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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-288

Medical Review(s)

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of Original NDA

NDA	21-288
Applicant	Debio Recherche Pharmaceutique SA Case Postale Route du Levant 146 CH – 1920 Martigny Switzerland
Submission Type	Original NDA
Drug	
Established name	Triptorelin pamoate for injectable suspension
Trade name	Trelstar™ LA
Chemical class	Synthetic decapeptide
Chemical name	Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH2 pamoate salt ($D\text{-}Trp^{6}$-GnRH)
Drug Class	Gonadotropin releasing hormone (GnRH) agonist
Proposed Indication	Palliative treatment for advanced prostate cancer.
Route of Administration	Intramuscular injection
Dosage Form	Suspension
Dosing Regimen	Administered once every 84 days (every 12 weeks)
Dose	11.25 mg per dosing
Dates	
Submitted	June 29, 2000
CDER stamp date	June 29, 2000
PDUFA date	June 29, 2001
Related NDAs	20-715
Related INDs	IND (Prostate cancer) IND (Endometriosis)
Medical Reviewer	Scott Monroe MD
Date Review Completed	June 15, 2001

FINAL

(June 28, 2001)

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EXECUTIVE SUMMARY

1 RECOMMENDATIONS

1.1 Recommendation Regarding Approval

1.1.1 Approvability

It is recommended that the 84-day formulation of triptorelin pamoate (Trelstar™ LA) be approved for the proposed indication of *"palliative treatment of advanced prostate cancer"* conditional upon the Sponsor's agreeing to (1) the labeling changes and the Phase IV commitment described below in Section 1.2

1.1.2 Basis for Recommendation Regarding Approvability (Risk/Benefit Assessment)

Benefits. Surgical castration is the standard against which hormonal therapies for the palliative management of advanced prostate cancer have been compared. The goal of androgen suppression therapy is to reduce serum testosterone concentrations to levels comparable to those observed following orchiectomy (i.e., ≤ 1.735 nmol/L or ≤ 50 ng/dL). Superactive GnRH agonists that suppress serum testosterone to castrate levels have been shown to have comparable long-term efficacy as orchiectomy, as assessed by time to disease progression and survival. Achievement of castrate levels of serum testosterone is generally obtained by 1 month after the start of therapy with a superactive GnRH agonist.

The results of Study DEB-96-TRI-01-Phase 1, the principal efficacy and safety study in support of NDA 21-288, indicated that the 84-day formulation of triptorelin pamoate suppressed serum testosterone to ≤ 1.735 nmol/L within 29 days of first dosing and maintained serum testosterone at ≤ 1.735 nmol/L through 3 dosing cycles (252 days) in greater than 90% of patients. In addition, the 84-day formulation was not statistically inferior to the 28-day formulation of triptorelin pamoate that was approved by the FDA in June 2000 for the treatment of advanced prostate cancer. These finding, along with the limited data provided by the Sponsor regarding the frequency and magnitude of increases in serum testosterone levels within 48 hours after repeat dosing, are sufficient to support the efficacy of the 84-day formulation of triptorelin pamoate for the palliative treatment of advanced prostate cancer.

Risks. In contrast to surgical castration, treatment with a superactive GnRH agonist initially results in a significant, albeit temporary (~1 to 2 weeks), increase in gonadal androgen secretion before reducing serum testosterone to castrate levels. The initial rise in serum testosterone may cause a temporary worsening of symptoms referred to as "a flare." Most commonly, the androgen-induced flare consists of an increase in bone pain in patients with advanced prostate cancer. Less frequently, more serious complications such as compression of the spinal cord with motor impairment can occur. This potential complication is a labeled warning for all superactive GnRH agonists. The likelihood of neurologic complications is diminished with earlier diagnosis of prostate cancer, as is occurring today in the United States. The risk of a clinically serious complication resulting from the initial surge of testosterone at the onset of treatment with the 84-day formulation of triptorelin should be no different than that associated with the use of other presently approved superactive GnRH analogs.

As a class, superactive agonists of GnRH have been found to be safe and well tolerated and are approved not only for the treatment of prostate cancer but also for benign estrogen-dependent gynecologic disorders and precocious puberty. Triptorelin, either as the acetate or pamoate salt, has been marketed outside of the United States in 28-day formulations for more than a decade for the treatment of advanced prostate cancer. In 1996, an 84-day formulation of triptorelin for the treatment of prostate cancer was approved in France and has subsequently received marketing approvals in a total of 10 countries. The Sponsor estimates that since the launch of a 28-day

formulation of triptorelin in 1986 and the 84-day formulation in 1997[. . . . and . .] treatment-months of the 2 formulations, respectively, have been sold world-wide by its licensee's Beaufour-Ipsen and Ferring.

Since GnRH analogs are small peptides, they have the potential to induce antibody formation and hypersensitivity reactions. The sponsor, in the initial and supplemental Safety Updates, provided information regarding post-marketing reports of allergic reactions in patients treated with any formulation of triptorelin. Based on information proved by the Sponsor and information in the FDA database for spontaneous reports of postmarketing adverse events, it appears that the risk of a patient developing a serious allergic reaction because of treatment with the 84-day formulation of triptorelin pamoate would not be significantly greater than that associated with treatment with other presently approved superactive GnRH agonists. The Sponsor's proposed labeling includes the following statement under WARNINGS: "Rare reports of anaphylactic shock and angioedema related to triptorelin administration have been reported."

In summary, based on safety and efficacy information contained in NDA 21-288, this reviewer believes that the sponsor has demonstrated that triptorelin pamoate 11.25 mg in the proposed 84-day formulation (Trelstar™ LA) is safe and effective for the proposed indication of palliative treatment of advanced prostate cancer.

1.2 Specific Recommendations to the Sponsor

Approval of Trelstar™ LA should be conditional on the following:

1. The Sponsor will make the labeling changes outlined in Section 11 (Package Insert) of this review.
2. The Sponsor will commit to conducting a Phase IV pharmacology study designed to obtain addition clinical data regarding increases in serum testosterone to levels > 1.735 nmol/L between 48 to 72 hours after repeat dosing with the 84-day formulation of triptorelin pamoate.

2 SUMMARY OF CLINICAL FINDINGS

2.1 Overview of Clinical Program

2.1.1 Drug

Triptorelin (D-Trp^6-GnRH) is a synthetic analog of naturally occurring gonadotropin releasing hormone (GnRH), in which D-tryptophan has replaced glycine in position 6 of the natural decapeptide. It is formulated as a sustained-release dosage form consisting of 11.25 mg of triptorelin in a matrix of poly (*dl*-glycolide-co-lactide). It is to be administered by IM injection once every 84-days and will be marketed under the trade name of Trelstar™ LA.

2.1.2 Clinical Program

The sponsor submitted data from 5 clinical studies that were conducted using an 84-day formulation of triptorelin. Four of the studies were conducted in men with cancer of the prostate, and 1 study was conducted in women with gynecologic disorders. Of the studies in men with prostate cancer, only one (Study DEB-96-TRI-01-Phase 1) was an adequate and well controlled trial that was conducted with the to-be-marketed 84-day formulation of triptorelin. All of the studies were conducted outside of the United States. Study DEB-96-TRI-01, which provided almost all of the safety and efficacy data in support of this NDA, was conducted in South Africa.

2.1.3 Design of the Controlled Study

DEB-96-TRI-01 was a multicenter, controlled (active comparator), randomized, open label clinical trial in which patients with advanced prostate cancer that might benefit from hormonal

therapy (i.e., reduction in androgen levels) were enrolled. Patients were randomly assigned in a 1:1 ratio to treatment with either the 84-day formulation of triptorelin or the active comparator (a 28-day formulation of triptorelin that was approved by the FDA in June 2000 for the palliative management of advanced prostate cancer). Patients assigned to the 84-day formulation group received a total of 3 IM doses of Study Drug, each dose separated by 84 days for a total treatment period of 252 days (3 x 84 days). Patients assigned to the triptorelin 28-day formulation group received a total of 9 IM doses of Study Drug, each dose separated by 28 days. Patients underwent efficacy and safety assessments at 28-day intervals.

2.2 Efficacy

2.2.1 Primary Efficacy Assessment and Efficacy Endpoints

Prostate cancer is an androgen-dependent tumor in most men at the time of initial presentation. The goal of hormonal therapy in prostate cancer is to suppress serum androgen levels to those normally observed following surgical castration. Based on these considerations, the FDA has accepted for this application, and prior applications for GnRH agonists, attainment of castration levels of testosterone (i.e., ≤ 1.735 nmol/L or ≤ 50 ng/dL) by treatment Day 29 and maintenance of these levels through at least 3 dosing cycles as a surrogate efficacy endpoint in clinical trials of the treatment of advanced prostate cancer.

The primary efficacy objective in Study DEB-96-TRI-01-Phase 1 was to demonstrate that the 84-day formulation of triptorelin was not inferior to the approved 28-day formulation as assessed by the following co-primary endpoints: (1) the proportion of patients with a serum testosterone of ≤ 1.735 nmol/L (i.e., medically castrate) on Day 29 and (2) the proportion of patients maintaining castrate levels of serum testosterone from Day 57 through Day 253. Based on a prior agreement with DRUDP, treatment with the 84-day formulation would be declared as non-inferior to that of the 28-day formulation if the lower bound of the 2-sided 95% CI for the difference (84-day formulation minus 28-day formulation) for the proportion of men with a serum testosterone of ≤ 1.735 nmol/L was not less than −10% for each of the co-primary endpoints.

2.2.2 Efficacy Results (Primary Endpoints)

The principal trial successfully achieved the co-primary efficacy endpoints as described below.

Achievement of medical castration by Study Day 29. In the intent to treat (ITT) population, 167 of 171 patients (97.7%) in the 84-day formulation group and 152 of 164 patients (92.7%) in the 28-day formulation group had a serum testosterone of ≤ 1.735 nmol/L on Day 29. The point estimate and 95% CI for the difference was 5.0% (95% CI: [-1.1%; 13.4%]). The results for the per protocol (PP) population were similar.

Cumulative maintenance of castration levels of testosterone from Study Day 59 through Study Day 253 (Kaplan-Meier analysis).). In the ITT population, the cumulative maintenance of castration was 94.4% for patients in the 84-day formulation group and 94.2% for patients in the 28-day formulation group. The point estimate and 95% CI for the difference in maintenance rates (84-day formulation minus 28-day formulation) was 0.2% (95% CI: [-4.9%; 5.3%]).

Maintenance of Medical Castration from Day 57 Through Day 253 (Kaplan Meier Analysis)

	Treatment					
	84-Day Formulation		28-Day Formulation		Percent Difference	
Population	N [1]	% Success	N	% Success	Value [2]	95% CI
Intent-to-treat	171	94.4	164	94.2	0.2	(-4.9, 5.3)
Per Protocol	166	94.1	159	95.3	-1.2	(-6.3, 3.9)

[1] Total number of patients in group.
[2] Difference in maintenance rates of medical castration (84-day formulation minus 28-day formulation).

