extent and response, additional scans of any type required to evaluate disease extent and response, electrocardiogram (EKG), chest x-ray, MUGA, and ejection fraction. Any x-rays, ultrasounds, or scans of any type of uninvolved organs that were not to be used for tumor measurement were required to be completed within 42 days of registration. Any bone scans needed to establish measurable disease were required to be completed within 30 days of registration. Any other radiographs (except bone scans) needed to establish measurable disease were required to be completed within 14 days of registration.

Every three weeks after treatment, subjects were required to have completed the following tests and evaluations: medical history, physical examination, performance status, weight, tumor measurement and assessment, and QOL assessment. Every six weeks after the start of treatment, subjects were required to have a skeletal survey or x-rays of areas of bony involvement and EKG. Every three months after the start of treatment, subjects were required to have tumor measurements and assessment, EKG, MUGA, and ejection fraction. QOL assessments were required at Weeks 6 and 12, then every 12 weeks and when the subject was taken off study. Bone scans were required between Days 56-63 and 115-125, then every 12 weeks.

Evaluations of known sites of disease that were assessable by physical examination were to be repeated every 3 weeks and, if assessable by radiograph (other than bone scan), every 6 weeks. CT scans, if initially abnormal, were to be repeated at the same intervals as bone scans. Skeletal surveys or x-rays were to be repeated if the bone scan was improved.

Endpoints: According to the protocol, the sample size calculations are based on overall survival, defined as the time between randomization and death. The median survival in the group, who receive only H and who have endocrine manipulation, is estimated to be 12 months. The median survival in the group, who receive only H and with more than one endocrine manipulation, is estimated to be 9 months. The sample size is computed to have 80% power to detect a 50% increase in the median survival of patients receiving M+H. Assuming that the survival time is exponentially distributed, and that approximately 100 per year will be accrued to this study, with 2/3 of patients having one endocrine manipulation and 1/3 of patients having more than one endocrine manipulation, using the methods of Berstein and Lagakos, with a two sided $\alpha=0.05$, a total of 220 patients are required. With a 5% of ineligibility rate, 232 would be accrued.

Secondary endpoints include time to treatment failure, response, duration of response, time to progression, and QOL.

Interim analysis: According to the protocol, there were 4 interim looks plus a final look scheduled, approximately when 20%, 40%, 60%, 80% of the expected number of failures occurred, using the Lan and DeMets analog of the O'Brien-Fleming group sequential boundaries, with an overall significance $\alpha=0.05$.

There was nothing mentioned in the submission about the status and results of these interim analyses.

Disease Categorization: For response analyses, subjects were categorized into one of three groups: measurable, evaluable, or bone only. Measurable disease was to take precedence over evaluable, and evaluable over bone only. The criteria for response in each of the following categories are defined in the protocol and are based on **tumor size, PSA levels, and performance status**.

Measurable Disease (Nonosseous). Subjects with measurable bidimensional or unidimensional nonosseous disease (e.g., palpable or visible lymph nodes, mediastinal, abdominal, or pulmonary masses, or hepatomegaly) were assessed using standard response criteria. In order to be considered measurable, masses visible by radiographic studies were to be ≥ 2 cm in two dimensions.

Evaluable Disease (Nonosseous). Malignant disease evident on clinical examination but not clearly measurable was to be considered evaluable. The only permissible examples of such disease were to be confluent or lymphangitic lung metastases or skin metastases.

Nonmeasurable (Bone Only) or Unevaluable Soft Tissue Disease. Subjects with disease that was neither measurable nor evaluable were to be assessed for response based on change in bone scan, PSA, and performance status. Elevated PSA was required to be eligible for this category.

Disease Response Assessment:

Unevaluable Tumor Response. The following were scored as an unevaluable tumor response: (1) if a follow-up disease assessment was not performed: or 2) if a subject who received treatment did not experience disease progression, died early, or did not satisfy the criteria for complete response, partial response, regression, or stable disease.

Mixed Response/Disease Progression. Simultaneous progression and regression of measurable lesions or other indices of response was deemed a mixed response and scored as disease progression for the purposes of this study.

Performance Status Assessment: Performance status was to be assessed using the following criteria: normal performance=0; decreased performance but ambulatory=1; increased time in bed, less than 50% of day=2; increased time in bed, more than 50% of day 3; and totally bedridden=4.

QOL Assessment: The following QOL instruments were used: Functional Living Index - Cancer (FLIC), Symptom Distress Scale (SDS), Sexual and Urologic Functioning, Functional Limitations Scale, and Impact of Pain on Daily Activities.

Duration of Treatment: Subjects with a complete or partial response or stable disease were to be treated until they developed progressive disease or reached a total Mitoxantrone dose of 160 mg/m^2. Subjects who developed progressive disease were to continue Hydrocortisone indefinitely. Crossover was not allowed. Subjects who developed progressive disease on either arm were not to receive anthracycline or further anthracenedione drugs but were allowed to receive other cytotoxic therapies if needed.

The following events mandated discontinuation at any time following enrollment: Progressive disease; Intercurrent illness that prevented further therapy; Unacceptable Grade 4 toxicity without evidence of antitumor response; Total Mitoxantrone dose of 160 mg/m^2; General or specific changes in the patient's condition that rendered the patient unacceptable for further treatment in the judgement of the Investigator.

Patients were considered off study when disease progression or treatment failure was documented. Follow-up after this point was for survival only. No information on subsequent therapy given after progression was collected.

2.B.2) EFFICACY RESULTS:

Statistical Methodology:

Time to Event Endpoints: Time to death was calculated from on-study date to death date or last date known alive. Time to progression was calculated from on-study date to date of progression or date last known alive or death date. Time to progression data were analyzed in two ways by the sponsor: in the first way all deaths were considered as censored observations (not events) and in the second way all deaths were considered as uncensored observations (events).

QOL Analyses: Baseline values for all QOL scores were defined for a subject as the first score recorded prior to Day 10 for each QOL score. In the only instance where two or more scores fell in that window prior to Day 10, the earliest score was used as baseline.

If dates for visits with QOL data were missing, the data were not used in any analyses. If answers were recorded that were less than 1 for instruments requiring values of 1 or more, these numbers were treated as missing in all analyses. Answers to questions for QOL module on pain were originally 0 to 10 in the database but adjusted to 1 to 11 in all analyses. Answers to FLIC questions 2, 3, 6, 9, 10, 11, 14, 16, 18, 19, 21, and 22 were rescaled so that in all cases a lower number reflected a clinically better response.

At baseline, for the FLIC, SDS, Sexual and Urologic Functioning, Functional Limitations

Scale, and impact of Pain on Daily Activities instruments, numerical answers for each instrument were summed to obtain scores for the baseline visit and summarized over subject for each instrument. For each instrument, if answers to some questions were missing for a subject on a particular visit, the score for that visit was prorated by multiplying the sum by the number of possible questions for that instrument divided by the number of answered (nonmissing) questions for that instrument.

Of the QOL domains available in the study, five QOL variables were retrospectively identified for analysis as most indicative of the effects of pain on QOL measures. These variables were FLIC question 11, FLIC question 13, SDS pain 1 item, SDS pain 2 item, and the total score (sum) for the Impact of Pain on Daily Activities questionnaire. For the Impact of Pain instrument, numerical answers to questions were summed to obtain a score for each visit. If answers to some questions were missing for a subject on a particular visit, the score for that visit was prorated as described above for the instruments at baseline.

For each of the five QOL selected variables, statistics were calculated over time in two ways:

> The value at Day 42 was defined as that value recorded at a visit within a $\pm$ 7-day window of day 42 (if more than one value fell in that window, the value closest to Day 42 was used).
>
> The best post-baseline value was defined as the value that was lowest in numerical value post-baseline.

Then, for each subject, change from baseline at Day 42 and best change from baseline were calculated as the value in the Day 42 window minus the value at baseline and the best value minus the baseline value, respectively. Percent change from baseline was change from baseline divided by the baseline value and multiplied by 100.

Statistical Procedures: Descriptive statistics were used to present demographic and baseline variables. Time to death and/or progression were estimated using Kaplan-Meier curves and compared using logrank tests. Rates for disease response categories were compared using Chi squared and Fisher' s exact tests. QOL-derived measures (Day 42$\pm$7 days, best value baseline, change, and percent change from baseline) were averaged over subjects and compared using both analysis of variance (two sided t-tests) and Wilcoxon rank-sum tests.

Results: A total of 242 subjects were enrolled in the study, with 119 randomized to receive Mitoxantrone plus Hydrocortisone (M+H) and 123 subjects randomized to receive Hydrocortisone only (H). Data were missing for some subjects. Follow-up data other than last alive dates were available for 209 subjects (86%) of the 242 subjects enrolled. Adverse event data were available for 206 subjects (85%). Disease response data were available for 181 subjects (75%). Baseline QOL data were available for 198 subjects (82%) but follow-up data were available for fewer subjects at the specified evaluation periods (6 and 11 weeks).

Demographic and Baseline Characteristics: The median age for both the M+H group and H group was 72 years. The age range for the M+H group was 43 to 84 years, and for the H group, 38 to 85. In the M+H group, 88% percent of subjects were white, 10% were black, and 2% were Hispanic. In the H group, 93% were white and 7% were black. Sponsor's Table 3 summarizes demographics (Attachment 3).

Baseline metastases, disease evaluability, and stratification factors data are presented in Sponsor's Table 4. There was no significant difference between the two treatment groups with respect to each of these parameters.

Sponsor's Table 5 contains the baseline lab values and Table 6 contains prior hormonal therapies. Baseline performance status and analgesic use data are summarized in Sponsor's Table 7 (Attachment 3).

Time to event endpoints: There was not any statistically significant difference between the two treatment groups in survival. There was some indication that patients in the treatment group had a longer time to progression than patients in the control group. Kaplan-Meier curves of time to event endpoints are given in Sponsor's Figures 1-3 (Attachment 3). The following table summarizes the efficacy results for the various time to event endpoints.

Table 1: Time to Death and Progression

	Treatment	Median (days)	N	Events	P-Value*
Time to Death	M+H	334	119	58	0.3298
	H	359	123	68	
Time to Progression	M+H	218		56	0.0654
	H	122		71	
Time to Progres-sion or Death	M+H	159		80	0.0723
	H	118		95	

* Logrank test.

The following tables summarize the efficacy results of Time to Progression for patients who had baseline analgesics, and patients who did not have any baseline analgesics. There was a statistically significant difference between the two treatment groups. There was some indication that the treatment group had a longer time to progression than the control group, for those patients who did not have any baseline analgesics. There were 13 patients with missing baseline analgesic use data. These patients were excluded from these analyses. Kaplan-Meier curves of time to progression are given in Reviewer's Figures 7-8 (Attachment 1) for these analyses.

Table 2 : Analysis of Time to Progression of patients who had baseline analgesics.

Time to Progression	Treatment (size)	Treatment Failures	Median (days)	P-value*
Analgesics at Baseline	M+H (n=73)	33	310	0.4275
	H (n=69)	41	132	
No Analgesics at Baseline	M+H (n=42)	21	218	0.0243
	H (n=45)	27	108	

*Logrank test

Table 3: Analysis of Time to Progression+Deaths of patients who had baseline analgesics.

Time to Progression+Deaths	Treatment (size)	Treatment Failures	Median (days)	P-value*
Analgesics at Baseline	M+H (n=73)	51	120	0.5354
	H (n=69)	58	121	
No Analgesics at Baseline	M+H (n=42)	27	208	0.0229
	H (n=45)	33	102	

*Logrank test

Response: There was not any statistically significant difference between the two treatment groups in the number of PR/SD between the two groups. The two-tailed Fisher's exact test p-value=0.20.

Table 4: Disease Response - All patients.

Response	M+H (N=119)	H (N=123)	P-value*
PR	10 (8.4%)	2 (1.6%)	0.018
PR/SD*	65 (54%)	57 (47%)	0.20
PD	31(26%)	45 (37%)	
Unevaluable	4 (3%)	3 (2%)	
Missing data	19 (16%)	18 (15%)	

*Fisher's two-tailed test

Change in PSA Levels: According to the sponsor, 10 patients had missing baseline PSA data, 3 in the M+H group and 7 in the H group. Median baseline PSA levels were similar for the two groups (155 μg/L for the M+H group and 145 μg/L for the H group). Three patients in each group had baseline PSA concentrations of < 5 μg/L. Sponsor's Table 9 includes the PSA data summary. The sponsor has also presented the following results:

Table 3: PSA Levels: Best value achieved (%)

% decrease from baseline	M+H (N=101)	H (N=100)	p-value*
$\geq$ 50%	31	17	0.023
$\geq$75%	14	7	0.112

*Two-sided t-test

QOL: Baseline QOL evaluation data were available for 198 subjects (82%) of the 242 subjects enrolled in this study and follow-up QOL data were available for fewer subjects. Not all evaluation data were complete due to evaluations that were not obtained or possibly data not entered into the database according to the sponsor. Based on the data available from the CALGB database, baseline QOL assessments for the two treatment groups were approximately the same.

The sponsor presented analyses of the components of the different QOL instruments as well as QOL components related to cancer-pain. Percent changes from baseline at various time points, and percent changes of best post-baseline values were analyzed. There were not any statistically significant differences observed between the two treatment groups. The same comments about the QOL data analysis made for the CCI-NOV22 study also apply to this study (see page 23).

Sponsor's Tables 12-32 summarize the QOL data analyses.

2.B.3) SUMMARY

There was not any statistically significant difference in survival between the two treatment groups. The median time to death was 334 days for the 119 patients in the M+H group (58 deaths), compared to 359 days for the 123 patients randomized to H group (68 deaths). The logrank p-value = 0.3298.

There was some indication that patients in the treatment group had a longer time to disease progression than patients in the control group. Time to disease progression was evaluated for all patients. If deaths are censored, patients in the M+H group had a median time to progression of 218 days, compared to 122 days for patients in the H group (p = 0.0654, logrank test). If deaths are not censored, patients in the M+H group had a median time to

progression of 159 days, compared to 118 days for patients in the H group (p = 0.0723, logrank test).

There was some indication that the treatment group had a longer time to disease progression than the control group, for those patients who did not have any baseline analgesics (p-value=0.0243).
There was not any statistically significant difference between the two treatment groups in the time to progression for patients who had baseline analgesics. This retrospective analysis should be interpreted cautiously.

There was not any statistically significant difference between the two treatment groups in the number of PR/SD between the two groups. There were 65 (54%) patients in the M+H group and 57 (47%) patients in the H group, who had PR/SD responses. The two-sided Fisher's exact test p-value=0.20.

There were not any statistically significant differences observed between the two treatment groups in the QOL instruments or in the QOL components related to cancer-pain. Percent changes from baseline at various time points, and percent changes from best post-baseline values were analyzed.

3) CONCLUSIONS AND RECOMMENDATIONS:

Study CCI-NOV22 showed a statistically significant difference between the two treatment groups (M+P vs P) in the "palliative response" endpoint, which was the primary endpoint, and in the time to disease progression, in favor of the M+P arm. These two endpoints correlate very well as they should, because the definition of the time to progression endpoint was mainly based on the "palliative response" endpoint. There was not any statistically significant difference between the two treatment groups in survival. All patients on this study used analgesics.

Study 9182 failed to show a statistically significant difference between the two treatment groups (M+H vs H) in survival, which was the primary endpoint. There was some indication, but not statistically significant, that patients in the treatment group had a longer time to progression than patients in the control group. The majority (155/232) of patients in this study had baseline analgesics. From a retrospective analysis, there was some indication that the treatment group had a longer time to progression than the control group, for those patients who did not have any baseline analgesics. There was not a statistically significant difference in time to progression between the two treatment group, for those patients who had baseline analgesics.

It is difficult to compare the time to progression endpoints of these two studies because they are both defined in a different way.

There were not any statistically significant improvements for the treatment arm vs the control arm in the various QOL instrument measures used in these studies.

RECOMMENDATION: Based on the data presented by the sponsor, the safety of Mitoxantrone has been demonstrated. According to the protocol specifications, evidence that Mitoxantrone is effective in the palliative treatment of patients with symptomatic Hormone-Resistant Prostate Cancer has also been shown. Approval of Mitoxantrone in patients with symptomatic Hormone-Resistant Prostate Cancer is recommended by this reviewer, as an alternative to other treatments, for the palliative treatment of patients with symptomatic Hormone-Resistant Prostate Cancer.

Antonis Koutsoukos, Ph.D.
Mathematical Statistician

concur: Dr. Gnecco C Gnecco 11/7/96

Dr. Chi Chi 11/7/96

cc:

Archival NDA 19-297
HFD-150/Dr. Beitz
HFD-150/Dr. Justice
HFD-150/Ms. Leslie Vaccari
HFD-344/Dr. Lisook
HFD-710/Dr. Chi
HFD-710/Dr. Gnecco
HFD-710/Dr. Koutsoukos
HFD-710/chron

Koutsoukos/ 11-28-1996/ WP6.1/ c:\nda19297\nova28.rvw
This review consists of pages (1-28) of text and 3 Attachments, Attachment 1, Attachment 2, and Attachment 3.

An addendum to this review contains the longitudinal data analyses of the primary endpoint PPI, and the analgesic scores.

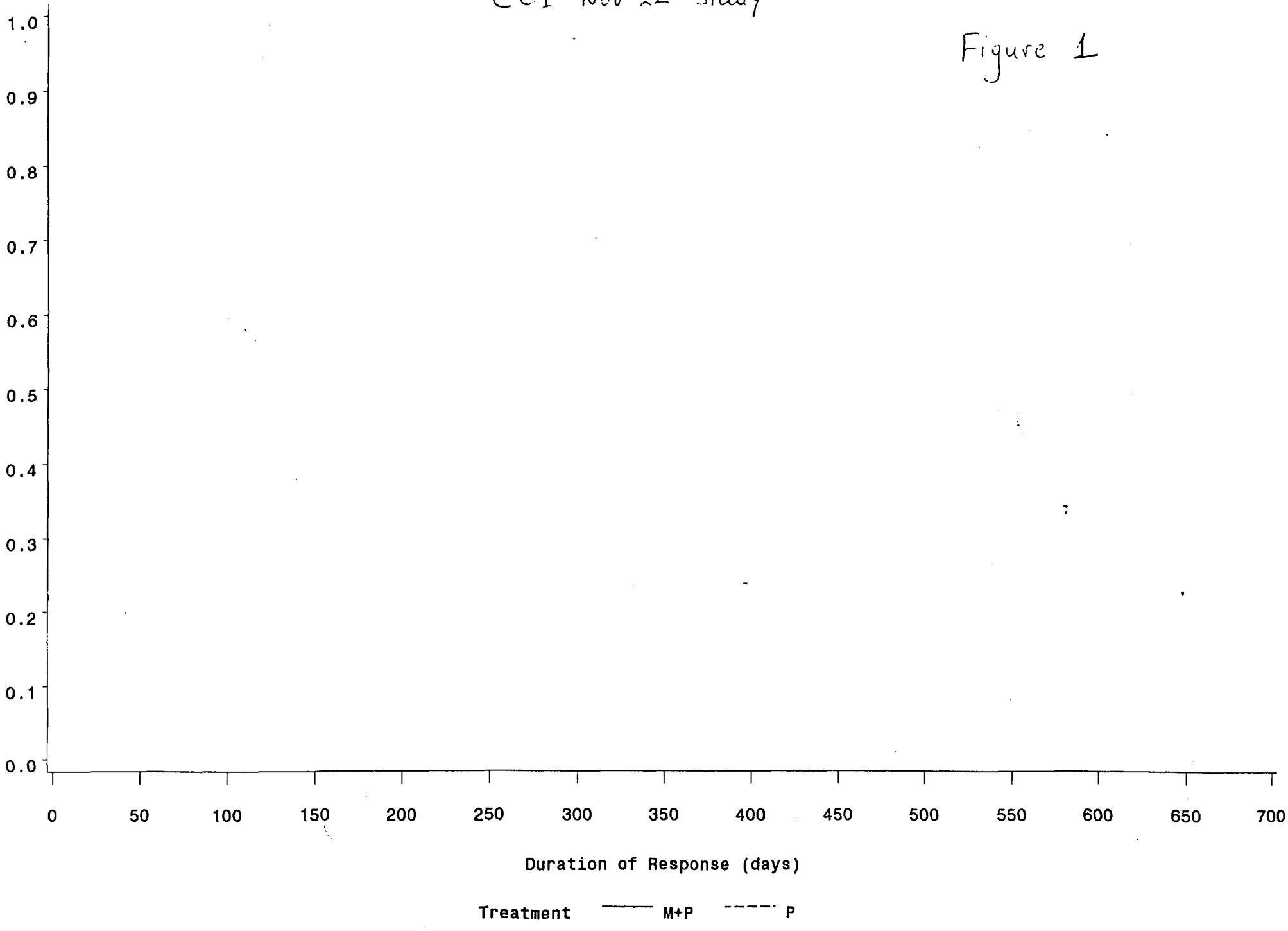
ATTACHMENT 1

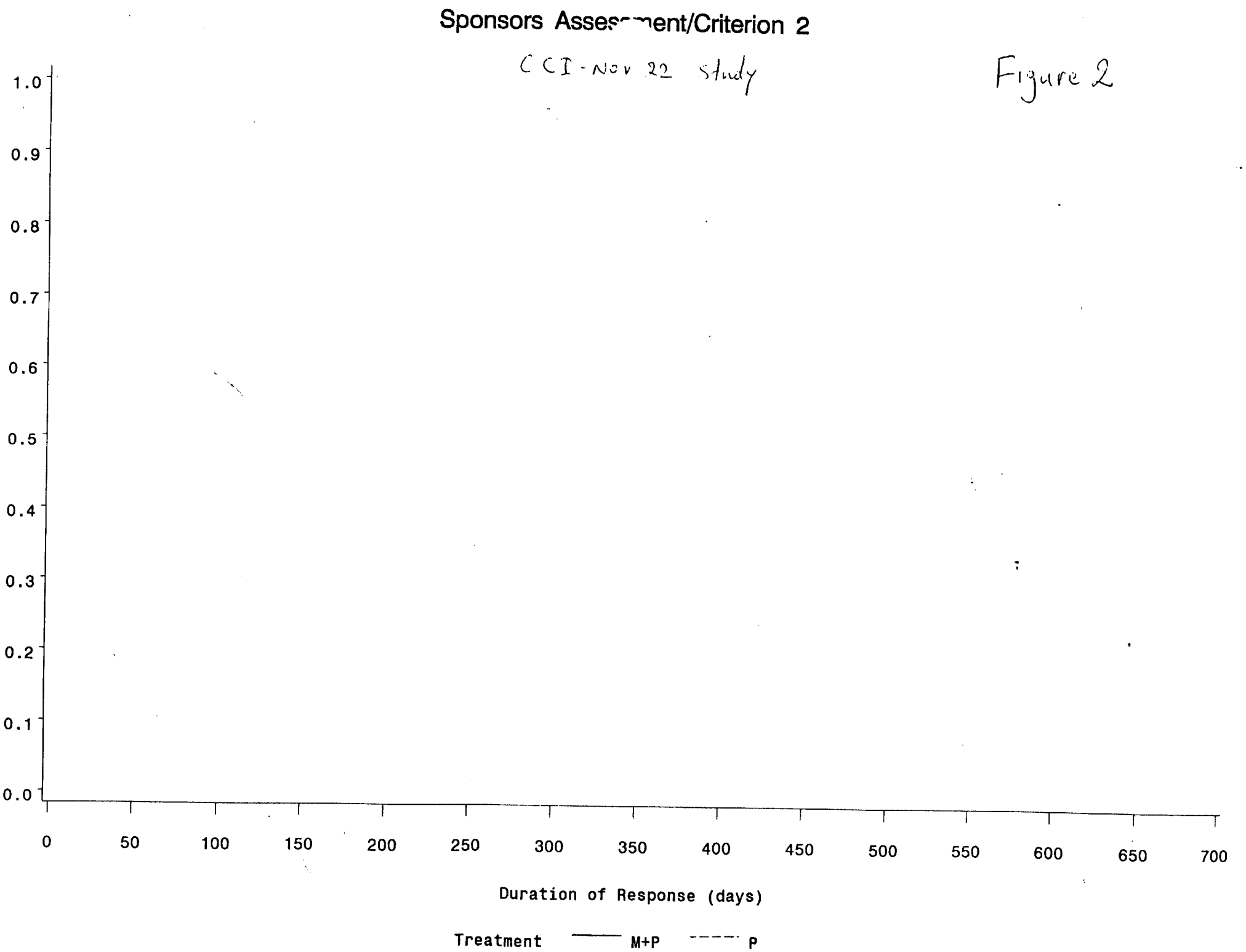
Reviewer's Figures 1-8.

Sponsors Asses ent/Criterion 1

CCI-Nov 22 Study

Figure 1




Sponsors Assessment/Criterion 2
CCI-Nov 22 study
Figure 2
1.0
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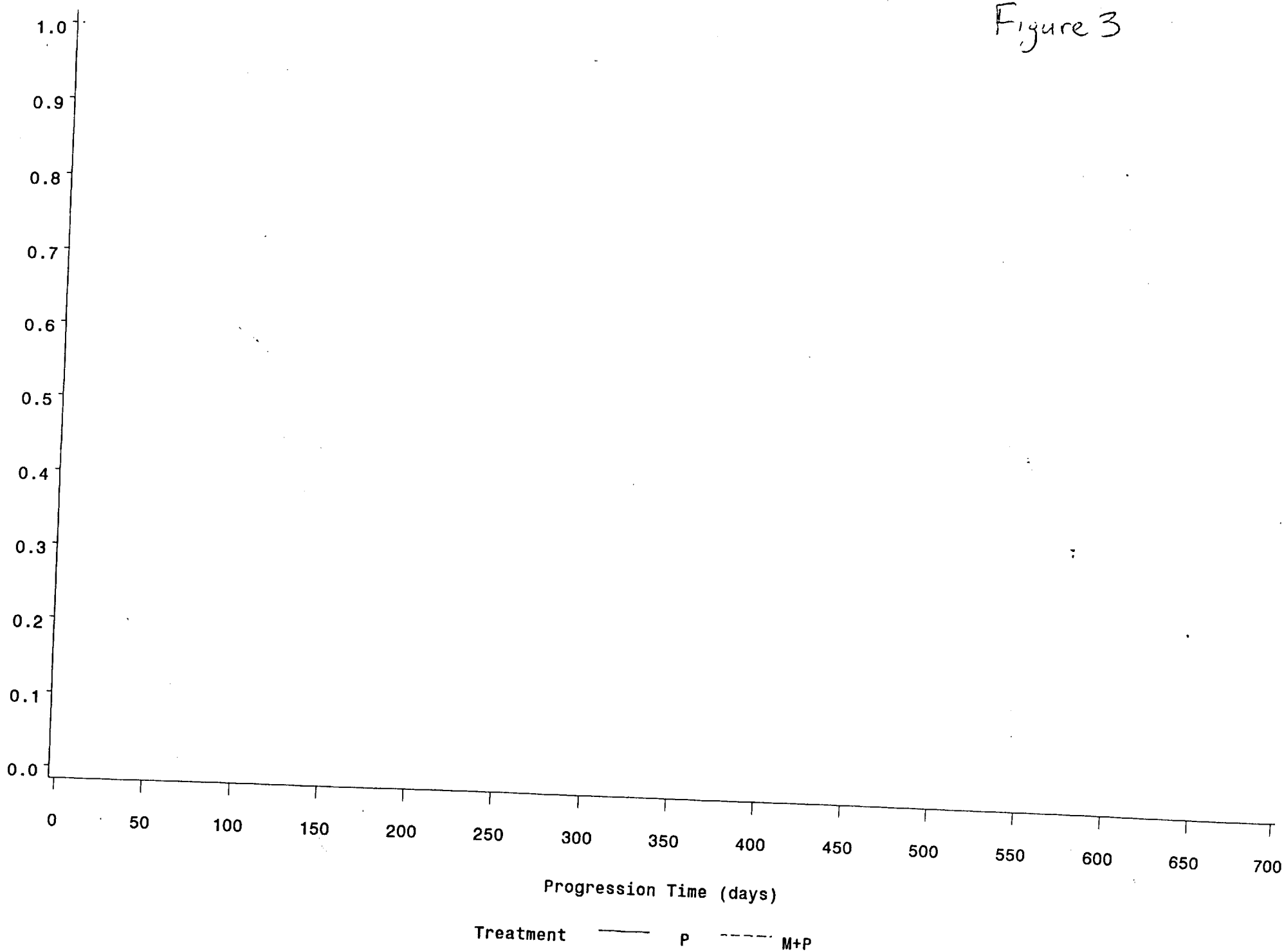
650
700
Duration of Response (days)
Treatment
M+P
P

Figure 3


TTP: P M+P
1.0
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0.5
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650
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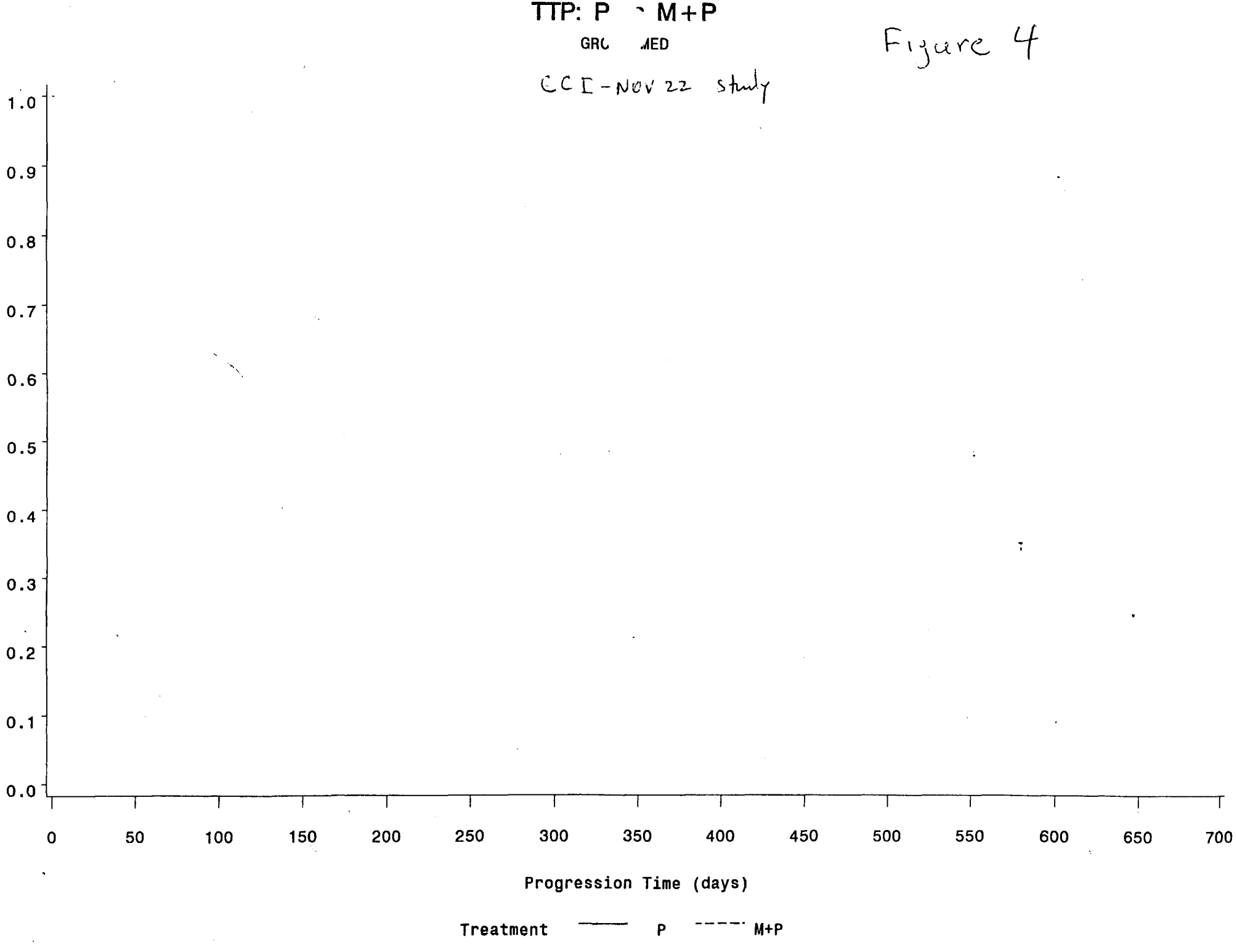
Progression Time (days)
Treatment
P
M+P


TTP: P - M+P
GRO MED
CCI-NOV 22 study
Figure 4
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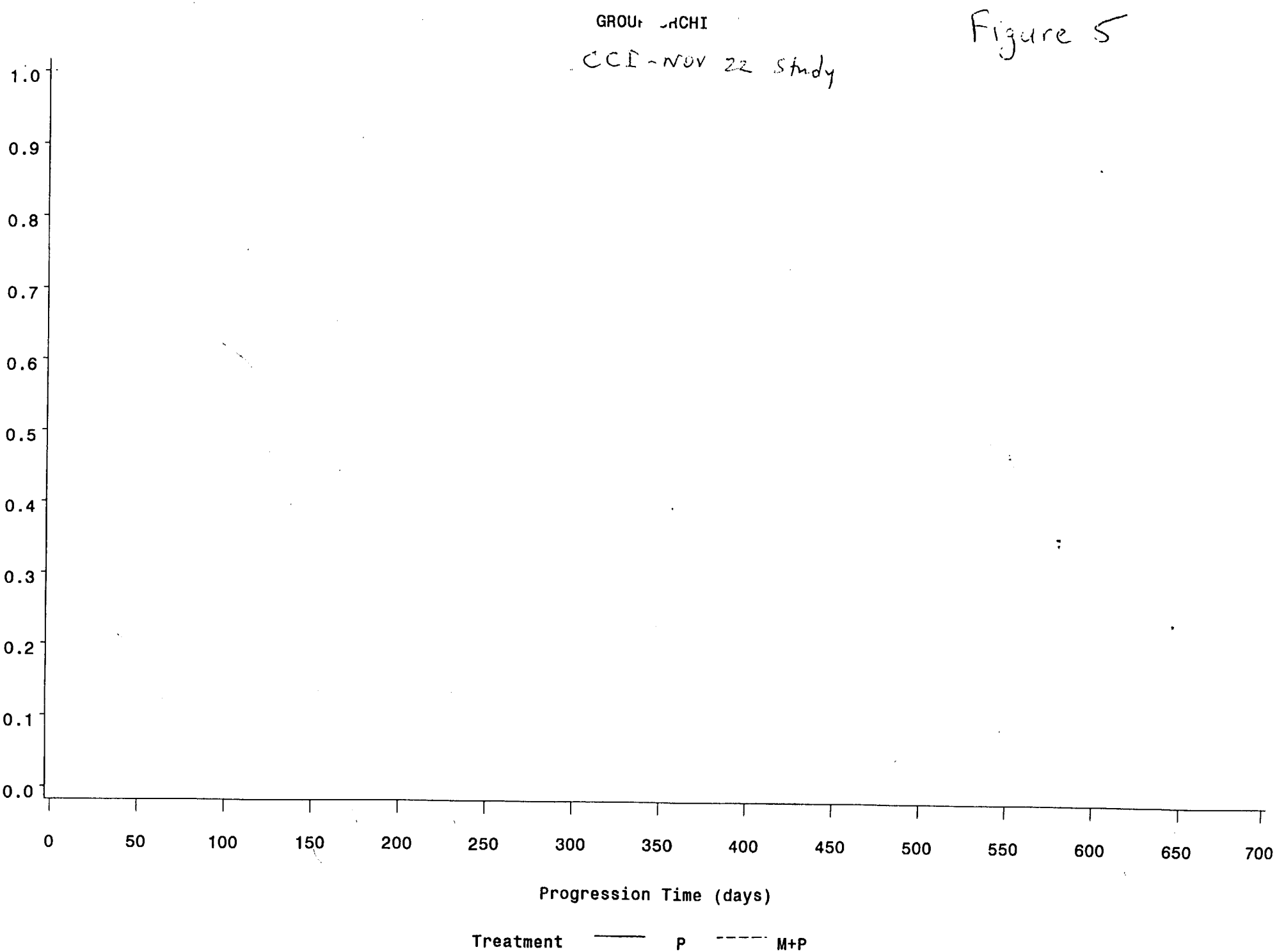
Progression Time (days)
Treatment
P
M+P


TTP: P M+P
GROUP ARCHI
CCI-NOV 22 Study
Figure 5
1.0
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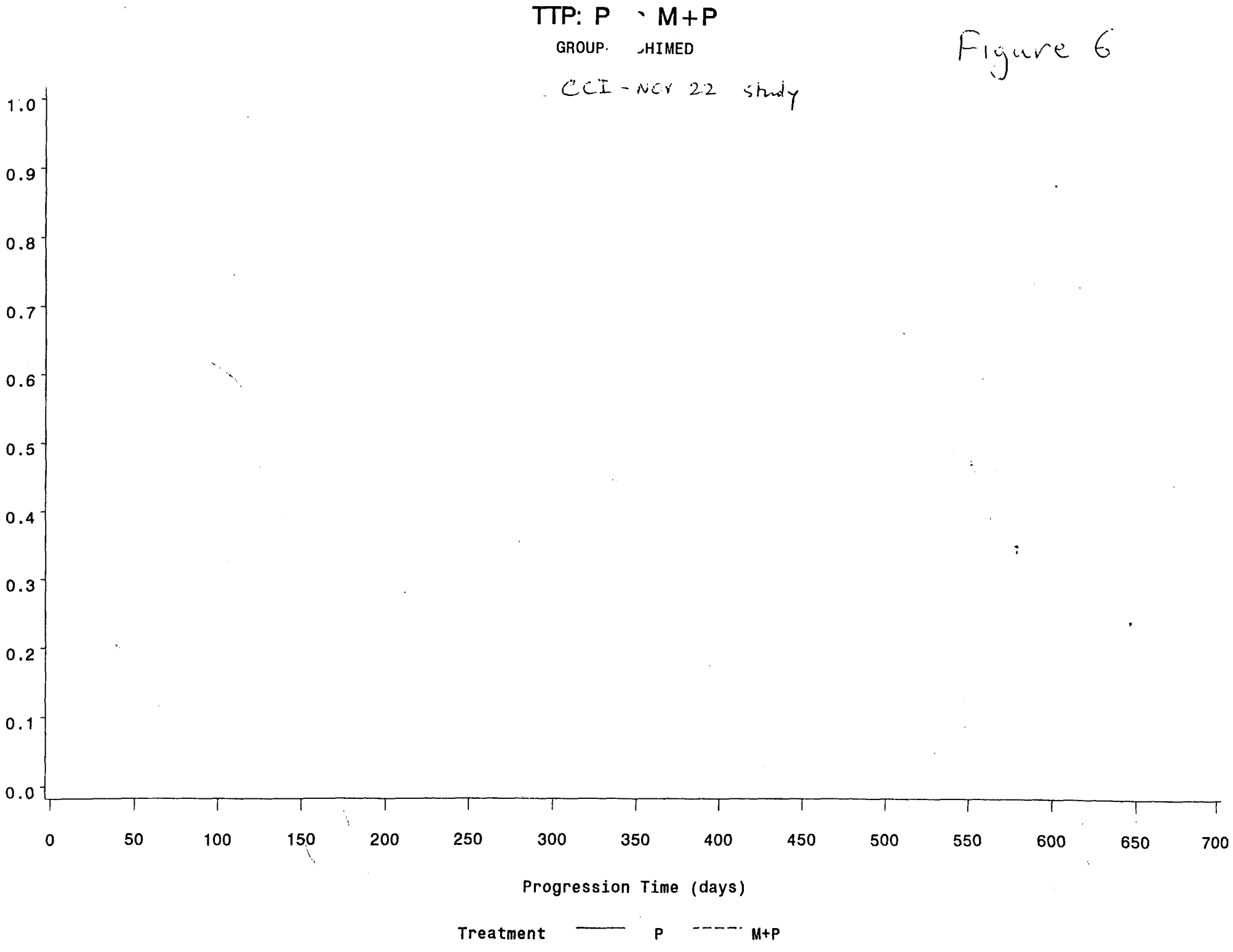
700
Progression Time (days)
Treatment
P
M+P


TTP: P M+P
GROUP: CHIMED
CCI-NCV 22 study
Figure 6
1.0
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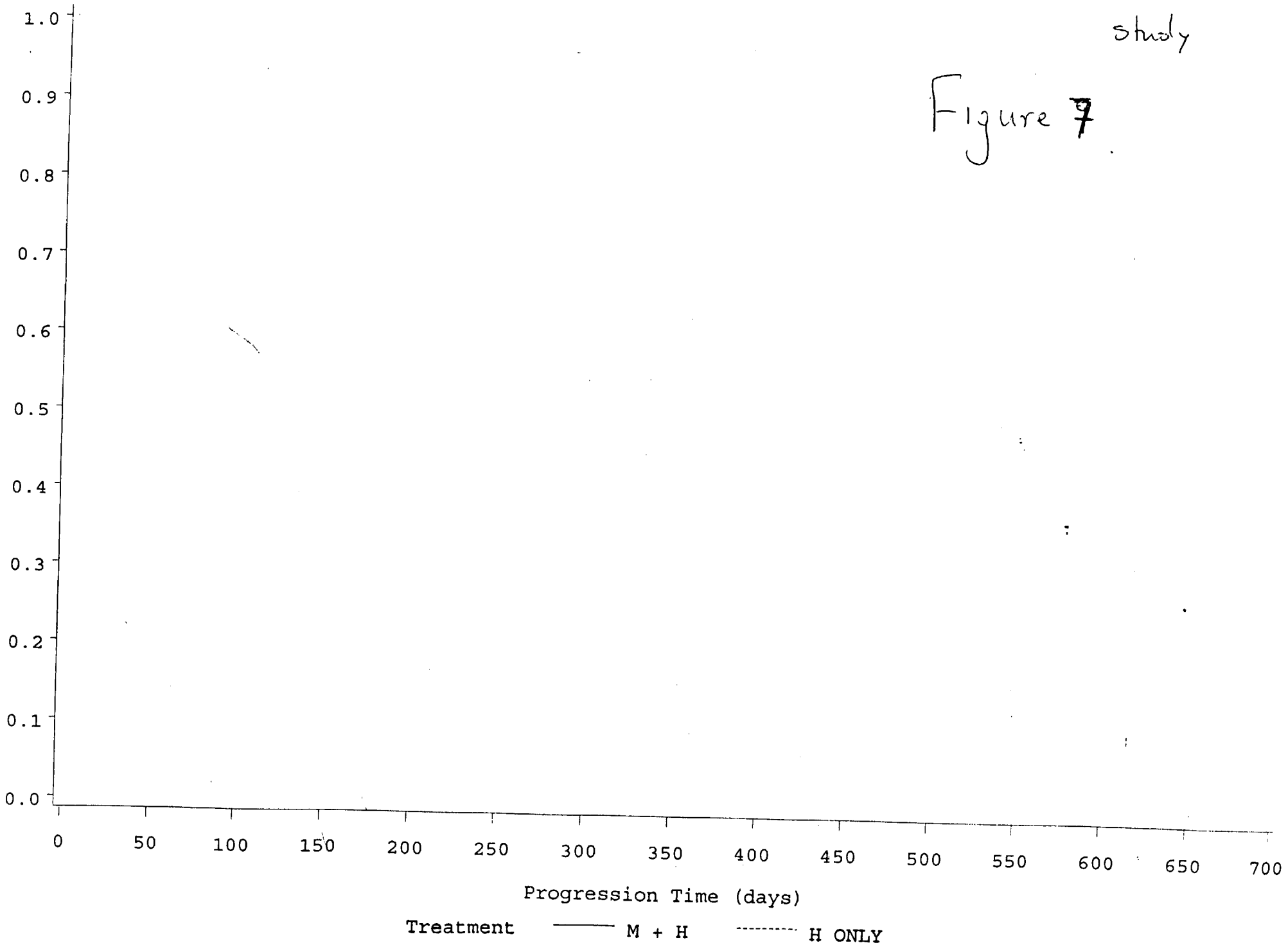
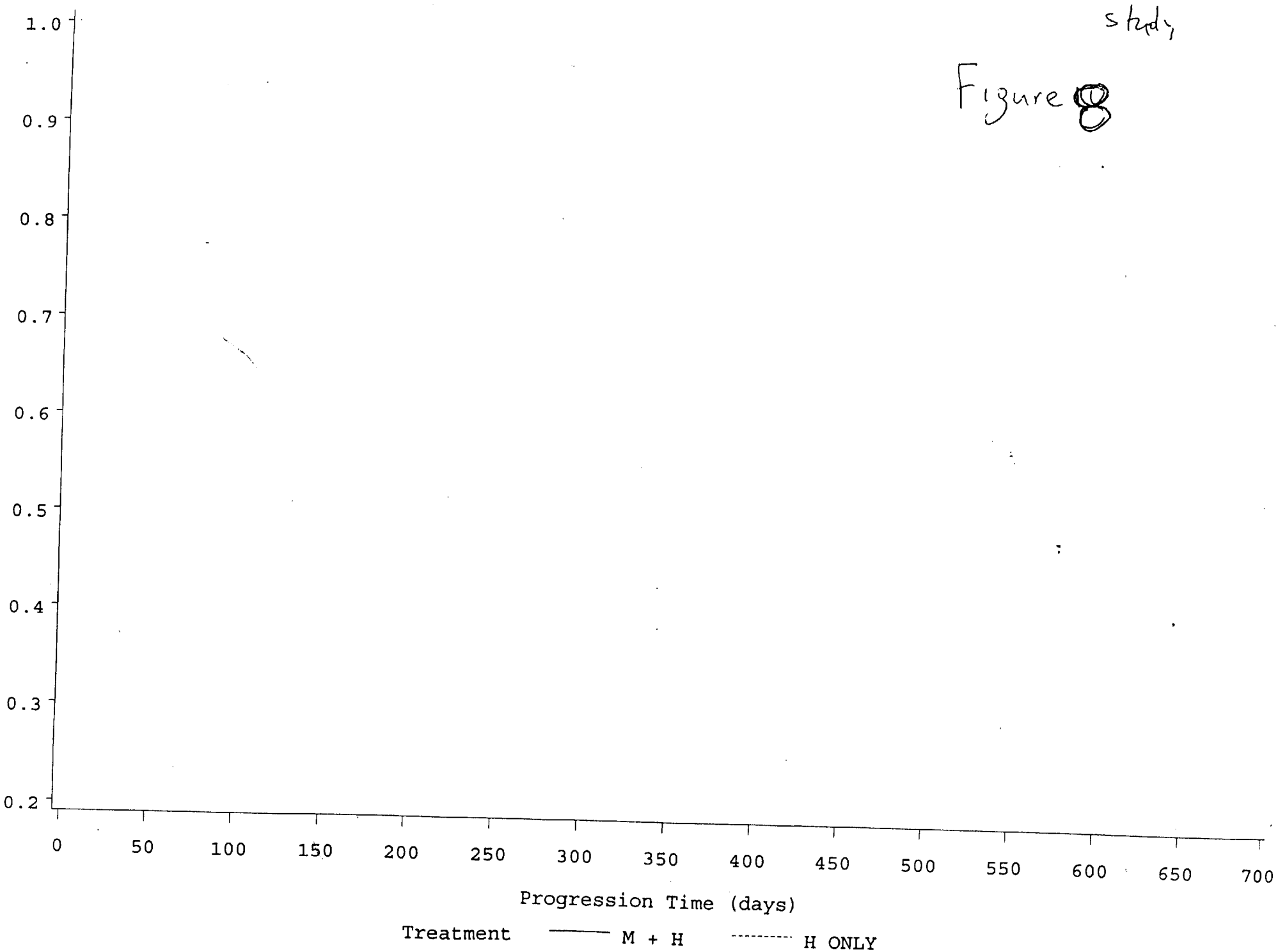
700
Progression Time (days)
Treatment P M+P

