CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-437

MEDICAL/STATISTICAL REVIEW(S)

Division of Drug Oncology Products

Medical Officer Review of
Watson's Responses to FDA "Complete Response"

NDA:	22-437
Applicant:	Watson Pharmaceuticals
Product:	TRELSTAR 22.5 mg (triptorelin pamoate for injectable suspension)
Indication:	Treatment of Advanced Prostate Cancer
CR Letter Date:	July 10, 2009
Resubmission Date:	September 10, 2009
Serial No:	0015
Reviewers:	Yang-Min (Max) Ning, MD, PhD, DDOP/OODP/ OND V. Ellen Maher, MD, DDOP/OODP/ OND

Background

The original New Drug Application (NDA #22-437) for TRELSTAR 22.5 mg (triptorelin pamoate for injectable suspension), submitted initially on September 11, 2008, received a Complete Response (CR) from DDOP/OODP/OND/FDA because of both clinical and CMC deficiencies identified from the reviews of the original submission. On September 10, 2009, the applicant provided responses to address those deficiencies listed in the FDA's Complete Response letter. In addition, the applicant submitted a revised product package insert based on the FDA reviewers' recommendations conveyed to the applicant prior to the CR letter. Moreover, the applicant provided a post-marketing safety update covering the period between November 2008 and July 2009. There were no new clinical or nonclinical data or any re-analysis of existing clinical or nonclinical data in the resubmission.

The clinical reviewers for this NDA evaluated the adequacy of the applicant's responses to the clinical deficiencies and the safety update. Below are the findings from the review of each listed clinical deficiency. Please note that the clinical review of the original submission can be found in DARRTs dated June 29, 2009.

Review of the Responses

The clinical deficiencies conveyed were as follows:

For Study DEB-TRI6M-301, you have provided testosterone levels using two different assay methods, immunoassay and liquid chromatography/tandem mass spectroscopy (LC/MS). The result of the analysis of the co-primary endpoint, maintenance of castrate testosterone levels from Day 57 to Day 337, using testosterone levels derived

from the immunoassay differs markedly from the result using testosterone levels derived from the assay using LC/MS. It is unclear whether the co-primary endpoint should be analyzed using the results of the immunoassay or of LC/MS.

a. Please provide your rationale for the use of testosterone levels from the LC/MS assay in your primary analyses. Please compare the testosterone assay used in your primary analyses to the methods used to assay testosterone levels in your own approved applications, in the approved applications of others (reviews available on the FDA website) and in published articles.

The applicant stated in the responses that the use of a validated LC/MS method to measure testosterone levels at a central laboratory was selected prior to the beginning of Study DEB-TRI6M-301 and that the results of these testosterone assays would be used in the primary analyses. The use of a chemiluminescence method (CHLIAs: (b) (4) was not considered for the primary analysis due to well-acknowledged analytical bias at hypogonadal testosterone levels and poorly documented analytical validation. However, for routine monitoring of patients during the study, the immunoassay method was employed in a local central laboratory (b) (4) since LC/MS methods are not practical for routine clinical measurement of testosterone levels.

The applicant also provided the basic characteristics of the two methods and comparison between them as well as information concerning possible differences or bias between the two methods.

Reviewer's Comments:

The applicant's responses clarified the concerns the reviewer had during the review of the initial submission, in which there was not a clear description as to which one of the two methods was supposed to be used for the primary efficacy analyses. With this clarification, the efficacy analysis results, as described in the original review, will remain unchanged since the LC/MS-measured testosterone levels were used by the reviewer in that review. Thus, the product was efficacious in suppressing and maintaining serum total testosterone production to the castrate levels of ≤1.735 nM in 93.3% (95% CI: 92.9% - 99.5%) of the patients during the 24-week study.