2.2.3 Other Efficacy Issues

A superactive GnRH agonist, in contrast to a true GnRH antagonist, has the potential to produce a transient postdosing increase in serum testosterone concentrations on repeat dosing in an otherwise adequately suppressed patient (i.e., serum testosterone ≤ 1.735 nmol/L). Such increases may be of potential harm to a patient with prostate cancer undergoing androgen deprivation therapy. In a subset of 30 patients (15 in each treatment group) at one Center, serum testosterone levels were measured through 48 hours after dosing on Study Days 85 and 169. In the 84-day formulation group, there were no postdosing testosterone values > 1.735 nmol/L after dosing on Day 85. After dosing on Day 169, however, 2 patients had serum testosterone levels > 1.735 nmol/L (maximum values of 1.79 nmol/L and 2.65 nmol/L). In the 28-day formulation group, no testosterone values > 1.735 nmol/L were observed after dosing on Days 85 or 169.

Because a sample size of only 15 patients may not provide a meaningful estimate of the actual incidence of transient postdosing testosterone increases in patients treated with the 84-day formulation of triptorelin, the Sponsor will be requested to investigate this further as part of a Phase IV clinical commitment.

2.2.4 Proposed Label Claim

The results of Study DEB-96-TRI-01-Phase 1 indicated that (1) the 84-day formulation of triptorelin pamoate suppressed testosterone to ≤ 1.735 nmol/L within 29 days of first dosing and maintained testosterone at ≤ 1.735 nmol/L through 3 dosing cycles (253 days) in greater than 90% of patients and (2) was not statistically inferior to the 28-day formulation in terms of achievement and maintenance of medical castration. These findings, along with the limited data provided by the Sponsor regarding postdosing acute increases in serum testosterone levels, are sufficient to support the Sponsor's label claim that "Trelstar™ LA is indicated in the palliative treatment of advanced prostate cancer."

2.3 Safety

2.3.1 Exposure to Study Drug

A total of 196 patients received one or more doses of the to-be-marketed 84-day formulation of triptorelin pamoate. Of these patients, 174 were in the principal safety and efficacy study, DEB-96-TRI-01-Phase 1. Of these 174 patients, 165 received 2 doses of the 84-day formulation (maximum exposure 168 days) and 156 received 3 doses (maximum exposure 152 days). Although the number of subjects treated with the to-be-marketed 84-day formulation of triptorelin is small, triptorelin acetate or triptorelin pamoate in 28-day formulations has been marketed worldwide for many years. In the present application, 172 patients also were exposed to the 28-day formulation for 28 to 252 days. As a class, superactive agonists of GnRH have been found to be safe and well tolerated. Based on the data in the present application and the overall experience with triptorelin in other countries, the exposure to the 84-day formulation of triptorelin is adequate to assess its general safety for the indication of management of advanced prostate cancer.

2.3.2 General Safety Findings

The types of reported adverse events and the proportion of patients reporting them in Study DEB-96-TRI-01-Phase 1 were compatible with the study population (men with advanced carcinoma of the prostate with a median age of 70 years). For most categories of adverse events, the reported frequencies were similar in the 84-day formulation and 28-day formulation groups. In the 84-day formulation group, 147 of 174 patients (84.5%) reported one or more treatment-related adverse events compared with 134 of 172 patients (77.9%) in the 28-day formulation group. In the 84-day formulation group, 30 patients (17.2%) experienced a total of 39 serious adverse events.

In the 28-day formulation group, 39 patients (22.7%) experienced a total of 45 serious adverse events. Thirteen patients (7.5%) in the 84-day formulation group and 13 patients (7.6%) in the 28-day formulation group were withdrawn because of an adverse event. Of these 26 adverse events, 1 in each treatment group was assessed as possibly related to treatment with Study Drug.

Changes in safety laboratory values also were generally similar across the 2 treatment groups. In the 84-day formulation group, mean or median increases of 10% or more above the baseline value were observed at the end of treatment for BUN, SGOT, SGPT, and alkaline phosphatase. Mean decreases of 10% or more below the baseline value were observed at the end of treatment for the measurements of leukocytes and prothrombin time. The mean change from baseline exceeded 20% for only one assessment. Mean SGPT increased from 19.11 U/L at baseline to 24.83 U/L at the last measurement. There were no statistically significant differences between the 84-day and the 28-day formulation treatment groups in terms of the change from baseline for any of the laboratory measurements. In the 84-day formulation group, measurements for which > 10% of patients had shifted to below the normal range by Study Day 253 were hemoglobin (21% of patients) and red blood cell count (27% of patients). Measurements for which > 10% of patients had shifted to above the normal range by Study Day 253 were glucose (27% of patients), BUN (17% of patients), SGOT (12% of patients), SGPT (13% of patients), and alkaline phosphatase (16% of patients). The relationship of these changes to drug treatment is difficult to assess in this population. However, the magnitude of the mean changes and the percentage of patients shifting either to above or below the normal range is consistent with the changes that might be expected during treatment with a therapy that induces medical castration in the study population (men with advanced carcinoma of the prostate with a median age of 70 years).

2.3.3 Patient Deaths

Twenty-six (26) patients (13 in each treatment group) died during or within 90 days of their participation in the Study. All deaths, with 2 exceptions, were considered by the Investigators as being *Not Related* to treatment with Study Drugs. The 2 exceptions (both assessed as having had an *Unlikely Relationship* to Study Drug) were due to a fatal pulmonary embolus (84-day formulation group) and a fatal cardiac arrest (28-day formulation group). In the 84-day formulation group, the 13 causes of death were related to progression of prostate cancer (n=5), cardiac or thromboembolic disease (n=3), sepsis other than that involving the urinary tract (n=2), syndrome of inappropriate ADH secretion (n=1), chronic obstructive airway disease (n=1), and a pulmonary mass (n=1, metastatic prostate cancer or primary lung tumor).

It is unlikely that treatment with triptorelin was responsible for any of these deaths. The fairly high percentage of deaths in this Study is not unexpected since all patients had advanced prostate cancer. All patients with on-treatment serum testosterone values who died of progressive disease, were medically castrate (testosterone ≤ 1.735 nmol/L) prior to their death.

In the 84-day formulation group, 7 of 66 Black patients (10.6%) and 4 of 81 Caucasian patients (4.9%) died. In the 28-day formulation group, 3 of 62 black patients (4.7%) and 9 of 84 Caucasian patients (10.7%) died. These differences in percentages of deaths by racial group in the 84-day formulation and the 28-day formulation groups are likely to be a result of the small number of events. Overall, the percentages of Black and Caucasian patients who died in Study DEB-96-TRI-01-Phase 1 (results for both formulations combined) were similar (10 of 130 black patients [7.7%] and 13 of 165 Caucasian patients [7.9%]).

2.3.4 Safety Issues of Particular Concern

There are no safety issues of special concern. Triptorelin, either as the acetate or pamoate salt, has been marketed in a 28-day formulation for more than a decade and was approved for marketing by the FDA in June 2000. As a class, superactive agonists of GnRH have been found

to be safe and well tolerated and are approved not only for the treatment of prostate cancer but also for benign estrogen-dependent gynecologic disorders and precocious puberty. The safety findings that were (1) observed in the primary safety study (DEB-96-TRI-01-Phase 1) and (2) reported in the Safety Updates are adequately and appropriately represented in the proposed labeling with the exception of those specific items listed in Section 11 (Package Insert) of this review.

2.4 Dosing

Although formal dose ranging studies do not appear to have been conducted with the 84-day formulation, the proposed dose of 11.25 mg administered every 84 days is reasonable. A somewhat higher dose of triptorelin, however, would likely provide somewhat more consistent suppression of serum testosterone to castrate levels at the end of each 84-day treatment period, the time at which the highest proportion of serum testosterone values are > 1.735 nmol/L in clinical data submitted by the Sponsor.

2.5 Special Populations

Women and children. The 84-day formulation of triptorelin (Trelstar™ LA) is to be used only for the management of advanced prostate cancer. This will limit its target population to men, primarily elderly men. It is not intended to be used in women or children.

Renal and hepatic impairment. Subjects with renal or hepatic impairment had a 2- to 4-fold higher exposure to triptorelin (higher AUC values) than young healthy males. Because superactive GnRH agonistic analogs have a high margin of safety, a dose reduction in patients with renal or hepatic impairment does not appear to be necessary.

Racial differences in efficacy and safety. Thirty eight (38) percent of the patients in Study DEB-96-TRI-01 were Black; consequently, secondary analyses for the co-primary efficacy endpoints, adverse events, and deaths (described previously) were performed separately for Black and Caucasian patients. In the 84-day formulation group, the proportion of patients who had castrate levels of testosterone on Day 29 was similar in Black and Caucasian patients (98.4% and 97.5%, respectively). However, the cumulative maintenance of medical castration was lower in Black patients (91.5%) compared to that in Caucasian patients (94.9%). Although the percentage of patients reporting one or more adverse events was similar in the Black and Caucasian groups, the percentages of patients experiencing adverse events in specific body system categories varied across the 2 racial groups. A numerically higher percentage of Caucasian patients experienced severe adverse events (44.4% versus 33.3%) while a higher percentage of Black patients experienced serious adverse events (16.7% versus 12.3%).

CLINICAL REVIEW

3 INTRODUCTION AND BACKGROUND

3.1 Drug

- **Established Name** Triptorelin pamoate for injectable
- **Proposed Trade Name** Trelstar™ LA
- **Drug Class** Gonadotropin releasing hormone (GnRH) agonist
- **Chemical Class** Synthetic decapeptide
- **Chemical name** Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH2-pamoate salt (D-Trp^6-GnRH)
- **Proposed Indication** Palliative treatment for advanced prostate cancer
- **Dosage Form** Suspension
- **Dose** 11.25 mg administered by intramuscular injection
- **Dosing Regimen** Administered once every 84 days (every 12 weeks)

3.2 Overview of Disease and Treatment Options

3.2.1 Carcinoma of the Prostate and Medical Therapy

Cancer of the prostate is the most frequent noncutaneous malignancy and the second most frequent cause of death from cancer in men over 50 years of age. When localized, prostate cancer can be cured by radical prostatectomy or radiation therapy. However, in a high percentage of men, it is discovered only in advanced stages with metastatic lesions. Although progress has been made in the diagnosis and treatment of prostate cancer, survival of patients with metastatic disease is usually less than 3 to 4 years.

Prostate cancer is an androgen-dependent tumor in most men at the time of initial presentation. Growth of prostate glandular tissue is regulated by a complex of growth factors of which androgens play a pivotal role. Surgical castration or treatment with high doses of estrogenic compounds (generally diethylstilbestrol [DES]) to suppress testicular androgen production were the mainstay of treatment for advanced prostate cancer for decades. However, the reluctance of many men to accept surgical castration for therapy and the adverse effects of estrogen therapy (particularly cardiovascular adverse events) encouraged investigators to develop alternative methods of medical castration. Today, treatment with superactive agonists of gonadotropin releasing hormone (GnRH) that suppress the secretion of testicular androgens have totally replaced estrogenic compounds as a palliative medical treatment for advanced prostate cancer. The first GnRH agonist approved by the FDA for this indication was leuprolide acetate (Lupron®, TAP Pharmaceuticals) in 1985. Other superactive GnRH agonists approved by the FDA for this indication include goserelin acetate (Zoladex®, AstraZeneca Pharmaceuticals) and triptorelin pamoate (Trelstar™ Depot, Debio Recherche Pharmaceutique). Because these peptide agonists are degraded and not pharmacologically active if taken orally, they are administered parenterally by means of long-acting biodegradable formulations. These long-acting formulations are generally administered at intervals ranging from 4 to 16 weeks.