Analges Required

Study

Figure 7




No Analgesics Required
study
Figure 8
1.0
0.9
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0.7
0.6
0.5
0.4
0.3
0.2
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100
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350
400
450
500
550
600
650
700
Progression Time (days)
Treatment
M + H
H ONLY

ATTACHMENT 2

CCI-NOV22 Study

Sponsor's Tables: 2, 3, 15-17
Sponsor's Figures: 6-20

STUDY CCI-NOV22

TABLE 2 - DEMOGRAPHIC SUMMARY

		MITOXANTRONE + PREDNISONE	PREDNISONE	TOTAL	P-VALUES*
AGE (yrs)	MEAN (SD)	68.0 (7.8)	67.2 (7.4)	67.6 (7.6)	0.499
	MEDIAN	67.0	67.0	67.0	
	RANGE	50.0 - 86.0	43.0 - 81.0	43.0 - 86.0	
	N	79	81	160	
WEIGHT (Kg)	MEAN (SD)	79.0 (14.5)	80.1 (11.6)	79.6 (13.1)	0.605
	MEDIAN	80.2	80.0	80.0	
	RANGE	48.5 - 134.8	57.2 - 109.4	48.5 - 134.8	
	N	78	79	157	
BODY SURFACE AREA (mSq)	MEAN (SD)	1.9 (0.2)	1.9 (0.1)	1.9 (0.2)	0.909
	MEDIAN	1.9	1.9	1.9	
	RANGE	1.5 - 2.5	1.7 - 2.3	1.5 - 2.5	
	N	78	51	129	
ECOG PERFORMANCE STATUS	0	5 (6.3 %)	3 (3.8 %)	8 (5.0 %)	0.906
	1	45 (57.0 %)	47 (58.8 %)	92 (57.9 %)	
	2	21 (26.6 %)	22 (27.5 %)	43 (27.0 %)	
	3	8 (10.1 %)	8 (10.0 %)	16 (10.1 %)	
TESTOSTERONE	MEAN (SD)	0.9 (1.2)	1.0 (1.4)	1.0 (1.3)	0.858
	MEDIAN	0.5	0.7	0.6	
	RANGE	0.0 - 7.4	0.2 - 12.0	0.0 - 12.0	
	N	79	79	158	
TIME FROM DIAGNOSIS (days)	MEAN (SD)	1487.0 (1267.5)	1277.9 (974.5)	1381.8 (1131.0)	0.241
	MEDIAN	1088.0	1067.0	1075.0	
	RANGE	56.0 - 5828.0	105.0 - 4537.0	56.0 - 5828.0	
	N	80	81	161	

* CMH ROW MEANS TEST FOR DATA PRESENTED AS MEAN / MEDIAN
CMH GENERAL ASSOCIATION TEST FOR DATA PRESENTED AS CATEGORICAL

SOURCE: BIOMETRICS PENG - DEMTAB (04APR96,10:55)

TABLE 2 - DEMOGRAPHIC SUMMARY

		MITOXANTRONE + PREDNISONE	PREDNISONE	TOTAL	P-VALUES+
TIME FROM METASTASIS (days)	MEAN (SD)	816.7 (734.6)	640.8 (529.4)	728.2 (643.7)	0.083
	MEDIAN	659.0	511.0	568.0	
	RANGE	3.0 -4559.0	6.0 -2974.0	3.0 -4559.0	
	N	80	81	161	
SITE - BONE	YES	78 (97.5 %)	77 (95.1 %)	155 (96.3 %)	0.416
SITE - LYMPH NODES	YES	18 (22.5 %)	15 (18.5 %)	33 (20.5 %)	0.533
SITE - VISCERA	YES	3 (3.8 %)	3 (3.7 %)	6 (3.7 %)	0.988
SITE - OTHER	YES	7 (8.8 %)	8 (9.9 %)	15 (9.3 %)	0.806
THERAPY - ORCHIDECTOMY	YES	46 (57.5 %)	50 (61.7 %)	96 (59.6 %)	0.586
THERAPY - ESTROGEN	YES	7 (8.8 %)	13 (16.0 %)	20 (12.4 %)	0.162
THERAPY - LHRH AGONIST	YES	17 (21.3 %)	10 (12.3 %)	27 (16.8 %)	0.132
THERAPY - CYPROTERONE ACETATE	YES	24 (30.0 %)	18 (22.2 %)	42 (26.1 %)	0.263
THERAPY - FLUTAMIDE	YES	24 (30.0 %)	10 (12.3 %)	34 (21.1 %)	0.006

+ CMH ROW MEANS TEST FOR DATA PRESENTED AS MEAN / MEDIAN
CMH GENERAL ASSOCIATION TEST FOR DATA PRESENTED AS CATEGORICAL

SOURCE: BIOMETRICS FENG - DEMTAB (04APR96,10:55)

STUDY CC1-NOV22

TABLE 3 - BASELINE ASSESSMENT SUMMARY

		MITOXANTRONE + PREDNISONE	PREDNISONE	TOTAL	P-VALUES+
PAP (U/L)	MEAN (SD)	78.0 (266.3)	62.0 (174.4)	69.9 (224.1)	0.670
	MEDIAN	16.3	10.7	13.8	
	RANGE	0.1 -2200.0	0.2 -1240.0	0.1 -2200.0	
	N	71	72	143	
PSA (ng/L)	MEAN (SD)	567.3 (924.9)	490.0 (960.8)	527.3 (941.1)	0.626
	MEDIAN	179.9	156.0	169.7	
	RANGE	0.2 -5170.0	2.8 -6290.0	0.2 -6290.0	
	N	68	73	141	
PRESENT PAIN INTENSITY	0	1 (1.3 %)	1 (1.2 %)	2 (1.2 %)	0.782
	1	30 (37.5 %)	23 (28.4 %)	53 (32.9 %)	
	2	30 (37.5 %)	37 (45.7 %)	67 (41.6 %)	
	3	15 (18.8 %)	15 (18.5 %)	30 (18.6 %)	
	4	4 (5.0 %)	5 (6.2 %)	9 (5.6 %)	
ANALGESIC SCORE	MEAN (SD)	25.5 (30.0)	18.9 (19.9)	22.1 (25.5)	0.104
	MEDIAN	17.7	14.0	15.0	
	RANGE	0.0 - 182.0	0.0 - 126.0	0.0 - 182.0	
	N	78	81	159	

+ CMH ROW MEANS TEST FOR DATA PRESENTED AS MEAN / MEDIAN
CMH GENERAL ASSOCIATION TEST FOR DATA PRESENTED AS CATEGORICAL

SOURCE: BIOMETRICS FENG - BLTAB (04APR96,11:11)

Figure 6 — LASA — PAIN
(MEAN OF SUBJECTS OVER TIME)

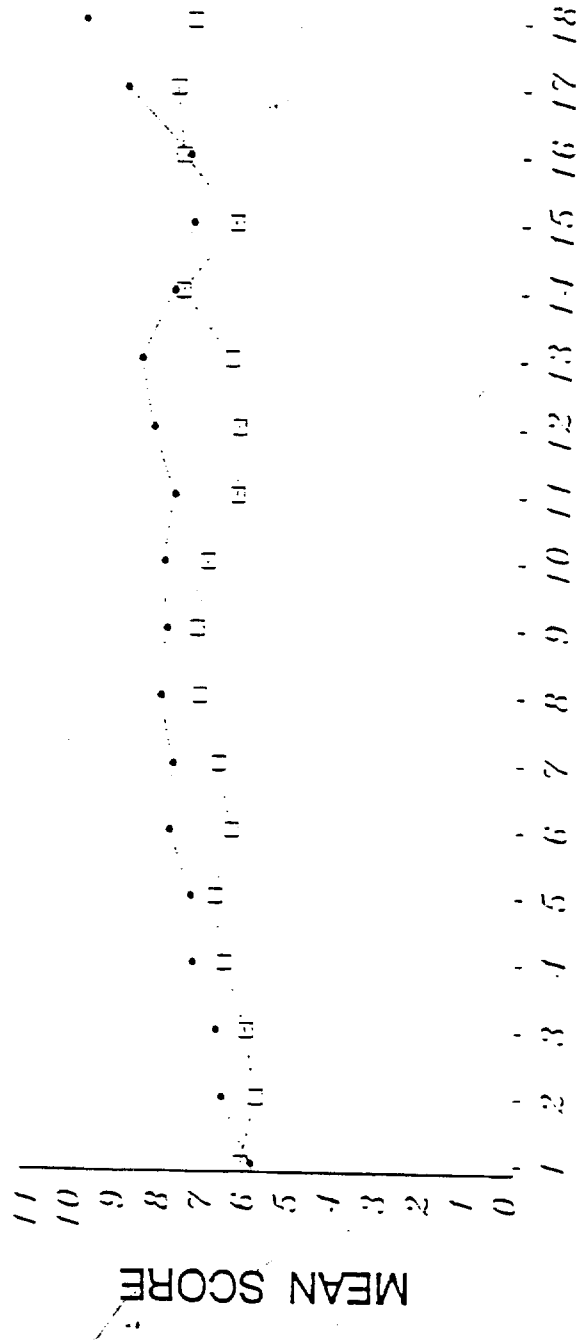


Figure 7 – LASA – PHYSICAL ACTIVITY
(MEAN OF SUBJECTS OVER TIME)

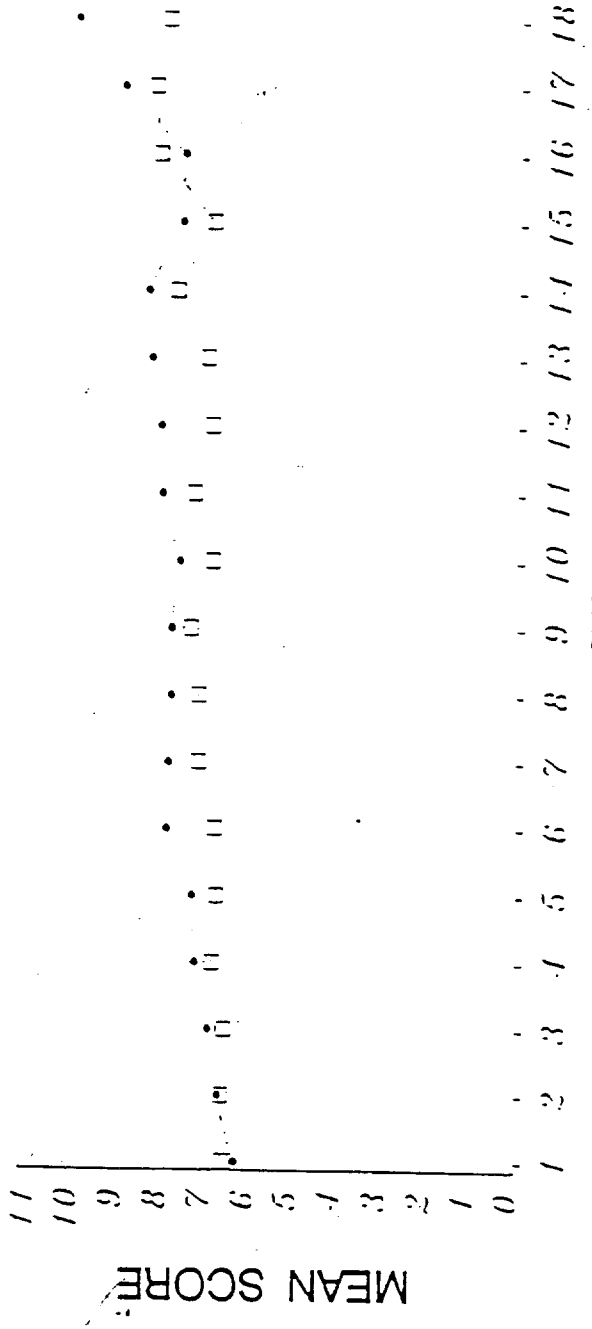


Figure 8 – LASA – FATIGUE
(MEAN OF SUBJECTS OVER TIME)

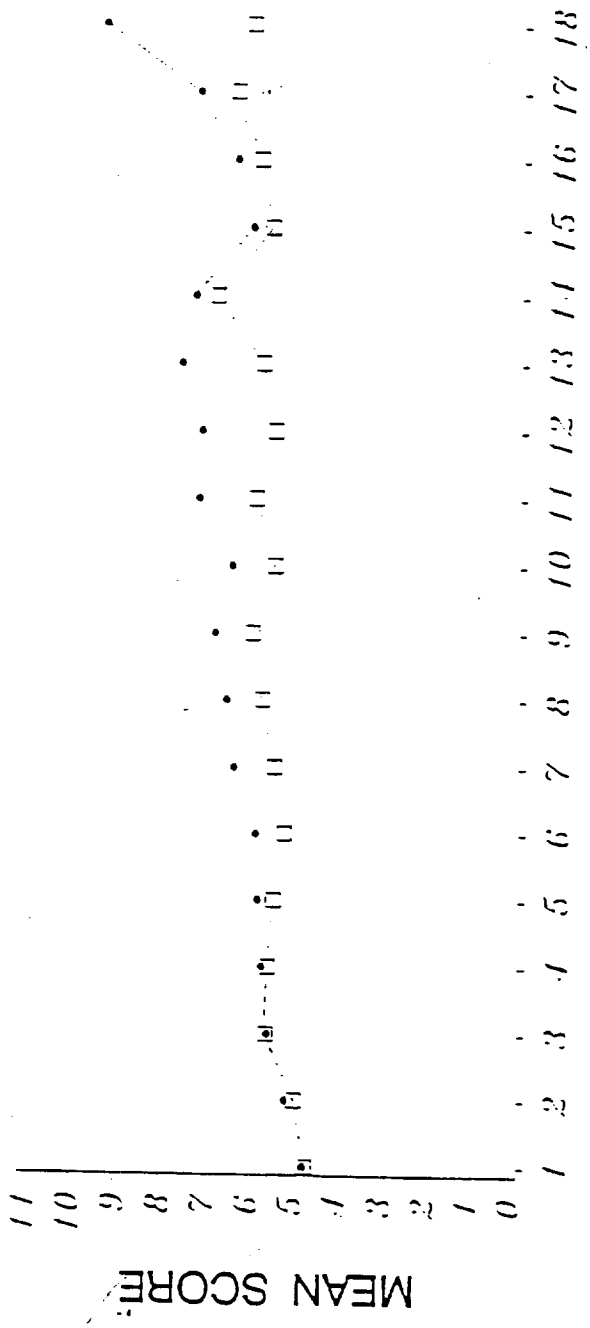


Figure 9 – LASA – APPETITE
(MEAN OF SUBJECTS OVER TIME)

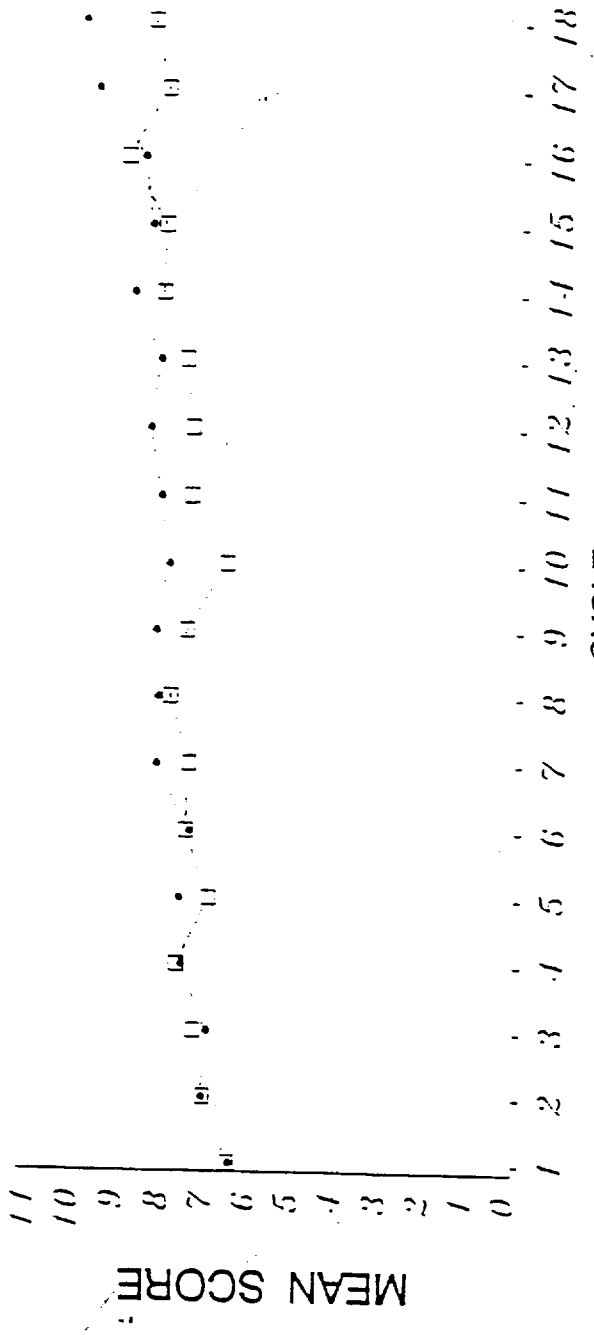


Figure 10 – LASA – CONSTIPATION
(MEAN OF SUBJECTS OVER TIME)

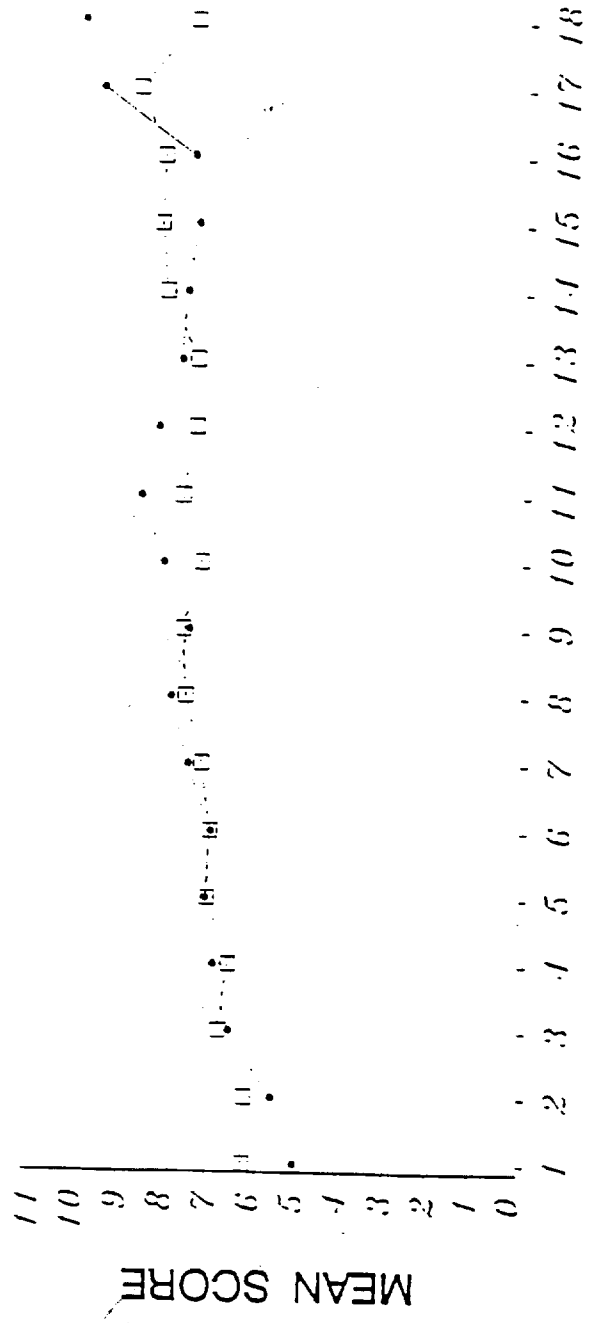


Figure 11 – LASA – FAMILY/MARRIAGE RELATIONSHIPS
(MEAN OF SUBJECTS OVER TIME)

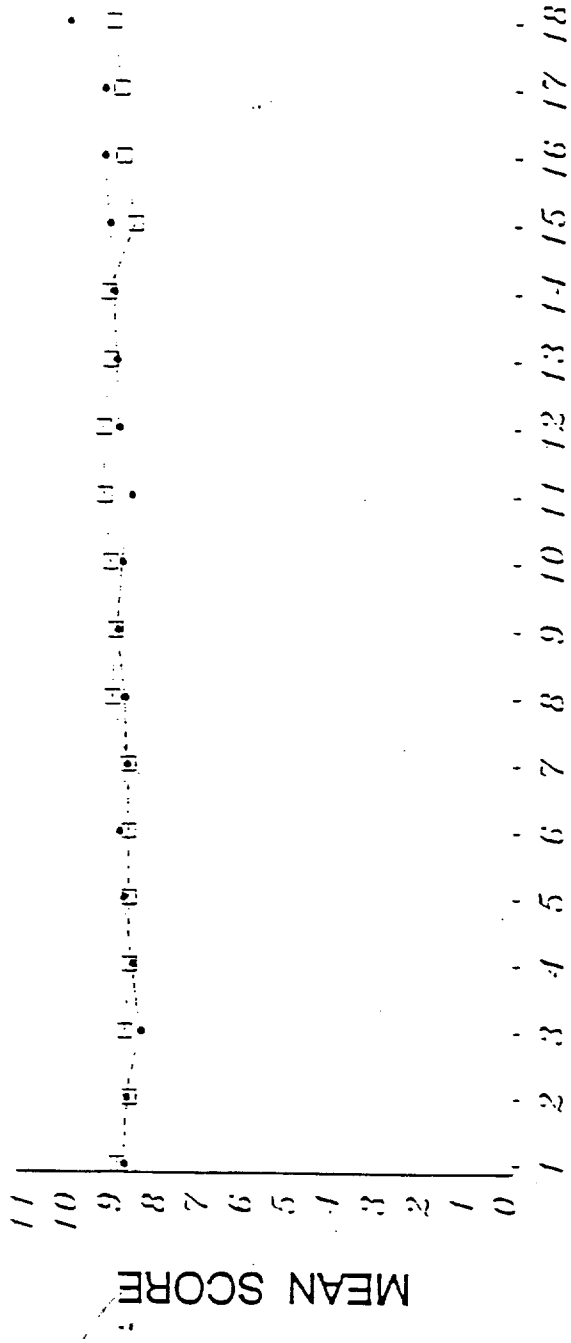


Figure 12 – LASA – MOOD
(MEAN OF SUBJECTS OVER TIME)

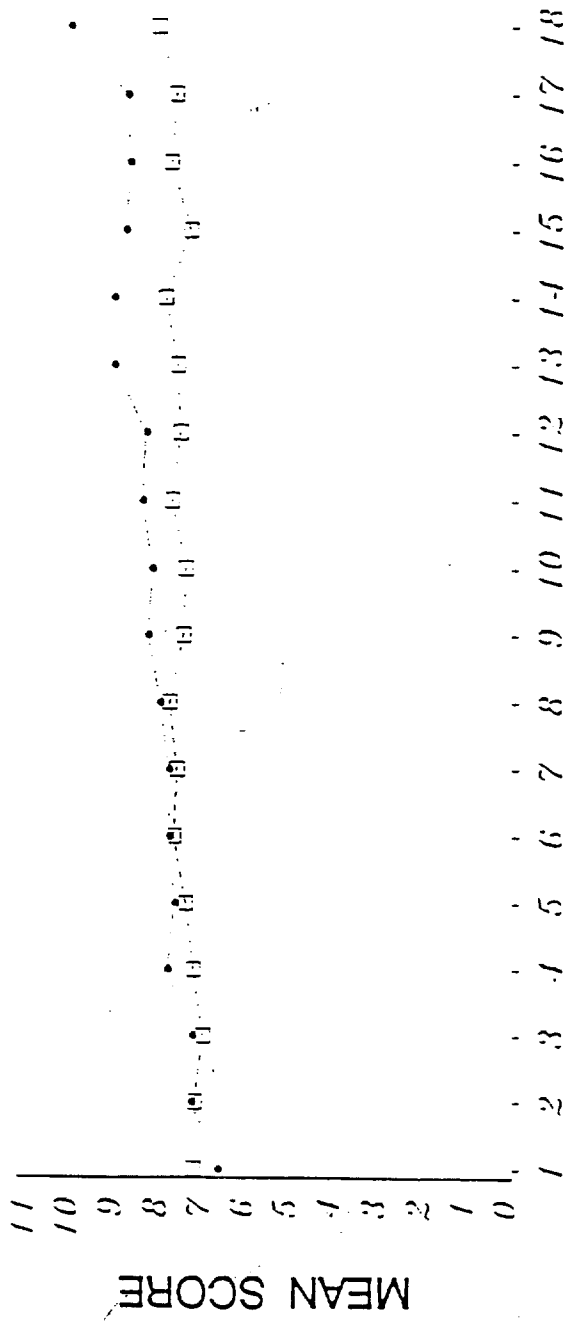


Figure 13 – LASA – PASSING URINE
(MEAN OF SUBJECTS OVER TIME)

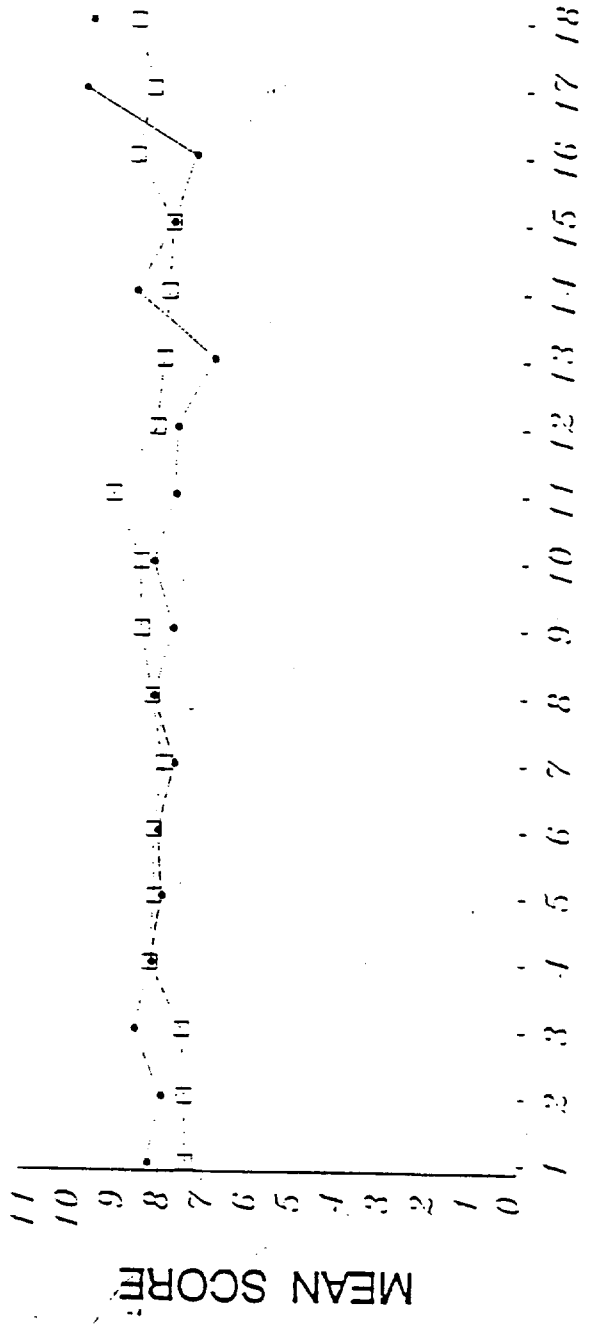


Figure 14 – LASA – OVERALL WELL-BEING (MEAN OF SUBJECTS OVER TIME)

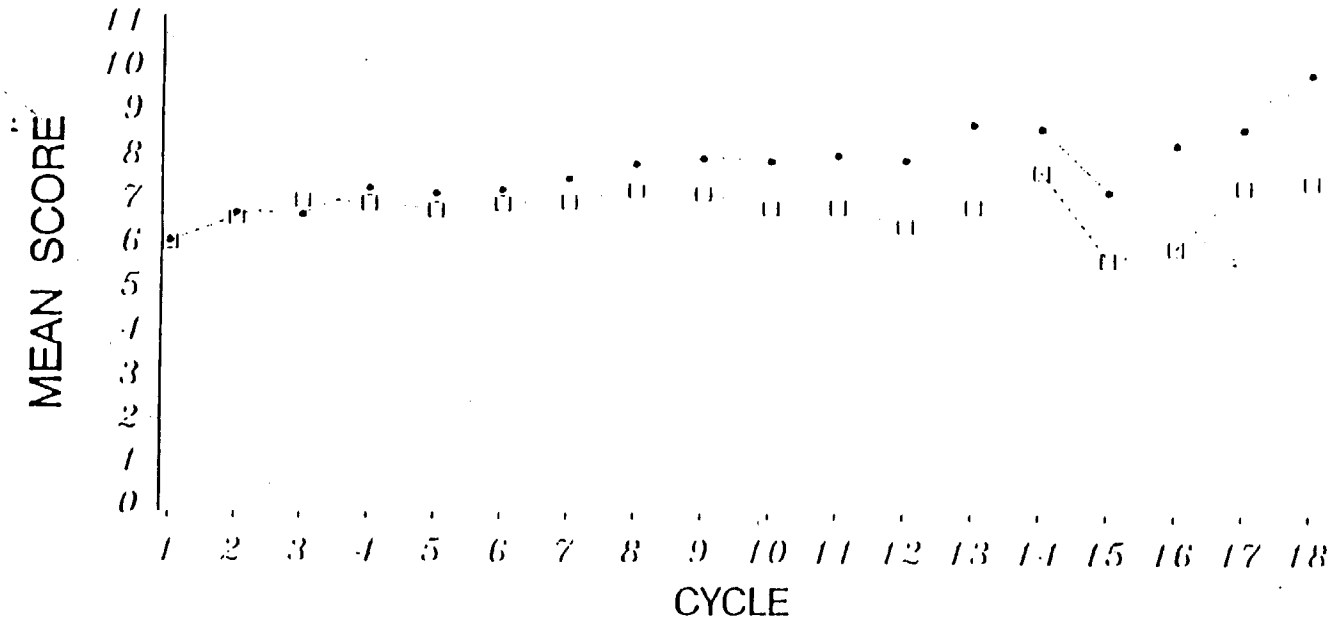
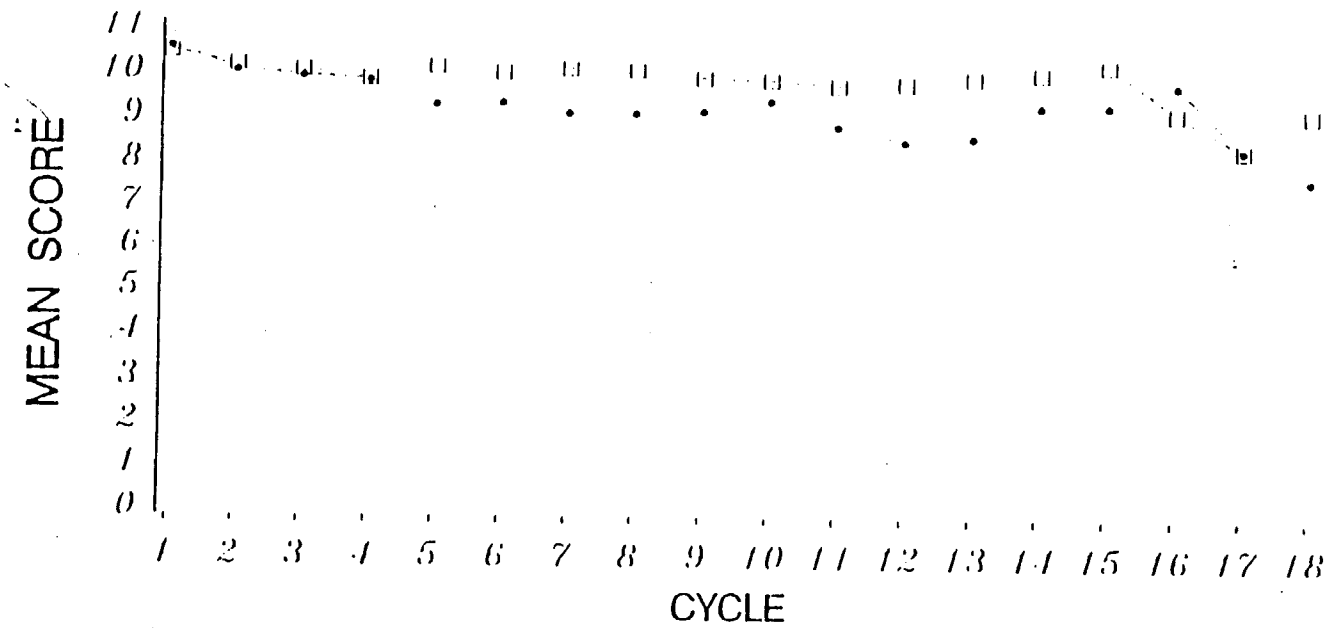


Figure 15 – QOL – SYMPTOMS AND PHYSICAL ACTIVITY (MEAN OF SUBJECTS' SUMS OVER TIME)



STUDY CCI-NOV22

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Figure 16 – QOL – FUNCTIONAL ACTIVITY
(MEAN OF SUBJECTS' SUMS OVER TIME)

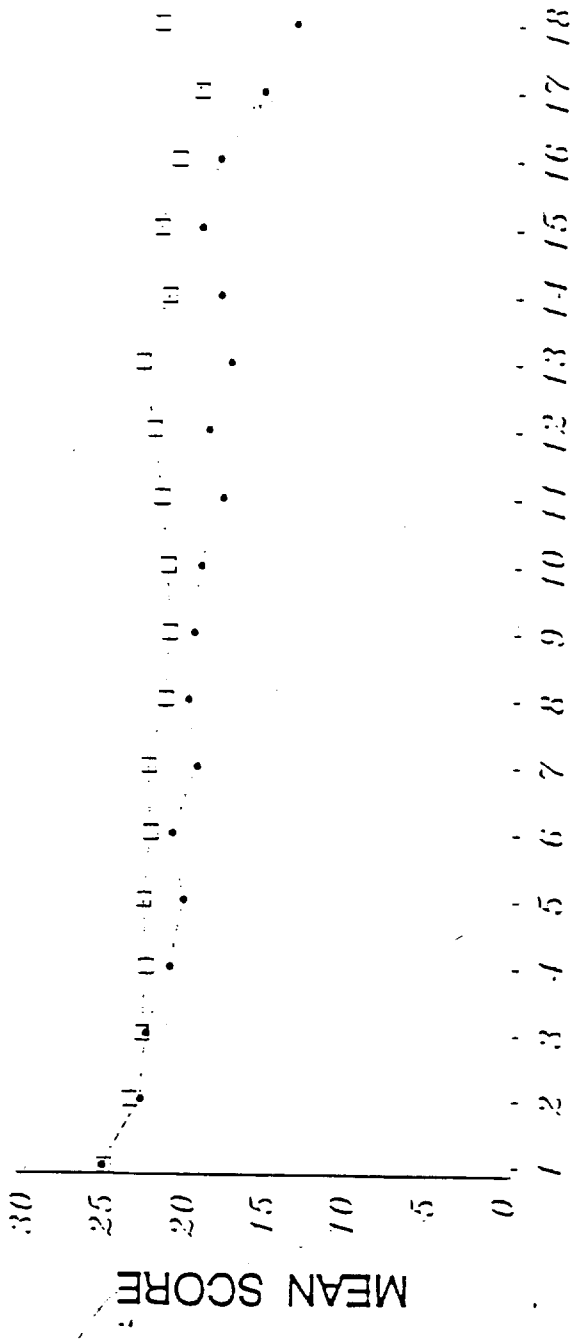


Figure 17 – QOL – PSYCHOSOCIAL
(MEAN OF SUBJECTS' SUMS OVER TIME)

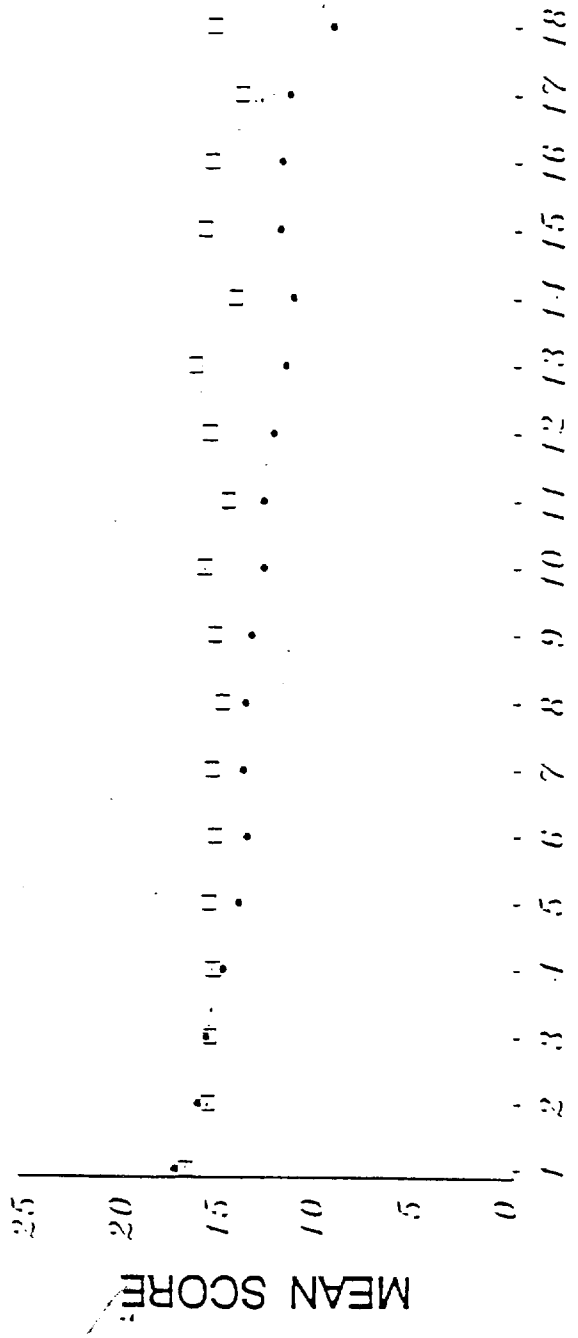


Figure 18 – QOL – OVERALL PHYSICAL
(MEAN OF SUBJECTS OVER TIME)

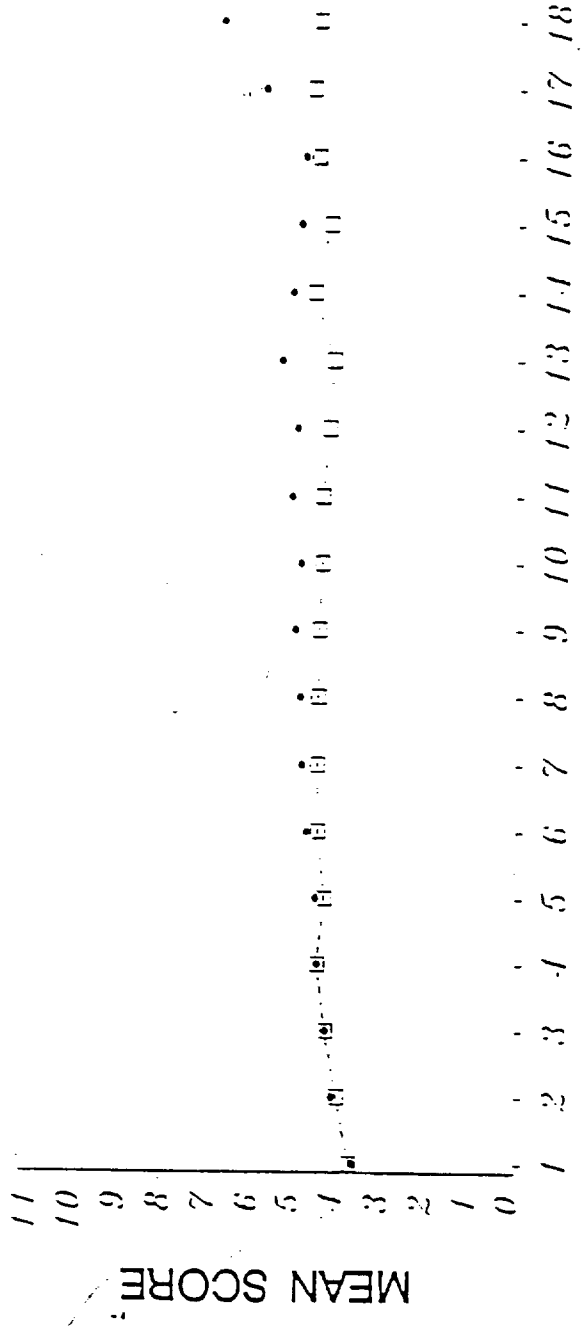


Figure 19 – QOL – OVERALL QUALITY OF LIFE
(MEAN OF SUBJECTS OVER TIME)

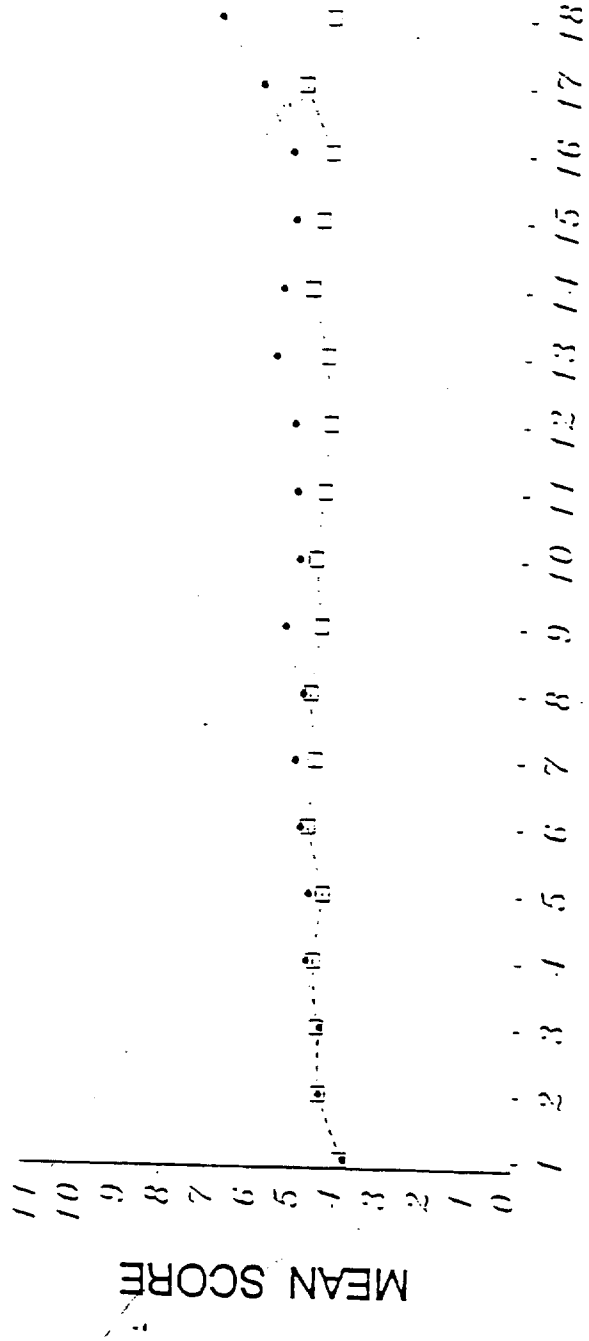
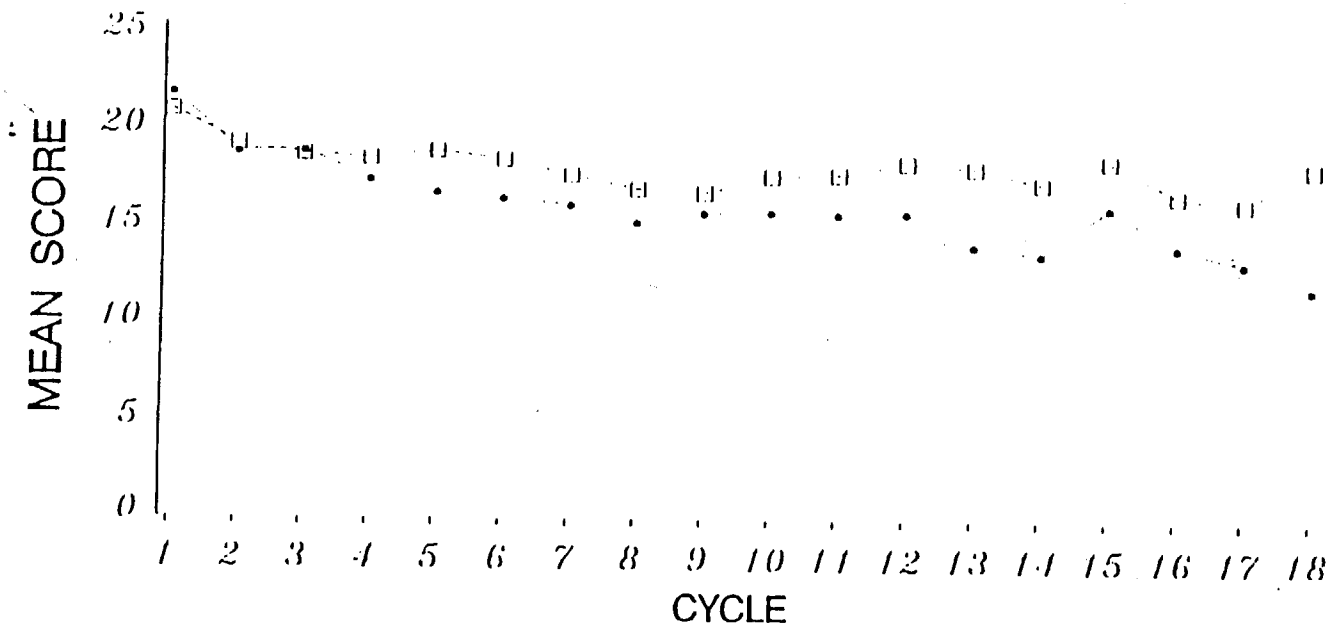