The reviewer concurred with the applicant's explanation of the differences between the two methods. Clearly, immunoassay-based measurement of testosterone levels can be affected by proteins (e.g., sex hormone binding protein) and cross-reactivity of testosterone antibody with other steroids, and has not been well characterized or validated for measuring testosterone below castrate levels or under hypogonodal conditions. It appears that the immunoassay method (CHLIA) could overestimate testosterone levels by 0.57 nM compared to the value obtained with LC/MS, which is regarded as the most sensitive and reliable method for measuring hypogonadal ranges of testosterone. The reviewer recognized that different testosterone levels did exist between the two methods because of the differences in the sensitivity and specificity of each method. The reviewer also acknowledged that variations in assay results from the same

sample could not be totally avoided in routine laboratory practice. The variations could be reduced by analyzing the same sample in triplicate in order to achieve a more accurate reading of testosterone in the sample. Regrettably, no triplicate or duplicate assays of a sample were performed under either method during the study. Since single sampling assay results of testosterone levels were used in the regulatory evaluation of other GnRH analogs, the reviewer considered that the LC/MS results from the study were adequate.

b. Please provide references to support your contention that the LC/MS method is preferred for the assay of hypogonadal testosterone levels. This should include a comparison of the intra-assay and inter-assay coefficient of variation using both of these assay methods.

The applicant provided a table showing the important information about the intra-assay coefficient variations of each method. The table as shown below is adopted from the resubmission as follows:

Characteristic	LC-MS/MS	CHLIAs
Method	Testosterone is extracted from sample (human serum) and calibration curve and QC standards (horse serum) by a (b) (4) (b) (4) method, then analyzed by LC-MS/MS. Testosterone is measured directly by monitoring the mass ratio of parent and product ions. Quantification is achieved using analyte to internal standard (trideuterated testosterone) peak area ratios. Concentrations are determined by the method of $(1/\chi^2)$ weighted least squares linear regression.	Competitive immunoassay in which testosterone in the sample competes with acridinium ester-labeled testosterone in the reagent for a limited amount of polyclonal rabbit anti-testosterone antibody bound to monoclonal mouse anti-rabbit antibody, which is coupled to paramagnetic particles in the solid phase. A releasing agent releases bound testosterone from the endogenous binding proteins in the sample. There is an inverse relationship between the amount of testosterone in the sample and the amount of relative light units detected by the system.
Sample volume	500 µl	15 µl
Sample preparation	(b) (4)	None
Specificity	No interferences	Cross-reactivities at 100 ng/mL spike: 5α-dihydrotestosterone: 5.4% androstenedione: 0.94% methyltestosterone : 0.68%
Linearity & range	0.1 – 10.0 nmol/L (r^2>0.99; 1.9% CV for validation curve gradients)	0.35 – 52 nmol/L (no characteristics of calibration curve reported; Master Calibration Curve provided with reagents)
Intrarun precision (CV%) **Interrun precision (CV%)**	At 0.1 nmol/L, 14% CV within-runs and 3.2% CV between-runs; At 3.1 nmol/L, 6.6% CV within runs and 0.6% CV between runs; At 8.8 nmol/L, 7.8% CV within-runs and 3.2% CV between-runs	At 3.3 nmol/L, 6.2% CV within runs and 4.4% CV between runs (7.6% CV total); At 35.0 nmol/L, 2.3% CV within runs and 1.4% CV between runs (2.7% CV total)
Recovery	Relative recoveries of testosterone of 69% at 8.8 nmol/L, 84% at 26.4 nmol/L, and 78% at 51.9 nmol/L; Relative recovery of internal standard calculated at 78%	Mean 95.6% recovery over testosterone concentrations from 0.87 to 1.94 nmol/L
Accuracy/Bias	100% average accuracy over the assay range	Accuracy not reported; Positive systematic bias reported in the literature (range: 0.53 to 1.19 nmol/L)
Stability	Sample stable at ambient for 4 hours prior to extraction, at 5°C up to 385 days, and at -20°C up to 578 days; Stable for three freeze-thaw cycles	Refrigerate specimens if assay not completed within 8 hours; Freeze samples below -20°C if assay not completed within 48 hours; Freeze samples only once

The applicant also examined the extent of agreement between the two methods based on the paired testosterone data that met the low limit of quantification for each method. Regression analysis showed a positive mean systematic bias of about 0.47 nM for the CHLIA methods as compared with the LC-MS/MS method. This finding was similar to the finding from a different analysis method.

c. Please provide information concerning the storage and shipment conditions used for the testosterone serum samples.