The presently approved FDA formulation of triptorelin pamoate is a 28-day depot formulation. The objective of the present NDA (NDA 21-288) is to obtain marketing approval of a new longer acting depot formulation of triptorelin (Trelstar™ LA, triptorelin pamoate for injectable suspension) that will require less frequent dosing (once every 84 days instead of every 28 days). An 84-day formulation will be more desirable for many patients with prostate cancer since they

may require treatment with a GnRH agonist for several years, and the drug generally must be administered by medical personnel.

3.2.2 Pharmacology of Triptorelin and Other Superactive GnRH Agonists

GnRH (also known as luteinizing hormone-releasing hormone or LHRH) is secreted by the hypothalamus and stimulates the pituitary gland to release the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH, in turn, stimulates the production and secretion of gonadal testosterone. A single injection of an aqueous formulation of a GnRH agonist induces a marked and prolonged release of LH and FSH. However, continuous stimulation of the pituitary gland by administration of a GnRH agonist in a long-acting or depot formulation initially stimulates and then suppresses the secretion of LH and FSH. Thus, chronic and continuous exposure to a GnRH agonist can reduce serum concentrations of testosterone to levels comparable to those observed following surgical orchiectomy.

Achievement of castration levels of serum testosterone (≤ 50 ng/dL or ≤ 1.735 nmol/L) is generally obtained by 1 month after the start of GnRH therapy. In contrast to surgical castration, however, treatment with a GnRH agonist initially results in a significant, albeit temporary (1 to 2 week), increase in gonadal androgen production and secretion, commonly referred to as a *testosterone surge*. The initial rise in serum testosterone may cause a temporary worsening of symptoms in some men, referred to as *a flare*. Most commonly, the immediate consequence of this initial increase in circulating androgen levels in men with advanced metastatic prostate cancer is an increase in bone pain. Less frequently, more serious adverse events can occur including ureteral obstruction, bladder neck outlet obstruction, spinal cord compression and paralysis, and rarely, death. For these reasons, superactive GnRH agonists must be used with caution in patients presenting with large local or metastatic lesions and their use is generally contraindicated in men with epidural or vertebral metastases. In clinical practice, anti-androgens are often used off-label at the onset of treatment with a GnRH agonist to prevent or reduce the severity of the androgen-induced flare.

3.2.3 Structure and Formulation of Triptorelin and Trelstar™ LA

Triptorelin is a synthetic analog of naturally occurring GnRH, characterized by the substitution of glycine with D-tryptophan in position 6 of the natural decapeptide. This structural modification increases both the resistance of the analog to enzymatic degradation and its affinity for pituitary GnRH receptors. The modification thus prolongs the drug's plasma half-life and increases its potency. The major structural difference between triptorelin and other GnRH analogs presently approved for the treatment of prostate cancer is the substitution of a different D-amino acid at position 6 and a modification at position 10. Table 1 presents a comparison of the amino acid sequence of native GnRH to that of leuprolide, goserelin, and triptorelin.

Table 1. Structure of Native GnRH and Superactive GnRH Agonists

	Amino Acid Sequence									
	1	2	3	4	5	6	7	8	9	10
GnRH	(pryo) Glu-	His-	Trp-	Ser-	Tyr-	**Gly**	-Leu-	Arg-	Pro –	**Gly-NH_2**
Leuprolide	(pryo) Glu-	His-	Trp-	Ser-	Tyr-	**D-Leu**	-Leu-	Arg-	Pro –	**Ethylamide**
Goserelin	(pryo) Glu-	His-	Trp-	Ser-	Tyr-	**D-Ser(tBu)**	-Leu-	Arg-	Pro –	**Gly(Az)-NH_2**
Triptorelin	(pryo) Glu-	His-	Trp-	Ser-	Tyr-	**D-Trp**	-Leu-	Arg-	Pro –	**Gly-NH_2**

Triptorelin, like other GnRH agonists, has a relatively short plasma half-life in vivo; therefore, it is formulated as a sustained-release dosage form. The triptorelin sustained-release formulation

for Trelstar™ LA consists of a polymeric matrix of poly (*dl*-glycolide-co-lactide) designed to release triptorelin over 84-days (12 weeks).

3.3 Important Milestones in the Development of Trelstar™ LA

3.3.1 Background of Clinical Development of Triptorelin

Initial clinical studies with a once monthly depot formulation of triptorelin were performed using a controlled release formulation of triptorelin acetate (3.75 mg) in microspheres of poly (*dl*-lactide-co-glycolide). These studies, which were conducted either entirely or primarily outside of the United States, supported the first marketing approval of triptorelin acetate (Decapeptyl LP 3.75 mg) in France in 1986 for the indications of prostate cancer and precocious puberty. This initial approval was followed by additional marketing approvals for triptorelin acetate in more than 40 countries worldwide. Subsequently, a monthly sustained-release formulation of triptorelin, free of chlorinated solvents, was developed. In this formulation, triptorelin pamoate salt is blended with poly (*dl*-lactide-co-glycolide) to form either microparticles or microgranules. Depot formulations of triptorelin pamoate in poly (*dl*-lactide-co-glycolide) that contain either (1) 3.75 mg triptorelin with an intended therapeutic effect of at least 28 days (e.g., Trelstar™ Depot) or (2) 11.25 mg triptorelin with an intended therapeutic effect of at least 84 days (e.g., Trelstar™ LA) have been developed. Trelstar™ Depot was approved by the FDA in June 2000 for the palliative treatment of advanced prostate cancer.

3.3.2 Significant Regulatory Interactions and Decisions

The NDA for the 28-day formulation of triptorelin pamoate for the treatment of advanced prostate cancer (NDA 20-715) was first submitted to the FDA in June 1996. Because of numerous deficiencies involving several review disciplines, the FDA notified Debio RP (the Sponsor) in a letter dated June 26, 1997 that the application could not be approved. The medical review indicated that the clinical data were inadequate to demonstrate that triptorelin pamoate was a safe and effective drug for the treatment of advanced prostate cancer.

In a meeting with the Division of Reproductive and Urologic Drug Products (DRUDP) on September 9, 1997, FDA staff suggested that resolution of the clinical deficiencies would require one well-controlled study that was adequately powered to rule out a clinically significant difference between triptorelin pamoate and an active comparator [a currently marketed GnRH agonist]. At the time of this meeting, a randomized, Phase III clinical trial sponsored by Debio RP (Study DEB-96-TRI-01) was ongoing. This study was intended to compare the efficacy of the 84-day formulation to that of the 28-day formulation. At the September 1997 meeting, DRUDP acknowledged that Study DEB-96-TRI-01 would be sufficient to allow filing of a supplemental NDA for the 84-day formulation of triptorelin after the 28-day formulation had been approved for marketing.

In October 1997, the sponsor submitted an amendment to IND [ ] that provided for adding a "second phase" to ongoing study DEB-96-TRI-01. The amended protocol permitted the continued study and treatment of patients already enrolled in DEB-96-TRI-01 but terminated further enrollment of patients who would be treated with the 84-day formulation. The original population of study patients, anticipated to be about 360 total patients, would represent the "first phase" of the revised two-phase study. In the second phase of revised Study DEB-96-TRI-01, patients would be (1) randomized to treatment with either the to-be-marketed 28-day formulation of triptorelin pamoate or the 28-day formulation of leuprolide acetate (Lupron, 7.5-mg) and (2) monitored by a study design very similar to that of the original protocol.

After completion of Phase 2 of Study DEB-96-TRI-01, Debio RP submitted a complete response on December 16, 1999 to the non-approval letter of June 1997 for NDA 20-715. The 28-day depot formulation of triptorelin pamoate (Trelstar™ Depot) was approved by the FDA on

June 15, 2000 for the palliative treatment of advanced prostate cancer. Following this approval, the Sponsor submitted NDA 21-288 for the 84-day (12-week) formulation of triptorelin pamoate.

3.3.3 Issues Arising during Clinical Trials

Several regulatory issues critical to the approvability of the 84-day formulation of triptorelin were reviewed earlier in Section 3.3.2. Another issue that was relevant to the approval of the 28-day formulation and remains critical to the approval of the 84-day formulation concerns the Sponsor's reluctance to measure serum testosterone levels in patients after repeat dosing with triptorelin to assess the frequency and magnitude of acute testosterone increases following re-dosing in otherwise suppressed patients. The sponsor instead measured serum concentrations of LH, both immediately prior to and 2 hours after dosing with Study Drug on Study Days 85 and 169. The sponsor claimed that an increase in LH of ≤ 1.0 IU/L would indicate that re-dosing was not associated with a significant increase in serum testosterone levels. The sponsor also stated in their version of the minutes of the November 18, 1997 teleconference with the Division "that Debio would use published literature and, if necessary, conduct a small pharmacology study, to establish the relationship between a 1 IU/L increase in LH and the corresponding increase in serum testosterone."

DRUDP informed the Sponsor both during a Teleconference on November 18, 1997 and in a written communication from Dr. Heidi Jolson on January 9, 1998 that using acute changes in serum LH levels as a surrogate for acute changes in serum testosterone levels would be difficult to interpret and might not be adequate. DRUDP requested that serum testosterone levels be measured at 4, 8, 12, and 24 hours after the second or third dose of the 84-day formulation of triptorelin.

Medical Officer's Comments

- *This is an important assessment since repeat dosing with a GnRH analog may be associated with a clinically significant, acute increase in serum testosterone levels.*
- *The Sponsor, at the request of the Medical Reviewer, submitted several scientific publications concerning the relationship between serum LH and testosterone levels in children with precocious puberty. None of the articles provided information about the relationship of a 1.0 IU/L increase in LH and the magnitude of the ensuing increase, if any, in serum testosterone levels. The Sponsor will be requested to conduct a Phase IV pharmacology study to obtain additional information regarding postdosing increases in serum testosterone levels.*

3.4 Other Relevant Information

3.4.1 Related Submissions

Study DEB-96-TRI-01-Phase 2, submitted to NDA 20-715 as part of the complete response to the deficiency letter of June 26, 1997, provides meaningful supportive safety data for the use of triptorelin pamoate (3.75 mg every 28 days) in the treatment of prostate cancer. In Phase 2 of Study DEB-96-TRI-01, men with prostate cancer were treated for up to 9 months with either 3.75 mg triptorelin pamoate (28-day formulation, n = 140) or 7.5 mg Lupron (n = 144).