Figure 20 – QOL – PROSTATE MODULE (MEAN OF SUBJECTS' SUMS OVER TIME)



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STUDY CCI NOV22

TABLE 15 - QUALITY OF LIFE SUMMARY
(BEST SCORES)

		MITOXANTRONE + PREDNISONE	PREDNISONE	TOTAL	P-VALUES*
FASA - PAIN*	MEAN (SD)	8.0 (2.1)	7.7 (2.1)	7.8 (2.1)	0.526
	MEDIAN	8.8	8.4	8.5	
	RANGE	0.1 - 10.0	0.3 - 10.0	0.1 - 10.0	
	N	80	81	161	
FASA - PHYSICAL ACTIVITY*	MEAN (SD)	8.1 (1.8)	8.1 (1.8)	8.1 (1.8)	0.932
	MEDIAN	8.5	8.7	8.6	
	RANGE	2.4 - 10.0	1.9 - 10.0	1.9 - 10.0	
	N	80	81	161	
FASA - FATIGUE*	MEAN (SD)	7.1 (2.5)	6.8 (2.2)	6.9 (2.2)	0.519
	MEDIAN	7.7	7.4	7.5	
	RANGE	1.6 - 10.0	0.9 - 10.0	0.9 - 10.0	
	N	80	81	161	
FASA - APPETITE*	MEAN (SD)	8.5 (1.9)	8.1 (2.5)	8.3 (2.3)	0.319
	MEDIAN	9.1	9.2	9.1	
	RANGE	2.6 - 10.0	0.7 - 10.0	0.7 - 10.0	
	N	80	81	161	
FASA - CONSTIPATION*	MEAN (SD)	8.0 (2.2)	8.1 (2.3)	8.0 (2.3)	0.705
	MEDIAN	8.8	8.9	8.9	
	RANGE	0.1 - 10.0	0.8 - 10.0	0.1 - 10.0	
	N	80	81	161	
FASA - FAMILY/MARRIAGE RELATIONSHIPS*	MEAN (SD)	9.4 (1.3)	9.3 (1.0)	9.3 (1.2)	0.855
	MEDIAN	9.7	9.7	9.7	
	RANGE	0.7 - 10.0	4.9 - 10.0	0.7 - 10.0	
	N	80	81	161	

+ CMH ROW MEANS TEST
* LARGER SCORE IS BETTER ** SMALLER SCORE IS BETTER

SOURCE: BIOMETRICS TEMP QOLTAB (04APR96,12:52)

STUDY CCI-NOV22

TABLE 15 - QUALITY OF LIFE SUMMARY
(BEST SCORES)

		MITOXANTRONE + PREDNISONE	PREDNISONE	TOTAL	P-VALUES+
FASA MOOD*	MEAN (SD)	8.5 (1.7)	8.5 (1.5)	8.5 (1.6)	0.929
	MEDIAN	9.0	8.9	9.0	
	RANGE	1.7 - 10.0	4.2 - 10.0	1.7 - 10.0	
	N	80	81	161	
FASA - PASSING URINE*	MEAN (SD)	9.1 (1.2)	8.9 (1.9)	9.0 (1.6)	0.413
	MEDIAN	9.7	9.7	9.7	
	RANGE	4.9 - 10.0	0.0 - 10.0	0.0 - 10.0	
	N	52	52	104	
FASA - OVERALL WELL-BEING*	MEAN (SD)	8.0 (1.7)	7.7 (2.3)	7.8 (2.0)	0.372
	MEDIAN	8.5	8.4	8.4	
	RANGE	3.4 - 10.0	0.5 - 10.0	0.5 - 10.0	
	N	80	81	161	
QOL - SYMPTOMS AND PHYSICAL ACTIVITY**	MEAN (SD)	9.1 (1.9)	9.4 (2.0)	9.2 (2.0)	0.484
	MEDIAN	9.0	9.0	9.0	
	RANGE	7.0 - 14.0	7.0 - 14.0	7.0 - 14.0	
	N	80	81	161	
QOL - FUNCTIONAL ACTIVITY**	MEAN (SD)	19.7 (5.2)	20.4 (5.8)	20.1 (5.5)	0.408
	MEDIAN	19.0	19.0	19.0	
	RANGE	12.0 - 32.0	12.0 - 37.0	12.0 - 37.0	
	N	80	81	161	
QOL - PSYCHOSOCIAL**	MEAN (SD)	13.8 (4.2)	13.8 (4.4)	13.8 (4.3)	0.985
	MEDIAN	13.0	13.0	13.0	
	RANGE	9.0 - 25.0	9.0 - 25.0	9.0 - 25.0	
	N	80	81	161	

+ CMH ROW MEANS TEST
* LARGER SCORE IS BETTER ** SMALLER SCORE IS BETTER

SOURCE: BIOMETRICS FENG - QOLTAB (04APR96,12:52)

TABLE 15 - QUALITY OF LIFE SUMMARY
(BEST SCORES)

		MITOXANTRONE + PREDNISONE	PREDNISONE	TOTAL	P VALUES+
QOL - OVERALL PHYSICAL*	MEAN (SD)	5.0 (1.2)	4.8 (1.3)	4.9 (1.2)	0.491
	MEDIAN	5.0	5.0	5.0	
	RANGE	1.0 - 7.0	2.0 - 7.0	1.0 - 7.0	
	N	80	81	161	
QOL - OVERALL QUALITY OF LIFE*	MEAN (SD)	5.2 (1.2)	5.0 (1.2)	5.1 (1.2)	0.361
	MEDIAN	5.0	5.0	5.0	
	RANGE	2.0 - 7.0	2.0 - 7.0	2.0 - 7.0	
	N	80	81	161	
QOL - PROSTATE MODULE**	MEAN (SD)	16.0 (5.1)	16.7 (5.5)	16.4 (5.3)	0.423
	MEDIAN	14.3	15.4	14.7	
	RANGE	11.0 - 28.6	11.0 - 34.1	11.0 - 34.1	
	N	80	81	161	

+ CMH ROW MEANS TEST
* LARGER SCORE IS BETTER ** SMALLER SCORE IS BETTER

SOURCE: BIOMETRICS TEMG - QOLTAB (04APR96,12:52)

STUDY CCI-NOV22

TABLE 16 - QUALITY OF LIFE SUMMARY
(BEST CHANGE FROM BASELINE)

		MITOXANTRONE + PREDNISONE	PREDNISONE	TOTAL	P-VALUES+
FASA - PAIN*	MEAN (SD)	2.2 (2.1)	1.7 (1.9)	1.9 (2.0)	0.105
	MEDIAN	1.6	1.0	1.4	
	RANGE	0.0 - 8.7	0.0 - 6.9	0.0 - 8.7	
	N	79	80	159	
FASA - PHYSICAL ACTIVITY*	MEAN (SD)	1.9 (1.8)	1.7 (2.1)	1.8 (2.0)	0.426
	MEDIAN	1.4	0.7	1.3	
	RANGE	0.0 - 7.0	0.0 - 8.7	0.0 - 8.7	
	N	80	81	161	
FASA - FATIGUE*	MEAN (SD)	2.3 (2.1)	2.1 (2.1)	2.2 (2.1)	0.621
	MEDIAN	2.0	1.6	1.8	
	RANGE	0.0 - 7.2	0.0 - 7.5	0.0 - 7.5	
	N	80	80	160	
FASA - APPETITE*	MEAN (SD)	2.1 (2.5)	1.7 (2.2)	1.9 (2.4)	0.305
	MEDIAN	1.1	0.6	0.9	
	RANGE	0.0 - 8.8	0.0 - 8.2	0.0 - 8.8	
	N	80	81	161	
FASA - CONSTIPATION*	MEAN (SD)	3.0 (2.7)	1.9 (2.5)	2.4 (2.7)	0.016
	MEDIAN	2.1	0.8	1.5	
	RANGE	0.0 - 8.7	0.0 - 9.4	0.0 - 9.4	
	N	79	81	160	
FASA - FAMILY/MARRIAGE RELATIONSHIPS*	MEAN (SD)	0.7 (1.4)	0.5 (1.0)	0.6 (1.2)	0.558
	MEDIAN	0.5	0.0	0.1	
	RANGE	0.0 - 9.1	0.0 - 7.2	0.0 - 9.1	
	N	79	79	158	

+ CMH ROW MEANS TEST
* LARGER SCORE IS BETTER ** SMALLER SCORE IS BETTER

SOURCE: BIOMETRICS FLNG - QOLTAB (04APR96,12:52)

STUDY CCI-NOV22

TABLE 16 - QUALITY OF LIFE SUMMARY
(BEST CHANGE FROM BASELINE)

		MITOXANTRONE + PREDNISONE	PREDNISONE	TOTAL	P-VALUES+
FASA - MOOD^	MEAN (SD)	1.9 (2.0)	1.3 (1.8)	1.6 (1.9)	0.058
	MEDIAN	1.2	0.7	0.9	
	RANGE	0.0 - 7.2	0.0 - 7.8	0.0 - 7.8	
	N	80	81	161	
FASA - PASSING URINE^	MEAN (SD)	1.0 (1.3)	1.6 (2.5)	1.3 (2.0)	0.151
	MEDIAN	0.4	0.3	0.4	
	RANGE	0.0 - 4.9	0.0 - 8.8	0.0 - 8.8	
	N	44	42	86	
FASA - OVERALL WELL-BEING^	MEAN (SD)	1.9 (2.0)	1.7 (2.0)	1.8 (2.0)	0.454
	MEDIAN	1.2	0.9	1.1	
	RANGE	0.0 - 7.9	0.0 - 8.1	0.0 - 8.1	
	N	80	81	161	
QOL - SYMPTOMS AND PHYSICAL ACTIVITY^^	MEAN (SD)	-1.4 (1.4)	-1.1 (1.4)	-1.3 (1.4)	0.125
	MEDIAN	-1.0	-1.0	-1.0	
	RANGE	-6.0 - 0.0	-5.0 - 0.0	-6.0 - 0.0	
	N	80	81	161	
QOL - FUNCTIONAL ACTIVITY^^	MEAN (SD)	-5.3 (4.8)	-4.5 (4.3)	-4.9 (4.6)	0.229
	MEDIAN	-4.0	-5.0	-4.0	
	RANGE	-19.0 - 0.0	-17.0 - 0.0	-19.0 - 0.0	
	N	80	81	161	
QOL - PSYCHOSOCIAL^^	MEAN (SD)	-3.5 (4.0)	-3.0 (3.1)	-3.3 (3.6)	0.299
	MEDIAN	-2.0	-2.0	-2.0	
	RANGE	-16.0 - 0.0	-12.0 - 0.0	-16.0 - 0.0	
	N	80	81	161	

+ CMH ROW MEANS TEST
^ LARGER SCORE IS BETTER ^^ SMALLER SCORE IS BETTER

SOURCE: BIOMETRICS FEDG - QOLTAB (06APR96,12:52)

TABLE 16 - QUALITY OF LIFE SUMMARY
(BEST CHANGE FROM BASELINE)

		MITOXANTRONE + PREDNISONE	PREDNISONE	TOTAL	P-VALUES+
QOL - OVERALL PHYSICAL^	MEAN (SD)	1.4 (1.1)	1.2 (1.1)	1.3 (1.1)	0.267
	MEDIAN	1.0	1.0	1.0	
	RANGE	0.0 - 4.0	0.0 - 4.0	0.0 - 4.0	
	N	80	81	161	
QOL - OVERALL QUALITY OF LIFE^	MEAN (SD)	1.4 (1.2)	1.2 (1.2)	1.3 (1.2)	0.185
	MEDIAN	1.0	1.0	1.0	
	RANGE	0.0 - 5.0	0.0 - 5.0	0.0 - 5.0	
	N	79	81	160	
QOL - PROSTATE MODULE^^	MEAN (SD)	-5.6 (5.6)	-4.1 (4.5)	-4.9 (5.1)	0.052
	MEDIAN	-4.4	-2.2	-3.3	
	RANGE	-23.1 - 0.0	-17.4 - 0.0	-23.1 - 0.0	
	N	80	80	160	

+ CHI ROW MEANS TEST
^ LARGER SCORE IS BETTER ^^ SMALLER SCORE IS BETTER

SOURCE: BIOMETRICS FENG - QOLTAB (04APR96,12:52)

STUDY CCI-NOV22

TABLE 17 - QUALITY OF LIFE SUMMARY
(BEST %CHANGE FROM BASELINE)

		MITOXANTRONE + PREDNISONE	PREDNISONE	TOTAL	P-VALUES+
FASA - PAIN*	MEAN (SD)	105.3 (356.7)	41.4 (68.2)	73.1 (257.2)	0.117
	MEDIAN	25.4	12.5	20.3	
	RANGE	0.0 -2900.0	0.0 - 344.4	0.0 -2900.0	
	N	79	80	159	
FASA - PHYSICAL ACTIVITY*	MEAN (SD)	44.5 (64.0)	63.0 (185.8)	53.8 (139.2)	0.399
	MEDIAN	20.2	9.3	16.7	
	RANGE	0.0 - 388.9	0.0 -1242.9	0.0 -1242.9	
	N	80	81	161	
FASA - FATIGUE*	MEAN (SD)	116.5 (233.8)	164.7 (643.1)	140.5 (481.8)	0.529
	MEDIAN	36.2	32.0	33.3	
	RANGE	0.0 -1500.0	0.0 -5300.0	0.0 -5300.0	
	N	80	79	159	
FASA - APPETITE*	MEAN (SD)	145.8 (538.3)	135.7 (648.2)	140.8 (594.0)	0.914
	MEDIAN	15.2	8.5	11.1	
	RANGE	0.0 -4400.0	0.0 -5700.0	0.0 -5700.0	
	N	80	80	160	
FASA - CONSTIPATION*	MEAN (SD)	161.6 (327.5)	274.9 (1360.1)	219.0 (995.3)	0.475
	MEDIAN	39.7	10.0	19.9	
	RANGE	0.0 -2150.0	0.0 -9400.0	0.0 -9400.0	
	N	78	80	158	
FASA - FAMILY/MARRIAGE RELATIONSHIPS*	MEAN (SD)	39.2 (214.8)	8.6 (30.9)	23.9 (153.8)	0.212
	MEDIAN	3.1	0.0	1.1	
	RANGE	0.0 -1820.0	0.0 - 266.7	0.0 -1820.0	
	N	79	79	158	

+ CMH ROW MEANS TEST
* LARGER SCORE IS BETTER ** SMALLER SCORE IS BETTER

SOURCE: BIOMETRICS FENG - QOLTAB (04APR96,12:52)

TABLE 17 - QUALITY OF LIFE SUMMARY
(BEST %CHANGE FROM BASELINE)

		MITOXANTRONE + PREDNISONE	PREDNISONE	TOTAL	P-VALUES+
FASA - MOOD*	MEAN (SD)	48.4 (77.4)	29.1 (60.2)	38.8 (69.8)	0.081
	MEDIAN	17.1	8.4	11.4	
	RANGE	0.0 - 423.5	0.0 - 352.6	0.0 - 423.5	
	N	80	80	160	
FASA - PASSING URINE*	MEAN (SD)	20.6 (39.9)	86.9 (225.8)	52.6 (161.9)	0.059
	MEDIAN	4.3	4.3	4.3	
	RANGE	0.0 - 208.3	0.0 -1071.4	0.0 -1071.4	
	N	44	41	85	
FASA - OVERALL WELL BEING*	MEAN (SD)	79.3 (266.1)	51.8 (128.9)	65.5 (208.1)	0.404
	MEDIAN	18.2	9.9	15.6	
	RANGE	0.0 -2150.0	0.0 -1012.5	0.0 -2150.0	
	N	79	81	160	
QOL - SYMPTOMS AND PHYSICAL ACTIVITY**	MEAN (SD)	-12.9 (12.4)	-10.2 (11.9)	-11.5 (12.2)	0.151
	MEDIAN	-10.0	-8.3	-10.0	
	RANGE	-46.2 - 0.0	-41.7 - 0.0	-46.2 - 0.0	
	N	80	81	161	
QOL - FUNCTIONAL ACTIVITY**	MEAN (SD)	-20.3 (15.6)	-17.4 (15.1)	-18.8 (15.4)	0.225
	MEDIAN	-20.0	-15.4	-17.4	
	RANGE	-60.0 - 0.0	-50.0 - 0.0	-60.0 - 0.0	
	N	80	81	161	
QOL - PSYCHOSOCIAL**	MEAN (SD)	-18.6 (18.1)	-17.0 (15.7)	-17.8 (16.9)	0.555
	MEDIAN	-12.5	-13.3	-13.3	
	RANGE	-64.0 0.0	-57.1 0.0	-64.0 0.0	
	N	80	81	161	

+ THE ROW MEANS TEST
* LARGER SCORE IS BETTER ** SMALLER SCORE IS BETTER

SOURCE: BTOMETRICS FENG QOLTAB (04APR96,12:52)

TABLE 17 - QUALITY OF LIFE SUMMARY
(BEST %CHANGE FROM BASELINE)

		MITOXANTRONE + PREDNISONE	PREDNISONE	TOTAL	P-VALUES+
QOL - OVERALL PHYSICAL*	MEAN (SD)	53.0 (65.2)	48.6 (66.4)	50.8 (65.7)	0.672
	MEDIAN	33.3	33.3	33.3	
	RANGE	0.0 - 400.0	0.0 - 300.0	0.0 - 400.0	
	N	80	81	161	
QOL - OVERALL QUALITY OF LIFE*	MEAN (SD)	64.8 (98.5)	51.1 (92.5)	57.9 (95.5)	0.364
	MEDIAN	33.3	25.0	25.0	
	RANGE	0.0 - 500.0	0.0 - 500.0	0.0 - 500.0	
	N	79	81	160	
QOL - PROSTATE MODULE**	MEAN (SD)	-23.7 (20.2)	-18.3 (17.2)	-21.0 (18.9)	0.072
	MEDIAN	-21.1	-15.4	-16.7	
	RANGE	-66.7 - 0.0	-56.8 - 0.0	-66.7 - 0.0	
	N	80	80	160	

+ CHI ROW MEANS TEST
* LARGER SCORE IS BETTER ** SMALLER SCORE IS BETTER

SOURCE: BIOMETRICS FENG QOLTAB (04APR96,12:52)

ATTACHMENT 3

Study

Sponsor's Tables: 3-7, 9, 12-32
Sponsor's Figures: 1-3

TABLE 3 - DEMOGRAPHIC SUMMARY

	TREATMENT ->	M + H	H ONLY	TOTAL
AGE (Yrs.) +	MEAN (SD)	71.0 (7.0)	70.0 (8.4)	70.5 (7.8)
	MEDIAN	71.8	72.0	71.8
	MIN - MAX	43 - 84	38 - 85	38 - 85
	N	119	123	242
SEX	MALE	119/119 (100%)	123/123 (100%)	242/242 (100%)
RACE	WHITE	105/119 (88%)	114/123 (93%)	219/242 (90%)
	HISPANIC	2/119 (2%)		2/242 (1%)
	BLACK	12/119 (10%)	9/123 (7%)	21/242 (9%)
WT LOSS IN LAST 6 MONTHS	NONE	71/111 (64%)	67/114 (59%)	138/225 (61%)
	< 5% OF BODY WT	22/111 (20%)	24/114 (21%)	46/225 (20%)
	5-10% OF BODY WT	5/111 (5%)	11/114 (10%)	16/225 (7%)
	> 10% OF BODY WT	13/111 (12%)	12/114 (11%)	25/225 (11%)

+ IN PARTIAL DATES, MISSING BIRTH DAY IS TREATED AS DAY 15

SOURCE: BIOMETRICS RAVI - DEMOGSUM (15APR96, 9:53)

TABLE 4 - BASELINE DATA SUMMARY - METASTASES, DISEASE AND STRATIFICATION FACTORS

	TREATMENT ->	M + H	H ONLY	TOTAL
METASTASES BONE	n/N (%)	105/116 (91%)	104/116 (90%)	209/232 (90%)
METASTASES LYMPH NODE	n/N (%)	34/116 (29%)	32/116 (28%)	66/232 (28%)
METASTASES LUNG	n/N (%)	10/116 (9%)	10/116 (9%)	20/232 (9%)
METASTASES LIVER	n/N (%)	8/116 (7%)	7/116 (6%)	15/232 (6%)
METASTASES BRAIN	n/N (%)		1/116 (1%)	1/232 (0%)
METASTASES SUBCUTANEOUS	n/N (%)	2/116 (2%)		2/232 (1%)
METASTASES PLEURA	n/N (%)	4/116 (3%)	4/116 (3%)	8/232 (3%)
METASTASES BONE MARROW	n/N (%)	4/116 (3%)	3/116 (3%)	7/232 (3%)
DISEASE MEASURABILITY ASSESSMENT	MEASURABLE	35/116 (30%)	34/116 (29%)	69/232 (30%)
	EVALUABLE	81/116 (70%)	80/116 (69%)	161/232 (69%)
PERFORMANCE STATUS (USED FOR STRATIFICATION)	0-1	102/119 (86%)	109/123 (89%)	211/242 (87%)
	2	17/119 (14%)	14/123 (11%)	31/242 (13%)
TUMOR MEASURABILITY (USED FOR STRATIFICATION)	NO	85/119 (71%)	83/123 (67%)	168/242 (69%)
	YES	34/119 (29%)	40/123 (33%)	74/242 (31%)
NUMBER OF ENDOCRINE MANIPULATIONS (USED FOR STRATIFICATION)	1	72/119 (61%)	71/123 (58%)	143/242 (59%)
	2	43/119 (36%)	46/123 (37%)	89/242 (37%)
	3	4/119 (3%)	5/123 (4%)	9/242 (4%)
	4		1/123 (1%)	1/242 (0%)

NOTE1: FOR METASTASES BIOPSY PROVEN AND CLINICAL WERE COMBINED.
NOTE2: MISSING ENDOCRINE MANIPULATIONS WERE SUBSTITUTED AS 1.

SOURCE: BIOMETRICS RAVI - BLTHRSUM (15APR96, 9:56)

STUDY [redacted] 9182

TABLE 5 - BASELINE DATA SUMMARY - LAB VALUES

	TREATMENT ->	M + H	H ONLY	TOTAL
PSA	MEAN (SD)	605.58 (1349.7)	471.84 (869.22)	538.71 (1134.7)
	MEDIAN	167.0	166.5	167.0
	MIN - MAX	3.00 - 9098.0	1.00 - 5180.0	1.00 - 9098.0
	N	116	116	232
ALKALINE PHOSPHATE	MEAN (SD)	252.63 (220.27)	263.90 (219.67)	258.24 (219.54)
	MEDIAN	164.5	163.0	164.0
	MIN - MAX	45.00 - 988.00	37.00 - 947.00	37.00 - 988.00
	N	110	109	219
CREATININE	MEAN (SD)	1.15 (0.31)	1.15 (0.30)	1.15 (0.30)
	MEDIAN	1.1	1.1	1.1
	MIN - MAX	0.60 - 2.00	0.60 - 2.00	0.60 - 2.00
	N	116	116	232

SOURCE: BIOMETRICS RAVI - BLLABSUM (15APR96, 9:59)

STUDY [redacted]9182

TABLE 6 - PRIOR HORMONAL THERAPY SUMMARY

TREATMENT ->	M + H	H ONLY	TOTAL
SURGICAL CASTRATION n/N (%)	67/116 (58%)	73/116 (63%)	140/232 (60%)
LHRH ANALOGUE n/N (%)	52/116 (45%)	47/116 (41%)	99/232 (43%)
ESTROGEN n/N (%)	9/116 (8%)	13/116 (11%)	22/232 (9%)
PROGESTRONE AGENT n/N (%)	8/116 (7%)	22/116 (19%)	30/232 (13%)
ANTI-ANDROGEN n/N (%)	77/116 (66%)	90/116 (78%)	167/232 (72%)

SOURCE: BIOMETRICS RAVI - PRTHRSUM (15APR96,10:02)

STUDY [redacted]_9182

TABLE 7 - BASELINE DATA SUMMARY - PERFORMANCE STATUS AND ANALGESIC USE

	TREATMENT ->	M + H	H ONLY	TOTAL
PERFORMANCE STATUS	0=FULLY ACTIVE	49/116 (42%)	41/115 (36%)	90/231 (39%)
	1=AMBULATORY, CAPABLE OF LIGHT WORK	50/116 (43%)	58/115 (50%)	108/231 (47%)
	2=IN BED <50% OF TIME	17/116 (15%)	16/115 (14%)	33/231 (14%)
PERFORMANCE STATUS=0 OR 1	n/N (%)	99/116 (85%)	99/115 (86%)	198/231 (86%)
ANALGESIC USAGE	0=NO ANALGESICS REQUIRED	42/115 (37%)	45/114 (39%)	87/229 (38%)
	1=NON-NARCOTIC ANALGESICS (OCCASIONALLY)	13/115 (11%)	13/114 (11%)	26/229 (11%)
	2=NON-NARCOTIC ANALGESICS (REGULARLY)	13/115 (11%)	11/114 (10%)	24/229 (10%)
	3=ORAL AND/OR PARENTERAL NARCOTIC ANALGESICS (OCCASIONALLY)	17/115 (15%)	20/114 (18%)	37/229 (16%)
	4=ORAL AND/OR PARENTERAL NARCOTIC ANALGESICS (REGULARLY)	30/115 (26%)	25/114 (22%)	55/229 (24%)

SOURCE: BIOMETRICS RAVI - BLOODSUM (15APR96,10:44)

STUDY [redacted]9182

TABLE 9 - PSA DATA SUMMARY

TREATMENT ->		M + H	H ONLY	TOTAL
PSA @ BASELINE (FOR ONLY PTS. WHO HAVE FU PSA)	MEAN (SD)	490.78 (1069.6)	392.01 (725.75)	441.64 (913.89)
	MEDIAN	150.0	127.0	141.0
	MIN - MAX	3.00 - 8000.0	1.00 - 4781.0	1.00 - 8000.0
	N	101	100	201
#PTS. WITH %DECREASE ≥50% FROM BASELINE PSA	NO	70/101 (69%)	83/100 (83%)	153/201 (76%)
	YES	31/101 (31%)	17/100 (17%)	48/201 (24%)
#PTS. WITH %DECREASE ≥75% FROM BASELINE PSA	NO	87/101 (86%)	93/100 (93%)	180/201 (90%)
	YES	14/101 (14%)	7/100 (7%)	21/201 (10%)

SOURCE: BIOMETRICS RAVI - PSASUM (02MAY96,15:54)

STUDY [redacted]9182

TABLE 12 - BASELINE QUALITY OF LIFE

QUALITY OF LIFE INSTRUMENT (SCALE)	TREATMENT ->	M + H	H ONLY
FUNCTIONAL LIVING INDEX - CANCER (22-154)	MEAN (SD)	66.23 (22.51)	68.86 (20.23)
	MEDIAN	64.8	67.5
	MIN - MAX	28.60 - 131.00	28.00 - 114.00
	N	94	104
SYMPTOM DISTRESS SCALE (13-65)	MEAN (SD)	24.68 (6.88)	26.03 (7.57)
	MEDIAN	24.0	25.0
	MIN - MAX	13.00 - 43.00	14.00 - 47.00
	N	92	100
SEXUAL AND UROLOGIC FUNCTIONING (7-28)	MEAN (SD)	16.92 (3.73)	16.23 (4.12)
	MEDIAN	17.0	17.0
	MIN - MAX	7.00 - 25.00	7.00 - 26.00
	N	93	99
FUNCTIONAL LIMITATIONS SCALE (8-40)	MEAN (SD)	19.18 (9.18)	20.38 (8.58)
	MEDIAN	18.0	19.0
	MIN - MAX	8.00 - 40.00	8.00 - 39.00
	N	90	100
IMPACT OF PAIN ON DAILY ACTIVITIES (7-77)	MEAN (SD)	29.10 (17.91)	29.96 (17.36)
	MEDIAN	28.0	28.0
	MIN - MAX	7.00 - 68.00	7.00 - 70.00
	N	92	97

NOTE: THE LOWEST POSSIBLE SCORE FOR EACH SCALE IS THE OPTIMAL SCORE FOR THAT SCALE

SOURCE: BIOMETRICS SHELDON - BLOSSOM (16APR96,10:23)

TABLE 13 - FUNCTIONAL LIVING INDEX, CANCER - HOW UNCOMFORTABLE DO YOU FEEL TODAY
ALL SUBJECTS

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) DISCOMFORT	MEAN (SD)	3.08 (1.93)	3.04 (1.61)
	MEDIAN	3.0	2.8
	MIN - MAX	1.00 - 7.00	1.00 - 6.00
	N	43	34
DISCOMFORT AT DAY 42 ♦	MEAN (SD)	2.34 (1.69)	2.59 (1.78)
	MEDIAN	1.5	2.0
	MIN - MAX	1.00 - 7.00	1.00 - 6.00
	N	43	34
RAW CHANGE, DAY 42 - B/L, DISCOMFORT	MEAN (SD)	-0.74 (2.01)	-0.46 (1.51)
	MEDIAN	0.0	0.0
	MIN - MAX	-6.00 - 4.50	-4.00 - 3.50
	N	43	34
PCT CHANGE, DAY 42 - B/L, DISCOMFORT	MEAN (SD)	-4.57 (73.37)	-7.34 (48.41)
	MEDIAN	0.0	0.0
	MIN - MAX	-85.71 - 300.00	-80.00 - 140.00
	N	43	34

♦:NOTE1 - RESPONSES GIVEN BETWEEN THE 35th AND 49th DAYS AFTER STUDY START ARE INCLUDE IN THE DAY 42 VALUE.
NOTE2 - THE QUESTION HAS POSSIBLE ANSWERS BETWEEN 1 AND 7, 1 BEING OPTIMAL.

SOURCE: BIOMETRICS SHELDON - Q11142_1 (15APR96,14:34)

TABLE 14 - FUNCTIONAL LIVING INDEX, CANCER - DISCOMFORT INTERFERING WITH DAILY ACTIVITIES (D/I)
ALL SUBJECTS

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) D/I	MEAN (SD)	3.46 (2.10)	3.45 (2.03)
	MEDIAN	3.0	3.0
	MIN - MAX	1.00 - 7.00	1.00 - 7.00
	N	45	38
D/I AT DAY 42 ♦	MEAN (SD)	2.87 (2.14)	3.12 (1.88)
	MEDIAN	2.0	2.0
	MIN - MAX	1.00 - 7.00	1.00 - 7.00
	N	45	38
RAW CHANGE, DAY 42 - B/L, D/I	MEAN (SD)	-0.59 (1.52)	-0.33 (1.61)
	MEDIAN	0.0	0.0
	MIN - MAX	-5.00 - 2.00	-4.00 - 2.50
	N	45	38
PCT CHANGE, DAY 42 - B/L, D/I	MEAN (SD)	-11.07 (48.07)	4.50 (54.85)
	MEDIAN	0.0	0.0
	MIN - MAX	-75.00 - 200.00	-71.43 - 166.67
	N	45	38

♦:NOTE1 - RESPONSES GIVEN BETWEEN THE 35th AND 49th DAYS AFTER STUDY START ARE INCLUDE IN THE DAY 42 VALUE.
NOTE2 - THE QUESTION HAS POSSIBLE ANSWERS BETWEEN 1 AND 7, 1 BEING OPTIMAL.

SOURCE: BIOMETRICS SHELDON - Q11342_1 (15APR96,15:01)

STUDY [redacted]9182

TABLE 15 - SYMPTOM DISTRESS SCALE - FREQUENCY OF PAIN
ALL SUBJECTS

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) PAIN FREQUENCY	MEAN (SD)	2.79 (1.51)	2.60 (1.19)
	MEDIAN	3.0	2.0
	MIN - MAX	1.00 - 5.00	1.00 - 5.00
	N	42	35
PAIN FREQUENCY AT DAY 42 ♦	MEAN (SD)	2.24 (1.43)	2.31 (1.28)
	MEDIAN	2.0	2.0
	MIN - MAX	1.00 - 5.00	1.00 - 5.00
	N	42	35
RAW CHANGE, DAY 42 - B/L, PAIN FREQUENCY	MEAN (SD)	-0.55 (1.13)	-0.29 (0.99)
	MEDIAN	0.0	0.0
	MIN - MAX	-4.00 - 1.00	-2.00 - 2.00
	N	42	35
PCT CHANGE, DAY 42 - B/L, PAIN FREQUENCY	MEAN (SD)	-13.37 (32.63)	-7.00 (38.98)
	MEDIAN	0.0	0.0
	MIN - MAX	-80.00 - 100.00	-66.67 - 100.00
	N	42	35

♦:NOTE1 - RESPONSES GIVEN BETWEEN THE 35th AND 49th DAYS AFTER STUDY START ARE INCLUDE IN THE DAY 42 VALUE.
NOTE2 - THE QUESTION HAS POSSIBLE ANSWERS BETWEEN 1 AND 7, 1 BEING OPTIMAL.

SOURCE: BIOMETRICS SHELDON - 02P142_1 (15APR96,15:13)

STUDY [redacted]9182

TABLE 16 - SYMPTOM DISTRESS SCALE - INTENSITY OF PAIN
ALL SUBJECTS

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) PAIN INTENSITY	MEAN (SD)	2.08 (1.10)	1.94 (0.89)
	MEDIAN	2.0	2.0
	MIN - MAX	1.00 - 5.00	1.00 - 4.00
	N	38	34
PAIN INTENSITY AT DAY 42 ♦	MEAN (SD)	1.74 (0.89)	1.79 (0.84)
	MEDIAN	1.5	2.0
	MIN - MAX	1.00 - 4.00	1.00 - 4.00
	N	38	34
RAW CHANGE, DAY 42 - B/L, PAIN INTENSITY	MEAN (SD)	-0.34 (0.88)	-0.15 (0.66)
	MEDIAN	0.0	0.0
	MIN - MAX	-3.00 - 1.00	-2.00 - 1.00
	N	38	34
PCT CHANGE, DAY 42 - B/L, PAIN INTENSITY	MEAN (SD)	-8.60 (30.43)	-1.47 (34.17)
	MEDIAN	0.0	0.0
	MIN - MAX	-75.00 - 100.00	-66.67 - 100.00
	N	38	34

♦:NOTE1 - RESPONSES GIVEN BETWEEN THE 35th AND 49th DAYS AFTER STUDY START ARE INCLUDE IN THE DAY 42 VALUE.
NOTE2 - THE QUESTION HAS POSSIBLE ANSWERS BETWEEN 1 AND 5, 1 BEING OPTIMAL.

SOURCE: BIOMETRICS SHELDON - Q2P242_1 (15APR96,15:28)

STUDY [redacted]0182

TABLE 17 - IMPACT OF PAIN ON DAILY ACTIVIVIES (IPDA)
ALL SUBJECTS

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) IPDA SUM	MEAN (SD)	24.58 (18.12)	27.84 (18.24)
	MEDIAN	19.5	24.0
	MIN - MAX	7.00 - 64.00	7.00 - 63.00
	N	40	33
IPDA SUM AT DAY 42♦	MEAN (SD)	20.93 (16.46)	26.61 (19.18)
	MEDIAN	14.5	18.0
	MIN - MAX	7.00 - 62.00	7.00 - 67.00
	N	40	33
RAW CHANGE, DAY 42 - B/L, IPDA SUM	MEAN (SD)	-3.65 (12.99)	-1.24 (14.69)
	MEDIAN	-2.0	0.0
	MIN - MAX	-52.00 - 22.00	-47.00 - 28.00
	N	40	33
PCT CHANGE, DAY 42 - B/L, IPDA SUM	MEAN (SD)	1.82 (78.22)	3.96 (45.57)
	MEDIAN	-7.8	0.0
	MIN - MAX	-85.25 - 314.29	-78.33 - 112.50
	N	40	33

♦:NOTE1 - RESPONSES GIVEN BETWEEN THE 35th AND 49th DAYS AFTER THE START OF DOSING ARE INCLUDE IN THE DAY 42 VALUE.
NOTE2 THE QUESTIONAIRE CONSISTED OF 7 QUESTIONS, EACH WITH POSSIBLE ANSWERS BETWEEN 1 AND 11, 1 BEING OPTIMAL

SOURCE: BIOMETRICS SHELDON - Q55M42_1 (15APR96,15:38)

TABLE 18 - FUNCTIONAL LIVING INDEX, CANCER - HOW UNCOMFORTABLE DO YOU FEEL TODAY
SUBJECTS ON ANALGESICS AT BASELINE

	TREATMENT ->	M + H	H ONLY
BASELINE DISCOMFORT	MEAN (SD)	3.42 (1.93)	3.66 (1.41)
	MEDIAN	3.5	4.0
	MIN - MAX	1.00 - 7.00	1.00 - 6.00
	N	25	19
DISCOMFORT AT DAY 42 +	MEAN (SD)	2.98 (1.89)	2.82 (1.68)
	MEDIAN	3.0	2.0
	MIN - MAX	1.00 - 7.00	1.00 - 6.00
	N	25	19
RAW CHANGE, DAY 42 - B/L, DISCOMFORT	MEAN (SD)	-0.44 (2.12)	-0.84 (1.40)
	MEDIAN	0.0	-1.0
	MIN - MAX	-4.00 - 4.50	-3.00 - 1.00
	N	25	19
PCT CHANGE, DAY 42 - B/L, DISCOMFORT	MEAN (SD)	7.43 (86.17)	-17.96 (45.46)
	MEDIAN	0.0	-25.0
	MIN - MAX	-75.00 - 300.00	-75.00 - 100.00
	N	25	19

+:NOTE1 - RESPONSES GIVEN BETWEEN THE 35th AND 49th DAYS AFTER STUDY START ARE INCLUDE IN THE DAY 42 VALUE.
NOTE2 - THE QUESTION HAS POSSIBLE ANSWERS BETWEEN 1 AND 7, 1 BEING OPTIMAL.

SOURCE: BIOMETRICS SHELDON - Q11142A1 (15APR96,15:53)

STUDY [redacted]9182

TABLE 19 - FUNCTIONAL LIVING INDEX, CANCER - DISCOMFORT INTERFERING WITH DAILY ACTIVITIES (D/I)
SUBJECTS ON ANALGESICS AT BASELINE

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) D/I	MEAN (SD)	4.37 (2.10)	4.22 (1.84)
	MEDIAN	5.0	4.0
	MIN - MAX	1.00 - 7.00	1.50 - 7.00
	N	26	23
D/I AT DAY 42 ♦	MEAN (SD)	3.44 (2.26)	3.43 (1.88)
	MEDIAN	3.0	3.0
	MIN - MAX	1.00 - 7.00	1.00 - 7.00
	N	26	23
RAW CHANGE, DAY 42 - B/L, D/I	MEAN (SD)	-0.92 (1.71)	-0.78 (1.51)
	MEDIAN	-0.5	-0.5
	MIN - MAX	-5.00 - 2.00	-4.00 - 2.00
	N	26	23
PCT CHANGE, DAY 42 - B/L, D/I	MEAN (SD)	-19.93 (31.84)	-13.82 (42.66)
	MEDIAN	-16.1	-7.7
	MIN - MAX	-75.00 - 40.00	-71.43 - 100.00
	N	26	23

♦:NOTE1 - RESPONSES GIVEN BETWEEN THE 35th AND 49th DAYS AFTER STUDY START ARE INCLUDE IN THE DAY 42 VALUE.
NOTE2 - THE QUESTION HAS POSSIBLE ANSWERS BETWEEN 1 AND 7, 1 BEING OPTIMAL.

SOURCE: BIOMETRICS SHELDON - Q11342A1 (15APR96,16:02)

STUDY [redacted]_9182

TABLE 20 - SYMPTOM DISTRESS SCALE - FREQUENCY OF PAIN
SUBJECTS ON ANALGESICS AT BASELINE

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) PAIN FREQUENCY	MEAN (SD)	3.33 (1.46)	2.90 (1.17)
	MEDIAN	3.5	2.5
	MIN - MAX	1.00 - 5.00	1.00 - 5.00
	N	24	20
PAIN FREQUENCY AT DAY 42 ♦	MEAN (SD)	2.54 (1.56)	2.45 (1.23)
	MEDIAN	2.0	2.0
	MIN - MAX	1.00 - 5.00	1.00 - 5.00
	N	24	20
RAW CHANGE, DAY 42 - B/L, PAIN FREQUENCY	MEAN (SD)	-0.79 (1.35)	-0.45 (1.10)
	MEDIAN	0.0	0.0
	MIN - MAX	-4.00 - 1.00	-2.00 - 2.00
	N	24	20
PCT CHANGE, DAY 42 - B/L, PAIN FREQUENCY	MEAN (SD)	-19.79 (30.86)	-10.58 (42.17)
	MEDIAN	0.0	0.0
	MIN - MAX	-80.00 - 25.00	-66.67 - 100.00
	N	24	20

♦:NOTE1 - RESPONSES GIVEN BETWEEN THE 35th AND 49th DAYS AFTER STUDY START ARE INCLUDE IN THE DAY 42 VALUE.
NOTE2 - THE QUESTION HAS POSSIBLE ANSWERS BETWEEN 1 AND 7, 1 BEING OPTIMAL.

SOURCE: BIOMETRICS SHELDON - Q2P142A1 (15APR96,16:15)

STUDY [redacted]9182

TABLE 21 - SYMPTOM DISTRESS SCALE - INTENSITY OF PAIN
SUBJECTS ON ANALGESICS AT BASELINE

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) PAIN INTENSITY	MEAN (SD)	2.45 (1.14)	2.20 (0.95)
	MEDIAN	3.0	2.0
	MIN - MAX	1.00 - 5.00	1.00 - 4.00
	N	22	20
PAIN INTENSITY AT DAY 42 ♦	MEAN (SD)	1.91 (0.92)	2.05 (0.89)
	MEDIAN	2.0	2.0
	MIN - MAX	1.00 - 4.00	1.00 - 4.00
	N	22	20
RAW CHANGE, DAY 42 - B/L, PAIN INTENSITY	MEAN (SD)	-0.55 (1.10)	-0.15 (0.81)
	MEDIAN	0.0	0.0
	MIN - MAX	-3.00 - 1.00	-2.00 - 1.00
	N	22	20
PCT CHANGE, DAY 42 - B/L, PAIN INTENSITY	MEAN (SD)	-12.58 (38.48)	2.50 (41.98)
	MEDIAN	0.0	0.0
	MIN - MAX	-75.00 - 100.00	-66.67 - 100.00
	N	22	20

♦:NOTE1 - RESPONSES GIVEN BETWEEN THE 35th AND 49th DAYS AFTER STUDY START ARE INCLUDE IN THE DAY 42 VALUE.
NOTE2 - THE QUESTION HAS POSSIBLE ANSWERS BETWEEN 1 AND 5, 1 BEING OPTIMAL.

SOURCE: BIOMETRICS SHELDON - Q2P242A1 (15APR96,16:19)

STUDY [redacted]9182

TABLE 22 - IMPACT OF PAIN ON DAILY ACTIVITIES (IPDA)
SUBJECTS ON ANALGESICS AT BASELINE

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) IPDA SUM	MEAN (SD)	32.13 (19.55)	35.53 (16.43)
	MEDIAN	33.0	37.0
	MIN - MAX	7.00 - 64.00	7.00 - 63.00
	N	23	19
IPDA SUM AT DAY 42♦	MEAN (SD)	27.09 (18.55)	32.68 (18.63)
	MEDIAN	27.0	36.0
	MIN - MAX	7.00 - 62.00	7.00 - 63.00
	N	23	19
RAW CHANGE, DAY 42 - B/L,IPDA SUM	MEAN (SD)	-5.04 (15.93)	-2.84 (13.68)
	MEDIAN	-2.0	1.0
	MIN - MAX	-52.00 - 22.00	-24.00 - 28.00
	N	23	19
PCT CHANGE, DAY 42 - B/L,IPDA SUM	MEAN (SD)	-0.21 (77.00)	-4.89 (43.74)
	MEDIAN	-5.3	2.1
	MIN - MAX	-85.25 - 314.29	-75.00 - 80.00
	N	23	19

♦:NOTE1 - RESPONSES GIVEN BETWEEN THE 35th AND 49th DAYS AFTER THE START OF DOSING ARE INCLUDE IN THE DAY 42 VALUE.
NOTE2 THE QUESTIONAIRE CONSISTED OF 7 QUESTIONS, EACH WITH POSSIBLE ANSWERS BETWEEN 1 AND 11, 1 BEING OPTIMAL

SOURCE: BIOMETRICS SHELDON - Q5SM42A1 (16APR96, 8:32)

STUDY [redacted]9182

TABLE 23 - FUNCTIONAL LIVING INDEX, CANCER - HOW UNCOMFORTABLE DO YOU FEEL TODAY
BASELINE, BEST POST BASELINE ,AND (RAW AND PERCENTAGE) CHANGES FROM BASELINE TO BEST POST BASELINE VALUES (BY SUBJECT)
ALL SUBJECTS

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) DISCOMFORT RESPONSE	MEAN (SD)	3.21 (1.86)	3.26 (1.80)
	MEDIAN	3.0	3.0
	MIN - MAX	1.00 - 7.00	1.00 - 7.00
	N	68	76
BEST POST B/L DISCOMFORT RESPONSE (BEST)	MEAN (SD)	2.37 (1.72)	2.54 (1.61)
	MEDIAN	2.0	2.0
	MIN - MAX	1.00 - 7.00	1.00 - 6.00
	N	68	76
RAW CHANGE, BEST - B/L, DISCOMFORT	MEAN (SD)	-0.84 (2.06)	-0.72 (1.82)
	MEDIAN	-0.8	-0.5
	MIN - MAX	-6.00 - 4.50	-6.00 - 2.50
	N	68	76
PCT CHANGE, BEST - B/L, DISCOMFORT	MEAN (SD)	-7.94 (74.79)	-9.05 (53.47)
	MEDIAN	-33.3	-18.3
	MIN - MAX	-85.71 - 300.00	-85.71 - 200.00
	N	68	76

NOTE: THE QUESTION HAD POSSIBLE ANSWERS BETWEEN 1 AND 7, 1 BEING OPTIMAL.