The applicant provided a detailed description of how patients' samples were stored and shipped during the study.

Reviewer's Comments:
The described sampling and storage method for testosterone levels evaluation appear reasonable in laboratory practice. The long term stability established during assay validation was 578 days at -20°C in the central laboratory. This stability result appears to be consistent with the findings that showed the testosterone concentration in serum samples was not affected during long-term cryostorage [Koziris LP et al. (2003) Stability of serum testosterone concentration in long-term cryostorage. Medicine & Science in Sports & Exercise: 35: S330].

Review of the Safety Update
The safety information, as shown in the following table, was provided voluntarily in the current submission. This was based on post-marketing adverse events reported to the approved triptorelin formulations during the period from November 2008 (the time point of the 120 safety update submission for the NDA) to July 2009 (the time when CR letter was issued).

MedDRA System Organ Class and Preferred Term	AEs	SAEs
Total events	26 (100%)	3 (100%)
Blood and lymphatic system disorders		
Anaemia	1	---
Eye disorders		
Visual acuity reduced	1	---
Gastrointestinal disorders		
Constipation	1*	---
General disorders & administration site disorders		
Asthenia	1	---
Condition aggravated	1	---
Drug ineffective	4	---
Injection site haematoma	1	---
Oedema peripheral	2*	---
Injury, procedural and procedural complications		
Drug administration error	1*	---
Investigations		
Liver function test abnormal	---	1
Prostatic specific antigen increased	1*	---
Musculoskeletal & connective tissue disorders		
Back pain	1*	---
Pain in extremity	1*	---
Nervous system disorders		
Dizziness	1*	---
Headache	1	---
Psychatric disorders		
Disorientation	1	---
Skin & subcutaneous tissue disorders		
Rash	3**	---
Hot flush	4	---
Vascular disorders		
Cardiovascular insufficiency	---	1
Circulatory collapse	---	1

* One case has been reported in other indications
** Two cases have been reported in other indications

Reviewer's Comments:
The listed adverse events have been reported previously with the approved triptorelin products. Since these events were collected from voluntary reporting, their attribution to triptorelin would be hard to establish. Therefore, this safety update does not change the safety findings described in the initial review of the NDA for the triptorelin 22.5 mg formulation, nor does the risk to benefit profile of the product.

Summary

In the reviewer's opinion, the applicant has satisfactorily addressed the clinical deficiencies as listed in the CR letter. The applicant's responses do not affect the original clinical review findings and conclusions dated June 29, 2009. Therefore, the reviewer recommends regular approval of the TRELSTAR 22.5 mg formulation for the treatment of patients with advanced prostate cancer.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22437	ORIG-1	WATSON LABORATORIES INC	TRELSTAR [redacted] (b) (4)

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/s/

YANGMIN NING
02/19/2010

VIRGINIA E MAHER
02/22/2010

Summary Review for Regulatory Action

Date	July 10, 2009
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	22-437
Applicant Name	Watson Laboratories, Inc.
Date of Submission	September 12, 2008
PDUFA Goal Date	July 12, 2009
Proprietary Name / **Established (USAN) Name**	Trelstar/ triptorelin pamoate
Dosage Forms / Strength	For injectable suspension / 22.5 mg
Proposed Indication(s)	Palliative treatment of advanced prostate cancer, (b) (4) [redacted]
Action/Recommended Action for NME:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	X
Statistical Review	X (combined clinical and statistical review)
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	X
Clinical Pharmacology Review	X
DDMAC	
DSI	X
CDTL Review	X
OSE/DMEPA	X
OSE/DDRE	
OSE/DRISK	
Other	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

Trelstar (triptorelin pamoate for injectable suspension) is a GnRH agonist. This application seeks approval of Trelstar 22.5 mg for administration every 24 weeks for the indication of "palliative treatment of advanced prostate cancer. (b) (4) This review will summarize the conclusions and recommendations of each review discipline.