3.4.2 Foreign Marketing Status

According to the Sponsor, triptorelin 3.75 mg (28-day formulation) is marketed as the acetate or pamoate salt in over 60 countries for treatment of advanced prostate cancer, and in some countries for the treatment of endometriosis and precocious puberty as well. Triptorelin is marketed in most countries under the trade-name Decapeptyl® and is distributed in the foreign countries by Debio's licensees. In some instances, Decapeptyl is also manufactured by these licensees (e.g., Beaufour-Ipsen group [France] and Ferring [Sweden]). Countries in which the

3.75 mg pamoate formulation is approved for marketing include Canada, Mexico, Sweden, Switzerland and several South American countries.

The 84-day formulation contains 11.25 mg of triptorelin and is available only as the pamoate salt. It is approved for marketing in 2 different formulations – one manufactured by Beaufour-Ipsen of France and the other manufactured by Debio RP (the formulation under review in this NDA). See Table 2 for a listing of the countries in which each formulation has been approved for marketing. The formulations differ in the composition of the poly (glycolic/lactic acid) and the quantity of excipients. The 84-day *microparticle* formulation manufactured by Ipsen (formulation A) was first approved for marketing in France in 1996 and subsequently received marketing approval in Belgium, Ireland, Italy, Lebanon, Portugal, and Spain. The *microgranule* formulation manufactured by Debio (formulation B) has been approved for marketing in Mexico, Argentina, and Canada The sponsor states in the Safety Update of October 24, 2000 that "None of the triptorelin formulations have been withdrawn from marketing in any country for any reason relating to safety or effectiveness."

Table 2. Triptorelin 84-Day (12-Week) Formulations: World Wide Status of Product Approvals for Prostate Cancer

Licensee	Country	Formulation	Date of First Approval	Date of Launch
Ipsen	Belgium	A [1]	Jun 1998	July 1999
	France	A	Jun 1996	Feb 1997
	Ireland	A	Oct 1998	Nov 1998
	Italy	A	Dec 1998	Jan 1999
	Lebanon	A	Jul 1998	Mar 2000
	Portugal	A	Apr 1999	Jun 1999
	Spain	A	Jul 1997	Sep 1997
Pharmacia & Upjohn	Mexico	B [2]	Oct 1997	
	Canada	B	May 2001	
SIDUS	Argentina	B	Feb 1999	Oct 2000

[1] Formulation A: Microparticles consisting of triptorelin pamoate (11.25 mg triptorelin) + poly (glycolic/lactic acid) 1:1 (~188 mg) and mannitol 63.75 mg, NaCMC 22.50 mg, and Polysorbate 80 (1.5 mg). Microparticles are resuspended in sterile water containing mannitol.

[2] Formulation B: Microgranules consisting of triptorelin pamoate (11.25 mg triptorelin) + poly (glycolic/lactic acid) 1:3 (~145 mg) and mannitol 85 mg, NaCMC 30 mg; and Polysorbate 80 (2 mg). Microgranules are resuspended in sterile water.

Source: Submission of June 7, 2001; answer to question No. 1.

3.4.3 Issues with Other Pharmacologically Related Agents

A superactive GnRH analog (Lupron) was first approved by the FDA for the treatment of advanced prostate cancer in 1985. Two other GnRH analogs were subsequently approved for this indication. Postmarketing data have not raised any concerns about either the safety or efficacy of these drugs when used for the palliative treatment of advanced prostate cancer.

Medical Officer's Comments

- *Although the 28-day formulation of triptorelin pamoate was approved for marketing by the FDA in June 2000, it has not been launched in the US and no postmarketing US safety data are therefore available.*
- *Although the sponsor states in their application that "None of the triptorelin formulations have been withdrawn from marketing in any country for any reason relating to safety or*

effectiveness" this statement does not appear to be entirely correct. In NDA 21-715, the Sponsor states on pg. 86, Volume 7.1 that in 1996 Ferring introduced dextran into the reconstitution diluent for triptorelin. This change was followed by several reports of serious allergic/immunologic adverse reactions. Consequently, Ferring voluntarily withdrew this formulation from marketing for precocious puberty. Neither the 28- nor the 84-day formulation of triptorelin pamoate that is manufactured by Debio RP contains dextran.

4 CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

4.1 Toxicology Review

No new toxicology data were submitted in NDA 21-288. The toxicology of triptorelin was previously reviewed under NDA 20-715, the NDA for triptorelin pamoate (28-day formulation) that was approved in June 2000. No toxicology issues were identified during the review of NDA 20-715.

4.2 Clinical Pharmacology and Biopharmaceutics Review

According the primary reviewer (Dr. V. Jarugula), there are no biopharmaceutical findings that would preclude the approval of the 84-day formulation of triptorelin pamoate for the proposed indication of prostate cancer.

4.3 Chemistry Review

According the primary reviewer (Dr. David Lin), there are no chemistry issues that would preclude the approval of the 84-day formulation triptorelin pamoate for the proposed indication.

The sponsor intends to supply Trelstar™ LA in 2 different configurations: (1) a configuration that includes only a single lyophilized vial of triptorelin pamoate and (2) a configuration that includes a single lyophilized vial of triptorelin pamoate and a prefilled syringe containing 2 ml of sterile water for injection.

5 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

5.1 Pharmacokinetics

Prostate cancer patients. The pharmacokinetic parameters of triptorelin following a single IM injection of the 84-day formulation (11.25 mg) or a total of 3 IM injections of the 28-day formulation (3.75 mg /injection) on Days 169, 197, and 225 in men with prostate cancer are listed in Table 3. The C_{max} for plasma triptorelin following administration of the 84-day formulation was 2-fold greater than that after administration of the 28-day formulation. However, the geometric mean triptorelin plasma AUC values during the assessment period (Study Days 169-253) were comparable in the 2 groups (2428 ng•h/mL and 2374 ng•h/mL, respectively.

Table 3. Pharmacokinetic Parameters of 84-Day and 28-Day Formulations of Triptorelin Pamoate (Study DEB-96-TRI-01-Phase 1) [1]

Dose (No. of subjects)	C_{max} (ng/mL)	T_{max} (h)	AUC (ng•h/mL)
84-day formulation (11.25 mg) (n=13)	48.5 [2] (32.1 – 88.1)	4.0 [3] (2.0 - 6.0)	2428 [2] (1412 – 3903)
28-day formulation (3.75 mg x 3 doses) (n=14)	21.3 [2] (14.1 – 31.1)	2.0 [3] (2-4)	2374 [2] (1221 – 5431)

[1] Based on serum triptorelin concentrations during last 3 months of treatment (Days 169-253).
[2] Geometric mean (range); [3] Median (range)
Source: Table 6, pg. 177, Vol. 1 of original submission.

Renal or hepatic insufficiency. Administration of a single IV bolus dose of 0.5 mg triptorelin to subjects with renal or hepatic insufficiency indicated that these subjects had a decrease in total triptorelin clearance compared to healthy volunteers (Table 4). The decrease in triptorelin clearance was most pronounced in subjects with liver insufficiency. In subjects with renal disease, the increase was proportional to the decrease in creatinine clearance. Subjects with renal or hepatic impairment had a 2- to 4-fold higher exposure to triptorelin (higher AUC values) than young healthy males.

Table 4. Pharmacokinetic Parameters (Mean ±SD) of Triptorelin in Volunteers with Renal or Hepatic Insufficiency

Group	C_{max} (ng/mL)	AUC_{inf} (h•ng/mL)	Cl_p [1] (mL/min)	Cl_{renal} [2] (mL/min)	Cl_{creat} [3] (mL/min)
6 healthy male volunteers	48.2 (±11.8)	36.1 (±5.8)	211.9 (±31.6)	90.6 (±35.3)	149.9 (±7.3)
6 males with moderate renal impairment	45.6 (±20.5)	69.9 (±24.6)	120.0 (±45.0)	23.3 (±17.6)	39.7 (±22.5)
6 males with severe renal impairment	46.5 (±14.0)	88.0 (±18.4)	88.6 (±19.7)	4.3 (±2.9)	8.9 (±6.0)
6 males with liver disease	54.1 (±5.3)	131.9 (±18.1)	57.8 (±8.0)	35.9 (±5.0)	89.9 (±15.1)

[1] Total plasma clearance of triptorelin
[2] Renal clearance of triptorelin
[3] Creatinine clearance
Source: Proposed Physician Package Insert.

The metabolism of triptorelin in humans is not known, but is unlikely to involve hepatic microsomal enzymes (cytochrome P-450). Pharmacokinetic data suggest that C-terminal fragments produced by tissue degradation are either completely degraded in the tissues, rapidly degraded in plasma, or cleared by the kidneys.

Medical Officer's Comment

- *Because superactive GnRH agonistic analogs have a high margin of safety, a dose reduction in patients with renal or hepatic impairment does not appear to be necessary.*

5.2 Pharmacodynamics

The pharmacodynamic effects of triptorelin on serum concentrations of pituitary gonadotropins LH and FSH) and testosterone are presented and discussed in the efficacy section of this review (Sections 8.4.2 and 8.4.3.1).

6 DESCRIPTION OF CLINICAL DATA AND SOURCES

6.1 Clinical Data Submitted in Support of NDA 21-288

6.1.1 Clinical Trials

The sponsor submitted data from 5 clinical studies that were conducted using a 84-day formulation of triptorelin pamoate. Four of the studies were conducted in men with cancer of the prostate, and 1 study was conducted in women with gynecologic disorders. Of the studies in men with prostate cancer, only one (DEB-96-TRI-01-Phase 1) was an adequate and well controlled trial that was conducted with the to-be-marketed 84-day formulation of triptorelin. All of the studies were conducted outside of the United States. Study DEB-96-TRI-01 was conducted in South Africa. See Section 6.2 for further details.

6.1.2 Secondary Sources of Clinical Data

Triptorelin, either as the acetate or pamoate salt, has been marketed outside of the US since 1985. On October 24, 2000, the sponsor provided (1) a brief, general safety update concerning recent marketing experience with triptorelin and other ongoing clinical trials and (2) a more detailed safety update (the Periodic Safety Update Report [PSUR] for March 5, 1999 to March 5, 2000) that was prepared by the Beaufour-Ipsen Group (a licensee of Debio RP). On June 7, 2001 the Sponsor provided a supplemental Safety Update that included an abridged PSUR from Beaufour-Ipsen for the period March 5, 2000 through October 31, 2000.

6.2 Overview of Clinical Studies Included in the NDA

Study reports for 5 clinical trials were submitted as part of NDA 21-288 to support the safety and efficacy of triptorelin pamoate microgranules (84-day formulation) for the palliative treatment of advanced prostate cancer. These reports were:

1. Comparative testosterone pharmacodynamics and therapeutic efficacy of 1-month and 3-month formulations of triptorelin pamoate in patients with advanced prostate cancer (first phase). Debio Clinical Report No. *DEB-96-TRI-01 (first phase)*, July, 1999.
2. A phase II, randomized, asymmetric, open, multicenter study investigating the bioequivalence and pharmacokinetics of two different sustained-release formulations of triptorelin in patients with prostate cancer. Ipsen Biotech Final Clinical Report *UK DCP 94-090*, July 26, 1999.
3. Effectiveness and tolerance of new triptorelin sustained release formulations (triptorelin pamoate 11.25 mg, 1 cycle of 3 months) to induce a pharmacological castration in patients suffering from prostate carcinoma. *Clinical Study Report DEB-95-TRI-01*, December 13, 1996.
4. Clinical pharmacology study of triptorelin pamoate (3-month formulation) in patients with advanced prostate cancer. *Clinical Study Report DEB-99-TRI-01*, February 2000.
5. Phase II, open, multicenter study to evaluate the pharmacodynamic and pharmacokinetic parameters of a sustained release formulation of triptorelin in female patients-part 1. *Clinical Study Report E5452014 099*, September 1998.