SOURCE: BIOMETRICS SHELDON - Q111MIN (16APR96, 8:39)

STUDY [redacted]9182

TABLE 24 - FUNCTIONAL LIVING INDEX, CANCER - DISCOMFORT INTERFERING WITH DAILY ACTIVITY (D/I)
BASELINE, BEST POST BASELINE ,AND (RAW AND PERCENTAGE) CHANGES FROM BASELINE TO BEST POST BASELINE RESPONSE (BY PT)
ALL SUBJECTS

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) D/I RESPONSE	MEAN (SD)	3.42 (2.02)	3.61 (1.95)
	MEDIAN	3.0	3.3
	MIN - MAX	1.00 - 7.00	1.00 - 7.00
	N	71	78
BEST POST BASELINE D/I RESPONSE(BEST)	MEAN (SD)	2.57 (1.87)	2.72 (1.59)
	MEDIAN	2.0	2.0
	MIN - MAX	1.00 - 7.00	1.00 - 7.00
	N	71	78
RAW CHANGE, BEST - B/L, D/I RESPONSE	MEAN (SD)	-0.85 (1.54)	-0.89 (1.67)
	MEDIAN	-0.5	-0.5
	MIN - MAX	-6.00 - 2.00	-6.00 - 2.00
	N	71	78
PCT CHANGE, BEST - B/L, D/I RESPONSE	MEAN (SD)	-17.52 (44.61)	-14.22 (41.71)
	MEDIAN	-23.1	-12.7
	MIN - MAX	-85.71 - 200.00	-85.71 - 100.00
	N	71	78

NOTE: THE QUESTION HAD POSSIBLE ANSWERS BETWEEN 1 AND 7, 1 BEING OPTIMAL

SOURCE: BIOMETRICS SHELDON - Q113MIN (16APR96, 8:53)

TABLE 25 - SYMPTOM DISTRESS SCALE - PAIN QUESTION 1 - PAIN FREQUENCY
BASELINE, BEST POST BASELINE ,AND (RAW AND PERCENTAGE) CHANGES FROM BASELINE TO BEST POST BASELINE RESPONSE (BY PT)
ALL SUBJECTS

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) PAIN FREQUENCY RESPONSE	MEAN (SD)	2.73 (1.39)	2.61 (1.25)
	MEDIAN	3.0	2.0
	MIN - MAX	1.00 - 5.00	1.00 - 5.00
	N	67	75
BEST POST-BASELINE PAIN FREQUENCY RESPONSE(BEST)	MEAN (SD)	2.09 (1.28)	2.13 (1.22)
	MEDIAN	2.0	2.0
	MIN - MAX	1.00 - 5.00	1.00 - 5.00
	N	67	75
RAW CHANGE, BEST - B/L, PAIN FREQUENCY	MEAN (SD)	-0.64 (1.05)	-0.48 (1.13)
	MEDIAN	0.0	0.0
	MIN - MAX	-4.00 - 1.00	-4.00 - 2.00
	N	67	75
PCT CHANGE, BEST - B/L, PAIN FREQUENCY	MEAN (SD)	-17.76 (31.06)	-12.76 (36.64)
	MEDIAN	0.0	0.0
	MIN - MAX	-80.00 - 100.00	-80.00 - 100.00
	N	67	75

NOTE: THE QUESTION HAD POSSIBLE ANSWERS BETWEEN 1 AND 5, 1 BEING OPTIMAL

SOURCE: BIOMETRICS SHELDON - Q2P1MIN (16APR96, 9:04)

STUDY [redacted]_9182

TABLE 26 - SYMPTOM DISTRESS SCALE - PAIN INTENSITY
BASELINE, BEST POST BASELINE ,AND (RAW AND PERCENTAGE) CHANGES FROM BASELINE TO BEST POST BASELINE RESPONSE (BY PT)
ALL SUBJECTS

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) PAIN INTENSITY RESPONSE	MEAN (SD)	2.08 (1.00)	2.04 (0.90)
	MEDIAN	2.0	2.0
	MIN - MAX	1.00 - 5.00	1.00 - 4.00
	N	63	71
BEST POST-BASELINE PAIN INTENSITY RESPONSE(BEST)	MEAN (SD)	1.70 (0.82)	1.87 (0.94)
	MEDIAN	2.0	2.0
	MIN - MAX	1.00 - 4.00	1.00 - 4.00
	N	63	71
RAW CHANGE, BEST - B/L, PAIN INTENSITY	MEAN (SD)	-0.38 (0.83)	-0.17 (0.91)
	MEDIAN	0.0	0.0
	MIN - MAX	-3.00 - 1.00	-2.00 - 2.00
	N	63	71
PCT CHANGE, BEST - B/L, PAIN INTENSITY	MEAN (SD)	-11.27 (29.46)	2.11 (55.42)
	MEDIAN	0.0	0.0
	MIN - MAX	-75.00 - 100.00	-66.67 - 200.00
	N	63	71

NOTE: THE QUESTION HAD POSSIBLE ANSWERS BETWEEN 1 AND 5, 1 BEING OPTIMAL

SOURCE: BIOMETRICS SHELDON - Q2P2MIN (16APR96, 9:12)

STUDY [redacted]9182

TABLE 27 - IMPACT OF PAIN ON DAILY ACTIVITIES (IPDA)
BASELINE, BEST POST BASELINE ,AND (RAW AND PERCENTAGE) CHANGES FROM BASELINE TO BEST POST BASELINE VALUES (BY SUBJECT)
ALL SUBJECTS

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) IPDA SUM	MEAN (SD)	26.35 (17.36)	28.87 (17.77)
	MEDIAN	21.0	27.0
	MIN - MAX	7.00 - 68.00	7.00 - 70.00
	N	68	70
BEST POST BASELINE IPDA SUM (BEST)	MEAN (SD)	21.82 (16.10)	24.76 (17.57)
	MEDIAN	17.5	18.0
	MIN - MAX	7.00 - 62.00	7.00 - 66.00
	N	68	70
RAW CHANGE, BEST - B/L,IPDA SUM	MEAN (SD)	-4.53 (13.86)	-4.10 (14.67)
	MEDIAN	-2.0	-1.0
	MIN - MAX	-52.00 - 27.00	-59.00 - 33.17
	N	68	70
PCT CHANGE, BEST - B/L,IPDA SUM	MEAN (SD)	-3.29 (67.39)	-2.49 (65.86)
	MEDIAN	-10.6	-9.8
	MIN - MAX	-85.25 - 314.29	-89.39 - 331.67
	N	68	70

NOTE1: THE QUESTIONAIRE CONSISTED OF 7 QUESTIONS, EACH WITH POSSIBLE ANSWERS BETWEEN 1 AND 11, 1 BEING OPTIMAL.
NOTE2: BECAUSE NOT ALL QUESTIONS WERE ANSWERED BY ALL PTS AT ALL VISITS,QOL RESPONSE SUMS WERE NORMALIZED BY MULTIPLYING THE MEAN PER-QUESTION SCORE OF THE QUESTIONS ANSWERED PER PT PER VISIT, BY 7 (THE TOTAL NUMBER OF QUESTIONS).

SOURCE: BIOMETRICS SHELDON - [illegible]MIN (16APR96,11:29)

STUDY [redacted]9182

TABLE 28 - FUNCTIONAL LIVING INDEX, CANCER - HOW UNCOMFORTABLE DO YOU FEEL TODAY
BASELINE, BEST POST BASELINE ,AND (RAW AND PERCENTAGE) CHANGES FROM BASELINE TO BEST POST BASELINE RESPONSE (BY SUBJECT)
SUBJECTS ON ANALGESIC AT BASELINE

	TREATMENT ->	M + N	N ONLY
BASELINE (B/L) DISCOMFORT RESPONSE	MEAN (SD)	3.63 (1.85)	3.71 (1.81)
	MEDIAN	4.0	4.0
	MIN - MAX	1.00 - 7.00	1.00 - 7.00
	N	39	40
BEST POST B/L DISCOMFORT RESPONSE (BEST)	MEAN (SD)	2.73 (1.86)	2.73 (1.54)
	MEDIAN	2.0	2.5
	MIN - MAX	1.00 - 7.00	1.00 - 6.00
	N	39	40
RAW CHANGE, BEST - B/L, DISCOMFORT	MEAN (SD)	-0.90 (2.15)	-0.99 (1.72)
	MEDIAN	-1.0	-1.0
	MIN - MAX	-4.50 - 4.50	-6.00 - 2.00
	N	39	40
PCT CHANGE, BEST - B/L, DISCOMFORT	MEAN (SD)	-8.13 (79.02)	-14.16 (57.58)
	MEDIAN	-33.3	-25.0
	MIN - MAX	-81.82 - 300.00	-85.71 - 200.00
	N	39	40

NOTE: THE QUESTION HAD POSSIBLE ANSWERS BETWEEN 1 AND 7, 1 BEING OPTIMAL

SOURCE: BIOMETRICS SHELDON - Q111MINA (16APR96, 9:26)

STUDY [redacted]9182

TABLE 29 - FUNCTIONAL LIVING INDEX, CANCER - DISCOMFORT INTERFERING WITH DAILY ACTIVITY (D/I)
BASELINE, BEST POST BASELINE ,AND (RAW AND PERCENTAGE) CHANGES FROM BASELINE TO BEST POST BASELINE RESPONSE (BY SUBJECT)
SUBJECTS ON ANALGESICS AT BASELINE

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) D/I RESPONSE	MEAN (SD)	4.30 (1.92)	4.18 (1.83)
	MEDIAN	5.0	4.0
	MIN - MAX	1.00 - 7.00	1.50 - 7.00
	N	41	44
BEST POST BASELINE D/I RESPONSE (BEST)	MEAN (SD)	3.17 (1.96)	3.15 (1.58)
	MEDIAN	3.0	3.0
	MIN - MAX	1.00 - 7.00	1.00 - 7.00
	N	41	44
RAW CHANGE, BEST - B/L, D/I RESPONSE	MEAN (SD)	-1.13 (1.55)	-1.03 (1.67)
	MEDIAN	-1.0	-1.0
	MIN - MAX	-5.00 - 1.00	-5.50 - 2.00
	N	41	44
PCT CHANGE, BEST - B/L, D/I RESPONSE	MEAN (SD)	-24.50 (29.82)	-18.37 (38.35)
	MEDIAN	-25.0	-23.6
	MIN - MAX	-81.82 - 33.33	-84.62 - 100.00
	N	41	44

NOTE: THE QUESTION HAD POSSIBLE ANSWERS BETWEEN 1 AND 7, 1 BEING OPTIMAL

SOURCE: BIOMETRICS SHELDON - Q113MINA (16APR96, 9:39)

STUDY [redacted]9182

TABLE 30 - SYMPTOM DISTRESS SCALE: - PAIN FREQUENCY
BASELINE, BEST POST BASELINE ,AND (RAW AND PERCENTAGE) CHANGES FROM BASELINE TO BEST POST BASELINE RESPONSE (BY PT)
SUBJECTS ON ANALGESIC AT BASELINE

	TREATMENT ->	M + N	N ONLY
BASELINE (B/L) PAIN FREQUENCY RESPONSE	MEAN (SD)	3.29 (1.31)	2.95 (1.23)
	MEDIAN	3.0	3.0
	MIN - MAX	1.00 - 5.00	1.00 - 5.00
	N	38	39
BEST POST-BASELINE PAIN FREQUENCY RESPONSE(BEST)	MEAN (SD)	2.42 (1.43)	2.49 (1.27)
	MEDIAN	2.0	2.0
	MIN - MAX	1.00 - 5.00	1.00 - 5.00
	N	38	39
RAW CHANGE, BEST - B/L, PAIN FREQUENCY	MEAN (SD)	-0.87 (1.23)	-0.46 (1.25)
	MEDIAN	-1.0	0.0
	MIN - MAX	-4.00 - 1.00	-4.00 - 2.00
	N	38	39
PCT CHANGE, BEST - B/L, PAIN FREQUENCY	MEAN (SD)	-23.55 (30.60)	-9.66 (40.36)
	MEDIAN	-20.0	0.0
	MIN - MAX	-80.00 - 33.33	-80.00 - 100.00
	N	38	39

NOTE: THE QUESTION HAD POSSIBLE ANSWERS BETWEEN 1 AND 5, 1 BEING OPTIMAL

SOURCE: BIOMETRICS SHELDON - Q2P1MINA (16APR96, 9:46)

TABLE 31 - SYMPTOM DISTRESS SCALE - PAIN INTENSITY
BASELINE, BEST POST BASELINE ,AND (RAW AND PERCENTAGE) CHANGES FROM BASELINE TO BEST POST BASELINE RESPONSE (BY PT)
SUBJECTS ON ANALGESIC AT BASELINE

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) PAIN INTENSITY RESPONSE	MEAN (SD)	2.43 (1.04)	2.32 (0.90)
	MEDIAN	3.0	2.5
	MIN - MAX	1.00 - 5.00	1.00 - 4.00
	N	37	38
BEST POST-BASELINE PAIN INTENSITY RESPONSE(BEST)	MEAN (SD)	1.89 (0.88)	2.21 (0.93)
	MEDIAN	2.0	2.0
	MIN - MAX	1.00 - 4.00	1.00 - 4.00
	N	37	38
RAW CHANGE, BEST - B/L, PAIN INTENSITY	MEAN (SD)	-0.54 (1.02)	-0.11 (0.98)
	MEDIAN	0.0	0.0
	MIN - MAX	-3.00 - 1.00	-2.00 - 2.00
	N	37	38
PCT CHANGE, BEST - B/L, PAIN INTENSITY	MEAN (SD)	14.23 (35.62)	7.89 (59.75)
	MEDIAN	0.0	0.0
	MIN - MAX	-75.00 - 100.00	-66.67 - 200.00
	N	37	38

NOTE: THE QUESTION HAD POSSIBLE ANSWERS BETWEEN 1 AND 5, 1 BEING OPTIMAL

SOURCE: BIOMETRICS SHELDON - Q2P2MINA (16APR96, 9:57)

STUDY [redacted]_9182

TABLE 32 - IMPACT OF PAIN ON DAILY ACTIVITIES (IPDA)
BASELINE,BEST POST BASELINE ,AND (RAW AND PERCENTAGE) CHANGE FROM BASELINE TO BEST POST BASELINE RESPONSE (PER SUBJECT)
SUBJECTS TAKING ANALGESICS

	TREATMENT ->	M + H	H ONLY
BASELINE (B/L) IPDA SUM	MEAN (SD)	33.10 (18.02)	34.89 (17.87)
	MEDIAN	33.0	36.0
	MIN - MAX	7.00 - 68.00	7.00 - 70.00
	N	40	38
BEST POST BASELINE IPDA SUM (BEST)	MEAN (SD)	27.70 (18.05)	30.80 (18.60)
	MEDIAN	27.5	34.0
	MIN - MAX	7.00 - 62.00	7.00 - 63.00
	N	40	38
RAW CHANGE, BEST - B/L,IPDA SUM	MEAN (SD)	-5.40 (16.01)	-4.09 (16.17)
	MEDIAN	-2.0	-2.0
	MIN - MAX	-52.00 - 27.00	-59.00 - 33.17
	N	40	38
PCT CHANGE, BEST - B/L,IPDA SUM	MEAN (SD)	-5.55 (65.62)	-1.82 (68.77)
	MEDIAN	-7.8	-7.0
	MIN - MAX	-85.25 - 314.29	-89.39 - 331.67
	N	40	38

NOTE: THE QUESTIONAIRE CONSISTED OF 7 QUESTIONS, EACH WITH POSSIBLE ANSWERS BETWEEN 1 AND 11, 1 BEING OPTIMAL.

SOURCE: BIOMETRICS SHELDON - Q5SMMINA (16APR96,10:07)

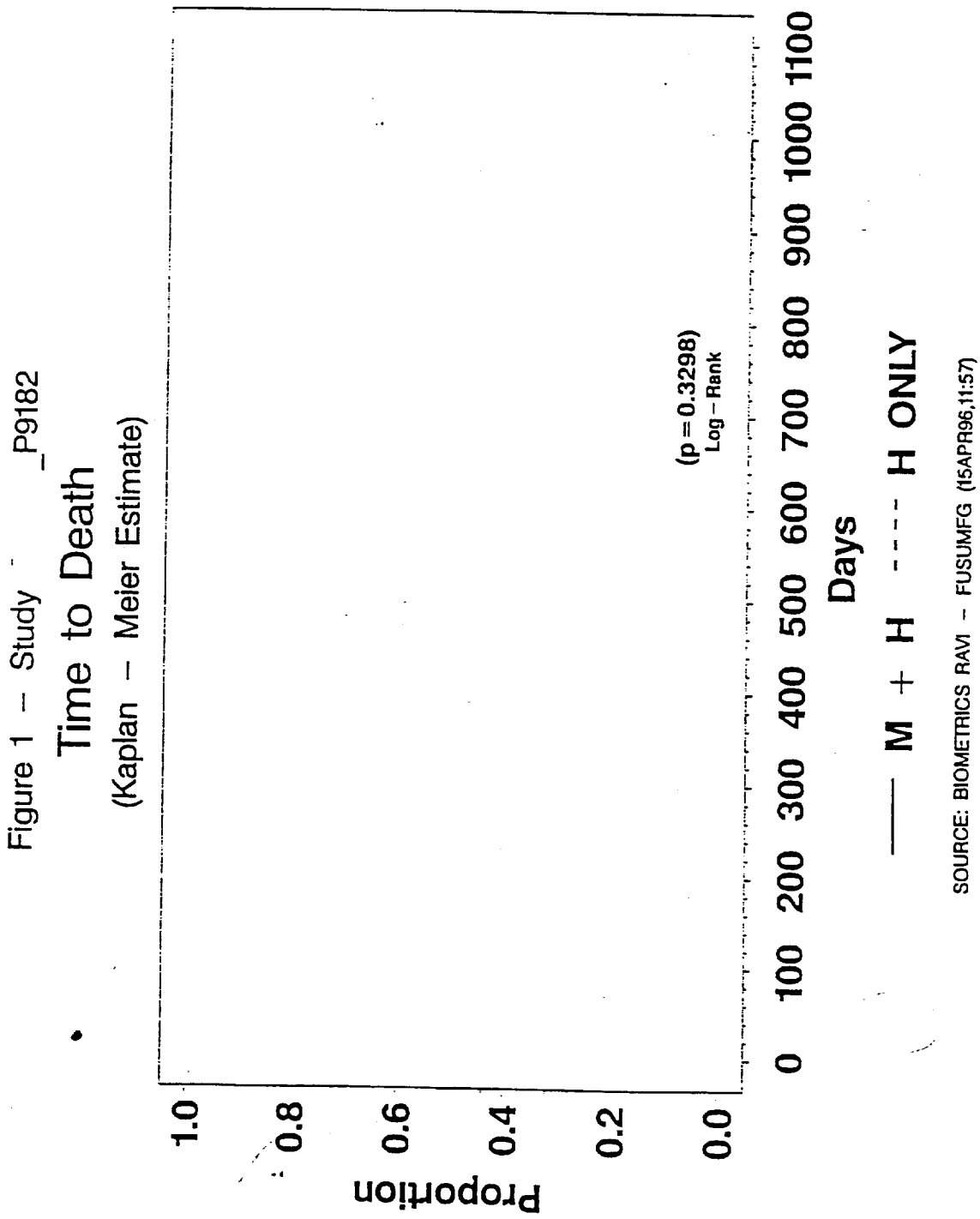
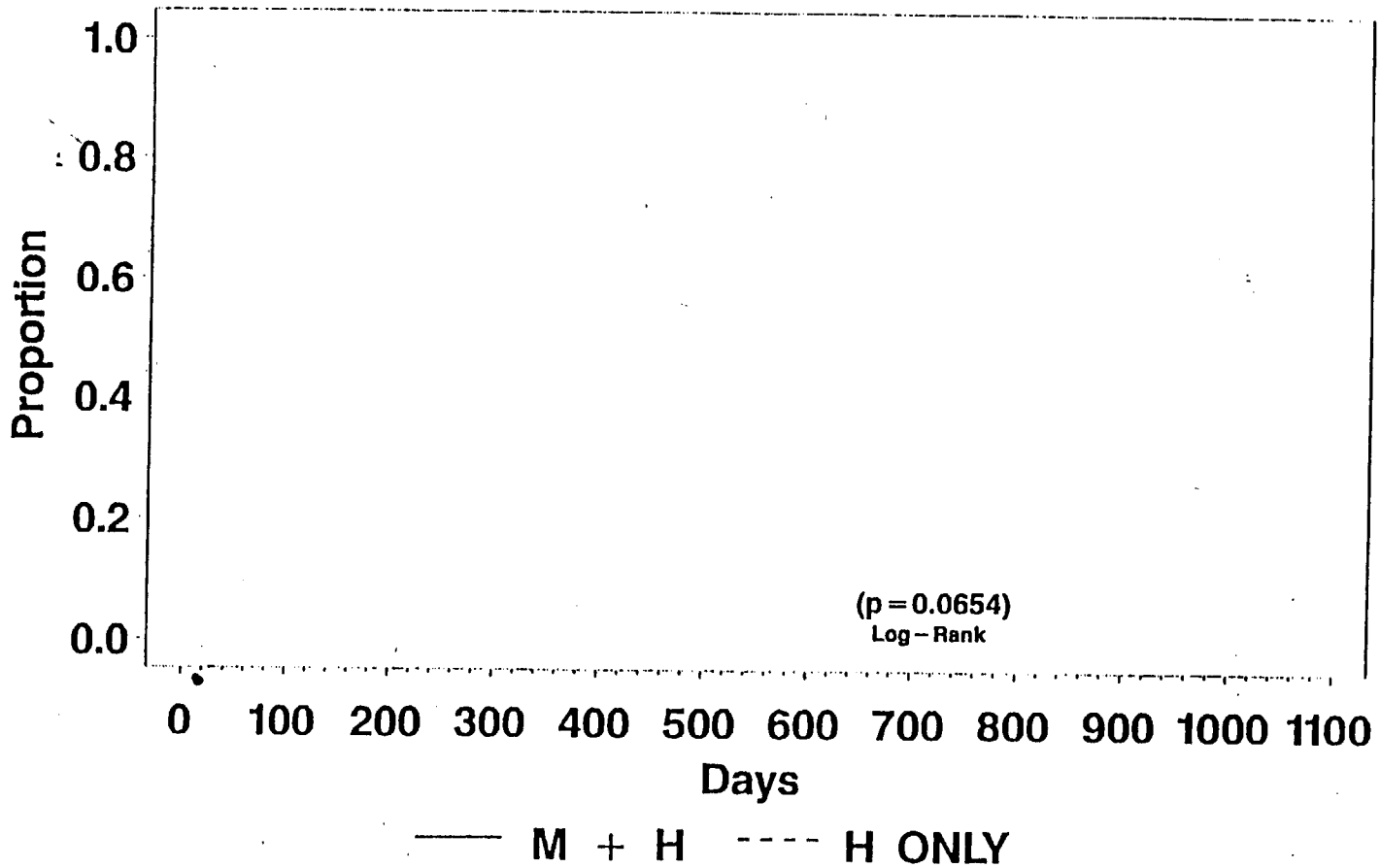


Figure 1 – Study _P9182
Time to Death
(Kaplan – Meier Estimate)
Proportion
1.0
0.8
0.6
0.4
0.2
0.0
(p = 0.3298)
Log – Rank
0 100 200 300 400 500 600 700 800 900 1000 1100
Days
M + H
H ONLY
SOURCE: BIOMETRICS RAVI – FUSUMFG (15APR96,11:57)

Figure 2 – Study _P9182

Time to Progression

(Kaplan – Meier Estimate)

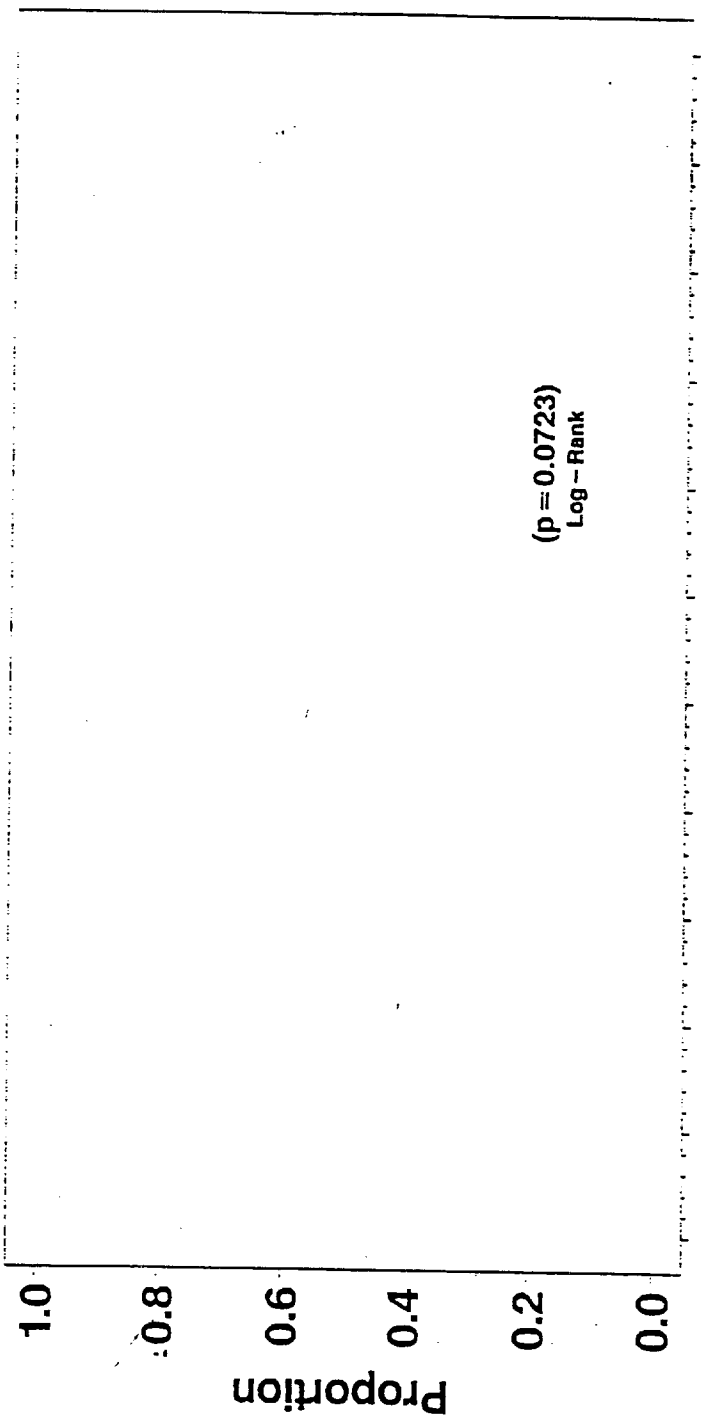


SOURCE: BIOMETRICS RAVI – FUSUMFG (15APR96,11:57)

Figure 3 – Study P9182

Time to Progression or Death

(Kaplan – Meier Estimate)



SOURCE: BIOMETRICS RAVI – FUSUMFG (15APR96,11:57)

Addendum to Statistical Review and Evaluation

NDA#: 19-297

NOV 7 1996

Title: Phase III Trial of Mitoxantrone Plus Low-Dose Prednisone Versus Low-Dose Prednisone for Symptomatic Hormone-Resistant Prostate Cancer

Applicant: Immunex

Name of Drug: Novantrone (Mitoxantrone Hydrochloride Concentrate for injection)

Indication: Hormone Resistant Prostate Cancer (HRPC)

Documents Reviewed: Volumes 9-12 of submission dated May 13, 1996, Volume 1 of submission dated October 4, 1996, and Volume 1 of submission dated November 4, 1996.

Medical Reviewer: Julie Beitz, M.D.

This review consists of: A) an exploratory longitudinal data analysis on PPI (Present Pain intensity), the primary endpoint of the CCI-NOV22 study, and B) some additional analyses requested by the ODAC members from the ODAC meeting on 9/11/1996 regarding the pain intensity endpoint of the CCI-NOV22 study, and the analgesic use and the pain intensity endpoints from the 9182 study.

LONGITUDINAL DATA ANALYSIS OF PPI (CCI-NOV22 Study):

The sponsor did not provide any formal longitudinal analyses that could be used to assess time trends on the quality of life data. This reviewer performed an exploratory longitudinal data analysis on PPI (Present Pain intensity), the primary endpoint of the CCI-NOV22 study. This type of analysis enables one to assess the time trend of the PPI for both groups, the treatment group (M+P) and the control group (P) over the 18 cycles of treatment. This review will not include any methodological details.

Longitudinal data analyses are looking at the patterns of the data over time and are taking into account the within patient correlation of the repeated measurements. One of the most important considerations in performing longitudinal data analysis is to assess the missing data mechanism. Under the 'ignorable' missing data mechanism (Little 1995), missing completely at random (MCAR) or missing at random (MAR), one can use all the available data for assessing time trends. Random missingness means that the time trend is the same for those patients who completed the study (completers) and for those who did not (drop-outs), by treatment arm. For example, one can define completers as those patients who had treatment for a minimum number of cycles. If the patterns of the drop-out patients in each group are not the same, and that is the case in most cancer clinical trials where patients either die fast, or they drop out for toxicity or other

reasons faster in one arm than the other, then we look at the time trends of those patients who completed the study and those who dropped out before the end of the study separately. In addition, correlation of the repeated measurements within each patient is an important consideration for the type of methodology to be used for the longitudinal data analysis. It is usually very difficult to choose one type of methodology over another when dealing with this problem.

Longitudinal data analyses are known as "Growth Curves" analyses. The most common methodologies for approaching this problem are the mixed effects models (Laird and Ware, 1982) and "estimating equations" (Liang and Zeger 1986, with different ways of estimating the within patient correlation) for determining trends of the treatment effect (if any) over time. One hopes that these different methods will give consistent results. Hence, the robustness of the results is also a very important factor for assessing the validity of these type of exploratory analyses.

The following table contains the baseline distribution of the PPI scores between the two treatment groups. These results were provided by the sponsor.

Table 1: Baseline assessments of PPI

PPI	0	1	2	3	4	5	
M+P	1	30	30	15	4	0	80
P	1	23	37	15	5	0	81

*Two-sided Chi-squared p-value=0.782

Figure 1 presents the PPI data available per treatment group at each cycle. We observe that the drop out rates of patients in each group are about the same at each cycle of treatment. There were 18 cycles of treatment, from 1 to 18. In this graph and all subsequent figures included in this review the cycles of treatment are translated from 0 to 17. More than 50% of the patients dropped-out at about or after cycle 8. Figure 2 present the PPI time trends for the control group and the treatment group, after applying the Liang and Zeger methodology of "estimating equations". The following model was applied separately for each treatment group:

$$PPI = Intercept + Cycle + Cycle^2.$$

We observe that the PPI is decreasing faster in the M+P group than in the P group up to about cycle 9, but then the PPI is increasing faster in the M+P group than the P group up to the end of the study. One has to take into account that the attrition rates are high after cycle 9. The main assumption here is that the missing data mechanism is 'ignorable'. These time trends are not different between the two treatment groups.

Next we assume that the missing data mechanism is not 'ignorable'. If we define completers as those patients who had at least 9 cycles (half a year) of treatment, and the rest of the patients as drop-outs, then we observe in Figure 3 that the time trend of the completers is about the same as

the time trend of the drop-out patients in treatment arm P. However, the time trend of the completers is not the same as the time trend of the drop-out patients in treatment arm M+P. This really means that the missing data mechanism is not 'ignorable'. The PPI was initially higher and decreased faster for the drop-outs than for the completers in the M+P group. We also observe that the time trends of PPI for the drop-outs between the two treatment groups are different. We observe that pain is decreasing very fast in the beginning for the drop-outs in the treatment group than for those in the control group. This steep reduction in pain in the treatment group lasted for about 4 to 6 cycles and then pain returned. That is probably why patients dropped out. The time trends of the PPI for the completers are about the same in both treatment groups. Completers in the treatment group started with a lower pain score than did the control completers. Pain decreased for about 9 cycles of treatment and then returned. One has to take into account that the attrition rates are high after cycle 9.

In conclusion, patients who stayed on the study long enough in either treatment group had a very small reduction in PPI that lasted for about 9 to 10 cycles and gradually increased thereafter. The PPI time trends between the two treatment groups for these patients were not different. Patients who dropped out in the treatment group M+P had a more rapid reduction in PPI than those patients who dropped out in the treatment group P. This reduction of PPI lasted for about 5 to 6 cycles. PPI then increased faster in the M+P group than the P group. As expected, such patients in either group stopped treatment at that point. The PPI time trends between the two treatment groups for these patients were different.

The following table includes the number of completers and drop-outs who were assessed as responders by the Medical Reviewer based on the definition of Criterion 1 for response.

Table 2: Number of responders who were classified as either completers or drop-outs for the longitudinal data analysis of PPI

Treatment	Responders	Completers	Drop-outs
M+P	21	12	9
P	10	8	2

Similar analyses were performed on the analgesic scores as for the PPI. There were some scores of more than 100 that were excluded from this analysis. This decision was taken after consultation with the Medical Reviewer. Figure 4 presents the analgesic scores time trends for the control group and for the treatment group respectively. We observe that analgesic use is increasing in the P group and is decreasing in the M+P group. The time trends are different between the two treatment groups in favor of the treatment group.

Figures 5 and 6 show that the time trends of the analgesic use of the completers are the same as the time trends of the drop-out patients for each treatment group. This really means that the missing data mechanism is 'ignorable', and hence, one could use all the data.

In conclusion, the analgesic use time trends favor the treatment arm over the control, indicating that patients in the treatment arm reduced their analgesic use.

Conclusion: We can not ignore the missing data mechanism between the two groups for the PPI scores since the time trends of the PPI for the drop-outs were different from those of the completers in the M+P group . But, this was not the case for analgesic use: the time trends were similar for both the drop-outs and the completers in each treatment group. These analyses show that there are some patients who had a reduction in their pain and quite a lot of patients who had a decrease in the analgesic use in the treatment arm compared to the control arm.

B) Additional analyses requested by the ODAC members from the ODAC meeting on 9/11/1996

CCI-NOV22 Study: The committee's statistical consultant, Dr. Simon suggested that we look at and compare the time trends in pain intensity (a) of those patients in the P arm who crossed over to the M+P arm with those remaining in the P arm and (b) of those patients in the P arm who had stable disease and crossed over to the M+P arm with those remaining in the P arm.

This reviewer performed the following analysis suggested by Dr. Simon: A linear regression model was fitted to each individual's data of pain intensity over time, and the slope of each line was calculated. Then, a t test was performed to compare the individual slopes between the two patient groups.

There were 48 (out of 80) patients in the P arm who crossed over to the M+P arm. The median number of crossover cycles was 5 cycles of treatment with a range of 2 to 12 cycles of treatment. The means of the slopes are 0.05 and -0.25 for the 48 patients in the P arm who crossed over to the M+P arm and the remaining 22 patients who stayed in the P arm, respectively. The two sided t test p-value is 0.012 in favor of those patients who did not cross over. Hence, the pain intensity of those patients who crossed over from the P arm to the M+P arm was worse. That is probably why these patients crossed over.

The means of the slopes are 0.07 and -0.25 for the 18 patients in the P arm who had stable disease before they crossed over to the M+P arm and the 22 patients who never crossed over, respectively. The two sided t test p-value is 0.05 in favor of those patients who did not cross over. Hence, the pain intensity of those patients who had stable disease and crossed over from the P arm to the M+P arm was worse.

Study 9182: This reviewer performed the same analysis as in the CCI-NOV22 Study, on both the analgesic use and the pain intensity. Pain intensity was not collected as an individual endpoint. Pain intensity was part of the SDS (Symptom Distress Scale), item #2. Both analgesic use and pain intensity were supposed to be collected at baseline, at 6-week intervals and at the end of the study. In actuality, data were collected very infrequently on these parameters. A linear

regression model was fitted to each individual's data of analgesic use and pain intensity over time, and the slope of each line was calculated. Then, a t test was performed to compare the slopes between the two treatment groups.

Analgesic use: There were 69 (out of 123) patients in the H arm and 73 (out of 119) patients in the M + H arm, who had analgesic use at baseline. The means of the slopes are 0.08 for the H arm and -0.05 for the M+H arm. Even though these results are not statistically significant, there is an indication that the analgesic use in the M+H arm is decreasing over time and the analgesic use in the H arm is increasing over time.

Pain intensity: There were 81 (out of 123) patients in the H arm and 79 (out of 119) patients in the M + H arm, who had at least 2 observations on pain intensity over time. The means of the slopes are similar, -0.001 for the H arm and -0.002 for the M+H arm. These results are not statistically significant.

Sponsor's analyses: The sponsor performed analyses on the analgesic use and pain intensity based on mean best percent changes from baseline. The following Table presents the mean best percent change in analgesic use for all subjects requiring analgesics at baseline and for subsets of patients based on the baseline level of analgesic use:

Sponsor's Table: Mean Best Percent Change in Analgesic Level

	M+H		H		
Baseline analgesics	Number of patients	Mean best % change	Number of patients	Mean best % change	P-value**
Level 1-4	61	-17	61	+17	0.014
Level 1,2	21	-21	23	+72	0.006
Level 3,4	40	-15	38	-16	0.951

* A negative value corresponds to a decrease in analgesic level, and a positive value corresponds to an increase in analgesic level

** CMH means test

*** 0= no analgesic use
1= non narcotic analgesic, occasionally
2= non narcotic analgesic, regularly
3= narcotic, occasionally
4= narcotics, regularly

The following Table presents the mean best percent change in pain intensity for all subjects requiring analgesics at baseline and for subsets of patients based on the baseline level of analgesic use:

Sponsor's Table: Mean Best Percent Change in Pain Intensity

	M+H		H		
Baseline analgesics	Number of patients	Mean best % change	Number of patients	Mean best % change	P-value**
Level 1-4	37	-14	38	+8	0.057
Level 1,2	13	-4	13	+4	0.735
Level 3,4	24	-20	25	+10	0.024

* A negative value corresponds to a decrease in pain intensity
** CMH means test
*** Pain scale of 1-5, where 1 is better (less pain).

Conclusions: Patients who crossed over from the P arm to the M+P arm seem to perform worse than those patients who did not, in their pain intensity scores. There was a statistically significant difference between these two cohorts of patients.

There is some indication that the analgesic use in the M+H arm is decreasing over time and the analgesic use in the H arm is increasing over time for patients with analgesic use at baseline. The difference between the M+H arm and the H arm was not statistically significant for this endpoint. The mean best percent change difference between the two treatment groups in analgesic use for all subjects requiring analgesics at baseline was statistically significant in favor of the M+H arm. For the subset of patients who had non narcotic analgesic use at baseline, the difference in the mean best percent changes in analgesic use was statistically significant in favor of the M+H arm.

OVERALL CONCLUSIONS: The longitudinal data analyses show that there is a benefit in the pain intensity for some patients who received the M+P treatment. Patients in the M+P arm had a statistically significant decrease in their analgesic use compared to patients in the P arm, who actually had an increase in their analgesic use.

Patients who crossed over from the P arm to the M+P arm seem to perform worse than those patients who did not, in terms of their pain intensity scores. There was a statistically significant difference in their pain intensity between these two cohorts of patients.

There is some indication that the analgesic use in the M+H arm is decreasing over time and the analgesic use in the H arm is increasing over time for patients with analgesic use at baseline. The difference between the analgesic use scores of the M+H arm and of the H arm

was not statistically significant for this endpoint. The mean best percent change difference between the two treatment groups in analgesic use for all subjects requiring analgesics at baseline was statistically significant in favor of the M+H arm. For the subset of patients who had non narcotic analgesic use at baseline, the difference in the mean best percent changes in analgesic use was statistically significant in favor of the M+H arm. The mean best percent change difference between the two treatment groups (M+H vs H) in the pain intensity for all subjects requiring analgesics at baseline was not statistically significant.

RECOMMENDATION: Based on the data presented by the sponsor, the retrospective analysis performed on the 9182 study supports the findings of the pivotal study (CCI-NOV22 Study), for the analgesic use endpoint. On the other hand, the retrospective analysis performed on the 9182 study does not support the findings of the pivotal study (CCI-NOV22 Study), for the pain intensity endpoint. This could be due to the fact that pain intensity was not collected as an individual endpoint. Pain intensity was part of the SDS (Symptom Distress Scale) questionnaire. Evidence that Mitoxantrone is effective in the palliative treatment of patients with symptomatic Hormone- Resistant Prostate Cancer has been shown. Approval of Mitoxantrone in patients with symptomatic Hormone-Resistant Prostate Cancer is recommended by this reviewer, as an alternative to other treatments, for the palliative treatment of patients with symptomatic Hormone-Resistant Prostate Cancer.

ACKNOWLEDGMENTS: I would like to thank Dr. Masahiro Takeuchi and Dr. Clare Cnecco for their constructive suggestions which substantially improved this review.

Antonis Koutsoukos

Antonis Koutsoukos, Ph.D.
Mathematical Statistician

concur: Dr. Gnecco C Gnecco 11/7/96

Dr. Chi Chi 11/7/96

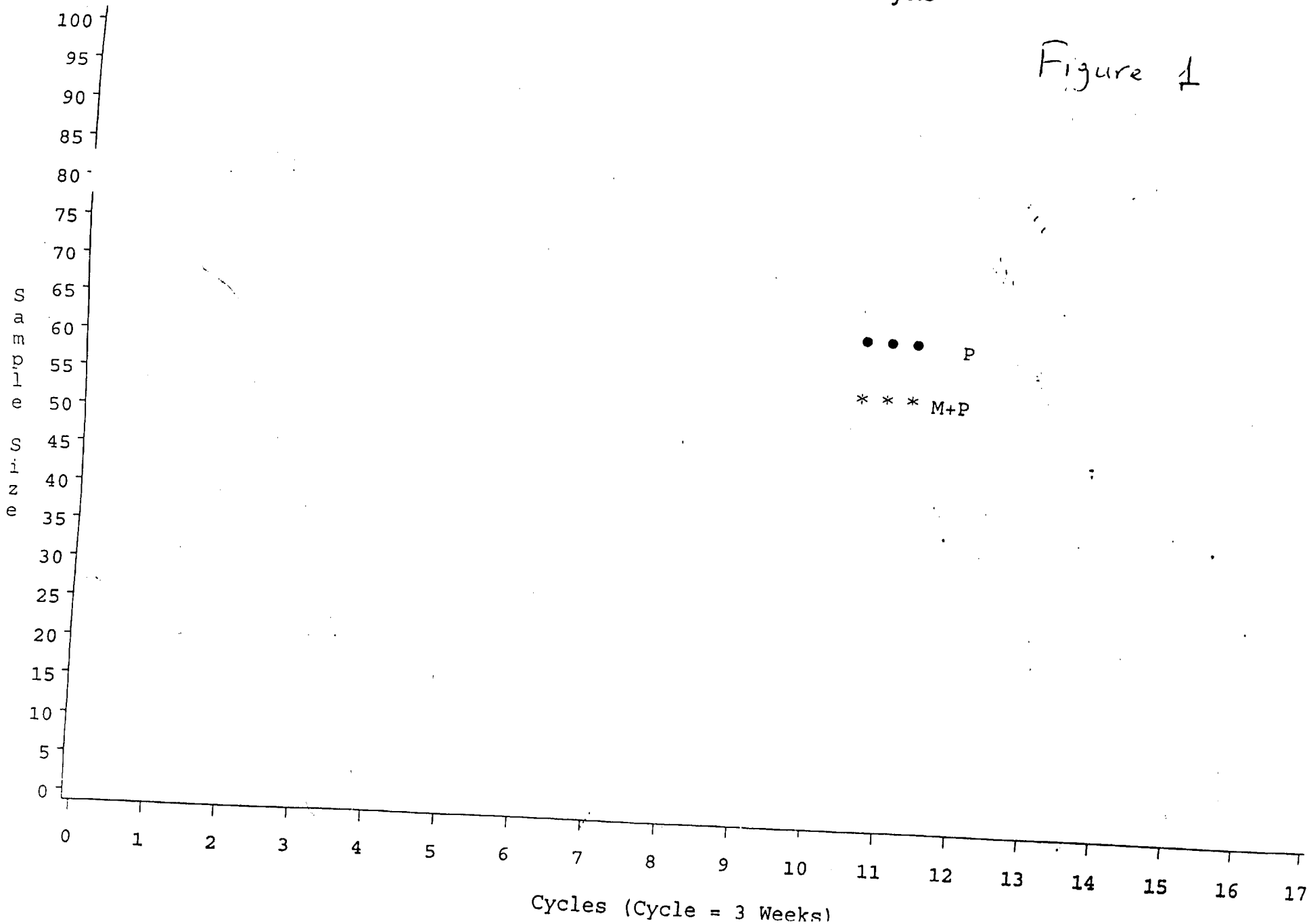
cc:
Archival NDA 19-297
HFD-150/Dr. Beitz
HFD-150/Dr. Justice
HFD-150/Ms. Leslie Vaccari
HFD-344/Dr. Lisook

HFD-710/Dr. Chi
HFD-710/Dr. Gnecco
HFD-710/Dr. Koutsoukos
HFD-710/chron

Koutsoukos/ 10-21-1996/ WP6.1/ c:\nda19-297\novalng2:rvw
This review consists of 8 pages (1-8) of text and 6 pages of graphs (Figures 1-6).