2. Background

Trelstar Depot 3.75 mg (NDA 20-715) is approved for monthly IM injection. Trelstar LA 11.25 mg (NDA 21-288) is approved for administration every 12 weeks. Trelstar 22.5 mg is intended to allow for every 24 week administration. As will be discussed in the Clinical Review and CDTL Review, approvals of GnRH agonists and antagonists have been traditionally based on the achievement and maintenance of castrate levels of testosterone.

3. CMC/Device

The Chemistry Review of 6/16/09 made the following recommendations and conclusion on approvability.

A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

The application CANNOT BE APPROVED from the Chemistry, Manufacturing and Controls (CMC) perspective based on major deficiencies in the application. An acceptable and complete response to the following deficiencies is needed before approval can be recommended from a CMC perspective.

The deficiencies are summarized as follows (see exact wording to be conveyed at end of the review):

1. DMFs (b) (4) (drug substance), 8084 (WFI syringes) and (b) (4) (release polymer) are not adequate. Deficiency letters have been sent to the agent for each file.
2. Additional information is requested on the drug substance analytical methods.
3. Additional information is requested on the stopper extractables/leachables study.
4. Clarification is requested regarding the responsiblities for the proposed manufacturing and control sites.
5. Additional information is requested regarding the drug product manufacturing process.
6. Additional information is requested regarding the validation studies for the drug product analytical methods.
7. Revision and justification is requested for the proposed drug product specification for impurities.
8. Acceptance specifications for the drug product packaging components have been requested.
9. Revisions are requested for the proposed protocol for post approval stability studies.
10. The stability information supporting the proposed expiry period and label storage statement is not adequate.
11. Revisions are requested for the CMC sections of the proposed labels and labeling.

In addition, an overall recommendation has yet to be provided by the Office of Compliance on the proposed manufacturing and control sites, and the microbiology review is currently pending.

The Product Quality Microbiology review of 7/19/09 recommended approval. However, see final CMC recommendation below for further discussion.

The final CMC recommendation of 7/9/09 on this NDA is quoted below.

> NDA 22-437 (triptorelin pamoate for injection suspension, 22.5 mg) was initially submitted on 12-SEP-2008 and was granted a standard review by the Agency. Chemistry Review #1 (dated 16-JUN-2009) identified eleven (11) Chemistry, Manufacturing and Controls (CMC) deficiencies which were subsequently communicated to the Applicant. These deficiencies have not been resolved to date. At the time of the Chemistry Review, a final recommendation from the Office of Compliance had not yet been issued, and the microbiology review was not completed.
>
> This memo serves to update that determination. The microbiology review recommends approval of this NDA and was finalized on 19-JUN-2009. However, the Office of Compliance issued an overall withhold recommendation for this application on 07-JUL-2009.
>
> Several CMC deficiencies were conveyed to the Applicant in a 16-JUN-2009 letter. While the majority of these items remain as outstanding CMC issues, two (5d and 9b) were partially covered as part of the subsequent microbiology review dated 19-JUN-2009. Therefore, these two deficiencies were discussed in an informal teleconference on 08-JUL-2009 (Dr. J. McVey, Dr. V. Pawar, Dr. S. Pope, and Dr. M. Adams participating). As a result of that discussion, a decision was made to slightly revise deficiency 5d to read "Verify that the procedures and parameters for the sterilization and depyrogenation of vials and stoppers in this application are the same as those validated and approved in NDA 20-715 and NDA 21-288." Additionally, the participants collectively decided to delete deficiency 9b, as it was already covered by the microbiology review. These revisions were made in the action letter language.
>
> Three of the proposed manufacturing sites received withhold recommendations from the Office of Compliance. While only one of the sites (Debio) was actually inspected, all three sites (Debio, (b) (4)) will be mentioned in the action letter as having received withhold recommendations.
>
> NDA 22-437 has outstanding CMC deficiencies, as well as an overall withhold recommendation from the Office of Compliance. Accordingly, from a CMC perspective, approval of NDA 22-437 cannot be recommended until any related deficiencies are resolved.