Study DEB-96-TRI-01-Phase 1 was a randomized, controlled, Phase III clinical trial that provided virtually all of the data in this submission supporting the efficacy and safety of triptorelin pamoate microgranules (84-day formulation, 11.25 mg) for the palliative treatment of advanced prostate cancer. The other studies that were conducted in men with prostate cancer (Studies UK DCP 94-090, DEB-95-TRI-01, and DEB-99-TRI-01) were supportive safety or pharmacology studies. Additional information concerning all of these studies is provided in Table 5.

Medical Officer's Comment

- *Data from Study UK DCP 94-090 and from 10 of the 20 subjects in study DEB-95-TRI-01 are of limited values since they were not conducted with the to-be-marketed formulation of triptorelin.*

Table 5. Tabular Listing of Studies Supporting Safety and Efficacy of Triptorelin Pamoate (11.25 Mg Microgranules)

Study No. Study Title	Study Design Status	No. Sites Country	No. Patients (Safety) Age Range Race	No. Patients (Safety population) Treatment (formulation) Dose/Route/Regimen Duration of Drug Exposure
Principal Efficacy and Safety Study in Men with Prostate Cancer				
DEB-96-TRI-01(first phase) "Comparative testosterone pharmacodynamics and therapeutic efficacy of 1-month and 3-month formulations of triptorelin pamoate in patients with advanced prostate cancer (first phase)"	Phase 3 Multicenter Open-label Controlled Randomized Study Complete	19 Sites South Africa	346 men 45-96 years 165 Caucasian 130 Black 51 Colored	174 patients triptorelin pamoate micro-granules 11.25 mg IM q 84 d x 3 doses 9 months 172 patients triptorelin pamoate micro-granules 3.75 mg IM q 28 d x 9 doses 9 months
Supportive Safety and Pharmacology Studies in Men with Prostate Cancer				
UK DCP 94-090 "A phase II, randomized, asymmetric, open, multicenter study investigating the bioequivalence and pharmacokinetics of two different sustained-release formulations of triptorelin in patients with prostatic cancer-part 2."	Phase 2 Multicenter, Open-label Comparative Randomized Study Complete	7 Sites UK	77 men 52-86 years 77 Caucasian	53 patients triptorelin pamoate micro-spheres [A] 11.25 mg IM (single dose) 3 months 24 patients triptorelin acetate micro-spheres 3.75 mg IM q 28 d x 3 doses 3 months
DEB-95-TRI-01 "Effectiveness and tolerance of new triptorelin sustained release formulations (triptorelin pamoate 11.25 mg, 1 cycle of 3 months) to induce a pharmacologic castration in patients suffering from prostatic carcinoma"	Phase 2 Single center Open-label Comparative Study Complete	1 Site Bulgaria	20 men 56-83 years 20 Caucasian	20 patients triptorelin pamoate micro-granules [B] 11.25 mg IM (single dose) 3 months
DEB-99-TRI-01 "Clinical pharmacology study of triptorelin pamoate (3-month formulation) in patients with advanced prostate cancer"	Phase 1 Single center Non-comparative, Study Complete	1 Site South Africa	12 men 55-81 years 12 Black	12 patients triptorelin pamoate micro-granules 11.25 mg IM (single dose) 3 months
Supportive Safety Study in Women with Gynecologic Disorders				
E5452014 099 "Phase II, open, multicenter study to evaluate the pharmacodynamic and pharmacokinetic parameters of a sustained release formulation of triptorelin in female patients-part 1"	Phase 2 Multicenter Non comparative Study complete	4 sites France (2) UK Ireland	14 women 24-38 years 11 Caucasian 2 Black 1 Oriental	14 patients triptorelin micro-particles[A] 11.25 mg IM (single dose) 3 months

[A] Not the same formulation as that which is to-be-marketed in the United States.
[B] Two different formulations administered. Ten (10) of 20 patients received the to-be-marketed formulation.
Source: Modification of Table 2, pg. 167, Vol. 1 of original submission.

7 CLINICAL REVIEW METHODS

7.1 Materials Consulted during Medical Review

The following materials were consulted during the conduct of this review:

Submissions to NDA 21-288

- Original NDA 21-288; Submission Date of June 29, 2000
  - Volumes 1, and 28-43
  - Electronic case report forms (CRFs) and electronic case report tabulations (CRTs)
- Submission of October 4, 2000 (data for requested supplemental measurements of serum testosterone levels to assess acute postdosing changes in serum testosterone levels)
- Submission of October 24, 2000 (Safety Update)
- Submission of January 26, 2001 (response to request for additional and modified electronic data files)
- Submission of January 29, 2001 (requested clarifications/corrections based on Medical Reviewer's questions of January 8, 2001)
- Submissions of April 23, 2001 (cumulative CIOMS Reports from a licensee of triptorelin [Ferring] for the period from 1995-2000)
- Submission of April 27, 2001 (requested supplemental efficacy and safety analyses in sub-populations [effects of race] and correction of errors [primarily laboratory analyses] in the original submission that were identified during the medical review)
- Submission of June 7, 2001 (response to request from Medical Officer for updated safety information and world-wide regulatory status of the 84-day formulation)

Other Submissions

- Annual Report for IND [ ] submitted on July 4, 2000 and all medically-related correspondence submitted to the IND since submission of the annual report)
- Volume 1.1 of NDA 20-715 (Original Submission for Trelstar 28-day formulation)
- Volume 7.1 of NDA 20-715 (Complete Response to the Non Approvable Letter of June 1997 for Trelstar 28-day formulation)
- Medical Officers' Primary Reviews of (a) Original NDA 20-715 and (b) the Complete Response to the Non Approvable Letter of June 1997 for the 28-day formulation
- Minutes of regulatory meetings and telephone conferences with Sponsor that were contained in Division files for IND [ ]

7.2 Review Processes and Procedures

7.2.1 Materials Reviewed

All documents listed in Section 7.1 were reviewed. The review conducted by this Medical Officer focused on Study DEB-96-TRI-01-Phase 1 and those supplemental materials specifically requested during the course of the review. All materials submitted in paper and electronic format for Study DEB-96-TRI-01-Phase 1 and the requested items were examined during the conduct of this review. Reviews of supplemental studies UK DCP 94-090, DEB-95-TRI-01, and DEB-99-TRI-01 focused on safety issues, namely, drug-related serious adverse events, adverse events

leading to patient withdrawal from the clinical trial, allergic reactions and deaths. Pharmacodynamic data from Study DEB-99-TRI-01 also were reviewed.

7.2.2 Safety and Efficacy Reviews

The accuracy of the Sponsor's primary efficacy analyses for maintenance of testosterone suppression were reviewed and confirmed by Dr. David Hoberman, FDA statistician. Dr. Hoberman's review did not identify any issues that would invalidate the sponsor's analyses (see Section 8.7). In addition, the medical reviewer also prepared separate supplemental efficacy tabulations and spreadsheets for both treatment groups of Study DEB-96-TRI-01-Phase 1 for (a) serum testosterone levels and (b) acute changes in serum LH and testosterone levels after repeat dosing to permit a more thorough assessment of the effects of treatment with Study Drugs on these efficacy assessments. A reanalysis of the cumulative maintenance of testosterone suppression for the intervals Days 29-253 and Days 57-253, based on a modification of the Sponsor's per protocol population was conducted by Dr. Hoberman at the request of the medical reviewer (Section 8.7).

Analyses and summary tables relating to major protocol violations, serious adverse events, and deaths were confirmed or modified using the data listings or electronic case report forms provided by the Sponsor. In addition, queries were submitted to the Sponsor to confirm or correct information that did not appear to be correct in the original submission. The sponsor also provided additional and corrected safety analyses pertaining to changes in laboratory assessments (serum chemistries and hematology measurements) at the request of the Medical Reviewer both for the entire safety population in Study DEB-96-TRI-01-Phase 1 as well as selected subgroups.

Medical Officer's Comments

- *The analyses and data listings for Study DEB-96-TRI-01 contained minor errors and inconsistencies. Examples of these errors and inconsistencies included (1) reporting an incorrect year for a patient's death in the AE listing, (2) safety laboratory data that were not likely to be correct because of their extreme values, and (3) inconsistent reporting of AE termination dates if a patient died on-study.*
- *These errors, however, were not of sufficient magnitude to invalidate the conclusions derived from this study.*

7.3 Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audits. Three study centers that participated in both Phase 1 and Phase 2 of the pivotal clinical trial (DEB-96-TRI-01) were audited by the Division of Scientific Investigation (DSI) in the spring of 2000. Records from 30 of 181 patients enrolled in DEB-96-TRI-01 at these 3 sites were inspected. Violations of varying importance to the integrity of the clinical trial were noted at each of the sites. All of the sites had violations related to IRB and/or patient consent form issues. In addition, protocol-related violations that were identified included: (1) unspecified deviations from the protocol (Center 4); (2) enrollment of a patient (No. 7001) with a screening testosterone of < 5 nmol/L and administering an inappropriate (extra) dose of the 84-day formulation of Study Drug on Day 29 to Patient No. 7027 (Center 7); and (3) enrollment of 4 patients without documented bone scans and dosing of 3 patients outside of the protocol-approved window (Center 16). In spite of these violations, the DSI recommendation for each of the inspected sites was the following "Our review of the information provided to us regarding the inspection of this clinical investigator concludes that the data appear acceptable in support of the submitted NDA."

Financial disclosure statements. Based on information submitted by the Sponsor (pg. 9, Vol. 1 of the original NDA), there were no financial conflict-of-interest issues.

Medical Officer's Comments

- *This Medical Officer concurs that the deficiencies identified during the site audits are not of sufficient magnitude to negate the overall validity of the clinical data and the clinical trial. Inappropriate and out-of-window dosing, however, are significant protocol violations.*
- *Inappropriate dosing with Study Drug – including extra doses of the 84-day formulation, administration of the 28-day formulation to subjects receiving the 84-day formulation, and dosing outside of the protocol-allowed window – also occurred at other sites and was addressed by excluding such patients from the Sponsor's per protocol population and per protocol analyses.*

Central Laboratory. Reproductive hormone (testosterone, LH, and FSH) and prostate specific antigen (PSA) measurements for all centers were performed under the general supervision of South Africa. This laboratory participated in an international quality assessment program (Murex Quality Assessment Program). Information concerning the laboratory's relative performance as well as Levy-Jennings Charts for internal quality control samples were provided.