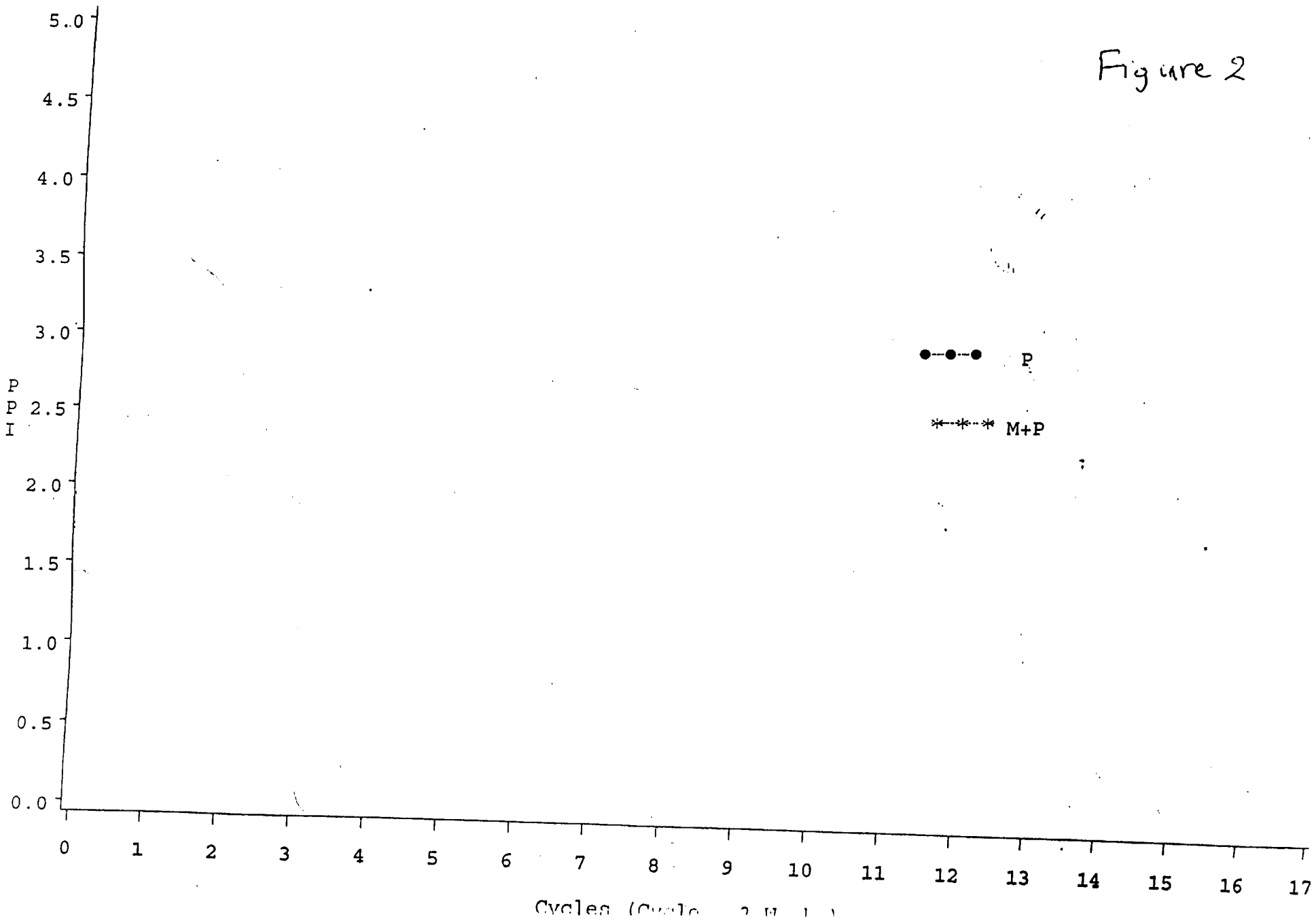
Sample size per treatment group
used in the Longitudinal data analysis

Figure 1



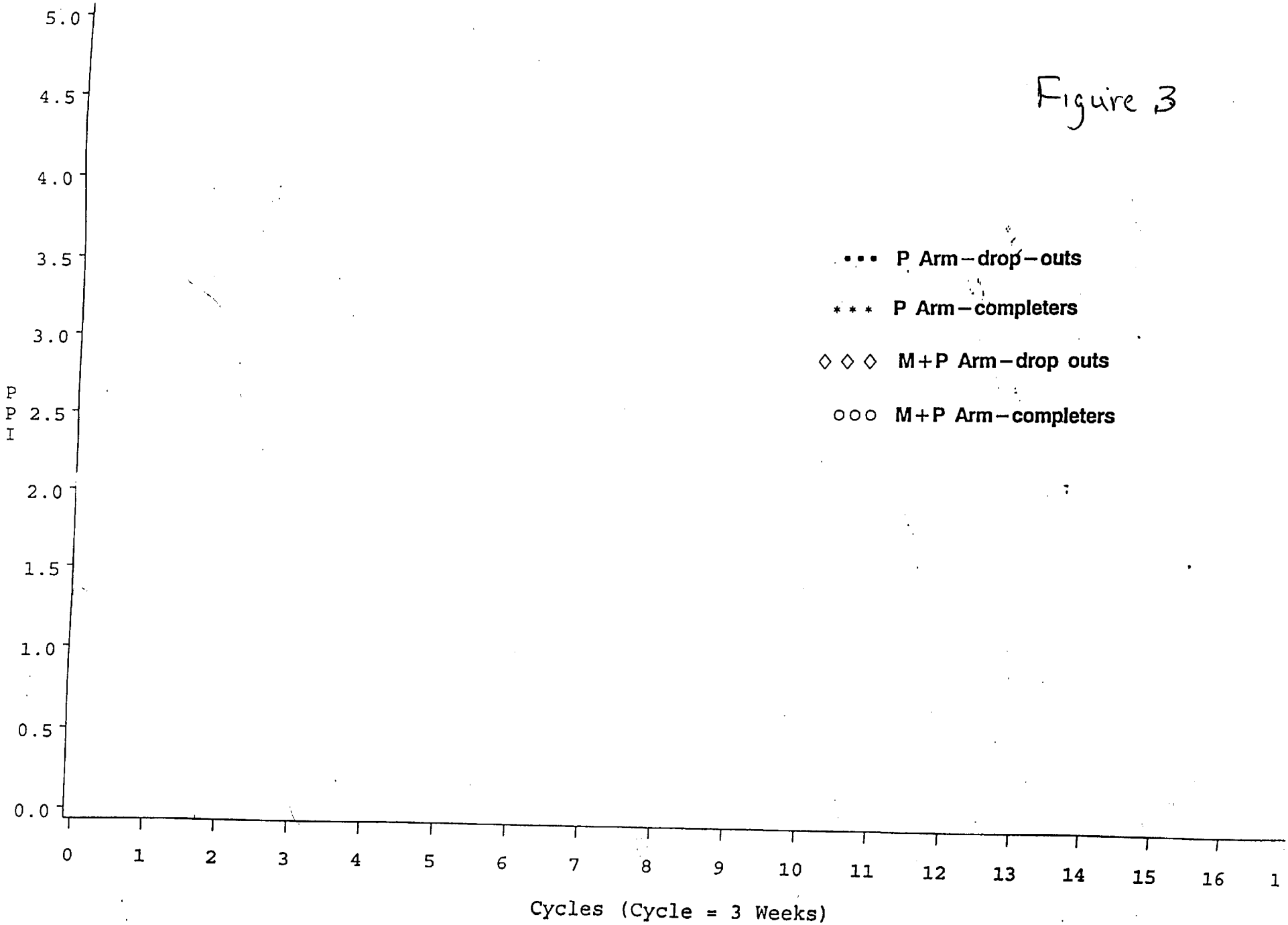
Longitudinal data analysis of PPI of all patients: Cycles 1–18
Ignorable missing data mechanism

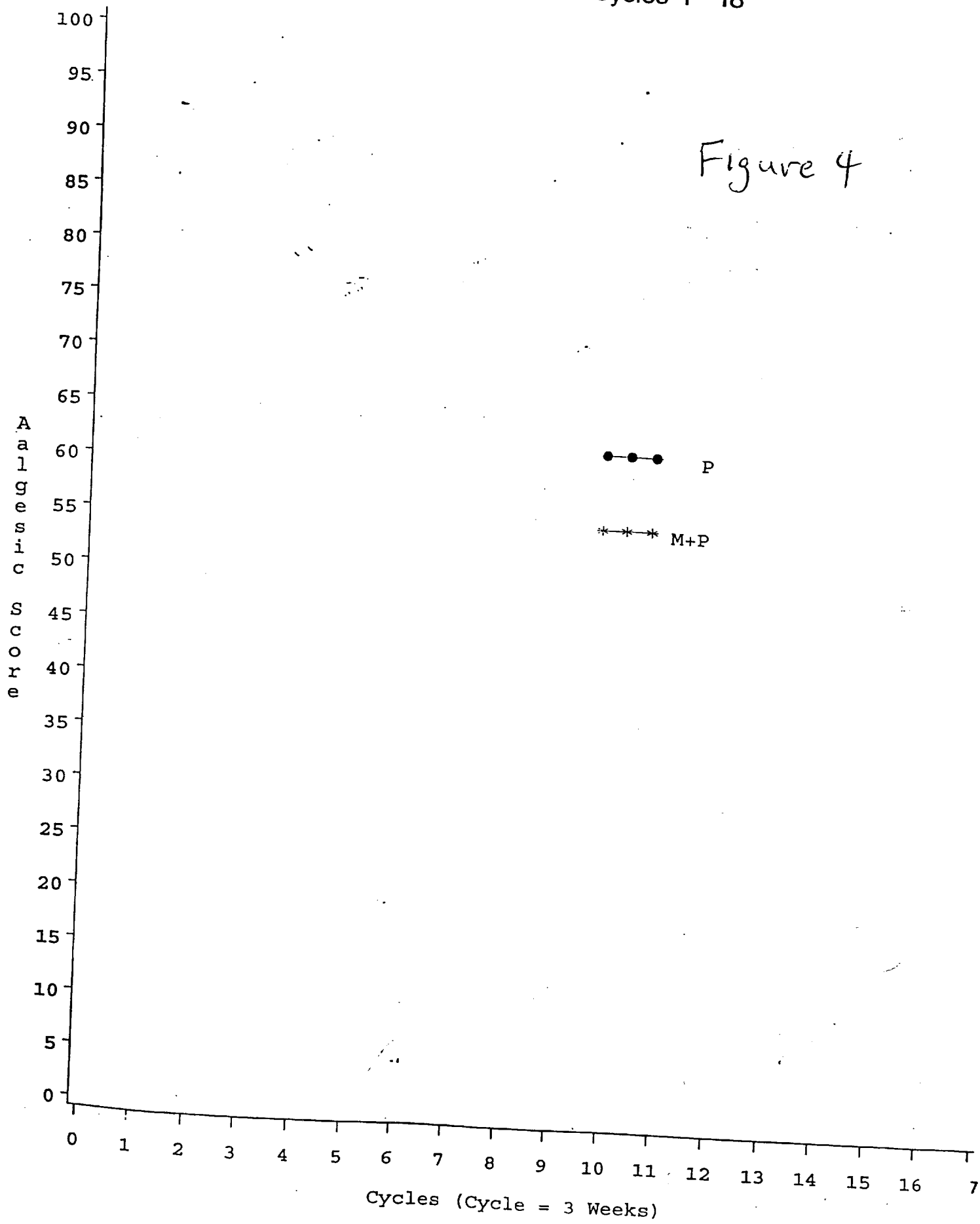
Figure 2



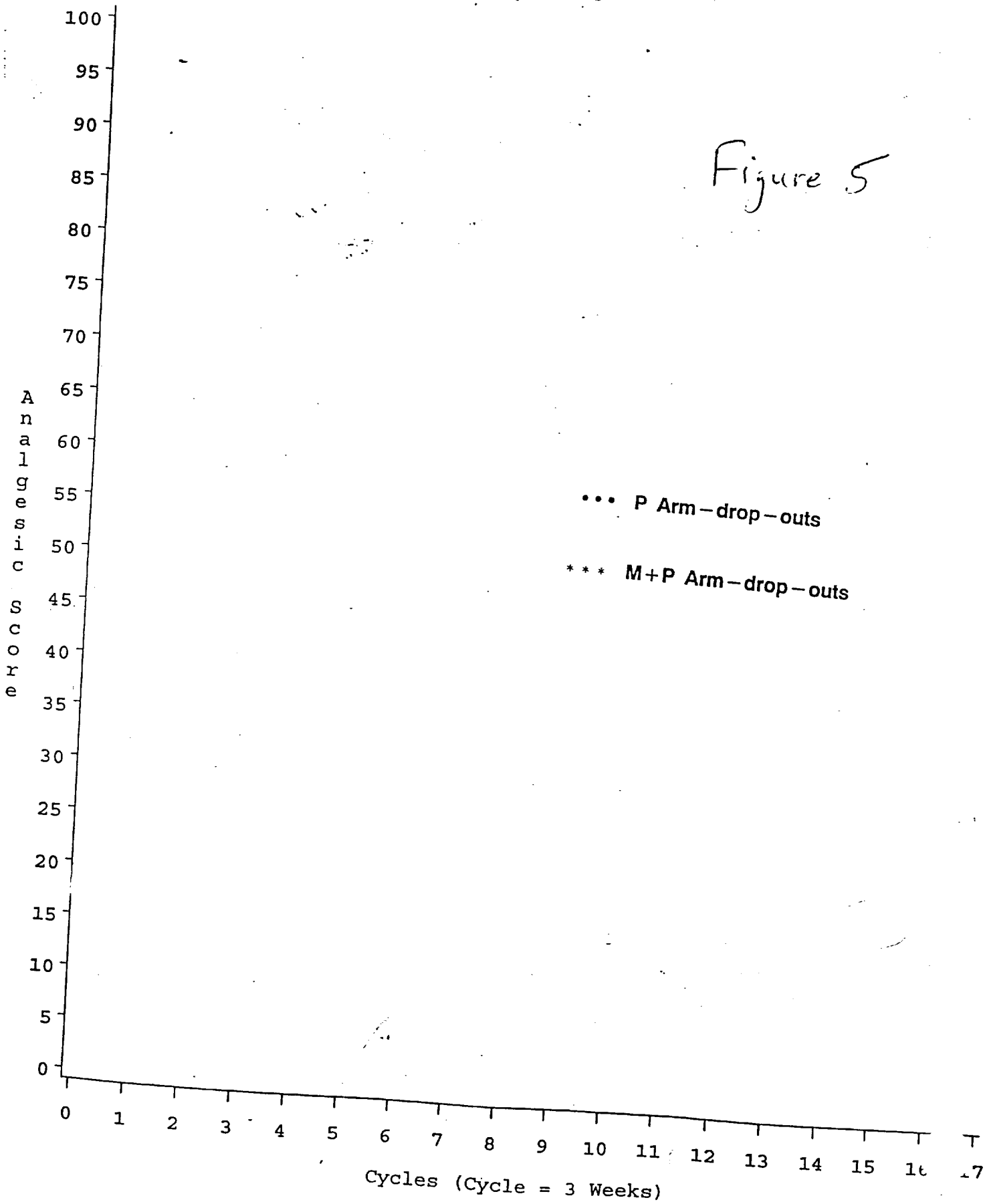
Longitudinal data analysis of PPI

Figure 3




Analgesic comparisons: Cycles 1–18
Figure 4
Analgesic Score
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
P
M+P
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
7
Cycles (Cycle = 3 Weeks)

Longitudinal data analysis of Analgesic Scores
Drop – outs



Longitudinal data analysis of Analgesic Scores
Completers

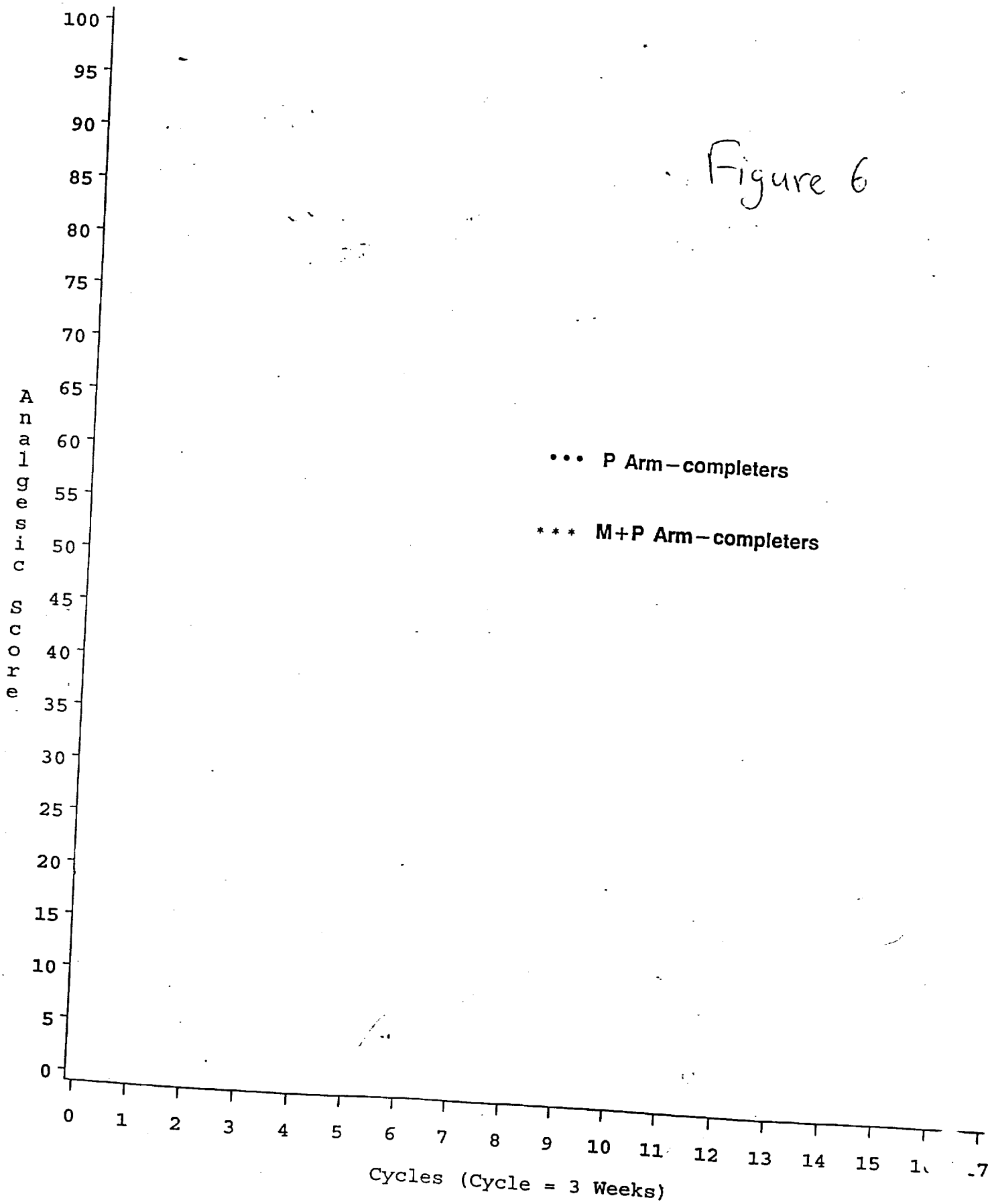


Figure 6

Chem

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
HFD-150 DODP	19-297

3. NAME AND ADDRESS OF APPLICANT *(City and State)*

Immunex Corporation
51 University Street
Seattle, Washington 98101-2936

4. AF NUMBER

5. SUPPLEMENT (S) NUMBER(S) DATES(S)

6. NAME OF DRUG	7. NONPROPRIETARY NAME		
Novantrone	mitoxantrone hydrochloride	SE_1-014	10-May-1996

8. SUPPLEMENT PROVIDES FOR:
approval for the treatment of hormonal refractive prostate cancer - a new indication for the approved drug. (Efficacy Supplement)

9. AMENDMENTS DATES
BC 01-OCT-1996

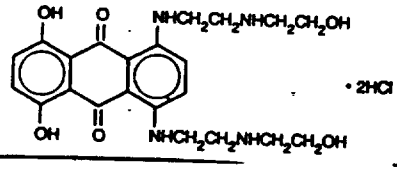
10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
antineoplastic	RX XX OTC __	

13. DOSAGE FORM(S)	14. POTENCY
concentrate for injection	2 mg /mL as base

15. CHEMICAL NAME AND STRUCTURE

1,4-dihydroxy-5,8-bis[[2-(2-hydroxy-ethyl)amino]ethyl]amino]-9,10- anthracene-dione hydrochloride

$C_{22}H_{28}N_4O_6 . 2HCl$



16. RECORDS AND REPORTS
CURRENT YES__NO__
REVIEWED YES__NO__

17. COMMENTS

Based on the submission date, the EA requirements for this supplement are covered by the ***Interim Directive, MaPP 5015.1,*** **dated November 14, 1995 and should meet the requirements of TIER 0.**

cc: Orig. NDA 19-297
HFD-150/Div. File
HFD-150/RPBarron
HF[redacted]
R/D init. by_____

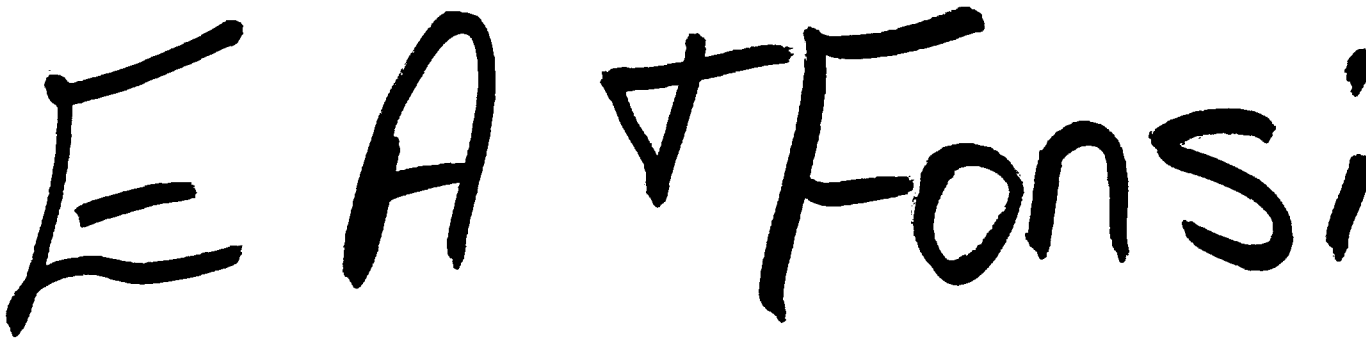
SKim for Rebecca Wood 10-11-96

18. CONCLUSIONS AND RECOMMENDATIONS

Based on the abbreviated EA (Tier 0) information and amendment dated 01-OCT-1996, A Finding of No Significant Impact is justified from the projected production levels of the product. for the proposed marketing for the new indications. Approval of the supplement is recommended.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Robert P. Barron	Robert P Barron	10/10/96

DISTRIBUTION ORIGINAL JACKET XX DIVISION FILE XX REVIEWER XX CSO XX SUP. CHEMIST XX



OCT 17 1996

ABBREVIATED ENVIRONMENTAL ASSESSMEMT

and

FINDING of NO SIGNIFICANT IMPACT

for

NOVANTRONE®

(mitoxantrone)
for Injection Concentrate

NDA 19-297 / SE_1-014

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Division of Oncologic Drug Products

HFD-150

FINDING OF NO SIGNIFICANT IMPACT

NDA 19-297

Novantrone®

(mitoxantrone)
for Injection Concentrate
(2 mg/mL as base)

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for the protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (Section 101), and provides procedures (Section 102) to carry out the policy.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their supplemental new drug application for Novantrone® (mitoxantrone for injection concentrate) for the treatment of hormonal refractive prostate cancer, a condition for which there is currently no available therapy, Immunex Corporation has prepared an abbreviated environmental assessment in accordance with 21 CFR 31a(b)(3) based on the infrequent use of the drug product. The new indication for the mitoxantrone has received orphan drug designation prusuant to Section 526 of the FD&C Act.

Mitoxantrone hydrochloride is a synthetic antineoplastic anthracenedione agent structurally similar to the anthracyclines. It exists under ambient conditions as a dark blue-black solid which has no odor and is only sparingly soluble in water.

Novantrone® was approved for the treatment of acute non-lymphocytic leukemia in adults in combination with other approved drugs on December 23, 1987 under the Orphan Drug Act [P.L. 97-414] as a concentrate which must be diluted with water or other suitable fluid prior to administration.

The bulk drug substance is manufactured in Germany. The firm has provided a letter confirming that all manufacturing operations in the production of mitoxantrone meet all local environmental regulations. The drug product is manufactured in Puerto Rico . A letter of compliance issued at the time of inspection from the Environmental Quality Board of the Government of Puerto Rico found the firm in compliance with the regulation for the control of hazardous and non-hazardous solid wastes. Occupational safety has been appropriately addressed and a Material Safety Data Sheet is attached. Approval of this new

indication and the resultant increase in the amount of drug product manufactured at the site is not expected to affect the ability of the firm to comply with all applicable regulations, nor is the increased use and disposal of drug expected to adversely affect the environment.

Novantrone® is classified as non-hazardous material under the Resource Conservation and Recovery Act (RCRA guidelines, 40 CFR Part 261). Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of by high temperature incineration at an EPA licensed waste treatment facility.

10/10/96
Date

Robert P. Barron
Prepared by
Robert P. Barron
Review Chemist
Division of Oncologic Drug Products, HFD-150

10/11/96
Date

SKM for Rebecca H Wood
Division Concurrence:
Rebecca H. Wood, Ph.D.
Chemistry Team Leader, DNDC I
Division of Oncologic Drug Products, HFD-150

10/13/96
Date

Nancy B Sager
Approved by
Nancy B. Sager
Team Leader
Environmental Assessment Team
Office of Pharmaceutical Sciences/CDER

cc: FDA 19-297 through L. Vaccari Original
HFD-004/FONSI File NDA 19-297
HFD-004/Docket File
HFD-019/FOI Copy

FDA ADDENDUM

In section 4.a. of the EA the applicant states that "The sponsor has discussed the proposed supplement with the FDA and was advised that an AEA is appropriated because the subject of this submission is an efficacy supplement to an approved NDA." The decision of whether an EA or AEA is appropriate is independent of the type of action (i.e., NDA, efficacy supplement). However, an AEA is appropriate for this action because the product is used to treat a rare disease or condition.

NOVANTRONE mitoxantrone for injection concentrate
Abbreviated Environmental Assessment

Table of Contents

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Not required for this submission.

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Section 1. Date
May. 1996

Section 2. Name of Applicant
Immunex Corporation

Section 3. Address
51 University Street
Seattle, Washington 98101-2936

Section 4. Description of the Proposed Action
4.a. Requested Approval:
Novantrone® (mitoxantrone for injection concentrate) is a synthetic antineoplastic anthracenedione for intravenous use. It is currently approved for use in combination with other approved drug(s) in the initial therapy of acute nonlymphocytic leukemia (ANLL) in adults. This category includes myelogenous, promyelocytic, monocytic, and erythroid acute leukemias. This indication was filed and approved under NDA 19-297.

Novantrone (mitoxantrone for injection concentrate) is a sterile aqueous solution containing mitoxantrone hydrochloride at a concentration equivalent to 2 mg mitoxantrone free base per mL. supplied in Type I glass multidose vials as follows:

10 mL/multidose vial (20 mg)
12.5 mL/multidose vial (25 mg)
15 mL/multidose vial (30 mg)

The Immunex Corporation has filed a supplemental NDA pursuant to section 505(b) of the Federal Food, Drug & Cosmetic Act for *Novantrone* (mitoxantrone hydrochloride) requesting approval of a new indication: "*Novantrone* in combination with corticosteroids is indicated as initial chemotherapy for treatment of patients with symptomatic prostate cancer, after failure of primary hormonal therapy." An AEA has been prepared and is being submitted pursuant to 21 CFR 25.31(a). The sponsor has discussed the proposed supplement with the FDA and was advised that an AEA is appropriate because the subject of this submission is an efficacy supplement to an approved NDA.

4.b. Need for Action:

Novantrone is currently licensed for marketing in the U.S. in parenteral formulations by Immunex Corporation. The product is also approved for several indications internationally and is distributed by a subsidiary of American Home Products Corporation. The need for the action is to obtain approval of an effective treatment for the palliation of pain related symptoms in patients with hormone refractory prostate cancer (HRPC); a condition for which there is currently no available therapy.

Assuming the approval of this application, the projected level of production of *Novantrone* is expected to increase approximately . The projected five (5) year production of Novantrone for total domestic use is provided below.

PRODUCTION YEAR	DOMESTIC
1996	
1997	
1998	
1999	
2000	

An application requesting orphan drug status for *Novantrone* for the treatment of hormone resistant prostate cancer was submitted to the FDA on April 3, 1996. To date, we have only received acknowledgment of receipt of the application; orphan drug status has not yet been granted. Based on data provided in the orphan drug application, it appears that the prevalence of patients who are eligible for chemotherapeutic treatment with *Novantrone* will plateau at approximately patients per year. Therefore, it is expected that the amount of drug for domestic use will not increase appreciably above the 5th year estimate provided above.

4.c. Manufacturing Locations:

4.c.i. Bulk Drug Manufacture:

Novantrone drug substance (mitoxantrone hydrochloride) is manufactured by

A complete description of the facility, method of manufacture and controls exercised during manufacture and for release of the bulk drug is on file in drug master file, type II. DMF

. A description of this plant site has been requested.

The bulk drug is stored and shipped at ambient temperature in double thickness polyethylene bags in fiber drums, sealed with locking rings.

4.c.ii. Parenteral Dosage Form Manufacture:
The bulk drug is formulated and packaged in 2 mg/ mL dosage strength vials at Product is filled at this concentration and marketed in three presentations: 1) a 10 mL vial (20 mg), 2) a 12.5 mL vial (25 mg), and 3) a 15 mL vial (30 mg).

It is a 19-acre plant site containing seven major buildings; the plant site is bounded by security fencing. These facilities are located in a populous area with a subtropical climate and flat terrain. Production is limited to sterile parenteral solutions, suspensions and lyophilized powders.

The manufacturing sites for bulk drug and final formulation are in compliance with applicable environmental regulations. Procedures are in place at both locations for handling and disposal of returned, expired and rejected drug product. Employee health and safety programs are also in place to assure containment of chemicals and minimize exposure of workers to mitoxantrone.

4.d. Location of Use and Disposal:
Novantrone is targeted for use by cancer patients throughout the United States. Patients will be treated in a hospital or clinic setting only, and empty or partially empty packages will be disposed according to hospital, pharmacy or clinic procedures.

Any rejected or out-of-specification bulk drug batches are disposed of by high temperature incineration at an EPA licensed waste treatment facility (refer to Reference 1, SOP 67-10-173, Disposition of Rejected Material, The drug formulation facility in has a contract to send any rejected waste product to the facility located in for incineration (RCRA TSD Permit #LAD 010395127P, expiration date March 21, 2001). This state and federally permitted facility is located on a 400 acre site in a rural setting, and in a climate that is temperate.

Master File, DMF

Currently, returned, rejected and expired commercial product is shipped to for subsequent disposal and destruction. This process will continue to be utilized after approval of the additional indication. According to established procedures (a copy of the Returned Goods Policy and Form is provided in Reference 2; a more detailed SOP is included in Confidential Appendix A), an inventory is taken of all returned goods and submitted to Immunex Corp. for confirmation. Each package of returned goods is inspected, the contents identified and classified, and the material tracked from the point of receipt through final disposal and destruction.

Returned materials processed at are stored in a separate inventory and then transferred to a contracted pharmaceutical disposal service

system to document and track the receipt and disposition of all incoming drug materials. A detailed description of all Immunex returned goods is captured upon receipt and forwarded to Immunex Customer Service. Waste materials are classified for proper disposal and destruction according to internal [redacted] procedures, and in accordance with local, state and Federal regulations.

Novantrone is classified as a non-hazardous material under the Resource Conservation and Recovery Act (RCRA guidelines, 40 CFR Part 261) (see also Reference 3). *Novantrone* returned goods are ultimately destroyed by high temperature incineration at an EPA permitted waste treatment facility - (RCRA Part B Permit #ADRO69748192, expiration date July 2, 1998). Each shipment of waste products to the facility leaves [redacted] with an attached shipping manifest, and a complete description of the materials and its packaging. [redacted] personnel confirm the receipt and destruction of each shipment. A confirmation copy of the shipping manifest, the Waste Material Data Sheet, (Reference 4) and a Certificate of Destruction are sent to Immunex Corporation. In this manner, Immunex has positive confirmation of the destruction of all waste drug product.

Section 5. Identification of Chemical Substances that are Subject to this Proposed Action

Novantrone is a synthetic antineoplastic anthracenedione for intravenous use. It is supplied as a concentrate and must be diluted prior to injection. The concentrate is a sterile nonpyrogenic, dark blue aqueous solution containing mitoxantrone hydrochloride equivalent to 2 mg/mL mitoxantrone free base, with sodium chloride (0.80% w/v), sodium acetate (0.005% w/v), and

acetic acid (0.046% w/v) as inactive ingredients. The solution has a pH of 3.0 to 4.5 and contains 0.14 mEq of sodium per mL. The product does not contain preservatives. The product is packaged in clear Type I glass vials stoppered with a gray butyl rubber plug, aluminum crimp seal and plastic cap.

The physical and chemical properties of *Novantrone* and the dosage form excipients/additives are summarized in this section. A material safety data sheet is provided for Novantrone (Reference 5).

A. Nomenclature:

i. USAN Name: mitoxantrone hydrochloride

ii. Brand/Proprietary Name: *Novantrone* mitoxantrone concentrate for injection

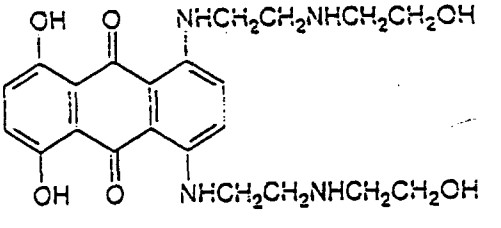
iii. Chemical Name: 1, 4-dihydroxy-5, 8-bis [[2- [(2-hydroxyethyl)amino]ethyl] amino]-9, 10-anthrancenedione dihydrochloride

B. CAS Registration No.: 70476-82-3

C. Molecular Formula: $C_{22}H_{28}N_4O_6 \cdot 2HCl$

D. Molecular Weight: 517.41

E. Structural (Graphic) Formula:



F. Physical Description: Dark blue aqueous solution

G. Additives:

Excipients:	Rationale
sodium chloride, USP	buffering agent
sodium acetate, USP	buffering agent
acetic acid	pH adjustment
water for injection, USP	diluent

H. Impurities

Specifications have been established for related compounds and degradation products in the bulk drug substance (mitoxantrone hydrochloride) as follows:

The specification established for total related compounds is not more than (NMT) 2.0%. Refer to Confidential Appendix B for Registration Specifications and a summary of process related compounds in the bulk drug substance.

Specifications have been established for impurities in *Novantrone* for Injection as follows:

Refer to Confidential Appendix C for Registration Specifications for *Novantrone* 2 mg/mL and stability testing results for 3 representative batches (one of each product presentation (20, 25 and 30 mg).

As can be noted from the product specifications, *Novantrone* has one related compound (CL 116,869) which has a limit of not more than (NMT) 3.0%. The related compound mentioned above was compared to mitoxantrone in a rat toxicity study. The related compound was shown to be 20 fold less toxic than the drug substance (summary report available upon request). A second related compound (CL 116,966) has a limit of NMT 1.5%. Total other related compounds cannot exceed (i.e., NMT) 2.0%. There are no other impurities present in the drug product which exceed the 1.0% level.

Section 6. Introduction of Substances into the Environment

Items 6a. - d. are addressed collectively in the following statements.

6.a. Substances expected to be emitted

6.b. Controls exercised

6.c. Citation of and statement of compliance with applicable emission requirements

6.d. Discussion of the effect of approval on compliance with current emission requirements

Drug substance:

The manufacturing process is in compliance with all local requirements, as noted in the attached environmental compliance certification from Reference 6). An updated statement has been requested from the manufacturer.

An MSDS for mitoxantrone hydrochloride is provided in Reference 7.

Drug product:

The product, *Novantrone* Mitoxantrone for Injection Concentrate, has been manufactured at this site for four (4) years. Approval of this application will not change the qualitative compliance related to emission requirements.

Manufacture of the drug product is in compliance with all applicable Federal, State and local emission requirements (Reference 8), as noted in the attached environmental compliance certification statement (Reference 9). A letter from Government of Puerto Rico, Environmental Quality Board summarizing the results of an inspection of the facility conducted on June 29, 1995 is also provided in Reference 10.

Approval of this efficacy supplement and the resultant increase in the amount of drug product manufactured is not expected to affect our ability to comply with all applicable regulations.

An MSDS for Novantrone is provided in Reference 5.

6.e. Impact due to use and disposal of products

The impact of total release into the environment of *Novantrone* is considered in the calculations provided. Calculation of maximum expected emitted concentration (MEEC), based on 5th year production estimates for *Novantrone* use in the United States is as follows:

MEEC (ppm in environment) =ibs/yr production X $8.9X10^{-9}$

This equation is derived from the following:

MEEC = (A)(B)(C)(D)(E)(F)

Where:

A= pounds/year

B= year/365 days

C= day person/150 gallons

D= 1/246 million

E= gallons/8.34 pounds

F= one million

Set 1

For total estimated *Novantrone* production expected for the year 2000:

$$MEEC = 2.3 \text{ kg/yr.} \times 2.2 \text{ lb/kg} \times 8.9X10^{-9}$$

$$= 4.5 X10^{-8} \text{ ppm}$$

Set 2

For additional *Novantrone* production expected by approval of this action:

$$MEEC = 0.58 \text{ kg/yr.} \times 2.2 \text{ lb/kg} \times 8.9X10^{-9}$$

$$= 1.1X10^{-8} \text{ ppm}$$

Note: assumes 1996 additional production = 200 g. Plus the 5th year additional = (2364 - 1984 = 380 g.
Or
380 + 200 = 580 g is the maximum concentration that could end up in the environment if everything was flushed.

The first set of calculations uses the fifth (5th) year maximum quantity production level, and assumes the complete disposal of all material. Therefore, this MEEC value represents the maximum amount of *Novantrone* which could enter the environment in the stated timeframe. The second set of calculations considers only the additional drug that would be used by

approval of this action. and therefore represents the additional maximum quantity that could enter the environment in the stated timeframe.

6.f. Conclusion

Novantrone bulk is manufactured within compliance of all applicable environmental requirements. established by the German government. *Novantrone* finished formulation is manufactured within compliance of all applicable environmental requirements. established by the local authorities in Carolina, Puerto Rico.

During manufacture of *Novantrone* air emissions are filtered through filters which operate with a 99.6-99.9% removal efficiency. The level of emissions is within compliance with all federal. state and local requirements.

All outdated or rejected materials are transported to a state and federal permitted treatment. storage and disposal facility for incineration. After commercialization, returned, rejected or expired goods will be incinerated in an EPA-licensed waste treatment and disposal facility.

Section 7. through Section 11.

Not required for this submission.

Section 12. List of Preparers/Contributors

Written by:

Mark W. Gauthier, Sr. Manager, Regulatory Affairs
Immunex Corporation

Jeff Palmer. Sr. Manager. Environmental Health and Safety
Immunex Corporation

Section 13. Certification

The undersigned official assures that the information presented is true, accurate and complete to the best of the knowledge of Immunex Corporation.

Mark W. Gauthier
Sr. Manager, Regulatory Affairs
Immunex Corporation

James F. Palmer
Sr. Manager, Environmental Health and Safety
Immunex Corporation

Section 14. References

1. SOP 67-10-173. Disposition of Rejected Material.

2. Immunex Corporation Customer Returned Goods form and instructions
3. Environmental Impact: Storage and Handling Wastes Resulting from the Manufacturing of *Novantrone*, March 2, 1990
4. Uniform Waste Data Sheet,
5. Material Safety Data Sheet, *Novantrone* Mitoxantrone for Injection Concentrate
6. Environmental Compliance Certification Statement from (drug substance manufacturer)
7. Material Safety Data Sheet, mitoxantrone hydrochloride
8. List of Applicable Federal, State and local emission requirements for

9. Environmental Compliance Certification Statement from drug product manufacturer)
10. Letter from Government of Puerto Rico, Environmental Quality Board - summary of June 29, 1995 facility inspection
11. Curriculum Vitae of contributors.

Section 15. Confidential Appendices

A. SOP # K-030-01. Immunex Corporation. Commercial Product Returns at Cardinal.

B. Mitoxantrone Hydrochloride - Registration Specifications and Summary of Process Related Compounds in the Bulk Drug Substance.

C. *Novantrone* Mitoxantrone for Injection Concentrate - Registration Specifications and stability testing results for 3 representative batches (one of each product presentation: 20, 25 and 30 mg) of the product.

MATERIAL SAFETY DATA SHEET

MANUFACTURER: AMERICAN CYANAMID COMPANY
LEDERLE LABORATORIES
MIDDLETOWN ROAD
PEARL RIVER, NY 10965

MSDS NO.: 09393-04
Supersedes: 09393-03
DATE: 10/27/93

EMERGENCY TELEPHONE: (914) 732-5000

I. PRODUCT IDENTIFICATION

PRODUCT NAME: NOVANTRONE® mitoxantrone HCl, 2 mg/ml:
(Product Code: 09393)

CAUTION! MAY CAUSE EYE IRRITATION.
MAY CAUSE EFFECTS ON THE BONE MARROW, KIDNEY, HEART, LYMPHOID ORGANS (SPLEEN, THYMUS, LYMPH NODES), GI TRACT, AND LIVER.

CHEMICAL/THERAPEUTIC FAMILY: Anthraquinone; Anti-cancer agent

II. HAZARDOUS INGREDIENTS AND EXPOSURE LIMITS

CHEMICAL AND COMMON NAMES	CAS NO.	%	RECOMMENDED AIRBORNE LEVELS OSHA	TLV (1992-93)	ACCO-TWA
Mitoxantrone HCl 1,4-Dihydroxy-5,8-bis®[2-[(2-hydroxyethyl)amino]ethyl]amino™-9,10-anthracenedione dihydrochloride; Mitozantrone HCl; CL 232,315; NSC-301379; "Big Blue"; NOVANTRONE®; NOVANTRON	[70476-82-3]	~0.2%	Not est.	Not est.	0.2 µg/m³#

#American Cyanamid Company has adopted a Permissible Exposure Limit (ACCO PEL) for MITOXANTRONE HCl of 0.2 µg/m³ (TWA-8).

III. PHYSICAL PROPERTIES

MOLECULAR WEIGHT: 517.5 (Mitoxantrone HCl)

EMPIRICAL FORMULA: $C_{22}H_{28}N_4O_6 \cdot 2HCl$ (Mitoxantrone HCl)

APPEARANCE AND ODOR: Sterile, dark blue aqueous solution; no odor.

BOILING POINT: 100°C (water)

MELTING POINT: Not applicable

VAPOR PRESSURE: Not available

SPECIFIC GRAVITY: Not applicable

VAPOR DENSITY: Not available

PERCENT VOLATILE: ~100% (water)

SOLUBILITY, ORGANIC SOLVENTS: Not applicable

SOLUBILITY, AQUEOUS (WATER): Not applicable

pH: 3.0 - 4.5

SATURATION IN AIR (BY VOLUME): Not available

EVAPORATION RATE: Not available

IV. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT: Not available (METHOD: Not applicable (N/A))

FLAMMABLE LIMITS: Not available LOWER: N/A UPPER: N/A

AUTOIGNITION TEMP.: Not available

HAZARDOUS COMBUSTION PRODUCTS: Not determined; combustion products will vary with fire conditions and oxygen supply to the flame. As with other organic materials, combustion may produce carbon monoxide, carbon dioxide, nitrogen oxides, irritating aldehydes, ketones and organic acids and, possibly, hydrogen cyanide. Fumes of hydrogen chloride (HCl) may also be generated.

EXPLOSION HAZARDS: Not available

V. REACTIVITY DATA

STABILITY: Stable CONDITIONS TO AVOID: N/A

POLYMERIZATION: Will not occur CONDITIONS TO AVOID: N/A

INCOMPATIBLE MATERIALS: Oxidizing agents, e.g., hypochlorite or permanganate.

DECOMPOSITION TEMPERATURE: Not available; bulk MITOXANTRONE HCl will decompose exothermically at 250°C.

HAZARDOUS DECOMPOSITION PRODUCTS: Chlorine gas is liberated when degraded with bleach or calcium hypochlorite (see § IX. SPILL OR LEAK PROCEDURES, below).

VI. SUMMARY OF TOXICITY AND HEALTH HAZARD DATA

SIGNS AND SYMPTOMS OF OVEREXPOSURE IN THE WORKPLACE:

EYES: May cause eye irritation.

SKIN: While not irritating to the skin, MITOXANTRONE HCl can be absorbed through abraded (broken) skin in toxic amounts. Accidental exposure would be expected to cause nausea, vomiting, loose stool, diarrhea, decreased white blood cell count, and increased susceptibility to infection.

INHALATION: Although low potential for exposures in excess of the ACGO PEL exists, overexposure would be expected to result in signs and symptoms similar to those described for SKIN exposure, above.

INGESTION: Although not an expected route of occupational exposure, MITOXANTRONE HCl would be expected to be an irritant to the GI tract.

MEDICAL CONDITIONS GENERALLY RECOGNIZED AS BEING AGGRAVATED BY EXPOSURE:

None known. In clinical use of NOVANTRONE® mitoxantrone HCl for treatment of leukemia and other cancers, the principal toxic side effect noted is a depression of the bone marrow (myelosuppression). This effect is seen clinically as a decrease in white blood cell and platelet counts (leukopenia and thrombocytopenia). Other, acute toxicities noted in clinical use

Continued...

VI. SUMMARY OF TOXICITY AND HEALTH HAZARD DATA

Continued...

MEDICAL CONDITIONS GENERALLY RECOGNIZED AS BEING AGGRAVATED BY EXPOSURE (continued...):
include nausea and vomiting, irritation of mucous membranes (mucositis), and hair loss (alopecia). Mild effects on the heart (cardiotoxicity) and liver (hepatotoxicity) are infrequently reported. A blue-green discoloration of the urine (due to compound excretion) is also occasionally reported. Signs and symptoms such as fever, fatigue, bleeding, infection, pain, and central nervous system disorders have also been reported in clinical use, but these may reflect the underlying disease being treated (leukemia), rather than be effects due to NOVANTRONE® mitoxantrone HCl treatment.

PRIMARY ROUTE(S) OF EXPOSURE/ENTRY:
Inhalation of mists or aerosols; eye or skin contact. MITOXANTRONE HCl may be absorbed through the abraded (broken) skin in toxic amounts. MITOXANTRONE HCl is poorly absorbed after oral administration.

CANCER INFORMATION:
MITOXANTRONE HCl is not listed by the National Toxicology Program (NTP) as a carcinogen. It has not been evaluated for carcinogenic potential by the International Agency for Research on Cancer (IARC). It is not regulated as a carcinogen by the Occupational Safety and Health Administration (OSHA).

MITOXANTRONE HCl was not carcinogenic in either rats or mice when administered intravenously once every 21 days for 2 years.

REPORTED HUMAN EFFECTS:
Pharmacologic (drug-related) effects noted during clinical use of NOVANTRONE® mitoxantrone HCl are discussed above under "MEDICAL CONDITIONS ..."

REPORTED ANIMAL EFFECTS:
The rat oral LD50 for MITOXANTRONE HCl is reported to be 582-721 mg/kg. MITOXANTRONE is absorbed through the skin, producing mortality at dose levels of 125 mg/kg or 500 mg/kg when applied to abraded rabbit and rat skin, respectively. Administered as a neat material, MITOXANTRONE produces significant ocular irritation, causing swelling, discharge, and reddening of the conjunctiva, and damage to the cornea and iris. The damage initially observed progressed in severity over time. Washing of the eye immediately after exposure prevented much of the damage from occurring. Ocular administration of a preparation of MITOXANTRONE HCl at 2 mg/ml in buffer caused only mild reddening of the conjunctiva. MITOXANTRONE did not cause dermal sensitization in guinea pigs (maximization test) nor was it a skin irritant.

In various studies, median lethal doses in rats and mice administered intravenous (IV) doses of MITOXANTRONE have ranged from 4.8 to 12.2 mg/kg, while the lowest lethal doses reported in dogs and monkeys following IV dosing were 0.5 and 1.0 mg/kg, respectively. When administered to mice and rats by intraperitoneal (IP) injection, the reported LD50s have ranged from 8.0 to 19.7 mg/kg. Target organs affected by single or multiple doses of

Continued...

VI. SUMMARY OF TOXICITY AND HEALTH HAZARD DATA

Continued...

REPORTED ANIMAL EFFECTS (continued...):
the drug include the bone marrow, lymphoid organs (spleen, thymus, lymph nodes), gastrointestinal tract, and the kidney; decreases in circulating red and white blood cells have also been seen.

No effects on fertility or reproductive performance were noted in rats. No evidence of teratogenicity was seen in rats or rabbits at doses that were slightly toxic to the mothers, although there was some evidence of slowed fetal kidney development, decreased fetal body weight, and premature delivery in pregnant rabbits. Since pharmacokinetic data indicate that MITOXANTRONE HCl does not cross the placenta, these effects were interpreted to have been an effect secondary to the maternal toxicity noted.

OTHER:
As would be expected with most anti-cancer drugs, MITOXANTRONE HCl was positive in the Ames test, producing mutations in bacteria, and has been shown to cause DNA damage and chromosomal aberrations in mammalian cells *in vitro*. Although the mechanism of action of MITOXANTRONE HCl is not fully understood, its toxic effects can be seen to be directly related to its therapeutic activity. It is believed that MITOXANTRONE HCl acts as a cytotoxic (cell-killing) agent by inhibiting nucleic acid (RNA and DNA) synthesis, resulting in the death of cells that are dividing and growing (proliferating) as well as those that are in resting (non-proliferative) stages.

VII. EMERGENCY AND FIRST AID PROCEDURES

EYES: Immediately flush eyes with plenty of cool, low-pressure water for at least 20 minutes. Contact a physician if irritation occurs.

SKIN: Promptly wash with soap and cool running water. Remove contaminated clothing. Contaminated clothing should be washed before reuse. Contact a physician if irritation occurs.

INHALATION: Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Call a physician.

INGESTION: Induce vomiting immediately as directed by medical personnel. Never give anything by mouth to an unconscious person. Never induce vomiting in an unconscious person. Call a physician.

VIII. EXPOSURE CONTROL METHODS

ENGINEERING CONTROLS:
Use closed-system handling. Laboratory bench hood or local exhaust ventilation to control dust or mist.

WORK PRACTICE CONTROLS:
Minimize excess handling. Keep container closed when not in use. Wash hands, face and exposed body parts at lunch and breaks, and at end of shift.

PERSONAL PROTECTION EQUIPMENT:
If the PEL is exceeded, wear an approved, full-faced, air-purifying respirator with high-efficiency cartridges adequate to control exposure, or a full-faced, supplied-air respirator.

Two pair of latex exam gloves should be worn to prevent contact with the skin. Eye protection should be worn.

IX. SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED:
Wearing disposable coveralls, plastic or rubber gloves and an approved, full-faced, supplied-air respirator, contain and collect spilled materials.

Decontaminate the spill site by wetting the spill with a mixture of water and household dish detergent, adding bleach until the blue color disappears (slight foaming may be observed). The amounts of water, detergent, and bleach used to validate this method were arbitrarily set at approximately 25:1:50, but variation on these proportions should still accomplish the decontamination provided the blue color is eliminated. Alternatively, decontaminate with 5.6 parts calcium hypochlorite in 13 parts by weight of water for each 1 part of MITOXANTRONE HCl.

CAUTION! CHLORINE GAS MAY BE GENERATED DURING EITHER OF THESE DECONTAMINATION PROCEDURES!

Once deactivation is completed, the residual material may be flushed to a sanitary sewer with water.

WASTE DISPOSAL:
Dispose of in accordance with all Federal, State, and local regulations. Incineration is recommended. This is not a RCRA-regulated hazardous waste.

X. STORAGE AND HANDLING

Maintain good housekeeping and personal hygiene procedures.

NOVANTRONE mitoxantrone HCl CONCENTRATE FOR INJECTION should be stored at controlled room temperature, 15 - 30°C (59 - 86°F); DO NOT REFRIGERATE OR FREEZE. NOVANTRONE has a shelf life of 2 years from manufacture.

XI. SARA SECTION 313 INFORMATION

Not applicable.

XII. APPENDIX

The information and statements herein are believed to be reliable but are not to be construed as a warranty or representation for which we assume legal responsibility. User should undertake sufficient verification and testing to determine the suitability for his own particular purpose of any information or products referred to herein. NO WARRANTY OF FITNESS FOR A PARTICULAR PURPOSE IS MADE.

MATERIAL SAFETY DATA SHEET

MANUFACTURER: AMERICAN CYANAMID COMPANY
LEDERLE LABORATORIES
MIDDLETOWN ROAD
PEARL RIVER, NY 10965

MSDS No.: 01258-03
Supersedes: 01258-02
DATE: 10/27/93

EMERGENCY TELEPHONE: (914) 732-5000

I. PRODUCT IDENTIFICATION

PRODUCT NAME: MITOXANTRONE HYDROCHLORIDE
(Product Code: 01258)

DANGER! HIGHLY TOXIC. POISON B. MAY BE FATAL IF ABSORBED THROUGH THE SKIN.
CAUSES SEVERE EYE IRRITATION.
MAY CAUSE EFFECTS ON THE BONE MARROW, KIDNEY, HEART, LYMPHOID ORGANS (SPLEEN, THYMUS, LYMPH NODES), GI TRACT, AND LIVER.

CHEMICAL/THERAPEUTIC FAMILY: Anthraquinone; Anti-cancer agent

II. HAZARDOUS INGREDIENTS AND EXPOSURE LIMITS

CHEMICAL AND COMMON NAMES	CAS NO.	RECOMMENDED AIRBORNE LEVELS OSHA	TLV (1992-93)	ACCO-TWA
Mitoxantrone HCl 1,4-Dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione dihydrochloride; Mitozantrone HCl; CL 232,315; NSC-301379; "Big Blue"; NOVANTRONE; NOVANTRON	[70476-82-3]	Not est.	Not est.	0.2 µg/m³*

*American Cyanamid Company has adopted a Permissible Exposure Limit (ACCO PEL) for MITOXANTRONE HCl of 0.2 µg/m³ (TWA8).

III. PHYSICAL PROPERTIES

MOLECULAR WEIGHT: 517.5 EMPIRICAL FORMULA: $C_{22}H_{28}N_4O_6 \cdot 2HCl$

APPEARANCE AND ODOR: Dark blue to blue-black, hygroscopic, crystalline solid; no odor.

BOILING POINT: Not available MELTING POINT: 205°C (not sharp)

VAPOR PRESSURE: Not available SPECIFIC GRAVITY: ~1.5

Continued...

NOTE - This MSDS has been developed for bulk MITOXANTRONE HCl; for information related to handling the formulated product (NOVANTRONE mitoxantrone HCl CONCENTRATE FOR INJECTION), see MSDS No. 09393.

III. PHYSICAL PROPERTIES

Continued...

VAPOR DENSITY: Not available PERCENT VOLATILE: 16% water (by wt.) lost up to 140°C

LIPID SOLUBILITY: Slightly soluble in methanol; practically insoluble in acetonitrile, chloroform, acetone.

WATER SOLUBILITY: Sparingly soluble, ~12%.

pH: 3.75 (0.05% solution)

SATURATION IN AIR (BY VOLUME): Not available

EVAPORATION RATE: Not available

IV. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT: Not available
(METHOD: Not applicable (N/A))

FLAMMABLE LIMITS: Not available
LOWER: N/A UPPER: N/A

AUTOIGNITION TEMP.: Not available

HAZARDOUS COMBUSTION PRODUCTS: Not determined; combustion products will vary with fire conditions and oxygen supply to the flame. As with other organic materials, combustion will produce carbon monoxide, carbon dioxide, nitrogen oxides, irritating aldehydes, ketones and organic acids and, possibly, hydrogen cyanide. Fumes of hydrogen chloride (HCl) may also be generated.

UNUSUAL FIRE & EXPLOSION HAZARDS: No thermal hazards are expected with crude, semi-finished, and/or finished MITOXANTRONE HCl. Their process temperatures will not exceed 50°C, and the adiabatic time-to-maximum rate for all 3 states of the material is over a year at 50°C.

Crude and semi-finished MITOXANTRONE showed no impact sensitivity at room temperature. No impact hazards are expected under normal handling or transportation conditions.

V. REACTIVITY DATA

STABILITY: Stable CONDITIONS TO AVOID: N/A

POLYMERIZATION: Will not occur CONDITIONS TO AVOID: N/A

INCOMPATIBLE MATERIALS: Oxidizing agents, e.g., hypochlorite or permanganate.

DECOMPOSITION TEMPERATURE: Decomposes exothermically at 250°C.

HAZARDOUS DECOMPOSITION PRODUCTS: Chlorine gas is liberated when degraded with bleach or calcium hypochlorite (see " IX. SPILL OR LEAK PROCEDURES, below).

VI. SUMMARY OF TOXICITY AND HEALTH HAZARD DATA

SIGNS AND SYMPTOMS OF OVEREXPOSURE IN THE WORKPLACE:

EYES: Causes severe irritation to the eye with possible damage to the cornea.

SKIN: While not irritating to the skin, MITOXANTRONE HCl can be absorbed through abraded (broken) skin in toxic amounts. Accidental exposure would be expected to cause nausea, vomiting, loose stool, diarrhea, decreased white blood cell count, and increased susceptibility to infection.

INHALATION: Although low potential for exposures in excess of the ACGO PEL exists, overexposure would be expected to result in signs and symptoms similar to those described for SKIN exposure, above.

INGESTION: Although not an expected route of occupational exposure, MITOXANTRONE HCl would be expected to be an irritant to the GI tract.

MEDICAL CONDITIONS GENERALLY RECOGNIZED AS BEING AGGRAVATED BY EXPOSURE:

None known. In clinical use of MITOXANTRONE HCl (NOVANTRONE) for treatment of leukemia and other cancers, the principal toxic side effect noted is a depression of the bone marrow (myelosuppression). This effect is seen clinically as a decrease in white blood cell and platelet counts (leukopenia and thrombocytopenia). Other, acute toxicities noted in clinical use include nausea and vomiting, irritation of mucous membranes (mucositis), and hair loss (alopecia). Mild effects on the heart (cardiotoxicity) and liver (hepatotoxicity) are infrequently reported. A blue-green discoloration of the urine (due to compound excretion) is also occasionally reported. Signs and symptoms such as fever, fatigue, bleeding, infection, pain, and central nervous system disorders have also been reported in clinical use, but these may reflect the underlying disease being treated (leukemia), rather than be effects due to MITOXANTRONE treatment.

PRIMARY ROUTE(S) OF EXPOSURE/ENTRY:

Eye or skin contact (MITOXANTRONE HCl may be absorbed through the abraded (broken) skin in toxic amounts); inhalation. MITOXANTRONE HCl is poorly absorbed after oral administration.

CANCER INFORMATION:

MITOXANTRONE HCl is not listed by the National Toxicology Program (NTP) as a carcinogen. It has not been evaluated for carcinogenic potential by the International Agency for Research on Cancer (IARC). It is not regulated as a carcinogen by the Occupational Safety and Health Administration (OSHA).

In studies done by American Cyanamid Company, MITOXANTRONE HCl was not carcinogenic in either laboratory rats or mice when administered intravenously once every 21 days for 2 years.

REPORTED HUMAN EFFECTS:

American Cyanamid Company has not received any reports of adverse effects in workers handling MITOXANTRONE HCl. Other effects noted during clinical use of the drug are discussed above under "MEDICAL CONDITIONS ..."

Continued

MSDS No.: 01258-03 DATE: 10/27/93 Page 4 of 5

VI. SUMMARY OF TOXICITY AND HEALTH HAZARD DATA

Continued...

REPORTED ANIMAL EFFECTS:

American Cyanamid Company has conducted extensive animal toxicity studies on MITOXANTRONE HCl. The rat oral LD50 for MITOXANTRONE HCl is reported to be 582-721 mg/kg. MITOXANTRONE is absorbed through the skin, producing mortality at dose levels of 125 mg/kg or 500 mg/kg when applied to abraded rabbit and rat skin, respectively. It also produced significant ocular irritation, causing swelling, discharge, and reddening of the conjunctiva, and damage to the cornea and iris. The damage initially observed progressed in severity over time. Washing of the eye immediately after exposure prevented much of the damage from occurring. Ocular administration of a preparation of MITOXANTRONE HCl at 2 mg/ml in buffer caused only mild reddening of the conjunctiva. MITOXANTRONE did not cause dermal sensitization in guinea pigs (maximization test) nor was it a skin irritant.

In various studies, median lethal doses in rats and mice administered intravenous (iv.) doses of MITOXANTRONE have ranged from 4.8 to 12.2 mg/kg, while the lowest lethal doses reported in dogs and monkeys following iv. dosing were 0.5 and 1.0 mg/kg, respectively. When administered to mice and rats by intraperitoneal (ip.) injection, the reported LD50s have ranged from 8.0 to 19.7 mg/kg. Target organs affected by single or multiple doses of the drug include the bone marrow, lymphoid organs (spleen, thymus, lymph nodes), gastrointestinal tract, and the kidney; decreases in circulating red and white blood cells have also been seen.

No effects on fertility or reproductive performance were noted in rats. No evidence of teratogenicity was seen in rats or rabbits at doses that were slightly toxic to the mothers, although there was some evidence of slowed fetal kidney development, decreased fetal body weight, and premature delivery in pregnant rabbits. Since pharmacokinetic data indicate that MITOXANTRONE HCl does not cross the placenta, these effects were interpreted to have been an effect secondary to the maternal toxicity noted.

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SKIN: Promptly wash with soap and cool running water. Remove contaminated clothing. Contaminated clothing should be washed before reuse. Contact a physician if irritation persists.

VII. EMERGENCY AND FIRST AID PROCEDURES

Continued...

INHALATION: Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Call a physician.

INGESTION: Induce vomiting immediately as directed by medical personnel. Never give anything by mouth to an unconscious person. Never induce vomiting in an unconscious person. Call a physician.

VIII. EXPOSURE CONTROL METHODS

ENGINEERING CONTROLS:
Use closed-system handling, laboratory bench hood or local exhaust ventilation to control dust or mist.

WORK PRACTICE CONTROLS:
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PERSONAL PROTECTION EQUIPMENT:
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Once deactivation is completed, the residual material may be flushed to a sanitary sewer with water.

WASTE DISPOSAL:
Dispose of in accordance with all Federal, State, and local regulations. Incineration is recommended. This is *not* a RCRA-regulated hazardous waste.

X. STORAGE AND HANDLING

Maintain good housekeeping and personal hygiene procedures.

Mitoxantrone HCl should be stored at controlled room temperature, 15 - 30°C (59 - 86°F); DO NOT REFRIGERATE OR FREEZE. Mitoxantrone HCl has a shelf life of 2 years from manufacture.

XI. SARA SECTION 313 INFORMATION

Not applicable.

XII. APPENDIX

The information and statements herein are believed to be reliable but are not to be construed as a warranty or representation for which we assume legal responsibility. User should undertake sufficient verification and testing to determine the suitability for his own particular purpose of any information or products referred to herein. NO WARRANTY OF FITNESS FOR A PARTICULAR PURPOSE IS MADE.

James (Jeff) Palmer
611 West Halladay Street
Seattle, Washington 98119-2528
(206) 283 - 5260

EDUCATION

9/82 - 10/84	Masters of Science in Public Health; Industrial Hygiene and Safety Management. Completed graduate course work - degree pending thesis, University of Washington, Seattle, Washington
9/78 - 6/82	Bachelor of Science; Environmental Health, University of Washington, Seattle, Washington

EMPLOYMENT

Sr. Manager Environmental Health & Safety
10/88 - present

Immunex Corporation
Seattle, Washington

Manage all aspects of an environmental compliance and employee safety program for a biotechnology - pharmaceutical company. Responsible for developing and implementing corporate occupational safety and environmental protection programs to ensure compliance with federal, state and local regulations. Health & safety program includes radiation protection, biological and chemical safety. Environmental programs include hazardous chemical and radioactive waste handling and disposal. Additional responsibilities include the coordination of emergency planning and loss prevention activities.

Safety Engineer
2/86 - 10/88

Intel Corporation
Portland, Oregon

Manage the Safety program for semiconductor research and development facility. Evaluate and approve new manufacturing equipment, facility design, chemicals and operating procedures. Implement and coordinate emergency response teams, safety committees and training.

Consultant
11/84 - 2/86

Self-employed Consultant
Portland, Oregon

Assessed safety program requirements and prepared special reports including: incident and accident analysis; personal protection policies; emergency response policies and procedures; computer applications.

Loss Control Representative
9/81 - 12/82

C.G. Aetna Insurance Company
Seattle, Washington

Conducted field surveys and developed risk assessment reports for small to medium size companies. Analyzed hazards and provided clients with recommendations to control hazards and reduce loss potential.

MARK W. GAUTHIER
3207 23rd Avenue W.
Seattle, Washington 98199
Work: (206) 389-4066
Home: (206) 285-3944

EDUCATION:

Northeastern Illinois University, Chicago, IL
B.S. degree in Biology
December 1982
3.46/5.0 GPA

Ferris State College, Big Rapids, MI
A.A.S. degree in Industrial Chemistry Technology
May 1974
2.74/4.0 GPA

EXPERIENCE:

Regulatory Affairs, Immunex Corporation
November 1995 - present, Senior Manager, Regulatory Affairs. Responsibilities include: soliciting, compiling, reviewing and submitting new INDs, amendments to INDs, original NDAs, supplements and amendments to NDAs and other registration applications that are complete and in compliance with regulations and other regulatory requirements; maintain active INDs and approved NDA and ELA/PLAs; provide regulatory advice to corporate project teams; develop and maintain two-way communication system with the FDA to assure rapid approval of submissions. Management responsibility for one Regulatory Affairs Associate including training, development, empowerment and guidance on assignments.

Pharmaceutical Regulatory Affairs Division, The Upjohn Company
January 1992 - November 1995, Regulatory Manager, Worldwide Pharmaceutical Regulatory Affairs. Responsibilities include: soliciting, compiling, reviewing and submitting new INDs, IINDs, amendments to INDs, original NDAs, IPRDs, supplements and amendments to NDAs and other registration applications that are complete and in compliance with regulations and other regulatory requirements; maintain active INDs and approved NDA and ELA/PLAS; provide regulatory advice to corporate project teams; develop and maintain two-way communication system with the FDA to assure rapid approval of submissions.

Manufacturing Division, The Upjohn Company

October 1986 - December 1991, Pharmaceutical Manufacturing Professional III, Manufacturing Project & Regulatory Mgmt. Responsibilities include: coordination of the CM & C section of new NDA's, NADA's, ELA's, PLA's, IPRD's, supplemental applications, responses to FDA inquiries; manage the Corporate New Product Register system; represent the Manufacturing Division on Corporate Project Teams; manage Manufacturing Project teams to approve and implement new and revised products from the development stage through manufacture and release of the first lot; interact frequently with all levels of personnel throughout the company on issues relating to the development, approval and introduction of new and revised products.

Upjohn Diagnostics, The Upjohn Company

September 1985 - October 1986. Biochemistry Assistant, Production and Distribution. Responsibilities: production planning and scheduling; development and stability testing of products; adherence to SOP's and cGMP's; purification of leukotrienes; iodination of peptides.

G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL

June 1983 - September 1985. Analytical Chemist, Research Analytical Group, Separations Dep't. HPLC, TLC and GC method development; pH stability studies; enantiomer separations; HPLC quantitation of biologically active materials in plasma.

May 1974 - June 1983. Technician II, 1974 - 1976; Technician III, 1976 - 1979; Biologist, 1979 - 1983. Responsibilities: development of RIA's, in vitro assays and in vivo models for contragestation and benign prostatic hyperplasia projects; enzyme purification; oral and written presentations; analysis of data.

OTHER:

The experience acquired after 21 years in the pharmaceutical industry has been multifaceted. My background includes biological research, analytical support, development and support of marketed products, preparation of regulatory documents for domestic and international registration of new and revised products and project management. While performing the usual aspects required for these functions, I have developed excellent communication skills. In my present position, it is essential that one have the ability to handle numerous projects at the same time and to be flexible to re-prioritize as needed to meet corporate objectives. I am very adaptable and work well with minimal supervision.

B. PHARMACOLOGIC CLASS, SCIENTIFIC RATIONALE, INTENDED USE AND POTENTIAL CLINICAL BENEFITS

B.1 PHARMACOLOGIC CLASS

Mitoxantrone, known also as dihydroxyanthracenedione dihydrochloride (DHAD), is a synthetic anthracenedione antineoplastic agent derived from the anthraquinone dye ametandrone. Mitoxantrone is structurally similar to the anthracyclines doxorubicin and daunorubicin, having a planar polycyclic aromatic ring structure. It is a hygroscopic, blue-black crystalline solid, with a molecular weight equal to 517.4 Daltons. Mitoxantrone is an anti-neoplastic agent that exerts its cytotoxic effects by intercalating deoxyribonucleic acid (DNA) by a hydrogen-bonding mechanism. The compound causes DNA-protein crosslinks and DNA-protein double- and single-stranded breaks. Mitoxantrone also exerts its cytotoxic activity by interfering with ribonucleic acid (RNA) molecules in the cell nucleus and by inhibiting topoisomerase II enzymatic activity (Faulds 1991).

The pharmacokinetic profile of mitoxantrone is well established. Mitoxantrone exhibits triexponential pharmacokinetics, with rapid initial (α) distribution phase, an intermediate (β) distribution phase, and a much slower (γ) elimination phase (Ehninger 1990). Autopsy studies in humans have shown extensive dose-related distribution into most tissues apart from the central nervous system (Stewart 1986). Mitoxantrone has a large volume of distribution (1000-4000 L) indicating that much of the drug is sequestered in tissues. For the most part, mitoxantrone is metabolized by the liver and eliminated in the bile. Renal clearance accounts for less than 10% of the total clearance of mitoxantrone. Details on the structure, mechanism of action, pharmacology, and pharmacokinetic parameters of this agent were included in the original NDA submission # 19-297.

B.2 SCIENTIFIC RATIONALE

In 1987, mitoxantrone was approved by the Food and Drug Administration (FDA) for the therapy of acute non-lymphocytic leukemia in adults. The scientific rationale for investigating mitoxantrone for the palliative treatment of patients with hormone-refractory prostate cancer (HRPC) is supported by its known antitumor activity in several malignancies and its favorable safety profile, even in older patients.

Prostate cancer is the most common cancer in men and the second leading cause of death due to cancer in men. The American Cancer Society estimates that about 317,000 men will be diagnosed with prostate cancer during 1996 and about 41,000 will die from the disease this year (Parker, 1996). The principal form of systemic therapy for prostate cancer is endocrine manipulation aimed at androgen ablation. The majority of patients treated with hormone therapy eventually experience disease progression due to the development of resistance to endocrine manipulation. The median duration of response from the beginning of hormone therapy to progression is approximately 3.5 years. The outcome of patients with HRPC is bleak due to rapid disease progression, poor performance status, and decreased quality of life (QOL). Patients with HRPC generally have bone pain due to diffuse skeletal metastases, dysuria, edema, fatigue, anorexia, depression, and weight loss. The median time to death of patients with HRPC is six to twelve months.

Currently, there is no cure for HRPC. The principal objective of current therapies is symptom palliation. Because prostate cancer occurs more frequently in older patients, usually over 60 years old, co-morbid conditions compromise the use of potentially effective but possibly toxic therapy. An agent must be effective and well tolerated in order to be clinically beneficial in this older patient population.

In Phase I and II trials, mitoxantrone has demonstrated substantial antitumor activity in a variety of malignancies including leukemia, lymphoma, breast cancer, and ovarian cancer. The safety profile of mitoxantrone has been found to be favorable when given at a dose averaging 12 mg/m^2 every three weeks, and its primary toxicity is neutropenia. At doses up to 28 mg/m^2 given every 3-4 weeks, dose-limiting toxicity is myelosuppression.

In the 1980s, Phase I and II studies were conducted to evaluate mitoxantrone given at various doses and schedules in HRPC. In these early trials, approximately 290 patients were reported to have received mitoxantrone alone or in combination with other cytotoxics. Overall, these trials confirmed that mitoxantrone has a favorable safety profile in this patient population and demonstrated a palliative benefit in 25 to 50% of patients with symptomatic disease. A Canadian Phase III, open-label, prednisone-controlled trial (CCI-NOV 22) was conducted in 161 subjects with HRPC using pain control as the primary endpoint for response. This pivotal trial

showed that, compared to single agent prednisone, the combination of mitoxantrone plus prednisone resulted in a significantly higher palliative response rate (29% vs. 12%, p = 0.011), a significantly longer duration of palliative response (median 229 days vs. 53 days, p = 0.0001), and a significantly longer time to disease progression (median 301 days vs. 132.5 days, p = 0.0001). These benefits were achieved with relatively low toxicity and had an overall positive effect on QOL. The favorable effect of mitoxantrone on pain reduction and improvement of QOL was confirmed in a recent Phase III trial conducted in the U.S. by the Cancer and Leukemia Group B in 242 subjects with HRPC Study 9182).

B.3 INTENDED USE

Mitoxantrone in combination with corticosteroids is indicated as initial chemotherapy for treatment of patients with prostate cancer after failure of primary hormonal therapy.

B.4 POTENTIAL CLINICAL BENEFIT

Two Phase III trials investigating mitoxantrone in combination with corticosteroids and the published reports of Phase I and II studies have shown that mitoxantrone provides substantial pain palliation in approximately 25 to 50% of patients with symptomatic HRPC. The Phase III pivotal trial CCI-NOV 22 has shown that the duration of palliative response is significantly longer than that achieved with prednisone alone. Decreased pain resulted in a decrease in analgesic use and a corresponding improvement in QOL measures in the two Phase III trials. These favorable responses led to an overall improvement in patient well-being. These results were obtained with relatively low toxicity and with no reports of unusual adverse events.

E. CLINICAL DATA SUMMARY

E.1 SUMMARY OF PIVOTAL TRIAL CCI-NOV 22 IN HRPC

Study CCI-NOV 22 was activated in September 1990 and closed to enrollment in April 1994. It was chaired by Ian Tannock, M.D., Ph.D., filed with the Canadian Health Protection Branch, and sponsored by In October 1995 the study database was transferred from to Immunex Corp. and the final clinical/statistical report was prepared.

The objective of the study was to compare the effectiveness of mitoxantrone plus low-dose prednisone to that of low-dose prednisone alone in providing relief of pain for subjects with symptomatic metastatic prostate cancer following failure of hormonal therapy. The study evaluated mitoxantrone, a marketed drug, in an investigational setting of HRPC. The study was designed to reflect typical oncology practice. It was conducted nationwide at 11 Canadian sites involving academic centers as well as community hospitals. It was open-labeled, and enrolled subjects with no limitation with respect to age or prior medical history. Because it was estimated that only 10 to 20% of subjects would respond to the treatment administered in the control arm, i.e., low-dose prednisone alone, the protocol permitted crossover to receive mitoxantrone.

E.1.a Study Objectives, Design, and Endpoints

The primary objective of the study was to assess improvement in pain as defined by a six-point pain scale, the present pain intensity (PPI) scale, without an increase in analgesic score and no evidence of disease progression.

The secondary objectives of the study were to compare the two randomized groups in terms of duration of response and survival, improvement in QOL, and disease response by National Prostate Cancer Project (NPCP) criteria.

This was a multicenter, prospective, open-label, randomized Phase III study with stratification according to baseline Eastern Cooperative Oncology Group (ECOG) performance status. Subjects with chemotherapy-naive HRPC were eligible if they had symptoms that could not be relieved by loco-regional therapy.

Subjects were randomized (central randomization) to receive mitoxantrone plus prednisone (M+P) or prednisone alone (P). All subjects received prednisone 5 mg orally (po) twice daily (BID) until death or serious toxicity occurred. Subjects randomized to the M+P arm also received mitoxantrone 12 mg/m^2 by intravenous (IV) push every 3 weeks. Mitoxantrone dose was increased or decreased by 2 mg/m^2 on the basis of nadir blood cell counts in the preceding cycle. Subjects in the M+P group achieving a palliative response continued on prednisone alone when they had reached the mitoxantrone cumulative dose of 140 mg/m^2. If disease progression occurred after stopping mitoxantrone, treatment could be restarted if a multigated acquisition (MUGA) scan or echocardiogram showed a normal left ventricular ejection fraction (LVEF). Subjects randomized to the P arm crossed over to receive mitoxantrone at the time of disease progression or could be crossed over if their disease was stable after six weeks of therapy.

All randomized subjects were evaluated for response based on the following prospectively defined endpoints that were considered indicative of a meaningful clinical benefit:

- A 2-point improvement in the 6-point PPI scale that was not accompanied by an increase in analgesic score and that was maintained for two successive visits three weeks apart. Subjects who had mild pain (1+) at baseline were to have complete relief of pain. The self-assessed PPI scale used consisted of the following six terms: no pain (0), mild pain (1+), discomforting pain (2+), distressing pain (3+), horrible pain (4+), and excruciating pain (5+).
- Time to disease progression (for responders only) that was measured from the date of first treatment with prednisone alone or prednisone plus mitoxantrone until evidence of progression defined by the occurrence of any of the following: increase in PPI by $\geq$ 1 point for 2 consecutive cycles, increase in analgesic score by $\geq$ 25%, and/or administration of palliative radiation therapy.
- Duration of survival.

Subjects recorded in a subject diary the name, strength, and number of analgesics for each day in the cycle. The daily analgesic score was calculated using a numerical scale. Each standard dose of non-narcotic analgesics was scored as 1. Each dose of oral narcotics was scored as 2. Each dose of parenteral narcotics was

scored as 4. Analgesic scores were summed for the last 7 days of each cycle and then averaged for one day to provide an estimate of the daily analgesic score.

The effect of therapy on QOL was evaluated in both arms using assessments that were self-administered by subjects during clinic visits. The following QOL instruments were used:

- EORTC QOL Questionnaire (EORTC - Q30C), consisting of 30 items grouped into 5 subscales that addressed symptoms and physical activity, functional activity, psychosocial interaction, overall physical assessment, and global QOL.
- Specific Prostate Module, an 11-item module including questions about pain and possible side effects from analgesic medication.
- A series of 9 linear analog self-assessment (LASA) scales evaluating various aspects of QOL.

E.1.b Subject Characteristics

A total of 161 subjects were enrolled in this study; 80 subjects were randomized to the M+P arm and 81 subjects were randomized to the P arm. Forty-eight subjects (59%) randomized to the P arm subsequently crossed over to receive mitoxantrone. Thus, a total of 128 subjects were treated with mitoxantrone in this study.

The two groups were similar with respect to baseline demographic characteristics. Median age was 67 years for both groups. Distribution of ECOG performance status scores was similar in the two treatment groups. Approximately 37% of subjects in each treatment group had an ECOG performance status of 2 or 3. All subjects had failed prior hormonal therapy. Similar numbers of subjects from both groups had metastases to bone, lymph nodes, viscera, and other sites. There was no difference in baseline prostate specific antigen (PSA) levels between the two groups. The baseline PPI scores were comparable between the two treatment groups with a median PPI score of 2 (range 0 - 4) in the two groups. The median baseline analgesic score was 17.7 in the M+P group and 14 in the P group. Median baseline scores for all QOL measures were comparable in both groups.

E.1.c Efficacy Summary

Palliative response (prior to crossover)

A palliative response, defined as a 2-point decrease in PPI without increase in analgesic score that was maintained for 2 consecutive cycles, was achieved in 23 subjects (29%) in the M+P group and 10 subjects (12%) in the P group ($p = 0.011$). The median times from study entry to achieving a palliative response were 65 days for the M+P group and 73.5 days for the P group.

Time to disease progression (responders only)

The Kaplan-Meier estimates of the median time to disease progression, defined as the time from the date of first treatment to the date of the assessment of progression, were 301 days in the M+P group and 132.5 days in the P group ($p = 0.0001$).

Duration of palliative response (responders only)

The Kaplan-Meier estimates of the median duration of response, defined as the time from the date of achieving a response (a 2-point decrease in PPI without increase in analgesic score that was maintained for 2 consecutive cycles) to the date of the assessment of progression, were 229 days in the M+P group and 53 days in the P group ($p = 0.0001$).

Overall palliative benefit

To assess overall palliative benefit, a second criterion of response was defined prospectively as a decrease in analgesic score of at least 50% from baseline without an increase in PPI at any time. Seven subjects in each group responded based on this second criterion. Thus, 30 subjects (37.5%) in the M+P group and 17 subjects (21%) in the P group satisfied either the primary or secondary criteria for palliative response, demonstrating a nearly double palliative response rate with M+P administration ($p = 0.025$).

Changes in PSA levels

Data on serial PSA concentrations were available in 83% of the subjects. A decrease of $\geq 75\%$ in PSA levels from baseline was achieved in 27% of subjects in the M+P group and 14% of subjects in the P group ($p = 0.077$).

Efficacy after crossover

Of the 48 subjects in the P group who crossed over to receive mitoxantrone, 9 (19%) demonstrated a palliative response as defined by the primary criterion of response (a 2-point decrease in PPI score without increase in analgesic score that was maintained for 2 consecutive cycles).

Effect of mitoxantrone dose on palliative response (M+P group only)

The 80 subjects in the M+P group received a median cumulative dose of mitoxantrone of 73 mg/m^2 (range 12 - 212 mg/m^2). The median individual dose administered was 12 mg/m^2 (range 2 - 18 mg/m^2). There was no significant difference in palliative response rates on the basis of the dose of mitoxantrone administered. There was a trend toward longer time to progression and duration of palliative response is subjects receiving higher mitoxantrone dose ($\geq$14 mg/m^2).

Effect of treatment on QOL

Subjects randomized to the M+P group had greater improvement in scores than subjects randomized to the P group for the following LASA scales: pain, physical activity, fatigue, appetite, mood, and overall well-being. Changes in LASA results were comparable in the two groups for the following scales: constipation, family relationships, and passing urine. Subjects randomized to the M+P group had consistently better scores than subjects randomized to the P group for all five domains evaluated by the EORTC-Q30C questionnaire (symptoms and physical assessment, functional activity, psycho social effect, overall physical activity, and overall QOL) and the Prostate Module.

Survival

Median time to death was similar for the two groups, as would be expected in a study that included crossover between groups. The Kaplan-Meier estimates of the median time to death were 338.5 days for the 80 subjects randomized to the M+P group and 324 days for the 81 subjects randomized to the P group ($p = 0.2324$).

The Kaplan-Meier estimates of median time to death were significantly longer for subjects in the M+P group (338.5 days) than for subjects in the P group (145 days) when subjects randomized to the P group who subsequently crossed over are excluded ($p = 0.0086$).

E.1.d Safety Summary

Deaths

Five subjects in the group randomized to M+P died while on study or within 30 days of the last dose of mitoxantrone: one subject died of pneumonia and four subjects died of malignant disease. Six subjects randomized to the P group and who subsequently crossed over died within 30 days of the last dose of mitoxantrone. All six subjects died of malignant disease.

Withdrawals

In the group randomized to M+P, 47 subjects withdrew due to progression, 11 due to adverse events, 6 died, 4 withdrew due to other reasons, and 2 refused further treatment. In the group randomized to P, 57 subjects withdrew due to progression, 8 for other reasons, 6 died, 3 refused further treatment, 3 withdrew due to protocol violations and 1 withdrew due to adverse event.

Serious adverse events (SAEs)

In total, 36 subjects experienced 43 SAEs during the course of the study. The 43 SAEs were reported in the two groups as follows: 21 SAEs in the M+P group and 22 SAEs in the P group (15 prior to crossover and 7 after crossover). The most frequently reported SAE was death. The second most frequently reported SAE was infection.

Adverse events (World Health Organization [WHO] Grading)

No Grade 3 or 4 adverse events occurred in ≥ 5% of subjects in either group. Events of any grade occurring in 10% or more of subjects randomized to the M+P group were nausea (61%), fatigue (31%), alopecia (29%), anorexia (25%), constipation (16%), and dyspnea (10%). Events of any grade occurring in 10% or more of subjects randomized to the P group were nausea (35%), constipation (16%), and fatigue (10%).

Cardiotoxicity

Seven of 128 subjects (5%) treated with mitoxantrone experienced a cardiac event, which was defined as any asymptomatic decrease in LVEF below normal, a congestive heart failure (CHF), or any myocardial ischemia. Three subjects had

symptoms of CHF. The cumulative dose of mitoxantrone received by these seven subjects ranged from 48 mg/m^2 to 212 mg/m^2.

Laboratory toxicity (National Cancer Institute [NCI] Common Toxicity Criteria)
Grade 3/4 laboratory toxicities occurring in ≥ 5% of subjects randomized to the M+P group consisted of neutropenia (81% of subjects), leukopenia (75%), elevated alkaline phosphatase (30%), elevated lactic dehydrogenase (LDH) (14%), and hyperglycemia (6%). Grade 3/4 laboratory toxicities occurring in ≥ 5% of subjects randomized to the P group (excluding data after crossover) consisted of elevated alkaline phosphatase (34% of subjects), elevated LDH (18%), and hyperglycemia (10%).

E.1.e Discussion and Conclusions

The rate of palliative response was significantly higher in the M+P arm than in the P arm (29% vs. 12%, p = 0.011). Median time to disease progression was significantly longer in the M+P arm than in the P arm (301 vs. 132.5 days, p = 0.0001). The median duration of palliative response was significantly longer in the M+P arm than in the P arm (229 days vs. 53 days, p = 0.0001). Median time to death for all subjects was comparable in the two arms (338.5 days vs. 324 days for the M+P and P groups respectively, p = 0.2324), not unexpected in a crossover study. When subjects randomized to the P group who subsequently crossed over were excluded from survival analyses, there was a 6-month increase in median survival for subjects in the M+P group (p = 0.0086).

The evaluation of overall palliative benefit was also in favor of the M+P arm: 37.5% of subjects randomized to M+P achieved an overall palliative benefit compared to 21% of subjects randomized to P only (p = 0.025), demonstrating a near doubling of the palliative response achieved with mitoxantrone.

There was a trend favoring mitoxantrone for a clinically meaningful decrease in PSA levels (≥ 75% decline). This was achieved in 27% of subjects randomized to the M+P arm compared to 14% of subjects randomized to the P arm (p = 0.077).

Nine of the 48 subjects (19%) randomized to the P arm who crossed over to receive mitoxantrone achieved a palliative response indicating that mitoxantrone activity is

not compromised by prior corticosteroid therapy. Median time to disease progression for the non-responders was 70 days for the M+P group and 54 days for the P group ($p = 0.0116$), indicating that failure to respond to mitoxantrone therapy does not worsen subsequent outcome.

The effect of therapy on QOL is more difficult to evaluate due to the complexity of the tools used and the multiple comparisons needed to assess the results. Following therapy, there were changes in QOL measures in both arms in varying directions. When evaluating the best score (most beneficial to patients) for each domain at any time during follow up, there was a consistent trend toward better results achieved in the M+P arm compared to the P arm. These scores were substantially better in the M+P group when QOL measures evaluating disease-related symptoms were assessed, but were less discriminative when evaluating global QOL measures.

When Study CCI-NOV 22 was conducted, the safety profile of mitoxantrone had been well established in previously reported Phase I-III trials and from the clinical experience gained since drug approval. This study did not reveal previously unreported adverse events. Most of the adverse events that occurred were of Grade 1 or 2 intensity; there were no adverse events of Grade 3 or 4 intensity that occurred in $\geq 5\%$ of patients in either group. The SAEs that occurred were not unusual for this patient population. There were reports of cardiac events in 5% of subjects treated with mitoxantrone (M+P arm and P arm after crossover). Some of these events occurred in patients who had a prior history of cardiac disease. Only three of these subjects developed CHF, the most serious cardiac complication of mitoxantrone. This incidence is comparable to the clinical experience with mitoxantrone. Grade 3 or 4 myelosuppression was the most frequent laboratory toxicity occurring in subjects who received mitoxantrone, a result comparable to that reported with this agent in clinical experience.

In conclusion, Study CCI- NOV 22 demonstrated that mitoxantrone plus prednisone is a safe and effective treatment for patients with HRPC. Mitoxantrone doubled the palliative response rate achieved with prednisone alone and significantly increased time to progression and duration of palliative response. This was achieved without significant toxicity in most patients and was associated with improved QOL in many patients.

E.2 OTHER INFORMATION ON MITOXANTRONE IN HRPC

E.2.a Summary of a Phase III U.S. Trial: Study 9182

Study 9182 was activated in October 1992 and closed to enrollment in September 1995. It was chaired by Philip W. Kantoff, M.D. and conducted under an IND granted It was sponsored initially by Lederle Oncology and then by Immunex Corp. In February 1996 the study database was transferred from to Immunex and a clinical/statistical report was prepared. Because the study had recently closed to enrollment, follow-up information was not available for some subjects.

The aim of the study was to compare the effectiveness of mitoxantrone plus hydrocortisone (M+H) to that of hydrocortisone alone (H) in subjects with metastatic prostate cancer following failure of hormonal therapy. The study evaluated mitoxantrone, a marketed drug, in an investigational setting of HRPC. The study was designed to reflect typical oncology practice. It was conducted groupwide by involved academic centers as well as affiliate hospitals, was open-labeled, and enrolled subjects with no limitation with respect to age or medical history. Because evaluation of survival was the primary endpoint of the study, the protocol did not permit crossover between treatments. It did allow the administration of further chemotherapy in the event of disease progression following administration of study drugs.

E.2.a.1 Study Objectives, Design, and Endpoints

The primary objective of the study was to compare the survival of subjects with metastatic HRPC treated with M+H to a control group treated with (H).

The secondary objective of the study was to compare the impact of M+H and H alone on QOL as assessed by questionnaires measuring physical functioning and cancer-related symptoms.

This was a randomized, open-label, groupwide, Phase III study with stratification based on performance status (0-1 vs. 2), disease status (measurable vs.

evaluable), and number of prior endocrine manipulations (1 vs. ≥ 2). Subjects were eligible if they had locally advanced or metastatic prostate cancer, had failed prior hormonal therapy, were previously untreated with chemotherapy for their prostate cancer, and had disease progression as demonstrated by clinical signs or symptoms, worsening imaging tests, and/or isolated rise in PSA levels.

In the H arm, subjects were administered 40 mg oral hydrocortisone daily. In the M+H arm, subjects were administered 14 mg/m^2 mitoxantrone IV every 21 days plus 40 mg oral hydrocortisone daily. The dose of mitoxantrone could be decreased by 25% or 50% based on nadir blood cell counts in previous cycles. Hydrocortisone was to be continued until death or serious toxicity occurred. The maximum cumulative mitoxantrone dose allowed was 160 mg/m^2. Crossover between treatments was not allowed, but additional cytotoxic therapy was permitted upon disease progression.

All subjects were evaluated for the following prospectively defined endpoints:

- Duration of survival.
- Response rates using NPCP criteria.
- Effect of therapy on PSA levels.
- Effect of therapy on analgesic use.