Safety laboratory measurements (with one exception) also were performed in the Safety laboratory measurements for Center 1 were analyzed in

Medical Officer's Comments

- *The Central Laboratory was not inspected by DSI. However, the overall quality control data submitted by the laboratory were adequate to obtain a general impression of the quality of the laboratory. Based on the quality control data included in this application, the testosterone data submitted in support of NDA 21-288 appear to be acceptable to assess suppression of serum testosterone to values of ≤ 1.735 nmol/L.*
- *It is not clear from the application if reproductive hormones for Center 1 were measured locally or in the*

Site monitoring. According to the Final Report for DEB-96-TRI-01-Phase 1, the study sites were monitored on a regular once monthly to every 2-month basis by from January 1997 through September 1998. Data entry was performed manually by using double data entry procedures. In addition, the Sponsor stated that 9 centers, the two central laboratories,) and the database were audited between November 1997 and March 1999 by Debio RP.

Medical Officer's Comments

- *is a well known Contract Research Organization widely used by the pharmaceutical industry to conduct and/or monitor drug clinical trials. The quality of monitoring to be expected from the local operation in South Africa, however, is not known.*
- *Review of electronic CRFs submitted with the NDA indicated that there was frequent communication between the CRO and study sites regarding resolution of CRF entry errors. In spite of this interaction, it was apparent that errors of varying degrees of importance were not always identified or corrected.*
- *These errors and omissions, however, would not be expected to invalidate the findings of Study DEB-96-TRI-01-Phase 1.*

8 INTEGRATED REVIEW OF EFFICACY (PRINCIPAL CLINICAL STUDY)

8.1 Efficacy Assessments

8.1.1 Primary Efficacy Assessment and Endpoints

The primary efficacy assessment in the principal Phase III Study DEB-96-TRI-01-Phase 1 was based on the patient's serum testosterone concentration during treatment with Study Drug. The primary efficacy objective was to demonstrate that the 84-day formulation of triptorelin was not inferior to the 28-day formulation as assessed by the rapidity and reliability of suppression of serum testosterone to levels normally observed following surgical orchiectomy (i.e., serum testosterone ≤ 1.735 nmol/L). The co-primary efficacy endpoints were:

1. The proportion of patients achieving castrate levels of serum testosterone (testosterone ≤ 1.735 nmol/L) on Study Day 29 (i.e., within 28 days following the initial injection of Study Drug) and
2. The proportion of patients maintaining castrate levels of serum testosterone from Study Day 57 through Study Day 253 during treatment with Study Drug.

8.1.2 Rationale for Surrogate Endpoint of Reduction and Maintenance of Serum Testosterone of ≤ 1.735 nmol/L (i.e., Castrate Testosterone Levels)

Surgical castration remains the standard against which all hormonal therapies for the palliative management of advanced prostate cancer have been and continue to be compared. To date no other therapy has been conclusively shown to increase survival time beyond that achieved by surgical castration. It is accepted that surgical castration exerts its therapeutic effect by markedly reducing serum androgen levels. A serum testosterone ≤ 1.735 nmol/L (equivalent to ≤ 50 ng/dL) is generally accepted as being within the range of concentrations observed following surgical castration. The goal of hormonal therapy in prostate cancer is to reduce serum concentrations of testosterone to castrate levels. Based on these considerations, the FDA has accepted for this application, and other current applications for GnRH agonists, attainment of castration levels of testosterone by Day 29 and maintenance of these levels through at least 3 dosing cycles as a surrogate efficacy endpoint in clinical trials for the palliative treatment of advanced prostate cancer. Absence of a testosterone surge following repeated dosing (referred to as the "acute on chronic testosterone response") also has been a required secondary efficacy endpoint (see Sections 3.3.3 and 8.1.3).

8.1.3 Secondary (Supportive) Efficacy Endpoints and Assessments

The secondary efficacy objectives of this study were to compare the two formulations in terms of:

1. The absence of serum LH and FSH increases following repeat administration of Study Drug, assessed just prior to dosing and at 2 hours postdosing on Study Days 85 (Month 3) and 169 (Month 6)
2. The regression in bone pain from baseline (Day 1) to the end of treatment (Day 253), assessed by Visual Analogue Scale (VAS) and analgesic use
3. The mean change in prostate specific antigen (PSA) from baseline throughout treatment
4. The mean change in Quality of Life (QoL) scales from baseline throughout treatment
5. The absence of triptorelin accumulation
6. Description of triptorelin pharmacokinetic parameters and triptorelin pharmacodynamic effects not specifically assessed by the primary efficacy endpoints or other secondary endpoints

Changes in Quality of Life (QoL) scales are not addressed in this review. Triptorelin pharmacokinetics and triptorelin pharmacodynamic effects not specifically related to the primary efficacy endpoints or other secondary endpoints are presented in the Biopharmaceutical Review.

8.1.4 Overview of Statistical Analyses for Primary Efficacy Endpoints

8.1.4.1 Achievement of Serum Tesfosterone of ≤ 1.735 nmol/L by Study Day 29

The proportion of patients with a serum testosterone of ≤ 1.735 nmol/L on Study Day 29 was calculated for the intent-to-treat (ITT) and the per protocol (PP) populations in each treatment arm. A noninferiority limit of -10% was applied to the lower bound of the 2-sided 95% confidence interval (CI) for the difference between the proportions in each of ~~the~~ treatment groups (i.e., 84-day formulation minus 28-day formulation). A CI with a lower bound no less than -10% for the difference was the criterion for success (i.e., noninferiority).

8.1.4.2 Maintenance of Castrate Levels of Serum Testosterone (≤ 1.735 nmol/L) from Study Day 57 through Study Day 253

Maintenance of castrate levels of serum testosterone (≤ 1.735 nmol/L) from Study Day 57 through Study Day 253 was analyzed by 2 different procedures.

1. Probability of maintaining castration levels of testosterone (Kaplan-Meier product limit-method). The probability of a patient maintaining castration levels of testosterone from Month 2 (Day 57) through Month 9 (Day 253) was estimated using survival analysis techniques (Kaplan-Meier product limit method). In this analysis, missing data were handled as follows: (a) for patients escaping castration levels at a certain visit, subsequent missing data was irrelevant; (b) patients maintaining castration levels up to a certain visit, with missing data afterwards (drop-outs due to non-drug related reasons), were treated as censored observations (i.e., a success); (c) patients maintaining castration levels up to a certain visit, with missing data afterwards (drop-out due to drug related reasons), were treated as having escaped medical castration; and (d) missing data between 2 visits where castration levels of testosterone were maintained at the visit following the missing visit were not treated as censored in the ITT analysis for that visit.

2. Observed monthly maintenance of castration levels of testosterone. The observed monthly maintenance of castration levels of testosterone within the time interval from Month 2 (Day 57) to Month 9 (Day 253) also was derived for each treatment group. This analysis was expressed as the ratio of the number of non-missing protocol-scheduled measurements with castration levels of testosterone (≤1.735 nmol/L) divided by the total number of non-missing scheduled measurements. Confidence limits for the difference in proportion of patients maintaining suppression in each of the treatment arms were not calculated for this analysis.

8.1.4.3 Populations Analyzed

Analyses were performed for both the intent-to-treat (ITT) and per protocol (PP) populations. These populations were defined as follows:

ITT population. The ITT population included all randomized patients who received Study Drug according to their assigned treatment, regardless of protocol deviations. The ITT population excluded patients who did not have a primary efficacy measurement (serum testosterone concentration value) on Study Day 29.

PP population. The PP population included all patients who received Study Drug according to the treatment they received and excluded patients who:

- received non-permitted treatments prior to study entry
- violated clinically relevant inclusion/exclusion criteria

- had no assessment before going off treatment due to loss-to-follow-up, refusal to continue treatment, or concurrent illness

For certain protocol violations (e.g., receiving forbidden concomitant medication, cross-over between Study Drugs, extra doses of Study Drug, or injections of Study Drug outside of protocol-defined time windows) patients were excluded from the PP analyses from the visit at which the protocol violation occurred onwards.

8.1.5 Overview of Statistical Analyses for Secondary Efficacy Endpoints

Selected analyses related to supportive efficacy endpoints that are discussed in this review are described below. Other analyses performed by the Sponsor are not described ~~in this~~ section.

Descriptive analyses of monthly testosterone values. The observed distribution of testosterone concentrations at each visit, expressed as mean and quartile testosterone values as well as the percentage of patients with serum testosterone ≤ 1.735 nmol/L at each visit also was presented.

Serum LH and FSH concentrations and acute LH responses. To assess the absence of gonadotropin stimulation following injection of Study Drug on Day 85 (Month 3) and Day 169 (Month 6), the proportion of patients showing an increase in serum LH of ≤1.0 IU/L from just prior to dosing (0 hour) to 2 hours post-injection was presented by treatment group. Exact two-sided 95% confidence intervals on the difference in group-specific proportions were calculated. The distribution of LH and FSH levels at each study visit also was presented.

Bone pain. Bone pain was assessed by both a VAS and the use of analgesics. The change in bone pain (Day 1 to Day 253) was summarized using descriptive statistics and presented by treatment. A comparison of the group-specific change from baseline in VAS was done using the Wilcoxon Rank Sum Test. The use of analgesics was summarized and the ratio of the number of days with analgesics use over total number of days in the assessment period was determined per visit for each treatment group.

PSA levels. For each treatment group, descriptive statistics of the change from baseline in serum PSA by visit were presented. The treatment groups were compared by calculating non-parametric point estimates and two-sided 95% confidence intervals for the difference in median changes from baseline by visit. In these analyses, only patients with non-missing baseline values were included and missing endpoint values were replaced by the last observation carried forward (LOCF). The percent changes from baseline PSA levels also were calculated and listed.

8.2 Principal (Pivotal) Clinical Trial to Support Efficacy Claim

8.2.1 Overall Study Design

Study DEB-96-TRI-01-Phase 1 was the primary clinical trial in NDA 21-288 supporting both the efficacy and safety of the 84-day formulation of triptorelin pamoate for the palliative treatment of advanced prostate cancer. DEB-96-TRI-01 was a multicenter, controlled (active comparator), randomized, open label clinical trial. The original protocol for this Study (later designated as Phase 1 of the Study) included only 2 treatment arms. Under the original protocol, men with advanced prostate cancer who met the entry criteria were randomly assigned in a 1:1 ratio to treatment with either the 84-day formulation or the 28-day formulation of triptorelin pamoate. Patients assigned to the 84-day formulation group received a total of 3 IM doses of Study Drug, each dose separated by 84 days for a total treatment period of 252 days (3 x 84 days). Patients assigned to the triptorelin 28-day group received a total of 9 IM doses of Study Drug, each dose separated by 28 days, also for a total treatment period of 252 days (9 x 28 days). The treatment

period was defined as the interval from the patient's first injection of Study Drug through either 84 or 28 days after his final injection, depending on the formulation. After completion of the study (Study Day 253), patients could continue to receive triptorelin pamoate 3.75 mg at the discretion of their physician.

A subset of 30 patients at Study Center 1 (15 patients in each treatment group) underwent additional blood sampling as part of a pharmacokinetic/pharmacodynamic substudy conducted within the primary study.