The effect of therapy on QOL was evaluated in both arms using assessments conducted during clinic visits (first assessment) or by phone (subsequent assessments). The following validated QOL instruments were used:

- The Functional Living Index - Cancer (FLIC), a 22-item cancer-specific questionnaire.
- The Symptom Distress Scale (SDS), a 13-item instrument developed to evaluate general symptoms in oncology patients.
- A sexual and urological functioning scale.
- A functional limitation scale.
- A scale evaluating the effect of pain on daily activity, a 7-item questionnaire aimed at evaluating the effect of pain on mood, relationship, walking ability, sleep, work, and enjoyment of life.

E.2.a.2 Subject Characteristics

A total of 242 subjects were enrolled at 62 sites; 119 subjects in the M+H arm and 123 subjects in the H arm. The two treatment groups had similar baseline demographic characteristics. Median age was 72 years in both groups. Distribution of performance status scores was similar in the two treatment groups, with 86% of subjects in the M+H arm and 89% of subjects in the H arm presenting with a performance status of 0 or 1. All subjects had failed prior hormonal therapy. Similar numbers of subjects from both groups had metastases to bone, lymph nodes, viscera, and other sites. Approximately 30% of subjects in each group had measurable disease. There was no difference in baseline PSA levels between the two groups. No analgesics were used at study entry in 37% of subjects in the M+H arm and in 39% of subjects in the H arm. Median baseline scores for all QOL measures were comparable in both treatment groups.

E.2.a.3 Efficacy Summary

Survival

At the time of database transfer, 58 subjects (49%) in the M+H group and 68 subjects (55%) in the H group were alive. The median time to death, estimated by the method of Kaplan-Meier, was 334 days for the M+H group and 359 days for the H group ($p = 0.3298$).

Disease response and progression after response

Using the NPCP criteria to define meaningful clinical response, a higher percentage of subjects randomized to the M+H group achieved a partial response (PR) or stable disease (SD) than in subjects randomized to the H group (54% vs. 47%, respectively). When only subjects with available data were assessed, 65 of 100 (65%) subjects in the M+H group and 57 of 105 (54%) subjects in the H group achieved a partial response or stable disease.

Based on the available data, 35 of the 65 subjects (54%) who achieved a PR or SD in the M+H group subsequently progressed compared to 40 of 57 subjects (70%) who achieved PR or SD in the H group and then progressed ($p = 0.064$). For all subjects enrolled, the Kaplan-Meier estimated median time to disease progression was 218 days in the M+H group and 122 days in the H group ($p = 0.0654$).

Effect on analgesic use

There was a trend toward reduced analgesic use over time in the M+H group compared to the H group.

Effect on PSA levels

Serial PSA levels were reported for 201 subjects (83%). Significantly more subjects had a decrease in PSA levels of $\geq$ 50% from baseline in the M+H group than in the H group, 31% versus 17% ($p = 0.023$). A decrease in PSA levels of $\geq$ 75% occurred in 14% of subjects in the M+H group and 7% of subjects in the H group ($p = 0.112$).

Effect on QOL

Of the five instruments evaluating various aspects of QOL used in the study, two FLIC questions, two SDS questions, and the Impact of Pain scale were identified retrospectively as indicative of an effect of pain on QOL and were analyzed. There was a trend toward more improvement over time in pain-related QOL measures in the M+H group than in the H group. This trend was more evident if the subset of subjects using analgesics at baseline was evaluated separately.

E.2.a.4 Safety Summary

Deaths

A total of 116 deaths have been reported: 61 deaths (51% of subjects) in the M+H group and 55 deaths (45% of subjects) in the H group. Causes of death were comparable in the two groups. Except for disease progression, there was no single cause of death that accounted for more than 5% of deaths in either group.

Withdrawals

Reasons for withdrawals were reported for 174 subjects. In the M+H group, 58 subjects withdrew due to progressive disease, 13 due to adverse events, 3 due to death, 2 due to patient refusal, and 5 due to other reasons. In the H group, 79 subjects withdrew due to progressive disease, 3 due to patient refusal, 2 due to death, 1 due to an adverse event, and 4 due to other reasons.

Serious Adverse Events

A total of 24 SAEs were reported: 15 SAEs in 8 subjects in the M+H group and 9 SAEs in 8 subjects in the H group. One SAE (cerebral hemorrhage in the M+H group) was considered possibly related to study drug by the Investigators and all other SAEs were considered unrelated. The SAEs that were reported in this study were consistent with the subjects' primary disease or comorbid conditions.

Adverse Events Grading)

Grade 3-5 clinical toxicities occurring in ≥ 5% of subjects in either treatment group were pain, either related to cancer or not (10% in the M+H group and 3% in the H group, p = 0.04) and sterility (6% in the M+H group and 4% in the H group, p = 0.6). The distribution and frequency of Grade 1-2 clinical toxicities were comparable in the two groups except for cardiac function anomalies that were noted in 16% of subjects in the M+H group compared to 1% of subjects in the H group.

Laboratory Toxicities Grading)

Grade 3-5 laboratory toxicities that occurred in ≥ 5% of subjects in the M+H group consisted of lymphopenia (65% of subjects), neutropenia (57%), leukopenia (57%), increased alkaline phosphatase (11%), hyperglycemia (7%), and anemia (5%). Grade 3-5 laboratory toxicities that occurred in ≥ 5% of subjects in the H group consisted of lymphopenia (13% of subjects), increased alkaline phosphatase (9%), and hyperglycemia (5%).

E.2.a.5 Discussion and Conclusions

There was no difference in survival times between the two treatment groups. These results were possibly confounded by therapies given after the failure of study drug treatments. For tumor response and duration of response, there was a trend for more subjects in the M+H group achieving a partial response or stable disease than in the H group (65% and 54% respectively). With the follow-up information currently available for subjects who achieved partial response or stable disease, fewer subjects in the M+H group had progressed compared to the H group (54% and 70% respectively, p = 0.064). Median time to disease progression was 218 days in the M+H group and 122 days in the H group (p = 0.0654). Median time to progression or death was 159 days for subjects in the M+H group and 118 days for subjects in the H group (p = 0.0723).

The data suggested a reduction in analgesic use over time in the M+H group compared to the H group. The power of this study to detect a statistically significant reduction in analgesic use may have been reduced by the enrollment of subjects without cancer-related pain (approximately one third of subjects reported no pain at entry). There were significantly more subjects who achieved a $\geq$ 50% decrease in PSA levels from baseline in the M+H group than in the H group (31% versus 17%, p = 0.023). There was a trend toward more subjects in the M+H group achieving PSA level decreases of $\geq$ 75% (14% versus 7%, p = 0.112).

Five parameters from the five QOL instruments used in the study were selected for analysis based on their applicability toward evaluating the impact of pain on QOL. When change from baseline and percent change from baseline were analyzed, a trend toward greater reduction in pain related QOL assessments was reported in the M+H group compared to the H group.

There were no unexpected safety findings in this study. The toxicity profile observed in this study that evaluated subjects with a median age of 72 years was no different than previously reported profiles. The causes of death reported are commonly seen in HRPC patients, and there was no single cause of death due to toxicity that accounted for more than 5% of deaths in either arm. There were few reports of SAEs (15 in the M+H group) and these SAEs were typical for HRPC patients. The incidence of Grade 3, 4, or 5 toxicities was low in both treatment groups. The majority of toxicities were of Grade 1 or 2 intensity. The only Grade 3-5 toxicity occurring in more than 5% of subjects in either treatment group that was significantly higher in the M+H group was pain, either related or unrelated to cancer (10% vs. 3% in the H group; p = 0.04). Grade 3-5 laboratory toxicities that were more frequent in the M+H group were leukopenia, lymphopenia, and neutropenia.

There was a higher incidence of cardiac function anomalies in the M+H group (18.3%) than in the H group (1.2%). These events were mainly of Grade 1 or 2 intensity. The higher incidence of cardiac events in the M+H group compared to the H group was not unexpected since mitoxantrone is known to be cardiotoxic. The rate of cardiotoxic events was not higher than the rates reported in other studies of mitoxantrone.

In conclusion, mitoxantrone, administered in conjunction with hydrocortisone, was safe and well tolerated in subjects with HRPC. Compared to the H group, the M+H group showed greater improvement in tumor response (PR and SD) and longer duration of response. Fewer subjects in PR or SD in the M+H group progressed compared to the H group. Median time to disease progression and time to progression or death was greater in the M+H group compared to the H group. There was a trend toward reduced analgesic usage over time in the M+H group compared to stable usage in the H group. For pain-related QOL endpoints, there was a trend toward greater improvement (less pain) for subjects in the M+H group for most parameters analyzed.

E.2.b Canadian Phase II Studies

E.2.b.1 Study CCI-NOV 6

Between February 1985 and June 1986, the use of a combination of IV mitoxantrone, 5-fluorouracil, and mitomycin was investigated in 41 patients with HRPC. Mitoxantrone at a dose of 10 mg/m^2 and 5-fluorouracil at a dose of 600 mg/m^2 were both administered IV every 3 weeks; mitomycin was given IV at a dose of 10 mg/m^2 every six weeks. Patient mean age was 67.6 years (range 48 - 83 years). The median cumulative dose of mitoxantrone was 34 mg/m^2 (range 8 - 70 mg/m^2) and the median single dose was 10 mg/m^2 (range 5 - 11 mg/m^2). Toxicity caused 24% of the treatments to be delayed. There were three responses (7%) based on the NPCP criteria and a response rate of 44% based on tumor measurement (4 of 9 patients). Palliative response based on analgesic use was 45% (14 of 31 patients). The Kaplan-Meier estimate of the median time to disease progression was 108 days (range 21 - 385 days), and the median survival was 252 days (range 53 - 700 days). WHO Grade 4 hematologic toxicity occurred in eight patients (20%). There were no reports of Grade 4 gastrointestinal toxicity and only one report of Grade 3 gastrointestinal toxicity. Other adverse events noted included sepsis (n = 2), neutropenic fever (n = 1), deep vein thrombosis (n = 2), transient ischemic attack (n = 1), acute renal failure (n = 1), and angina (n = 1).

E.2.b.2 Study CCI-NOV 14

A Phase II trial of single-agent mitoxantrone given IV every 3 weeks was conducted between February, 1984 and March, 1988 in 38 patients with HRPC. The initial dose of mitoxantrone was 12 mg/m^2 per cycle, and the dose could be adjusted up or down to achieve a Day 21 absolute granulocyte count in the 2,000 to 2,500/mm^3 range. Patient mean age was 67.7 years (range 39 - 87 years). Nine patients had measurable disease at study entry. Single doses of mitoxantrone ranged from 7 to 26 mg/m^2 and cumulative doses ranged from 10 to 154 mg/m^2. Measurable response rate was 22% (2 of 9 patients) and palliative response based on analgesic use was 35% (12 of 34 patients). The Kaplan-Meier estimate of the median time to disease progression was 80.5 days (range 21 - 252 days) and the median survival time was 237.5 days (range 40 - 570 days). WHO Grade 4 hematologic toxicity occurred in one patient (3%). There was one report of Grade 3 gastrointestinal toxicity, one case of pneumonia, and one report of dysgeusia.

E.2.b.3 Study CCI-NOV 16

The combination of mitoxantrone and prednisone was investigated in 27 patients with HRPC. Mitoxantrone was given IV at a dose of 12 mg/m^2 every 3 weeks with dose adjustment based on hematologic nadirs. Prednisone was given orally at a dose of 5 mg twice a day. Patient mean age was 69 years (range 54 - 87 years). The mean number of treatment courses was 4.7. Nine of 25 (36%) assessable patients achieved an overall palliative complete response (n = 4) or partial response (n = 5). By NPCP criteria, there was one PR which was maintained for 9 months and 12 patients had SD for > 2 months. A decrease in PSA levels of $\geq$ 50% was noted in 5 of 23 (22%) evaluable patients. Assessments of QOL showed a reduction in pain and improvement in social and emotional functioning. There were no Grade 3 non-hematologic toxicities reported. Grade 2 nausea was noted during 2% of cycles. Grade 3-4 neutropenia was noted in 65% of cycles and neutropenia < 500/mm^3 was noted in 15% of cycles. There were no reports of Grade 4 thrombocytopenia, febrile neutropenia, or cardiotoxicity. The favorable results observed in this pilot study led to the Phase III trial CCI-NOV 22.

E.2.c Other Published Studies

Other Phase I and II studies of mitoxantrone in HRPC were reported in the medical literature. These studies evaluated mitoxantrone given at various doses and schedules as a single agent or in combination with other agents. These studies demonstrated that mitoxantrone has modest cytoreductive activity, an effect comparable to that reported with other cytotoxic agents investigated in HRPC. Mitoxantrone, however, was generally well tolerated by this older patient population and was associated with substantial palliation of cancer-related pain. The table that follows lists the reported studies of mitoxantrone in HRPC.

Studies of Mitoxantrone in HRPC

Mitoxantrone Dose mg/m^2	Other Agents	No. of Subjects	Rates Palliative Response	Response by NPCP Criteria		Reference
Single-agent				n	%	
12 q3w	None	37	Not reported	7/35	20%	Osborne 1983
12 q3w	None	29	8 of 29 (28%)	14/29	48%	Raghavan 1986
12 q3w	None	38	11 of 34 (35%)	0	0	CCI-NOV 14
1.0-1.5/d x14	None	15	Not defined	5/15	33%	Kantoff 1993
3-4 qw	None	14	Not reported	5/14	36%	Rearden 1992
10 mg qw	None	10	Not reported	3/10	30%	Knop 1993
Combination						
8-12 q4w	Cisplatin	45	Not reported	NR	24%	Osborne 1992
13 q3-4w	Cisplatin	20	3 of 20 (15%)	3/30	15%	Kuhbock 1994
9-12 q3w	FU/leucovorin	14	Not reported	NR	77%	Magarotto 1994
10 q3w	FU/mitomycin	41	14 of 31 (45%)	3/41	7%	CCI-NOV 6
12 q3w	Prednisone	27	9 of 25 (33%)	3/27	11%	CCI-NOV 16
12 q3w	Prednisone	80/161	23 of 80 (29%)	NR	NR	CCI-NOV 22
14 q3w	Hydrocortisone	119/242	Not reported	65/100	65%	CALGB 9182

FU = 5-fluorouracil

NR = Not reported

q(x)w = Every (x) week

E.2.c.1 Single-Agent Mitoxantrone Given by a 3-Week Schedule

The Southwest Oncology Group (SWOG) conducted a Phase II trial of mitoxantrone in subjects with metastatic HRPC (Osborne 1983). Patients were stratified as good or poor risk, with poor risk defined as having any of the following: age over 70 years, heavy prior chemotherapy, poor tolerance to prior chemotherapy, or prior radiation therapy to more than 25% of bone marrow bearing areas. Patient median age was 65 years (range 54 - 81 years). Mitoxantrone was given by IV bolus injection every 21 days at a dose of 10 mg/m^2 per cycle to poor-risk patients (n = 20) and 12 mg/m^2 to good-risk patients (n = 17). Patients received a median of five courses of therapy. Two patients were not evaluable for tumor response (one was lost to follow-up after the first cycle and the other refused therapy after the first dose for reasons not related to drug toxicity). Of the 35 evaluable patients, two had objective partial tumor regression and five had stable disease. The response duration ranged from 7 months to more than 17 months. Mitoxantrone was well tolerated. Twenty-one patients (58%) had a nadir leukocyte count of less than 2,000/mm^3. Thrombocytopenia, nausea, and vomiting were uncommon. One patient with pre-existing diabetes mellitus and coronary artery disease died from refractory congestive heart failure after a cumulative mitoxantrone dose of 60 mg/m^2, although a direct relationship to mitoxantrone use could not be established.

Another Phase II trial of single-agent mitoxantrone given at 12 to 14 mg/m^2 IV every three weeks was conducted in 29 patients with HRPC (Raghavan 1986). Patient mean age was 67.8 years (range 50 - 76 years). The ECOG performance status was 2 or 3 in 62% of patients. Sixteen patients had received prior radiotherapy but none had received prior chemotherapy. Patients received 1 to 7 courses of therapy. The median cumulative mitoxantrone dose was 36 mg/m^2. One patient achieved a PR and 13 patients had SD as evaluated by tumor size reduction. Eight patients had clinical improvement as evidenced by less pain, weight gain, improved performance status, improvement in QOL measures which were evaluated by LASA scales and QOL questionnaires. The treatment was well tolerated. Neutropenia occurred in 8 patients, vomiting in 2, infection in 2, stomatitis in 1, cardiac toxicity in 1, and painful nail bed changes in 2.

E.2.c.2 Single-Agent Mitoxantrone Given by Other Schedules

A Phase I dose-finding study of mitoxantrone given by continuous infusion was conducted in 15 patients with HRPC (Kantoff 1993). Mitoxantrone planned dose-levels were 1.0, 1.25, 1.4, and 1.5 mg/m^2/day to be given by continuous IV infusion for 14 days followed by two weeks of rest. Patient mean age was 67 years (range 50 - 79 years). No patient had measurable disease. The patients received one to ten courses of therapy with the majority receiving one to three courses. Stable disease was evident in five patients, lasting 5 to greater than 11 weeks. Six of 14 evaluable patients had decreases in PSA levels. Baseline and follow-up QOL questionnaires were completed by 13 patients and showed improvement in physical activity, a slight improvement in mood and feelings of well being, decreased pain, increased ability to work, and increased social activity. The maximum tolerated dose of mitoxantrone was 1.25 mg/m^2/day for 14 days. The dose-limiting toxicity was neutropenia in four patients, although none of the patients required hospitalizations because of neutropenia. There were no instances of platelet counts less than 20,000/mm^3. Other adverse clinical experiences included nausea and vomiting, anorexia, constipation, tongue blisters, and mucositis. All adverse events were mild to moderate in intensity and most occurred in three or fewer patients.

A Phase II study of mitoxantrone given at a dose of 4 mg/m^2 IV every week was conducted in 14 patients with HRPC (Rearden 1992). Patients with prior pelvic irradiation received a lower dose of 3 mg/m^2 every week. A 15% dose escalation was carried out based on hematologic parameters in the preceding cycle. The median age of patients was 68 years. The median number of weeks of therapy was 9 (range 4 - 36 weeks). . The response rate was 36% based on NPCP evaluation criteria: One patient had a PR and four patients had SD. Three patients reported significant improvement in bone pain. The median survival time was 29 weeks (range 9 - 86 weeks). Toxicities were minimal and usually hematologic in nature. A leukocyte count of less than 2,000/mm^3 was reported in two patients and a platelet count of less than 50,000/mm^3 was reported in one. There were no reports of neutropenic fever, bleeding, or cardiac toxicity .

A Phase II study of weekly mitoxantrone administration was conducted in 10 patients with HRPC, three of whom had failed prior chemotherapy (Knop 1993).

All patients had either measurable or evaluable disease. Patient age ranged from 40 to 75 years. Mitoxantrone was administered by short IV injection at a weekly flat dose of 10 mg administered for 4 to 5 cycles, and then continued at a flat dose of 5 mg weekly until disease progression as evidenced by PSA and performance status. Three patients had a partial response (i.e., PSA levels decreasing by $\geq$ 50%) and five patients had stabilization of PSA levels for a period ranging from 18 to 102 weeks (median 20 weeks). No significant bone marrow toxicity was seen and no cardiac toxicity was reported.

E.2.c.3 Combination Chemotherapy with Mitoxantrone

The SWOG conducted a Phase II study of mitoxantrone and cisplatin in 45 patients with HRPC (Osborne 1992). All patients had measurable (n = 17) or evaluable (n = 28) disease. Thirty-six patients were considered poor risk based on age, performance status, or prior chemotherapy. Chemotherapy was given IV every four weeks and consisted of cisplatin 60 mg/m^2 and mitoxantrone 8 or 12 mg/m^2 depending on risk status. The response rate was 12% in patients with measurable disease and 12% in patients with evaluable disease. The estimates of median progression-free survival times were 2.7 months in patients with measurable disease and 4.1 months in patients with evaluable disease. The median survival times were 4.9 and 8.7 months, respectively. There was one treatment-related death due to congestive heart failure. The most common toxicity was myelosuppression, but only one patient developed a leukocyte count of less than 1,000/mm^3 and one patient had a platelet count of less than 25,000/mm^3. Events of moderate to severe nausea and vomiting were reported in 15 patients.

A risk-adapted chemotherapy was investigated in 20 patients with HRPC (Kuhbock 1994). Patient mean age was 63.9 years (range 40 - 74 years). Treatment consisted of mitoxantrone given on Day 1 at a dose of 13 mg/m^2 followed by cisplatin at a dose of 20 mg/m^2/day given daily for five days. Cycles were repeated every three to four weeks. Five of 20 patients with high-risk profiles (i.e., suspected history of cardiopathy, leukopenia, thrombocytopenia, or abnormal kidney and liver function tests) received fractionated doses of each agent on a weekly basis until the total dose noted above was reached for each cycle. Partial remission was noted in 3 of 20 patients (15%), stable disease in eight (40%), and subjective improvement in three (15%). Duration of response ranged from 3 to 14

months. The median overall survival was 9.2 months. One patient developed a hypotensive crisis with reversible myocardial hypoxemia and two patients developed sepsis.

A regimen of mitoxantrone, 5-fluorouracil, and high-dose folinic acid was evaluated in 14 patients with HRPC (Magarotto 1994). The median age of patients was 65 years (range 53 - 81 years). Mitoxantrone was given at a dose of 12 mg/m^2 on Day 1, 5-fluorouracil was given at 350 mg/m^2 Days 1, 2, and 3, and folinic acid was given at 100 mg/m^2, Day 1, 2, and 3. All drugs were given IV. Cycles were repeated every three weeks. The median number of cycles was 4 (range 3 - 9 cycles). The PR rate was 23% and SD rate was 54% using the NPCP criteria. The median duration of response was 4 months (range 3 - 6 months) and the median duration of survival was 10 months (range 3 - 26 months). A decline in PSA levels of $\geq$ 50% was noted in two patients. There were no reports of nausea or vomiting of Grade 2 intensity or above. Grade 2 mucositis was noted in two patients and Grade 3 mucositis in one patient. Grade 2 or 3 leukopenia was common. Grade 4 leukopenia was noted in four patients. One patient had a transient episode of atrial fibrillation, and two patients had a decrease of the left ventricular ejection fraction by at least 10%, but without clinical symptoms.

E.2.d Commercial Marketing Experience

Since its approval for marketing in 1988, mitoxantrone has been used in a variety of hematologic malignancies and solid tumors at doses ranging from 10 to 80 mg/m^2 per cycle given by short IV injection or by 24-hour continuous IV infusion.

E.2.d.1 Mitoxantrone for Leukemia

Mitoxantrone, in combination with other drugs, is indicated for the initial therapy of acute nonlymphocytic leukemia in adults. In a Phase III randomized trial, it was shown that the combination of mitoxantrone and cytarabine was superior to the combination of daunorubicin and cytarabine both in terms of efficacy and safety (Arlin 1990). Mitoxantrone was also shown to be active in the treatment of recurrent/refractory acute nonlymphocytic leukemia. Furthermore, mitoxantrone combination therapy appears to be less toxic than other commonly used regimens in the treatment of adults with acute nonlymphocytic leukemia. Mitoxantrone was also

reported to be active in the treatment of acute lymphocytic leukemia in adults and children. In this disease, mitoxantrone has been investigated in combination therapy with vincristine, cytarabine, methotrexate, etoposide, ifosfamide, asparaginase, and corticosteroids. Mitoxantrone was also reported to be active either as a single agent or in combination with other cytotoxics in the treatment of chronic lymphocytic leukemia and chronic myelogenous leukemia.

E.2.d.2 Mitoxantrone for Metastatic Breast Cancer

Mitoxantrone was extensively investigated in the treatment of metastatic breast cancer. Based on evidence of substantial single agent activity, mitoxantrone was combined with other cytotoxic agents such as cyclophosphamide and 5-fluorouracil (CNF regimen) or 5-fluorouracil and leucovorin (NFL regimen). In randomized comparative trials, mitoxantrone appears to be at least as active or, in some cases, slightly less active than doxorubicin. In the same trials, however, mitoxantrone consistently induced less toxicity than doxorubicin, with less mucositis, gastrointestinal toxicity, and cardiotoxicity. More recently, mitoxantrone has been investigated in combination with new agents, e.g., paclitaxel and vinorelbine.

E.2.d.3 Mitoxantrone for Lymphoma

Mitoxantrone in combination with other cytotoxic agents is commonly used in the treatment of patients with previously untreated or recurrent non-Hodgkin's lymphoma. The most frequently used regimen in intermediate and high grade lymphoma consists of the combination of mitoxantrone, cyclophosphamide, vincristine, and prednisone (CNOP regimen). The CNOP regimen was compared in several Phase III randomized trials with the standard combination of doxorubicin, cyclophosphamide, vincristine, and prednisone (CHOP regimen). In most of these randomized trials, the activity of the mitoxantrone-containing regimen appears to be comparable to the CHOP regimen but was associated with substantially less toxicity. Mitoxantrone has also been substituted for doxorubicin in third generation regimens commonly used for lymphoma (e.g., m-BNCOD, mNCOP-B, and CAP-BOP/m regimens). Mitoxantrone in combination with etoposide, ifosfamide, and mesna (MINE regimen) was shown to be active in the treatment of relapsed/refractory lymphoma; and the combination of mitoxantrone with thiotepa, vincristine, and prednisone (TNOP) was shown to be active and well

tolerated in older patients with lymphoma. A number of combination chemotherapy regimens with mitoxantrone were reported to be active in the treatment of low-grade lymphoma. The combination of mitoxantrone with fludarabine appears to be active in patients with follicular lymphoma.

E.2.d.4 Mitoxantrone in Other Malignancies Including HRPC

There are occasional reports of the use of mitoxantrone in the treatment of gastric, colorectal, lung, ovarian, soft tissue, and prostatic cancer. The information available on the off-label use in the U.S. of mitoxantrone in HRPC is limited. Because mitoxantrone is not a vesicant substance, it has also been administered intracavitary, i.e., by intraperitoneal injection in patients with ascites due to advanced ovarian cancer, by intravesical instillation in patients with superficial bladder cancer, and by intrapleural installation in patients with malignant pleural effusions. There are also reports of investigational use of mitoxantrone in sustained-release liposome-bound formulations.

E.2.d.5 High Dose Mitoxantrone in Solid Tumors

Because of its steep dose-response curve, its activity at standard dose, and its favorable safety profile, mitoxantrone is also used as a component of very high-dose combination chemotherapy regimens requiring hematopoietic stem cell support (i.e., bone marrow or peripheral blood stem cell transplant). The most frequently used regimens in this setting consist of the combination of mitoxantrone, carboplatin, and cyclophosphamide, and the combination of mitoxantrone, paclitaxel, and thiotepa. Most studies of high-dose mitoxantrone were reported in the treatment of patients with advanced ovarian and breast cancer.

E.2.d.6 Summary of Clinical Experience

Based on the data available in the published literature, mitoxantrone is an active agent in the treatment of a wide range of hematologic malignancies and solid tumors. The information available on the extent of the off-label use of mitoxantrone in HRPC is limited. The safety profile of mitoxantrone is predictable, well established, and consists primarily of myelosuppression. Its cardiotoxicity, mucosal toxicity, and gastrointestinal toxicity are of mild to moderate intensity.

E.3 SAFETY SUMMARY - GENERAL SAFETY.CONCLUSIONS

This section summarizes the safety profile of mitoxantrone administered IV at a dose of 12 to 14 mg/m^2 every 3 weeks in subjects with HRPC. This data presented is a compilation of information obtained from the pivotal Phase III trial CCI-NOV 22, the supporting Phase III trial Study 9182, three Phase II studies (CCI-NOV 6, 14, and 16), and the published literature on mitoxantrone in HRPC.

E.3.a Pivotal Trial in HRPC: Study CCI-NOV 22

E.3.a.1 Study Aim and Design

The aim of Study CCI-NOV 22 was to compare the effectiveness of mitoxantrone plus low-dose prednisone to that of low-dose prednisone in providing relief of pain for subjects with symptomatic metastatic HRPC. The study evaluated the use of mitoxantrone, a marketed drug, in an investigational setting of HRPC. The study was designed to reflect typical oncology practice. It was conducted nationwide in Canada, involved academic centers and community hospitals, was open-labeled, and enrolled subjects with no limitation with respect to age or medical history.

In this study, subjects were randomized to receive mitoxantrone plus prednisone (M+P) or prednisone alone (P). All subjects received prednisone 5 mg po twice BID until death or serious toxicity occurred. Subjects randomized to the M+P arm received a single dose of mitoxantrone 12 mg/m^2 by IV push every 3 weeks. Mitoxantrone dose was increased or decreased by 2 mg/m^2 on the basis of nadir blood cell counts in the preceding cycle. Subjects in the M+P group were to discontinue mitoxantrone if they had reached a cumulative dose of 140 mg/m^2. If disease progression occurred after stopping mitoxantrone, treatment could be restarted provided the LVEF was in the normal range. Subjects randomized to the P arm were to receive mitoxantrone at the time of disease progression or could be crossed over if their disease was stable after six weeks of P therapy.

E.3.a.2 Demographics

A total of 161 subjects were enrolled in this study; 80 subjects were randomized to the M+P arm and 81 subjects were randomized to the P arm. Forty-eight subjects

(59%) in the P arm subsequently crossed over to receive mitoxantrone. Thus, a total of 128 subjects were treated with mitoxantrone. Median age was 67 years for both groups. Approximately 37% of subjects in each treatment group had an ECOG performance status of 2 or 3.

E.3.a.3 Extent of Exposure

The 80 subjects in the M+P group received a median cumulative dose of mitoxantrone of 73 mg/m^2 (range 12 - 212 mg/m^2). The median number of cycles administered in the M+P group was 6.5 (range 1 - 18 cycles). The median individual dose of mitoxantrone administered was 12 mg/m^2 (range 2 - 18 mg/m^2). Thirty-nine subjects (49%) in the M+P group received at least one dose of mitoxantrone greater than 12 mg/m^2 and 18 (23%) received at least one dose less than 12 mg/m^2. Four subjects (5%) in the M+P group received cumulative doses of mitoxantrone greater than 140 mg/m^2. An additional 14 subjects received a cumulative mitoxantrone dose within 10 mg/m^2 of the maximum recommended dose of 140 mg/m^2.

Seven subjects randomized to the M+P arm (9%) and 5 subjects randomized to the P arm who crossed over (10%) did not receive mitoxantrone for one or more cycles. The reasons for not administering mitoxantrone for a scheduled cycle included thrombocytopenia, leukopenia, infection, mucositis, and other reasons.

As noted in Section D.3.a.1, the individual dose of mitoxantrone could be changed by $\pm$ 2 mg/m^2 on the basis of nadir blood cell counts in the preceding cycle. Because of this rule and since 7 subjects received no mitoxantrone for $\geq$ 1 cycles, a mitoxantrone dose-ratio was calculated. The dose-ratio was defined as cumulative dose/number of cycles not excluding cycles during which mitoxantrone was not administered. The median dose-ratio of mitoxantrone per cycle was 12 mg/m^2 (range 5.1 - 16.5 mg/m^2). Palliative responses were seen at all dose levels and there was no significant correlation between dose-level and response rates.

E.3.a.4 Deaths

In the group randomized to M+P, 5 subjects died while on study or within 30 days of the last dose of mitoxantrone: one subject died of pneumonia and four subjects

died of malignant disease. Six subjects randomized to the P group and who subsequently crossed over died within 30 days of the last dose of mitoxantrone. All six subjects died of malignant disease. The Kaplan-Meier estimates of the median time to death were 338.5 days for the 80 subjects randomized to the M+P group and 324 days for the 81 subjects randomized to the P group (p = 0.2324).

E.3.a.5 Withdrawals Due to Adverse Events

A list of reasons for withdrawals due to toxicity, death, subject decision, and other reasons is provided in the table that follows:

Subject Withdrawals Due to Toxicity or "Other" Reasons

Reason for Withdrawal	Details	M+P	P
Toxicity (n = 12)	Myelosuppression	3	0
	Sepsis	2	0
	Confusional state	1	0
	Gastrointestinal events	1	1
	Cardiac events	2	0
	No reason given	2	0
Other (n = 12)	Febrile neutropenia	1	0
	Surgery	1	0
	Diabetes	0	1
	Non-compliance	0	2
	Epigastric pain	0	1
	Renal failure	0	1
	Cardiac event	0	1
	Deep venous thrombosis	1	1
	Alternative therapy	0	1
	Disease progression	1	0
Refused treatment (n = 5)	Subject refusal	2	3
Death (n = 10)	Progressive disease	4	6

E.3.a.6 Serious Adverse Events

In total, 36 subjects experienced 43 SAEs during the course of the study. The distribution of the 43 SAEs in the two groups was as follows: 21 SAEs in the M+P group and 22 SAEs in the P group (15 prior to crossover and 7 after crossover). In the M+P group, the most frequent reported SAEs were infection-related (n = 9), death (n = 3), and cardiac events (n = 3). In the P group, the most frequent reported SAEs were thrombo-embolic events (n = 4) and death (n = 4).

E.3.a.7 Adverse Events

There were no adverse events of WHO Grade 3 or 4 intensity that occurred in ≥ 5% of subjects in either group. Events of any WHO grade occurring in 10% or more of subjects randomized to the M+P group were nausea (61%), fatigue (31%), alopecia (29%), anorexia (25%), constipation (16%), and dyspnea (10%). Events of any grade occurring in 10% or more of subjects randomized to the P group were nausea (35%), constipation (16%), and fatigue (10%).

E.3.a.8 Cardiotoxicity

Seven of 128 subjects (5%) treated with mitoxantrone experienced a cardiac event which was defined as any asymptomatic decrease in LVEF below normal, congestive heart failure, or any myocardial ischemia. Only three subjects had symptoms of congestive heart failure. The cumulative dose of mitoxantrone received by these seven subjects ranged from greater than 48 mg/m^2 to 212 mg/m^2.

E.3.a.9 Laboratory Toxicity (NCI Grading)

Grade 3 or 4 laboratory toxicities occurring in ≥ 5% of subjects randomized to the M+P group consisted of neutropenia (81% of subjects), leukopenia (75%), elevated alkaline phosphatase (30%), elevated LDH (14%), and hyperglycemia (6%). Grade 3 or 4 laboratory toxicities occurring in ≥ 5% of subjects randomized to the P group who did not crossover consisted of elevated alkaline phosphatase (34% of subjects), elevated LDH (18%), and hyperglycemia (10%).

E.3.a.10 Conclusions

Study CCI-NOV 22 was conducted in subjects whose median age was 67 years. Results demonstrated no adverse events that were not already known to occur with mitoxantrone administration. There were no WHO Grade 3 or 4 adverse events reported in > 5% of subjects. Cardiotoxicity was mild; only 3 of 128 subjects (2%) given mitoxantrone developed evidence of CHF. The most frequent laboratory toxicities were neutropenia and thrombocytopenia.

E.3.b Safety Data From Other Clinical Trials in HRPC

E.3.b.1 Study 9182

The aim of Study 9182 was to compare the effectiveness of mitoxantrone plus hydrocortisone to that of hydrocortisone in subjects with metastatic HRPC. The study evaluated the use of mitoxantrone, a marketed drug, in an investigational setting of HRPC. The study was designed to reflect typical oncology practice. It was conducted groupwide by involved academic centers and affiliate hospitals, was open-labeled, and enrolled subjects with no limitation with respect to age or medical history.

In this study subjects were randomized to receive mitoxantrone plus hydrocortisone (M+H) or hydrocortisone alone (H). All subjects received hydrocortisone 40 mg po daily. Subjects randomized to the M+H arm received mitoxantrone 14 mg/m^2 by IV push every 3 weeks. Mitoxantrone dose was decreased by 25% or 50% on the basis of nadir blood cell counts in the preceding cycle. Subjects in the M+H group were to discontinue mitoxantrone if they had reached a cumulative dose of 160 mg/m^2. Crossover between treatments was not permitted. A total of 242 subjects were enrolled in this study; 119 subjects were randomized to the M+H arm and 123 subjects were randomized to the H arm. Median age was 72 years for both groups.

As of February 1996, 116 deaths have been reported: 61 deaths (51% of subjects) in the M+H group and 55 deaths (45% of subjects) in the H group. Causes of death were comparable in the two groups. Except for disease progression, there was no single cause of death that accounted for $\geq$ 5% of all deaths in either group.

Reasons for withdrawals were reported for 174 subjects. In the M+H group, 58 subjects withdrew due to progressive disease, 13 due to toxicity, 3 due to death, 2 due to consent withdrawal, 5 due to other reasons, and 4 after completing study. In the H group, 79 subjects withdrew due to progressive disease, 3 due to consent withdrawal, 2 due to death, 1 due to toxicity, and 4 due to other reasons.

Eight subjects in the M+H group and eight subjects in the H group were reported to have experienced a total of 24 SAEs. One SAE (cerebral hemorrhage in the M+H group) was considered possibly related to study drug by the Investigator and all other SAEs were considered unrelated. The SAEs that were reported in this study were consistent with the subjects' primary diseases or comorbid conditions.

Grade 3-5 clinical toxicities occurring in ≥ 5% of subjects in either treatment group were pain, either related to cancer or not (10% in the M+H group and 3% in the H group, $p = 0.04$) and sterility (6% in the M+H group and 4% in the H group, $p = 0.6$). The distribution and frequency of Grade 1-2 clinical toxicities were comparable in the two groups except for cardiac function anomalies that were noted in 16% of subjects in the M+H group compared to 1% of subjects in the H group.

Grade 3-5 laboratory toxicities that occurred in ≥ 5% of subjects in the M+H group consisted of lymphopenia (65% of subjects), neutropenia (57%), leukopenia (57%), increased alkaline phosphatase (11%), hyperglycemia (7%), and anemia (5%). Grade 3-5 laboratory toxicities that occurred in ≥ 5% of subjects in the H group consisted of lymphopenia (13% of subjects), increased alkaline phosphatase (9%), and hyperglycemia (5%).

In conclusion, Study 9182 did not demonstrate any adverse event that was not already known to occur with mitoxantrone administration. The only Grade 3-5 adverse events reported in > 5% of subjects treated with mitoxantrone were pain and sterility. Cardiotoxicity was mostly of Grade 1 or 2 (incidence of 16%). The most frequent laboratory toxicities were neutropenia and thrombocytopenia.

E.3.b.2 Study CCI-NOV 6

A Phase II trial investigating the combination of mitoxantrone, 5-fluorouracil, and mitomycin was conducted by Murray et al in 41 patients (mean age 67.6 years) with HRPC. Mitoxantrone at a dose of 10 mg/m^2 and 5-fluorouracil at a dose of 600 mg/m^2 were both administered IV every 3 weeks; mitomycin was given IV at 10 mg/m^2 every 6 weeks. The 41 patients completed a total of 164 treatment cycles. Individual patients received between 1 and 7 cycles (mean 4 cycles). The cumulative dose of mitoxantrone ranged from 8 to 70 mg/m^2 (median, 34) and single doses ranged from 5 to 11 mg/m^2 (median 10 mg/m^2). The cumulative mitoxantrone dose ranged from 8 to 70 mg/m^2. Toxicity caused 24% of the treatments to be delayed. There were no withdrawals due to toxicity.

All 41 patients have died. The cause of death was not recorded in 4 cases. There were 7 deaths that were primarily attributed to causes other than cancer progression. These included two cases of pneumonia, and one case each of intracranial bleed, anemia, congestive heart failure, myocardial infarction, and acute renal failure. Interpretation of the cause of death data is difficult because deaths associated with an adverse event may also have been related to cancer progression.

The WHO system was used for toxicity grading. There was no reports of grade 4 gastrointestinal toxicity. Grade 3 gastrointestinal toxicity was reported in 1% of cycles, Grade 2 in 2% , and Grade 1 in 20% . Additional adverse events reported included sepsis (n = 1), neutropenic fever (n = 1), transient ischemic attack (n = 1), acute renal failure (n = 1), angina (n = 1), and deep vein thrombosis (n = 2). A cardiac event was reported in one patient (3%). This was a 76 year-old man who developed angina on Cycle 2 after receiving a cumulative mitoxantrone dose of 20 mg/m^2. His symptoms resolved and he then received a third cycle of therapy.

Grade 4 hematologic toxicities occurred in 8 patients (20%). Grade 3 or grade 4 leukopenia occurred in 32% of patients, granulocytopenia in 34%, thrombocytopenia in 22%, and anemia in 33%. Eighteen patients (44%) had a blood transfusion during the study.

E.3.b.3 Study CCI-NOV 14

A Phase II trial of single-agent mitoxantrone given IV every 3 weeks was conducted by Murray et al in 38 patients with HRPC. The initial dose of mitoxantrone was 12 mg/m^2 per cycle, with subsequent dose adjustment permitted to achieve a Day 21 absolute granulocyte count in the 2,000 to 2,500/mm^3 range. Single doses of mitoxantrone ranged from 7 to 26 mg/m^2 and cumulative doses ranged from 10 to 154 mg/m^2. Patient mean age was 67.7 years.

The 38 patients completed a total of 182 treatment cycles. Individual patients received between 1 and 8 cycles (mean 4.8 cycles). The cumulative mitoxantrone dose ranged from 10 to 154 mg/m^2 (median 60 mg/m^2). The single dose of mitoxantrone ranged from 7 to 26 mg/m^2 (median 14 mg/m^2). The dose of mitoxantrone was reduced to less than 12 mg/m^2 in 13% of the 182 treatment cycles. Omitting Cycle 1, 22 of the 144 treatment cycles (15%) were delayed due to toxicity. There were no reports of withdrawals from study due to toxicity.

All 38 patients have died. The cause of death was not recorded in 7 cases. There were 3 deaths that were primarily attributed to causes other than cancer progression. These included one case each of endocarditis, congestive heart failure, and cerebrovascular accident. Interpretation of the cause of death data is imprecise because deaths associated with an adverse event may also have been related to cancer progression.

The WHO system was used for toxicity grading. There were no reports of WHO Grade 4 gastrointestinal toxicity. Grade 3 gastrointestinal toxicity was noted in only one patient (3%) and Grade 1-3 gastrointestinal toxicity was reported in 20% of cycles. Mild to moderate alopecia was noted in 26% of cycles, and there were no reports of WHO Grade 3 or 4 alopecia. Additional adverse events included pneumonia in one patient and dysgeusia in another. Cardiotoxicity was reported in one patient (3%). This was a 74 year old man who developed congestive heart failure after receiving 6 treatment cycles and a mitoxantrone cumulative dose of 71 mg/m^2. He died from the consequences of congestive heart failure.

WHO Grade 4 hematologic toxicity was reported in one patient (3%). Combined Grade 3 and 4 leukopenia occurred in 11% of patients, granulocytopenia in 11%,

anemia in 11%, and thrombocytopenia in none. Six patients (16%) required a blood transfusion during the study.

E.3.b.4 Study CCI-NOV 16

The combination of mitoxantrone and prednisone was evaluated in 27 patients with HRPC. Mitoxantrone was given at a dose of 12 mg/m^2 every 3 weeks with dose adjustment based on hematologic nadirs. Prednisone was given orally at a dose of 5 mg twice a day. Patient mean age was 69 years (range 54 - 87 years). The 27 men completed a total of 126 treatment cycles. Patients received between 1 and 8 cycles (median 4 cycles) and nine patients (33%) completed the specified treatment of at least 8 cycles. The cumulative mitoxantrone dose ranged from 12 to 136 mg/m^2 (median 60 mg/m^2). Single doses of mitoxantrone ranged from 6 to 22 mg/m^2 (median 14 mg/m^2). Only one of the 25 patients (4%) who received a second treatment cycle had his mitoxantrone dose reduced by 2 mg/m^2 due to myelosupression according to protocol guidelines. Of the 16 patients who received a third treatment cycle, the mitoxantrone dose decreased by 2 mg/m^2 in 4 (25%). Overall, the dose of mitoxantrone was reduced to less than 12 mg/m^2 in ten men (37%) who experienced granulocytopenia. There were no dose reductions due to thrombocytopenia.

Three patients were withdrawn from study because of adverse events. One patient developed claustrophobia that was attributed to prednisone one week after entry on study. The other two patients developed concomitant illnesses that led to protocol violation and withdrawal from study. These illnesses consisted of deep vein thrombosis in one patient and hypercalcemia in another. Both patients were subsequently lost to follow-up. At the time of analysis, 25 of the 27 patients had died. There was one death resulting from an unrelated intercurrent cause (not related to toxicity or malignant disease).

Both nausea/vomiting and alopecia were solicited adverse drug reactions, i.e., patients were questioned specifically about these side effects at each visit. Nausea or vomiting was reported by 13 patients (48%) in a total of 31 of 123 treatment courses (25%). There were no reports of WHO grade 2 or higher episodes of nausea or vomiting. Mild alopecia was noted in 28% of cycles and there was no reports of grade 3 or 4 alopecia. An infection was reported in 3 patients (11%)

including one of each of the following: Herpes simplex infection, urinary tract infection, and thrush. Only anorexia (n = 4) and constipation (n = 3) were reported in more than 2 patients. Fever, loss of appetite, sore throat, and weakness were each reported by only one patient.

Granulocytopenia of < 500/mm^3 was reported in 44% of patients. One patient (4%) experienced Grade 4 anemia (hemoglobin < 6.5 g/dL). There were no reports of Grade 4 thrombocytopenia. Combined Grade 3 and 4 granulocytopenia occurred in 74% of patients, thrombocytopenia in 7%, and anemia in 4%. Four patients (15%) received a blood transfusion during the study.

E.3.b.5 Published Reports Of Single-Agent Mitoxantrone In HRPC

Several Phase I and II studies investigating the role of mitoxantrone in the treatment of HRPC were conducted in the U.S., Canada, and other foreign countries. These studies evaluated mitoxantrone given at various doses and schedules as a single agent, in combination with other cytotoxic agents, or in combination with corticosteroids. These studies demonstrated that mitoxantrone was generally well tolerated in this older patient population.

The SWOG conducted a Phase II trial of mitoxantrone in 37 patients (median age 65 years) with HRPC (Osborne 1983). Mitoxantrone was given by IV injection every 21 days for a median of 5 courses of therapy. Poor risk patients (n = 20) were given mitoxantrone at a dose of 10 mg/m^2 and good risk patients (n = 17) received mitoxantrone at a dose of 12 mg/m^2. The therapy was well tolerated. Twenty-one patients (58%) had a nadir leukocyte count of less than 2,000/mm^3. Thrombocytopenia, nausea, and vomiting were uncommon. One patient with pre-existing diabetes mellitus and coronary artery disease died from refractory congestive heart failure after a cumulative mitoxantrone dose of 60 mg/m^2, although a direct relationship to mitoxantrone use could not be established.