In October 1997, the Sponsor amended the Protocol for Study DEB-96-TRI-01 to allow the study to support separate NDA applications for both the 28-day and 84-day formulations of triptorelin. The amendment allowed for the following:

1. Discontinuation of enrollment of new patients into the originally described clinical trial (now designated as Phase 1 of Study DEB-96-TRI-01);
2. Continued treatment and monitoring of patients already enrolled into Phase 1 of the clinical trial; and
3. Addition of a second phase to the clinical trial. In Phase 2, patients were to be randomly assigned to 9 months of treatment with either the 28-day formulation of triptorelin or the 28-day formulation of Lupron (Lupron 7.5 mg).

Patient monitoring and assessment procedures conducted during Phase 2 of Study DEB-96-TRI-01 were identical to those conducted in Phase 1 with the exception of monthly dosing with Lupron, instead of treatment with the 84-day formulation of triptorelin, in one of the two treatment groups. The final report for Study DEB-96-TRI-01 submitted in the present NDA (NDA 21-288) included only data from Phase 1 of the clinical trial. Data from Phase 2, were submitted and reviewed previously as Part of the Complete Response to the Nonapproval Letter of June 1997 for NDA 20-715.

8.2.2 Patients

Patients with prostate cancer who might benefit from hormonal therapy (i.e., reduction in serum androgen levels) were considered for enrollment into Study DEB-96-TRI-01 if they met the following criteria:

Inclusion Criteria

- Histologically proven prostate cancer, T3-4NxMx, or TxN1-3Mx or TxNxM1 according to the Tumor, Lymph Nodes, Metastases (TNM) classification
- A recent bone scan (within the previous 3 months)
- Serum testosterone levels greater than 5 nmol/L
- Karnofsky performance index > 40
- Expected survival of ≥ 12 months
- Absence of another malignancy, other than dermatological, for 5 years
- Written informed consent given before entry into the study

Patients were excluded from participation if they met any of the following criteria:

Exclusion Criteria

- Prior hormonal treatment for prostate cancer including finasteride (Proscar®) treatment
- Presence of another neoplastic lesion or brain metastases

- Prior hypophysectomy or adrenalectomy
- Known or suspicion of vertebral metastases with risk of spinal compression
- Severe kidney or liver failure (creatinine ≥ 2 times the upper limit of normal [ULN], or aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥ 3 times ULN)
- Any concomitant disorder or resultant therapy that was likely to interfere with patient compliance or with the study
- Participation in another study with an experimental drug within 3 months before study start or within 5 drug half-lives of the investigational drug (whichever was the longer)
- Known hypersensitivity to any of the test materials or related compounds
- Known active use of recreational drug or alcohol dependence
- Any current use or use, within 6 months before start of treatment, of medications that were known to affect the metabolism and/or secretion of androgenic hormones: ketoconazole, aminoglutethimide, estrogens, and progesterone
- Use of corticosteroids, except topical application
- Use of anticoagulants, heparin and coumarin derivatives
- Inability to give informed consent or to comply fully with the protocol

8.2.3 Study Drugs

8.2.3.1 Study Drugs and Dose Selection

Study Drugs. The 84-day formulation of triptorelin (Trelstar™ LA) consisted of microgranules of triptorelin pamoate (11.25 mg of triptorelin base) plus poly (*dl*-lactide-co-glycolide, ~145 mg) and the excipients mannitol (85 mg), carboxymethylcellulose (30 mg), and Polysorbate 80 (2 mg). It was to be resuspended in 2 mL of sterile water immediately prior to IM injection and administered once every 84 days. The 28-day formulation of triptorelin pamoate, approved for the treatment of prostate cancer, contained 3.75 mg of triptorelin base in poly (*dl*-lactide-co-glycolide) and was to be administered once every 28 days.

Dose selection. The mean serum AUC values for triptorelin over an 84 day interval following either a single IM dose of 11.25 mg of triptorelin as the 84-day formulation (2428 ng•h/mL) or 3 doses of 3.75 mg of triptorelin as the 28-day formulation administered at 28-day intervals (2374 ng•h/mL) were similar (see Section 5.1 and the Biopharmaceutical Review). Based in part on these pharmacokinetic considerations and the pharmacodynamic findings regarding suppression of serum testosterone in supportive Clinical Trial DEB-95-TRI-01, a dose of 11.25 mg of triptorelin in poly (*dl*-lactide-co-glycolide) was selected for the 84-day formulation.

Medical Officer's Comments

- *Although formal dose ranging studies do not appear to have been conducted with the 84-day formulation, the proposed dose of 11.25 mg administered every 84 days is reasonable.*
- *A somewhat higher dose of triptorelin, however, would likely provide more consistent suppression of serum testosterone to castrate levels at the end of each 84-day treatment period, the time at which the highest proportion of serum testosterone values are > 1.735 nmol/L in clinical data submitted by the Sponsor.*

8.2.3.2 Assignment to Study Drug

Patients were randomly assigned in a 1:1 ratio to either the 84-day formulation (11.25 mg triptorelin) or the 28-day formulation (3.75 mg triptorelin, the active comparator). The randomization was stratified by center and balanced between the two treatment groups. Each Study Center was provided with a unique randomization list consisting of sealed randomization envelopes. Patient numbers were to be allocated according to the patient's chronological enrollment into the study. Patients assigned to the 84-day formulation received an IM injection of Study Drug every 84 days for a total of 3 doses. Patients assigned to 28-day formulation received an IM injection of Study Drug every 28 days for a total of 9 doses.

- *This was an open label study. According to the protocol, however, investigators and patients were to be blinded to the treatment assignment at the time of patient enrollment through the use of sealed randomization envelopes.*

8.3 Study Procedures and Study Conduct

8.3.1 Schedule of Study Assessments

During the screening period, the patient's eligibility for the study was determined according to the inclusion and exclusion criteria described in Section 8.2.2). After the first injection of Study Drug on Day 1, patients were to return to the Study Center every 28 days for clinical and laboratory assessments and dosing with Study Drug according to the schedule presented in Table 6.

8.3.2 Efficacy Assessments

All blood samples for efficacy and pharmacokinetic assessments were to be obtained in the morning prior to dosing with Study Drug unless otherwise indicated.

Serum concentrations of testosterone. Blood samples for the measurement of serum concentrations of testosterone were to be obtained at screening, and on Study Days 1, 29, 57, 85, 113, 141, 169, 197, 225, and 253.

Serum concentrations of LH and FSH. Blood samples for the measurement of serum levels of LH and FSH were to be taken on Study Days 1, 29, 57, 85, 113, 141, 169, 197, 225, and 253. On Study Days 1, 85, and 169, blood samples for LH and FSH measurements also were to obtained 2 hours after dosing to assess the acute LH and FSH responses to Study Drug.

Serum concentrations of PSA. Blood samples for the measurement of serum concentrations of prostate specific antigen (PSA) were to be obtained on Study Days 1, 85, 169, and 253.

Other efficacy assessments. Bone pain was to be assessed on Study Days 1, 29, 57, 85, 113, 141, 169, 197, 225, and 253 using a visual analogue scale (VAS). Analgesic use was to be recorded throughout the study. Quality of life (assessed by EORTC Quality of Life Questionnaire) was to be assessed on Study Days 1, 29, 57, 85, 169, and 253.

8.3.3 Pharmacokinetic Assessments

Blood collection for the measurement of trough concentrations of triptorelin were collected on Study Days 1, 29, 57, 85, 113, 141, 169, 197, 225, and 253 (prior to dosing with Study Drug on treatment days).

Table 6. General Schedule of Study Procedures and Assessments

END OF MONTH:		0	1	2	3	4	5	6	7	8	9
Study Day:	Screen	1	29	57	85	113	141	169	197	225	253
Injection of Study Drug											
Triptorelin 84-day formulation		X			X			X			
Triptorelin 28-day formulation		X	X	X	X	X	X	X	X	X	
Blood samples											
Testosterone	X	X	X	X	X	X	X	X	X	X	X
LH		X*	X	X	X*	X	X	X*	X	X	X
FSH		X*	X	X	X*	X	X	X*	X	X	X
PSA		X			X			X			X
Triptorelin		X	X	X	X	X	X	X	X	X	X
Assessments											
Bone pain (VAS)		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X**	X	X	X**	X	X	X**	X	X	X
Local tolerance		X			X			X			
Hematology and biochemistry	X	X***			X			X			X
QoL (EORTC)		X	X	X	X			X			X

* Sampling at 0h and 2h post-dosing in all patients (gonadotropin stimulation test).
** Vital signs were measured at 0h, 2h, and 4h post-dosing.
*** To be performed if not done during the pre-study visit (within 15 days prior to study start).
All single blood samples were taken in the morning and before dosing when applicable.
Source: Flow chart, pg. 106, Vol. 28 of original submission.

Table 7. Schedule of Study Procedures (Pharmacokinetic and Pharmacodynamic Subgroup)

END OF MONTH		0	1	2	3	4	5	6	7	8	9
Time (Day)	Screen	1	29	57	85	113	141	169	197	225	253
Injection:											
Triptorelin 84-day formulation		X			X			X			
Triptorelin 28-day formulation		X	X	X	X	X	X	X	X	X	
Blood samples:											
Testosterone	X	X#	X	X	X	X	X	X	X	X	X
LH		X*	X	X	X*	X	X	X*	X	X	X
FSH		X*	X	X	X*	X	X	X*	X	X	X
PSA		X			X			X			X
Triptorelin		X##	X	X	X##	X	X	X##	X###	X###	X
Assessments:											
Bone pain (VAS)		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X**	X	X	X**	X	X	X**	X	X	X
Local tolerance		X			X			X			
Hematology and biochemistry	X	X***			X			X			X
QoL (EORTC)		X	X	X	X			X			X

*: Sampling at 0h 2h, 4h, 6h, and 10h.
**: Vital signs were measured at 0h, 2h, and 4h post-dosing.
***: To be performed if not done during the pre-study visit (within 15 days prior to study start).
#: Profile of testosterone with sampling at 0h, 24h, 48h, 96h, and 144h (Day 7).
##: Triptorelin pharmacokinetics with sampling at: 0h, 2h, 4h, 6h, 10h, 24h, and 48h post-dosing.
###: Triptorelin pharmacokinetics with sampling at: 0h, 2h, 4h, 6h, 10h, 24h, and 48h post-dosing only in the subset of patients receiving the 28-day formulation.
Source: Flow chart, pg. 106, Vol. 28 of original submission.