A second trial of single-agent mitoxantrone given at 12 to 14 mg/m^2 IV every 3 weeks was conducted in 29 patients with HRPC (Raghavan 1986). Patients received 1 to 7 courses of therapy. The median cumulative mitoxantrone dose was 36 mg/m^2. Patient mean age was 67.8 years. The ECOG performance status was 2 or 3 in 62% of patients. Mitoxantrone was well tolerated. Neutropenia occurred

in eight patients, vomiting in two, infection in two, stomatitis in one, cardiac toxicity in one, and painful nail bed changes in two.

A Phase I dose-finding study of continuous infusion of mitoxantrone was conducted in 15 patients (mean age 67 years) with HRPC (Kantoff 1993). Mitoxantrone dose-levels were planned at 1.0, 1.25, 1.4, and 1.5 mg/m^2/day given by continuous IV infusion for 14 days followed by two weeks of rest. The patients received 1 to 10 courses of therapy with a majority receiving 1 to 3. The maximum tolerated dose of mitoxantrone was 1.25 mg/m^2/day for 14 days. The dose-limiting toxicity was neutropenia in four patients, although none of the patients required hospitalizations because of neutropenia. There were no instances of platelet counts less than 20,000/mm^3. Other adverse clinical experiences included nausea and vomiting, anorexia, constipation, tongue blisters, and mucositis. All adverse events were mild to moderate in intensity and most occurred in 3 or fewer patients.

A Phase II study of mitoxantrone given at a dose of 4 mg/m^2 IV every week was conducted in 14 patients (median age 68 years) with HRPC (Rearden 1992). Patients with prior pelvic irradiation received a lower dose of 3 mg/m^2 every week. A 15% dose escalation was carried out based on hematologic parameters in the preceding cycle. The median number of weeks of therapy was 9 (range 4 - 36 weeks). Toxicities were minimal and usually hematologic in nature. A leukocyte count of less than 2,000/mm^3 was noted in two patients and a platelet count of less than 50,000/mm^3 was noted in one. There were no reports of neutropenic fever, bleeding, or cardiac toxicity.

A Phase II study of mitoxantrone administered weekly was conducted in 10 patients with HRPC (Knop 1993). Patient age ranged from 40 to 75 years. Mitoxantrone was administered by short IV injection at a weekly flat dose of 10 mg administered for four to five cycles, and then continued at a flat dose of 5 mg weekly until disease progression as evidenced by PSA and performance status. No significant bone marrow toxicity was seen and no cardiac toxicity was noted.

E.3.b.6 Published Reports of Combination Therapy With Mitoxantrone In HRPC

The SWOG conducted a Phase II study of mitoxantrone and cisplatin in 45 patients with HRPC (Osborne 1992). Chemotherapy was given IV every 4 weeks and consisted of cisplatin 60 mg/m^2 and mitoxantrone 8 or 12 mg/m^2 based on risk status. There was one treatment-related death due to congestive heart failure. The most common toxicity was myelosuppression but only one patient developed a leukocyte count of less than 1,000/mm^3 and one patient had thrombocytopenia of less than 25,000/mm^3. Events of moderate to severe nausea and vomiting were reported in 15 patients. Alopecia was not reported.

A risk-adapted chemotherapy was investigated in 20 patients (mean age 63.9 years) with HRPC (Kuhbock 1994). Treatment consisted of mitoxantrone given IV on Day 1 at 13 mg/m^2 followed by cisplatin at 20 mg/m^2/day given IV daily for 5 days. Cycles were repeated every 3-4 weeks. Five of 20 patients with high-risk profiles (i.e., history of cardiopathy, leukopenia, thrombocytopenia, or abnormal kidney and liver function tests) received fractionated doses of each agent on a weekly basis until the total dose noted above was reached for each cycle. The therapy was well tolerated. One patient developed a hypotensive crisis with reversible myocardial hypoxemia and two patients developed sepsis.

A regimen of mitoxantrone, 5-fluorouracil, and high-dose folinic acid was evaluated in 14 patients (median age of 65 years) with HRPC (Magarotto 1994). Mitoxantrone was given IV at 12 mg/m^2 (9 mg/m^2 for Cycle 1) on Day 1, 5-fluorouracil was given IV at 350 mg/m^2 Days 1, 2, and 3, and folinic acid was given IV at 100 mg/m^2, Day 1, 2, and 3. Cycles were repeated every 3 weeks. The median number of cycles was 4 (range, 3 - 9). There were no reports of nausea or vomiting of Grade 2 intensity or above. Grade 2 mucositis was noted in two patients and Grade 3 mucositis in one patient. Grade 2 or 3 leukopenia was common. Grade 4 leukopenia was noted in four patients. One patient had a transient episode of atrial fibrillation, and two patients had a decrease of the left ventricular ejection fraction by at least 10%, but without clinical symptoms.

E.3.c Summary of Safety Information

Overall, the two Phase III trials of mitoxantrone in HRPC, the three Phase II trials, and the published literature showed that mitoxantrone given at doses ranging from 10 to 14 mg/m^2 every three weeks was well tolerated in this older patient population. The most common adverse event was myelosuppression, a common event with most cytotoxic agents. The incidence of myelosuppression can be decreased by increasing the interval between courses or by reducing the dose per cycle. Other adverse events often seen with cytotoxic therapy, e.g., nausea, vomiting, alopecia, and fatigue, were uncommon and usually of Grade 1 or 2. The incidence of cardiotoxicity, a toxicity noted in the label of mitoxantrone, was not increased in this patient population. The most common laboratory toxicities (> 10% of subjects) were leukopenia, neutropenia, thrombocytopenia, and increased alkaline phosphatase.

E.3.d U.S. IND Safety Reports In HRPC

There were no IND safety reports in the U.S. for mitoxantrone studies conducted in subjects with HRPC. The only available IND safety reports were submitted to the Health Protection Branch for the Phase II and III Canadian studies, CCI-NOV 6, 14, 16, and 22.

E.3.e Summary Of Post-Marketing Experience

The entire mitoxantrone post-marketing experience database was searched at Immunex for reportable events reported five or more times since U.S. approval. The table that follows lists all such events, their frequency of occurrence, and whether such events are not described in the mitoxantrone prescribing information.

Post-Marketing Adverse Experience Reports with ≥ 5 Occurrences

Body System	Adverse Event	No. Reports	Labeled
Body as a whole	death	19	no
	dehydration	5	no
	disease progression	6	no
	fever/sepsis	23	
Cardiovascular	cardiac disorder	6	
	heart failure	5	
Gastrointestinal	abdominal pain	5	
	nausea	8	
	vomiting	5	
Hemic	acute leukemia	11	
	leukopenia	12	
	marrow depression	6	
	neutropenia	8	
	thrombocytopenia	5	
Neurologic	subdural hematoma	5	no
Respiratory	pneumonia	6	
Skin	injection site reaction/pain	31	
	skin discoloration	10	no

The only unlabeled adverse events reported five or more times since approval are death, dehydration, disease progression, subdural hematoma, and skin discoloration. Dehydration is often a secondary complication of vomiting and diarrhea, both expected events with mitoxantrone. Disease progression is a frequent occurrence in patients with advanced cancer and is unrelated to mitoxantrone. Skin discoloration is associated with the blue color of mitoxantrone which may occasionally extravasate from an injection site. All reported deaths were due to events unrelated to mitoxantrone administration (e.g., progressive disease) or associated with adverse events known to occur with mitoxantrone administration (e.g., sepsis, hemorrhage, heart failure). The five reports of subdural hematoma were all contained in one publication in patients with acute myeloid leukemia with monoblastic component and were considered by the authors to be multifactorial, including meningeal infiltration with leukemia cells.

F. BENEFIT/RISK ASSESSMENT AND PROPOSED POST-MARKETING STUDIES

F.1 BENEFIT AND RISK ASSESSMENT

A common perception among medical oncologists is that non hormonal cytotoxic therapy is seldom effective in the management HRPC. The information obtained from the pivotal trial CCI-NOV 22, the supporting trial Study 9182, and Phase II studies indicate that mitoxantrone treatment provides a substantial clinical benefit in patients with locally advanced or metastatic prostate cancer who have failed prior hormonal therapy. Mitoxantrone therapy results in significant improvement of cancer-related symptoms, improves quality of life measures, and does not lead to significant toxicity in this older patient population.

F.1.a Pivotal Trial CCI-NOV 22

The pivotal trial CCI-NOV 22 showed that mitoxantrone plus prednisone results in clinically meaningful improvement or total resolution of cancer-related pain in about 40% of patients with HRPC who have persistent pain despite optimization of analgesic therapy prior to enrollment on study. This criterion of response was assessed using a well-defined 6-point pain scale and the response had to be maintained for two consecutive cycles, i.e., for a period of at least six weeks.

Compared to prednisone alone, mitoxantrone plus prednisone significantly increased the rate of primary palliative response from 12% to 29% ($p = 0.01$), the median duration of palliative response from 53 days to 229 days ($p = 0.0001$), and the median time to disease progression from 132.5 days to 301 days ($p = 0.0001$). Furthermore, the overall palliative response rate according to either the primary or the secondary criterion of response was 21% in the prednisone group compared to 37.5% in the mitoxantrone plus prednisone group ($p = 0.025$). As would be expected in a crossover study, there was no difference in survival times between the mitoxantrone plus prednisone group (median of 338.5 days) and the prednisone alone group (median of 324 days). Median time to death was significantly longer, however, for the mitoxantrone plus prednisone group (338.5 days) compared to the prednisone group (145 days), when subjects randomized to prednisone who subsequently crossed over are excluded ($p = 0.0086$).

A decrease in pain intensity and corresponding decrease in analgesic use resulted in overall improvement in patient functional activity, feeling of well being, and psychosocial interactions. This was evidenced by an improvement in quality of life evaluations assessed by two validated quality of life measures, the linear analog self-assessment scales (9 LASA scales) and the EORTC-Q30 quality of life questionnaire (30 questions). This improvement was more manifest for quality of life instruments assessing cancer-related symptoms and less distinct for quality of life instruments assessing general questions of well-being.

In addition to the favorable clinical responses noted above, a 75% or greater decrease in PSA levels was noted more often in subjects randomized to mitoxantrone plus prednisone (27%) compared to patients randomized to prednisone alone (14%), with $p = 0.077$. Because most patients with metastatic prostate cancer have bone lesions that are not readily measurable or evaluable by radiographs or bone scans, the role of mitoxantrone in tumor size reduction could not be consistently evaluated in this study.

The favorable results achieved with mitoxantrone in Study CCI-NOV 22 were obtained without undue toxicity or worsening of patient quality of life due to therapy-related adverse events. The most common adverse event was myelosuppression that made mitoxantrone dose adjustments necessary in 22.5% of subjects. There were no adverse events of grade 3 or 4 intensity that occurred in 5% or more of subjects treated with mitoxantrone plus prednisone. Events of any grade occurring in 10% or more of subjects treated with mitoxantrone plus prednisone consisted of nausea, fatigue, alopecia, anorexia, constipation, and dyspnea. Seven of 128 subjects (5%) treated with mitoxantrone experienced a cardiac event defined as any asymptomatic decrease in LVEF below normal, congestive heart failure, or any myocardial ischemia; only three subjects had symptoms of congestive heart failure. Grade 3 or 4 laboratory toxicities occurring in $\geq 5\%$ of subjects randomized to the mitoxantrone plus prednisone group consisted of neutropenia, leukopenia, elevated alkaline phosphatase, elevated LDH, and hyperglycemia.

F.1.b Supportive Phase III Trial Study 9182

Phase III Study 9182 showed that a clinically meaningful tumor response by NPCP criteria (stable disease or better) was achieved in 65% of subjects treated with mitoxantrone plus hydrocortisone compared to 54% of subjects treated with hydrocortisone alone. Median time to disease progression for all subjects randomized to mitoxantrone plus hydrocortisone was 218 days compared to 122 days for subjects randomized to hydrocortisone alone ($p = 0.0654$). The median time to death was comparable in the two groups; 334 days for mitoxantrone plus hydrocortisone and 359 days for hydrocortisone alone. This endpoint may have been confounded by additional therapy given after withdrawal from study.

A decrease in PSA levels $\geq$ 50% was achieved in significantly ($p = 0.023$) more subjects randomized to the mitoxantrone plus hydrocortisone arm (31%) compared to the hydrocortisone alone arm (17%). There was a trend toward more reduction in analgesic use over time in the mitoxantrone plus hydrocortisone group. There was also a trend toward more improvement over time in pain-related quality of life measures in the mitoxantrone plus hydrocortisone group. This trend was more apparent if the subset of subjects using analgesics at baseline.

Grade 3-5 clinical toxicities occurring in $\geq$ 5% of subjects in the mitoxantrone plus hydrocortisone group were pain (10%) and sterility (6%). The distribution and frequency of Grade 1-2 clinical toxicities were comparable in the two groups except for cardiac function anomalies that were noted in 16% of subjects in the mitoxantrone plus hydrocortisone group compared to 1% of subjects in the hydrocortisone group. Grade 3-5 laboratory toxicities that occurred in $\geq$ 5% of subjects in the mitoxantrone plus hydrocortisone group consisted of lymphopenia, neutropenia, leukopenia, increased alkaline phosphatase, hyperglycemia, and anemia.

F.1.c Phase II Trials in HRPC

Evidence of palliative response was also seen in numerous Phase I and II trials conducted in the U.S. and other countries investigating the role of mitoxantrone in HRPC. Overall, pain improvement was noted in 20 to 50% of patients receiving mitoxantrone every three weeks, once a week, or by continuous IV infusion, at

cumulative monthly doses ranging from 8 to 20 mg/m^2. These treatments were well tolerated, with myelosuppression being the predominant, albeit easily manageable, adverse event.

In conclusion, these results indicate that mitoxantrone provides clinical benefit to patients with HRPC for whom no approved alternative chemotherapy currently exists.

F.2 PROPOSED POST-MARKETING STUDIES

At present, Immunex does not intend to conduct Phase IV studies of mitoxantrone in subjects with advanced prostate cancer. While the clinical benefit of mitoxantrone plus prednisone for pain palliation in patients with HRPC was clearly demonstrated in study CCI-NOV 22, there are several ongoing investigator-initiated studies evaluating other doses and schedules of mitoxantrone alone or in combination with other cytotoxic drugs in patients with recurrent or newly diagnosed advanced prostate cancer. These studies aim at optimizing drug administration on the basis of the intended goal, e.g., pain palliation, tumor cytoreduction, or prevention of disease recurrence. A pharmacoeconomic study is now underway to evaluate the cost-benefit of the treatment of HRPC with mitoxantrone in a subset of patients enrolled on study CCI-NOV 22 .

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development(HF-35)
Food and Drug Administration 5600 Fishers Lane
Rockville, MD 20857

August 21, 1996

Immunex Corporation
Attention: Mr. Mark W. Gauthier
Senior Manager, Regulatory Affairs
51 University Street
Seattle, WA 98101

Dear Mr. Gauthier:

Reference is made to your orphan drug application of April 3, 1996 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of Novantrone® (mitoxantrone), as an orphan drug (application #96-966). We also refer to your amendment dated July 8, 1996.

We have completed the review of this application, as amended, and have determined that mitoxantrone qualifies for orphan designation for the treatment of hormone refractory prostate cancer. Please note that it is mitoxantrone and not its formulation that has received orphan designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity. Also please be advised that if mitoxantrone were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

In addition, please inform this office annually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of mitoxantrone as designated. If you need further assistance in the development of your product for marketing, please feel free to contact Dr. C. Carnot Evans at (301) 827-0987.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

cc:
HFD-85/M.A.Holovac
HFD-150/L.Vaccari ✓
HF-35/OP File #96-966
HF-35/C.Evans
HF-35/chron
HF-35/P.Vaccari 8/21/96 dsg.966

DEPARTMENT OF HEALTH & HUMAN SERVICES

P. Zimmerman
Public Health Service

Food and Drug Administration
Rockville MD 20857

Date MAY 16 1996
NDA No. 19-297

Need 45 day filing ltg
Sup Ack letter.

Immunex Corporation
51 University Street
Seattle, WA 98101

Attn: Mark Gauthier

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Novantrone (mitoxantrone for injection concentrate)

NDA Number: 19-297

Supplement Number: S-014

Date of Supplement: May 10, 1996

Date of Receipt: May 13, 1996

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research, HFD-150
Attention: Document Control Room ~~HFD-20~~
5600 Fishers Lane
Rockville, MD 20857

Paul F. Zimmerman for
Ruth Peace

Chief, Project Management Staff
Division of Oncology and Pulmonary
Drug Products

Request for Information: 6/24/96

NDA # 19-297, Supplement S-014
NOVANTRONE® (Mitoxantrone for Injection Concentrate)
Sponsor: Immunex Corporation

Information to be conveyed to the sponsor:

A. CCI-NOV22

Review of study CCI-NOV22 has raised questions regarding 1) palliative response evaluation, and 2) determination of the duration of the response in the patients described below. Please respond to the following requests and provide case report forms for each patient no later than the week of July 8, 1996.

1. Please justify assignment of palliative response for the following patients:

Patient [redacted]: response was noted to occur from cycle 5 to 8, but PI scores were missing for cycles 4 and 6 on Listing 4.

Patient [redacted]: response was noted to occur from cycle 6 to 14, but PI scores were missing for cycles 3, 5, 7, 9, and 12 on Listing 4.

Patient [redacted]: withdrawn for unknown reason after cycle 5, but response is noted to occur in "cycles" 6 through 9 (duration was 70 days).

Patient [redacted]: last course given was cycle 5; patient withdrawn for toxicity at "cycle" 6, and last follow-up date is "cycle" 7. Response is noted to occur in "cycles" 5 through 7 (duration was 77 days).

Patient [redacted]: completed treatment at cycle 11; follow-up 3 weeks later confirms response by PI score. However, since this is the last available score, the response duration was 0 days.

Patient [redacted]: refused treatment after cycle 3; follow-up 3 weeks later confirms response by PI score. However, since this is the last available score, the response duration was 0 days.

Patient [redacted] response was noted to occur from cycle 5 to 15 using PI scores (Listing 4), however, using Analgesic Scores, this patient would have progressed at cycle 3 (Listing 5) without ever achieving a response.

2. Please clarify the following discrepancies affecting calculation of the duration of palliative response/time to progression:

Patient [redacted]: progressed on prednisone at cycle 6 (8/21/92, Listing 11) or at cycle 18 (11/26/93,

Listing 20); evidence of progression at cycle 12 using analgesic score.

Patient [redacted]: patient is reported as not progressed on prednisone at cycle 11 (3/24/93, Listing 11) or as progressed at cycle 11 (5/5/93, Listing 20).

Patient [redacted]: received 10 cycles of M+P; patient is reported to have progressed at cycle 18 dated as 1/26/94 (Listing 7) or as 6/1/94 (Listing 20).

Patient [redacted]: received 12 cycles of M+P; patient is reported to have progressed at cycle 7 on 9/10/93 (Listing 11) or at cycle 12 on 12/23/93 (Listing 20).

Patient [redacted]: received 9 cycles of M+P; withdrawn immediately (2/4/94) for surgical procedure but patient is reported to have progressed at "cycle" 9 dated 10/31/94 (Listing 7). No PI scores were given after cycle 9 to document progression. What was the nature of the surgery?

Patient [redacted] reported to have progressed on prednisone at cycle 4 (5/18/94, Listing 20) or at cycle 6 (6/29/94, Listing 7). Using PI scores, progression occurred at cycle 6, however, using analgesic scores, progression occurred at cycle 5.

3. Please clarify the following additional discrepancies:

Patient [redacted]: withdrawn from treatment due to myelosuppression (Table 25) or due to disease progression (Listing 11)?

Patient [redacted]: reported to have disease progression at cycle 6 (Listing 7) but PI score missing; how was progression determined?

Patient [redacted] received 7 cycles of M+P; 3 weeks later, patient is reported as not progressed (Listing ~~11~~) or progressed (Listing 20); response affects whether patient is censored for TTP.

Patient [redacted]: received 8 cycles of M+P; 3 weeks later, patient is reported as not progressed (Listing 7) or progressed (Listing 20); response affects whether patient is censored for TTP.

4. Please submit case report forms for the following patients treated on study CCI-NOV22 who were either withdrawn for toxicity or experienced cardiotoxicity:

Purpose	Patient #
Withdrawn for Toxicity	
Cardiotoxicity	

B. CALGB 9182 Trial

1. Please indicate the basis (e.g., physical exam, radiographic, PSA decrease by 75%, etc.) upon which each partial response was assigned in the trial. Please provide the dates when individual assessments were made if these are available.

2. Please submit case report forms for the following patients treated on study 9182 who were withdrawn for toxicity and for patient

Purpose	Patient #
Withdrawn for Toxicity	
Death due to sepsis	

Julie Beitz 6/24/96

Julie Beitz, MD Date

cc:
NDA #19-297
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ L. Vaccari

FDA
TALK PAPER

FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

T96-74
Nov. 13, 1996

Susan Crusan
(301) 443-3285

FDA Approves New Use for Drug in Treating Prostate Cancer

FDA has approved a new use for Novantrone (mitoxantrone injection, as a chemotherapy for treatment of pain related to advanced prostate cancer that has progressed despite hormone therapy. Novantrone was approved within six months of its submission as initial chemotherapy for patients with advanced prostate cancer that has spread to bone. The following may be used to respond to questions.

Prostate cancer is the second leading cause of cancer deaths in the United States. About 310,000 new cases are expected to be diagnosed in 1996 and more than 40,000 of these will become resistant to hormone therapy. Advanced prostate cancer is often accompanied by intense pain as cancer cells multiply and spread to the bone. Novantrone in combination with steroids has been shown to reduce bone pain, and stabilize or reduce reliance on analgesics. The application was one of the first submitted after FDA announced its initiative to speed cancer drug approvals in 1996.

In a randomized controlled trial, Novantrone in combination with steroids significantly decreased pain in 38 percent of patients, compared to 21 percent treated with steroids alone.

-More-

Patients responding to Novantrone therapy experienced an average of eight months of pain relief compared to two months for patients on steroids alone. There was no difference in survival between the two treatments.

Adverse effects include neutropenia (decrease of white blood cells) and the usual side effects associated with chemotherapy such as nausea, vomiting and hair loss. Less frequently occurring side effects include congestive heart failure, tachycardia (rapid heartbeat), arrhythmias (irregular heart beats), chest pain and decreases in heart function.

In September 1996, FDA's Oncologic Drugs Advisory Committee voted in favor of approval for Novantrone for this new indication. Novantrone was first approved in the United States in 1987 for the treatment of acute non-lymphocytic leukemia.

The drug is marketed by Immunex Corporation, Seattle, Washington.

####

IMMUNEX

November 11, 1996

Robert DeLap, M.D.
Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike - 2nd Floor (HFD-150)
Rockville, MD 20852-1448

NOVANTRONE® (mitoxantrone for injection concentrate)
NDA 19-297 / S-014

Dear Dr. DeLap:

Enclosed is additional information pertaining to supplement S-014, submitted May 10, 1996 to NDA 19-297 for NOVANTRONE (mitoxantrone for injection concentrate). S-014 was submitted to request approval of a new indication for the product.

Included in this amendment is a revised draft package insert to include information pertaining to the new indication. The following changes, listed by page number have been made in response to a teleconference held on November 8, 1996 to discuss CDER comments regarding the draft package insert submitted to sNDA 19-297 / S-014 on May 10, 1996:

Page Two through Four
All references to NOVANTRONE within the CLINICAL PHARMACOLOGY section of the package insert have been changed to refer to the drug substance, mitoxantrone.

Page Four
Paragraph two, under has been changed to

Page Five
Within the palliative response analysis, two patients have been added as primary responders, such that 29% of patients randomized to N + P were responders, with p = 0.011 (as included in our original draft package insert, May 10, 1996). Explanation that the duration of response for these two patients is assigned a value of zero was also added.

The percentage of patients who achieved overall palliative response was changed to 38% of patients randomized to N + P and the associated p-value was revised to 0.025. Two patients have been added as primary responders as described above, these patients, by definition, also qualify as secondary responders.

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Within paragraph three, the word [redacted] has been added in front of the word [redacted] in four places in order to specify that the numbers apply to all patients in the analyses for time to progression.

Page Six
All information regarding the measure and analysis of quality of life has been removed.

Page Seven
Information pertaining to baseline performance status has been removed.

Page Nine
The wording for the additional indication has been modified to state:

Page Fourteen
Reference to children in the PRECAUTIONS section was changed to pediatric patients for greater precision.

Page Seventeen
Under Adverse Reactions, a statement to denote that no non-hematologic adverse events of Grade 3/4 were seen in > 5% of patients in the CCI-NOV 22 Trial was added.

Page Eighteen
A table entitled,
has been added as per your request based on the 4-month safety update for the trail (page 10-11 of the September 9, 1996 submission).

Page Nineteen
Information regarding use of NOVANTRONE, in combination with other antineoplastic agents, being associated with the development of acute leukemia has been relocated to appear directly under the heading of Hematologic adverse events, as this event is possibly associated with NOVANTRONE treatment in general and is not specifically related to the hormone-refractory prostate cancer indication.

Page Twenty
The wording for the hematologic adverse reactions in patients with hormone-refractory prostate cancer has been revised to indicate that the Grade 4 neutropenia observed in these patients was related to the dose escalation required in one trial.

All previous FDA recommendations have been incorporated; changes made by Immunex Corporation and agreed upon during the teleconference held on November 8, 1996 have been indicated by underline or strikethrough, as appropriate.

Please contact me at (206) 389-4066 if you have questions concerning the enclosed information.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Nancy Kercher
File 31100, 31543

TAM/tam

DUPLICATE

IMMUNEX

NDA SUPPL AMEND
SE1-014
(132)

October [redacted]

Robert DeLap, M.D.
Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike - 2nd Floor (HFD-150)
Rockville, MD 20852-1448

NOVANTRONE®, mitoxantrone for injection concentrate
NDA 19-297/S-014
Amendment #012 to unapproved supplement

Dear Dr. DeLap:

Please refer to your facsimile dated September 27, 1996 which provided comments from the pharmacokinetics (pK) and pharmacology/toxicology reviewers on the Novantrone package insert. On October 23, 1996, we informally provided copies of a number of literature articles for review to support changes we made to the CLINICAL PHARMACOLOGY section in response to the 9/27/96 facsimile. On October 24, we sent by facsimile a draft of the revised CLINICAL PHARMACOLOGY section for review. In the present submission, we offer our formal response to the comments in the 9/27/96 facsimile, supporting literature articles, and a copy of the annotated CLINICAL PHARMACOLOGY section of the package insert with references listed. The response, revised pK section (also on diskette in Word Perfect 6.0) and references are provided in Clinical, Pharmacokinetic and Archival section jackets.

We are also taking this opportunity to formally submit 2 other pieces of information to supplement (S-014) to NDA 19-297 which had been sent informally earlier. They are:

1. In response to a request from Dr. Koutsoukos we are providing, in Statistical and Archival section jackets, copies of data diskettes containing the updated datasets from our 10/18/96 response. A "desk copy" of the diskette was sent to Ms. Vaccari, Project Manager, on 10/23/96; and,

2. On 10/28/96, we sent via facsimile a copy of the final table for TTP for all patients in trial CCI-NOV22 in response to a request from Dr. Koutsoukos to Dr. Abbe Rubin received by telephone on 10/23/96. The enclosed table combines the answers included in our responses dated 10/11/96 and 10/18/96 to the FDA requests for additional information on TTP, and documents all changes from the analysis provided in the original submission of S-014 (5/10/96). Copies of the table are included in Clinical, Statistical and Archival section jackets.

For your information, we intend to incorporate all of the comments from the pharmacology/toxicology reviewer as relayed in the 09/27/96 facsimile into the appropriate sections of the package insert.

If you have any comments or questions regarding the contents of this submission, please contact me at (206) 389-4066.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

51 University Street, Seattle, Washington 98101-2936
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IMMUNEX

October 11, 1996

Robert DeLap, M.D.
Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike - 2nd Floor (HFD-150)
Rockville, MD 20852-1448

NOVANTRONE®, mitoxantrone for injection concentrate
NDA 19-297/S-014
Amendment #010 to unapproved supplement

Dear Dr. DeLap:

Attached please find our response to the questions from the Medical Reviewer provided in your facsimile dated 10/9/96. The facsimile requested clarification of information provided in our 10/4/96 submission, regarding TTP (time to progression) dates and status for patients in the CCI-NOV22 trial.

Our response is provided in Attachment 1. We have chosen to address parts a, b and c of your question in a single narrative answer and table with a brief explanation for the change from what was originally reported in supplement S-014 listings. Reasons for a change in status, i.e., either censored or not censored, for the patients listed are also provided.

If you have any comments or questions regarding the contents of this submission, please contact me at (206) 389-4066.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

51 University Street, Seattle, Washington 98101-2936
206.587.0430, Fax 206.587.0606 www.immunex.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: April 30, 1994
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*

NAME OF APPLICANT	DATE OF SUBMISSION
Immunex Corporation	96.10.11
ADDRESS *(Number, Street, City, State and Zip Code)*	**TELEPHONE NO.** (Include Area Code)
51 University Street Seattle, WA 98101	(206) 587-0430
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
	019-297

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME (If any)
Mitoxantrone for injection concentrate	NOVANTRONE®

CODE NAME *(If any)*	CHEMICAL NAME
N/A	1,4-dihydroxy-5,8-bis[[2-[(hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione dihydrochloride

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
njection concentrate	Intravenous Injection	10, 20, 25, 30mg

PROPOSED INDICATIONS FOR USE

NOVANTRONE in combination with cotricosteroids as initial chemotherapy for treatment of patients with prostrate cancer, after failure of primary hormonal therapy.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

IND #
IND #
DMF DMF
DMF DMF
DMF

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA)(21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE OF SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☒ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* 21 CFR 314.70

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

	1. Index
	2. Summary (21 CFR 314.50(c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d)(1))
	4. a. Samples (21 CFR 314.50 (e)(1))(Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50(e)(2)(i))
■	c. Labeling (21 CFR 314.50(e)(2)(ii))
	i. draft labeling (4 copies)
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50(d)(2))
	6. Human pharmacokinetics and bioavailability section(21 CFR 314.50(d)(3))
	7. Microbiology section (21 CFR 314.50(d)(4))
X	8. Clinical data section (21 CFR 314.50(d)(5))
	9. Safety update report (21 CFR 314.50(d)(5)(vi)(b))
	10. Statistical section (21 CFR 314.50(d)(6))
	11. Case report tabulations (21 CFR 314.50(f)(1))
	12. Case reports forms (21 CFR 314.50(f)(1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

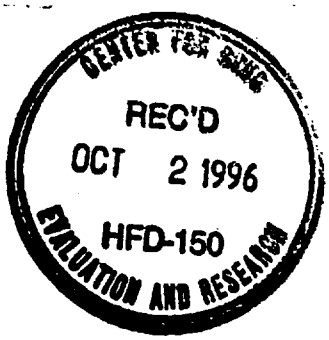
NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Mark Gauthier	Mark W. Gauthier	96.10.11

ADDRESS (Street, City, State, Zip Code)	TELEPHONE NO. (Include Area Code)
1 University Street, Seattle, WA 98101	(206) 389-4066

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Immunex Corporation

DUPLICATE



October 1, 1996

Robert DeLap, M.D.
Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike - 2nd Floor (HFD-150)
Rockville, MD 20852-1448

NOVANTRONE® (mitoxantrone for injection concentrate)
NDA 19-297 / S-014
Amendment 008

Dear Dr. DeLap:

Enclosed is an amendment (Amendment 008) to supplement S-014, submitted May 10, 1996 to NDA 19-297 for NOVANTRONE (mitoxantrone for injection concentrate). S-014 was submitted to request approval of a new indication for the product. Contained in this amendment are responses to FDA questions communicated to Immunex via telephone by Bob Barron, Ph.D., Chemistry Reviewer, on September 30, 1996.

In response to Dr. Barron's request for identification of the level of confidentiality of sections of the Abbreviated Environmental Assessment (AEA) (NDA 19-297 / S-014, page 03/18/086 through 03/18/0150), the following sections of the AEA are classified as releasable or confidential, as indicated:

Releasable	*Confidential*
Section 1 Date	*Section 15 Confidential Appendices*
Section 2 Name of Applicant	
Section 3 Address	
Section 4 Description of Proposed Action	
Section 5 Identification of Chemical Substances	
Section 5 Introduction of Substances into the Environment	
Section 7 through Section 11 not required	
Section 12 List of Preparers	
Section 13 Certification	
Section 14 References	

Information contained in Section 4 Description of the Proposed Action is releasable, with the exception of the projected five year production of Novantrone for total domestic use (NDA 19-297 / S-014, page 03/18/088); this information is confidential.

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In response to Dr. Barron's request for a justification for submission of an *Abbreviated* Environmental Assessment, attached (Attachment I) is a telephone contact report in which Ms. Nancy Sager, Office of Pharmaceutical Science, states that this supplement qualifies for an AEA. Attachment I also contains guidance for preparation of certain sections of the AEA, provided by Ms. Sager.

As further justification for submission of an AEA, a letter granting mitoxantrone orphan drug designation for the treatment of hormone refractory prostate cancer is attached (Attachment II).

Please contact me directly at (206) 389-4066 if you should have questions concerning the information in this submission.

Sincerely,

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Nancy Kercher
File 31100, 31543

TAM/tam

DUPLICATE

IMMUNEX

NDA SUPPL AMEND
SE1-014
(SU)

September 6, 1996

Robert DeLap, M.D.
Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike - 2nd Floor (HFD-150)
Rockville, MD 20852-1448

NOVANTRONE® (mitoxantrone for injection concentrate)
NDA 19-297 / S-014
Amendment 006

Dear Dr. DeLap:

Enclosed is an amendment (Amendment 006) to supplement S-014, submitted May 10, 1996 to NDA 19-297 for NOVANTRONE (mitoxantrone for injection concentrate). S-014 was submitted to request approval of a new indication for the product. The additional indication being sought is:

"NOVANTRONE in combination with coritcosteroids is indicated as initial chemotherapy for treatment of patients with prostate cancer, after failure of primary hormonal therapy."

Included in this amendment is the Four Month Safety Update Report (Item 9) for NDA 19-297 / S-014. The safety update report includes adverse events that occurred after the filing of the sNDA that were reported by subjects during off-study follow-up as well as events that occurred prior to filing of the sNDA but were not reported to Immunex until after the filing. Page number references made to the sNDA within this document refer to NDA 19-297 / S-014, submitted on May 10, 1996.

If you should have any questions concerning the information in this submission, please contact me directly at (206) 389-4066.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: File 31100, 31543
Nancy Kercher

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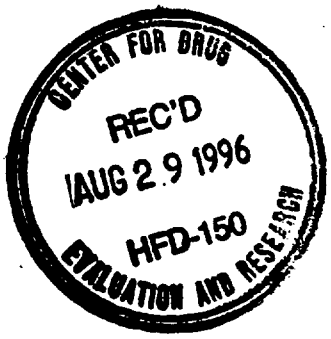
206.587.0430, Fax 206.587.0606 www.immunex.com

IMMUNEX

DUPLICATE



Robert DeLap, M.D.
Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike - 2nd Floor (HFD-150)
Rockville, MD 20852-1448

NOVANTRONE, mitoxantrone for injection concentrate
NDA 19-297/S-014
Amendment #005 to unapproved supplement

Dear Dr. DeLap:

Attached please find 3 copies of the slides we intend to present at the September 11, 1996 ODAC meeting. These are considered final, however, minor changes may be made in format prior to the meeting. We are providing them for information and would appreciate the opportunity to see a copy of the FDA slides prior to the meeting, if convenient.

Please note: the slides for the presentation include several analyses that have not previously been submitted to the Agency. The analyses are directly derived from the database and can be readily verified. Attachment 1 contains a table which summarizes the additional analyses presented. The slides themselves appear after attachment 1.

If you have any comments or questions regarding the contents of this submission, please contact me at (206) 389-4066.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

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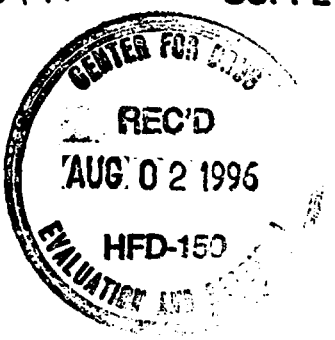
206.587.0430. Fax 206.587.0606 www.immunex.com

Immunex Corporation

ORIGINAL SUPPL NEW CORRES



August 1, 1996

Robert DeLap, M.D.
Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike - 2nd Floor (HFD-150)
Rockville, MD 20852-1448

NOVANTRONE® (mitoxantrone for injection concentrate)
NDA 19-297/S-014
Amendment 003

Dear Dr. DeLap:

Enclosed are eleven copies of Immunex Corporation's briefing package that has been prepared for the Oncologic Drugs Advisory Committee (ODAC) meeting on September 11, 1996. This package summarizes the data submitted to NDA 19-297, Supplement 014 for treatment of patients with hormone refractory prostate cancer (HRPC). Twenty copies of this document have also been provided to Ms. Jannette O'Neill-Gonzalez of the FDA's Advisors and Consultants Staff.

A total of 25 Immunex representatives and consultants will be present at the September 11, 1996 ODAC meeting. The following individuals will be making formal presentations to the committee: Ken Seamon, Ph.D. (Immunex), Ian Tannock, M.D. (Princess Margaret Hospital) and Richard Ghalie, M.D. (Immunex). A list of Immunex consultants who will be present at the meeting is attached.

Please contact me at (206) 389-4066 if you have questions regarding this information.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Nancy Kercher
File 31100, 31462

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206.587.0430, Fax 206.587.0606

Immunex Corporation

DUPLICATE

Robert DeLap, M.D.
Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
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Rockville, MD 20852-1448

NOVANTRONE, mitoxantrone for injection concentrate
NDA 19-297/S-014
Amendment to unapproved supplement

NDA SUPPL AMEN
SE1-014
(AZ)

Dear Dr. DeLap:

The attached submission is provided in response to questions received on supplement S-014, submitted May 10, 1996 to NDA 19-297 for Novantrone (mitoxantrone for injection concentrate). S-014 requested approval of a new indication for the product. The questions from the Medical Reviewer were received in a facsimile dated June 24, 1996. In addition, the Statistical Reviewer provided questions by phone on June 25, 1996. One archival copy and one reviewer copy (in appropriate jackets) are included. Diskettes, where requested, containing data or text are included in both the archival and reviewer copies.

The original supplement included a dataset for the EORTC Quality of Life (QOL) Prostate Module for trial CCI-NOV22. The data set for the prostate module consisted of 13 questions. The response to question 10 (parts A & B) was inadvertently omitted for all subjects in the analyses, listings and diskette submitted with the supplement. Tables 14 through 17 (pages 08/02/067-078 of S-014 submitted May 10, 1996), Figure 20 (page 08/02/0117 of S-014), and Listing 19 (pages 08/04/047-092 of S-014) have been updated to reflect addition of this data. Inclusion of the previously omitted data does not alter the statistical or clinical comparisons for the QOL instrument. New Tables 15A through 17A are included here as well. The analyses presented in new Tables 15A through 17A are identical to those in Tables 15 through 17 except that subjects with values at baseline only (without follow-up values) are excluded. This is provided for information.

The contents of the package include:

1. Response to Medical Reviewer's questions from June 24, 1996 facsimile, including case report forms;

2. Response to Statistical Reviewer's questions provided by phone on June 25, 1996, including diskettes with SAS codes;

3. Update to CCI-NOV22 QOL Prostate Module - Questions 10A and 10B, includes revised data listings and diskette as previously provided in Item 10, Statistical Section. Copies of the revised listings are included in the Archival, Clinical (Item 8) and Statistical (Item 10) sections; diskettes provided in Item 10 only.

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IMMUNEX

WordPerfect 6.0 versions of the draft package insert and CCI-NOV22 Clinical Trial Report, as requested by the Medical and Statistical Reviewers, respectively, will be provided under separate cover within the next 7-10 days.

On or about September 10, 1996, Immunex intends to submit the four month safety update for the trials (CCI-NOV22 and 9182) included in supplement S-014. Safety and follow-up information collected after analysis database was locked will be included in this update.

If you have any comments or questions regarding the contents of this submission, please contact me at (206) 389-4066.

Sincerely,

Mark W. Gauthier
Senior Regulatory Affairs Manager

Immunex Corporation

SUPPL NEW CORRESP

S-014
NC

IMMUNEX

Robert DeLap, M.D.
Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike - 2nd Floor (HFD-150)
Rockville, MD 20852-1448

NOVANTRONE, mitoxantrone for injection concentrate
NDA 19-297/S-014
Amendment to unapproved supplement

Dear Dr. DeLap:

The information included in this submission is provided in response to requests received regarding supplement S-014, submitted May 10, 1996 to NDA 19-297 for Novantrone (mitoxantrone for injection concentrate). S-014 was submitted to provide information sufficient for approval of an additional indication for the product.

Enclosed in this submission are three copies of a disk containing the WordPerfect 6.0 version of the draft package insert, as requested by the Medical Reviewer. One disk is provided for the Medical Reviewer, one for the Consumer Safety Officer and one for archival purposes. Please note that the structural formula diagram for the product (page 1) as well as the Immunex logo (page 18) did not properly convert to the WordPerfect format. The remainder of the document converted appropriately.

Also enclosed are three copies of a disk containing a WordPerfect 6.0 version of the CCI-NOV22 Clinical Trial Report, as requested by the Statistical Reviewer on June 25, 1996. One disk is provided for the Statistical Reviewer and one for archival purposes.

If you should have any questions concerning the information provided, please contact me directly at (206) 389-4066.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Nancy Kercher
File 31100, 31543

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206.587.0430, Fax 206.587.0606

Immunex Corporation

DUPLICATE

SUPPL NEW CORRESP

IMMUNEX

Robert DeLap, M.D.
Director
Division of Oncology Drug Products
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1451 Rockville Pike - 2nd Floor (HFD-150)
Rockville, MD 20852-1448

NOVANTRONE, mitoxantrone for injection concentrate
NDA 19-297/S-014
Amendment to unapproved supplement

Dear Dr. DeLap:

The information included in this submission is provided in response to requests received regarding supplement S-014, submitted May 10, 1996 to NDA 19-297 for Novantrone (mitoxantrone for injection concentrate). S-014 was submitted to provide information sufficient for approval of an additional indication for the product.

Enclosed in this submission are three copies of a disk containing the WordPerfect 6.0 version of the draft package insert, as requested by the Medical Reviewer. One disk is provided for the Medical Reviewer, one for the Consumer Safety Officer and one for archival purposes. Please note that the structural formula diagram for the product (page 1) as well as the Immunex logo (page 18) did not properly convert to the WordPerfect format. The remainder of the document converted appropriately.

Also enclosed are three copies of a disk containing a WordPerfect 6.0 version of the CCI-NOV22 Clinical Trial Report, as requested by the Statistical Reviewer on June 25, 1996. One disk is provided for the Statistical Reviewer and one for archival purposes.

If you should have any questions concerning the information provided, please contact me directly at (206) 389-4066.

Sincerely,

Mark W. Gauthier

Mark W. Gauthier
Senior Regulatory Affairs Manager

cc: Nancy Kercher
File 31100, 31543

51 University Street, Seattle, Washington 98101-2936
206.587.0430, Fax 206.587.0606

immunex

May 10, 1996

Robert L. Justice, M.D.
Acting Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Office Building
1451 Rockville Pike - 2nd Floor (HFD-150)
Rockville, MD 20852-1448

NOVANTRONE® mitoxantrone for injection concentrate
NDA 19-297/S-014
Efficacy supplement

Dear Dr. Justice:

Pursuant to 21 CFR 314.70, Immunex Corporation is submitting a supplemental application to request approval of a new indication for the product, NOVANTRONE mitoxantrone concentrate for injection. The additional indication being sought is:

"*NOVANTRONE in combination with corticosteroids is indicated as initial chemotherapy for treatment of patients with prostate cancer, after failure of primary hormonal therapy.*"

Results are presented from a randomized phase III clinical trial (CCI-NOV22) which demonstrates that Novantrone provides a significant benefit for relief of pain in symptomatic hormone resistant prostate cancer patients and suggests that overall quality of life (QOL) also improves as a result of Novantrone treatment. Also included are results from a second phase III trial 9182) which confirm the activity of Novantrone in Hormonal Resistant Prostate Cancer and the QOL improvement. Final clinical trial reports for the pivotal study (CCI-NOV22) and the supportive study 9182), including all data tabulations and listings, are located in Item 8, Volumes 2-4 and 5-7, respectively, and in Item 10, Volumes 10-12 and 13-15, respectively. Please refer to the table of contents for a detailed listing.

The safety update (Item 9) will be filed 4 months from the date of submission of this supplement.

As discussed at the meeting between Immunex and the Agency on December 20, 1995, we anticipate that the supplement will receive priority review status under the Prescription Drug User Fee Act of 1992, because there is no currently approved chemotherapy for palliative treatment in this patient population.

Prostate cancer is a disease which is receiving much attention in the media of late. Rapid approval of this new indication may be viewed by patients and the press as a positive result of the "Reinventing the Regulation of Cancer Drugs..." initiative recently announced by the FDA and President Clinton, at least in spirit if not literally. Therefore, we would appreciate

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the opportunity to work closely with the Division to facilitate review of this submission and to prepare for a September 1996 presentation to the Oncologic Drugs Advisory Committee, should that be required. The goal of our collaboration being to accelerate availability of this promising new treatment for patients with hormone resistant prostate cancer. Novantrone has a proven safety record based on nine years of post marketing surveillance.

I will follow up by phone within two weeks to discuss how we can help to facilitate review of this submission.

Electronic SAS datasets for the NOV22 and 9182 studies as requested by the Statistician are provided with this submission. Refer to Volume 17 for the key to the data set documentation, diskettes provided and directory of files.

If you have any comments or questions regarding the contents of this submission, please contact me at (206) 389-4066.

Sincerely,

Mark W. Gauthier
Senior Regulatory Affairs Manager

MG:nm

File: 31100, 31543