8.3.4 Special Pharmacokinetic and Pharmacodynamic Assessments

Additional blood samples were obtained from a subset of 30 patients (15 patients in each treatment group) at Center 1 for a more detailed assessment of (a) changes in serum concentrations of testosterone, LH and FSH after the first dose of Study Drug and (b) triptorelin pharmacokinetics (see Table 7). In addition to undergoing the efficacy assessments described previously in Section 8.3.2, these patients had additional blood sampling for:

- Measurement of serum testosterone levels at 24, 48, 96, and 144 hours after first dosing with Study Drug
- Measurement of serum LH and FSH levels at 2, 4, 6, and 10 hours post dosing on Study Days 1, 85, and 169
- Measurement of serum triptorelin levels at 2, 4, 6, 10, 24, and 48 hours post-dosing on Study Days 1, 85, and 169
- Measurement of serum triptorelin levels at 2, 4, 6, 10, 24, and 48 hours post-dosing on Study Days 1, 85; 169, 197, and 225 for those patients receiving the 28-day formulation of triptorelin

8.3.4.1 Laboratory Procedures for Efficacy and Pharmacokinetic Assessments

Serum testosterone concentrations were measured by the Clinical Assays™ GammaCoat Testosterone ^{125}I RIA Procedure. Serum concentrations of LH, FSH, and PSA were measured by Abbott IMx assays, which are proprietary Microparticle Enzyme Immunoassay (MEIA) procedures that employ monoclonal antibodies that bind with the protein to be measured. Specimens from all centers, with the possible exception of Center 1, were measured centrally under the supervision of

South Africa. The assay procedure for the measurement of serum concentrations of triptorelin is described in the Biopharmaceutical Review.

The lower limits of quantification (LLQ) for these assays as listed in the Final Study Report were: testosterone = 0.2 nmol/L, LH = 0.5 IU/L, FSH = 0.2 IU/L, and PSA = 0.2 µg/L. For statistical analyses, values reported by the laboratory to be below the limit of quantification were replaced with values one half those of the LLQ values.

Medical Officer's Comments

- *All of these assays were commercially available procedures.*
- *The Central Laboratory provided Quality Control data and evidence of participation in an international quality monitoring program (see Section 7.3).*
- *It appeared that assay results were reported to investigators who in turn recorded the values on case report forms (CRFs) Data from CRFs were subsequently entered manually into the study database. The likelihood of incorrect data in the final database would have been reduced had the laboratory provided electronic sets directly to the Sponsor's database or the Sponsor's data entry group.*

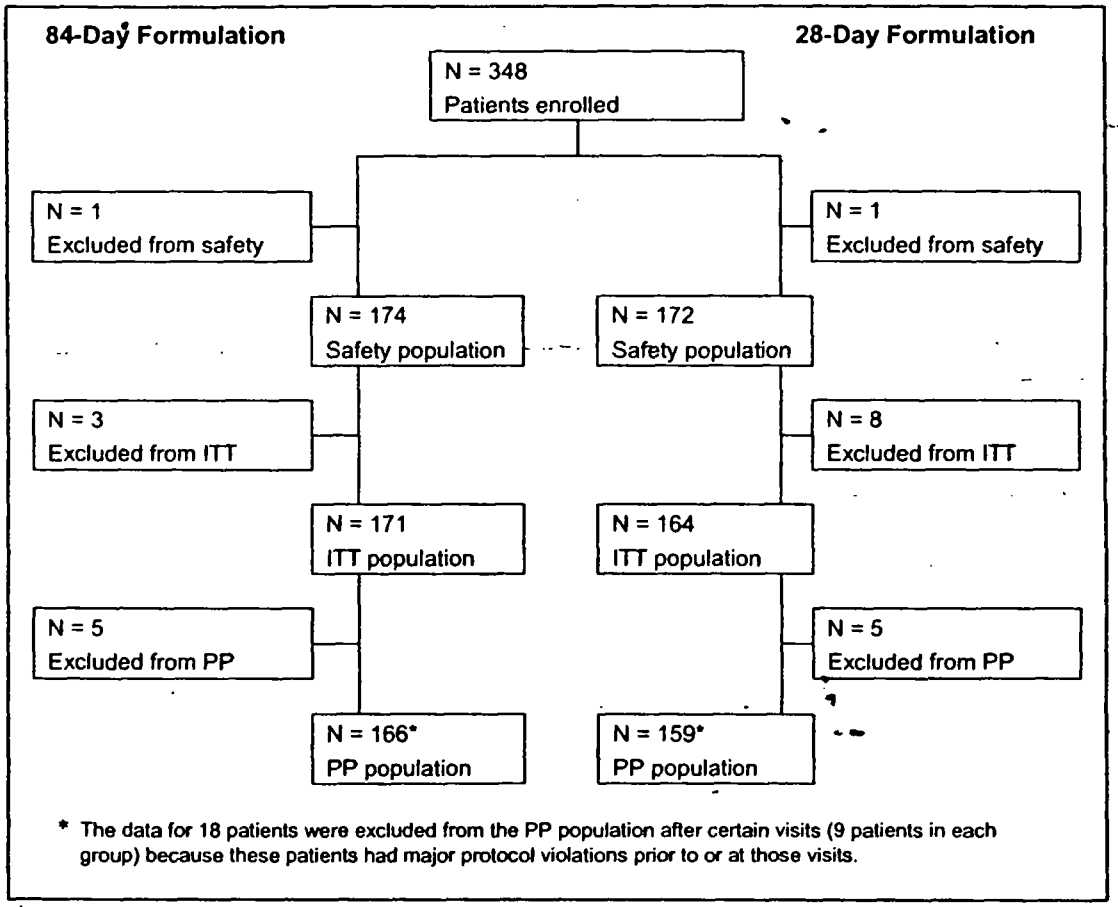
8.4 Results

8.4.1 Enrollment and Study Population

8.4.1.1 Study Population

This study was conducted at 19 Centers in South Africa. The first patient was enrolled on January 27, 1997 and the last patient completed his participation on September 4, 1998. A total of 348 patients were enrolled. The safety population consisted of 346 patients (174 and 172 patients in the 84-day formulation and 28-day formulation treatment groups, respectively). Two patients, one in each treatment group, did not receive any injection of Study Drug. Figure 1 summarizes the number of patients in the safety, intent to treat, and per protocol populations.

Figure 1. Study Populations



Source: Section 10.1, pg 50, Vol. 29 of original submission.

Three hundred and thirty-five (335) patients were included in the ITT population, 171 patients in the 84-day formulation group and 164 patients in the 1-month formulation group. In the 3-month formulation group, 3 patients were excluded from the ITT population because they had no primary efficacy data on Day 29. Eight (8) patients in the 1-month formulation group were excluded from the ITT population. Seven of these patients did not have primary efficacy data on Day 29 and 1 patient received the wrong study drug on his first visit.

Ten (10) patients (5 in each group) were excluded from the PP population. The reasons for exclusion included use of a prohibited medication prior to Study Day 29 (n=4), lack of histologic proof of prostate cancer or no pretreatment bone scan (n=3), a late Day 29 clinical visit (n=2) or a screening testosterone < 5 nmol/L (n=1).

The data of 18 patients (9 patients in each treatment group) were subsequently excluded from the PP population after certain visits since each of these patients had a major protocol violation prior to or at the respective visit. Patients were excluded from a specific visit onwards for 3 reasons:

- Out of schedule Study Drug administration
- Forbidden concomitant medication
- Cross-over of Study Drug (i.e., receiving the wrong Study Drug)

8.4.1.2 Major Protocol Violations

In the 3-month formulation group, 14 patients had major protocol violations and 25 patients had a total of 27 minor protocol violations. In the 1-month formulation group, 14 patients had major protocol violations (one patient had two major protocol violations) and 21 patients had a total of 22 minor protocol violations. Table 8 summarizes the major protocol violations.

Table 8. Summary of Major Protocol Violations

Type of violation	Specific Protocol violation	84-Day Formulation	28-Day Formulation
Entry Criteria	Exclusion criteria violated, forbidden medications prior to study entry	1	2
	Serum testosterone ≤ 5 nmol/L on Day -1	0	1
	No histological proof of prostate cancer	1	1
	No bone scan within 6 months of study start	0	1
On-Study Medication	Forbidden concomitant medications	2	1
Study Drug	Crossover between the two study treatments	5	1
	Out of schedule dosing at Day 29	2	0
	Out of schedule dosing other than at Day 29)	3	8
	Total	**14**	**15** [1]

[1] One patient had 2 violations.
Source: Tables 14.1.1.4 and 14.1.1.5, Vol. 29 of original submission.

8.4.1.3 Demographics and Baseline Disease Characteristics

Baseline demographic characteristics are listed in Table 9. The mean age of the patients in the safety population was 70.0 years (range:) in the 84-day group and 71.0 years (range 45-89 years) in the 28-day group. The mean weight of the patients in the safety population was 72.8 kg (range:) in the 84-day group and 72.9 kg (range) in the 28-day group. Just under 50% of the patients were Caucasian (47% in the in the 84-day group and 49% in the 28-day group). Thirty eight (38) percent and 37% of the patients in the 84-day and 28-day groups, respectively, were Black. Baseline serum testosterone concentrations were 11.3 nmol/L (range:) in the 84-day group and 12.2 nmol/L (range:) in the 28-day group.

Medical Officer's Comments

- *The 2 treatment groups were well balanced in terms of age, weight, and race.*
- *In contrast to most studies conducted in the US in men with advanced prostate cancer, slightly more than 50% of the patients in Study DEB-96-TRI-01-Phase 1 were not Caucasian.*
- *Pretreatment serum testosterone concentrations were statistically lower ($p < 0.05$) in the 28-day group. The mean difference (approximately 1 nmol/L) might bias the outcome of the study to some extent in favor of the 84-day formulation group.*

Table 9. Baseline Demographics

	84-Day Formulation			28-Day-Month Formulation		
	Safety N = 174	ITT N = 171	PP N = 166	Safety N = 172	ITT N = 164	PP N = 159
Age (yr.)						
Mean	70.0	69.8	69.7	71.0	70.8	70.8
Range						
Weight (kg)						
Mean	72.8	72.8	72.9	72.9	73.2	73.2
Range						
Race [n (%)]						
Caucasian	81 (47%)	80 (47%)	77 (46%)	84 (49%)	81 (49%)	77 (48%)
Black	66 (38%)	64 (37%)	62 (37%)	64 (37%)	59 (36%)	58 (37%)
Colored	27 (16%)	27 (16%)	27 (16%)	24 (14%)	24 (15%)	24 (15%)
Testosterone (nmol/L)						
Mean	11.3	11.2	11.1	12.2	12.3	12.3
Range						

Source: Tables 14.1.2.1, 14.1.2.2, and 14.1.2.3, Vol. 29.

Baseline disease characteristics are listed in Table 10. In the 84-day group, the mean and median duration of disease in the safety population was 6.5 and 1.0 months (range: 0-150). In the 28-day group, the mean and median duration of disease was 7.2 and 1.0 months (range: 0-155). Slightly more than 50% of the patients in both treatment groups had Stage C disease while slightly less than 50% of the patients had Stage D disease.

Table 10. Baseline Disease Characteristics

	84-Day Formulation			28-Day Formulation		
	Safety N = 174	ITT N = 171	PP N = 166	Safety N = 172	ITT N = 164	PP N = 159
Duration Disease (months)						
Mean	6.5	6.7	6.5	7.2	7.3	6.6
Median	1.0	1.0	1.0	1.0	1.0	1.0
Range						
Stage of Disease (%)						
Stage C	51.7	52.0	52.4	54.1	54.3	54.1
Stage D	48.3	48.0	47.6	45.3	45.1	45.9
Other	0.0	0.0	0.0	0.6	0.6	0.0

Source: Tables 14.1.2.5, 14.1.2.6, 14.1.2.7, and 14.1.2.10, Vol. 29.