I concur with the conclusions reached by the chemistry reviewers regarding the action on this NDA.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review is quoted below.

NDA 22-437 does not contain any new information on the toxicology of the product. Three pharmacokinetic studies have been submitted, indicating decreased levels of testosterone in response to the new formulation of triptorelin. The NDA relies on pharmacology and toxicology information submitted for triptorelin pamoate under NDA 20-715. There are no formulation differences that would be expected to change the pharmacological or toxicological activity between previous formulations and the formulation that is being proposed under NDA 22-437. Only the duration of activity should be expected to change. One of the excipients, (b) (4) Poly(D,Llactide-coglycolide), is a novel polymer in this formulation but the DMF relied upon (DMF (b) (4)) has been reviewed and relied upon for approved products in the past (significantly, it has been referred to for NDA 021731, an approved 6-month depot formulation of 45 mg leuprolide acetate). Furthermore, there is no change in proposed indication (palliative treatment of advanced prostate cancer). Given these facts, the pharmacology/toxicology review conducted for NDA 20-715 is sufficient and an additional pharmacology and toxicology review for this NDA is not needed.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that an additional pharmacology and toxicology review is not needed.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review of 6/18/09 provided the following executive summary and recommendations.

The Applicant seeks approval of NDA 22-437 for **TRELSTAR** (b) (4) (triptorelin pamoate injectable suspension) **22.5 mg** (6-month sustained-release formulation) to be used as a palliative treatment of advanced prostate cancer. **TRELSTAR** (b) (4) has the same indication, dosage form (injection), and route of administration (intramuscular) as for the approved triptorelin **3.75 mg** (1-Month) and **11.25 mg** (3-Month) sustained-release formulations.

In support of the efficacy and safety of **TRELSTAR** (b) (4) (22.5 mg triptorelin injectable suspension) in the advanced prostate cancer indication, the Applicant submitted a pivotal Phase 3 study in 120 patients (**Study 301**). In this study, all patients were given two intramuscular injections of triptorelin pamoate 22.5 mg at an interval of 6 months. The primary efficacy endpoint was to determine the percentage of patients who achieved castration levels of ≤ 0.5 ng/mL on Day 29 and the percentage of patients who maintained these levels from Day 57 through Day 337. The results of the study showed that for the intent-to-treat (ITT) population, 97% (117/120) achieved castration levels of testosterone on Day 29 and 93% (107/115) maintained these throughout study treatment.

The pharmacokinetics (PK: serum triptorelin) and the pharmacodynamics (PD: serum testosterone) were evaluated in a subset of **15 patients** in the pivotal **Study 301** after the **6-month formulation**. Fourteen patients (14/15, 93%) achieved castration **testosterone** serum levels of ≤0.5 ng/mL at **Day 29** and maintained these levels at **Days 57-337**. One patient did not maintain castration testosterone levels during this period. The 6-Month formulation of triptorelin was found to be at least as effective as the approved 1-month and the 3-Month formulations in achieving and maintaining castration level of testosterone.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the information contained in NDA 22-437 and found it acceptable from the clinical pharmacology perspective.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The following summary of the study design and efficacy results are from division's current version of the draft package insert.

> TRELSTAR 22.5 mg was studied in a non-comparative trial of 120 men with advanced prostate cancer. The clinical trial population consisted of 64% Caucasian, 23% Black, and 13% Other, with a mean age of 71.1 years (range 51-93). The response to triptorelin was comparable between racial groups. Patients received TRELSTAR 22.5 mg (N = 120) every 24 weeks for a total of 2 doses (maximum treatment period of 337 days). The primary efficacy endpoint included achievement of castration by Day 29 and maintenance of castration from Day 57 through Day 337.
>
> Castration levels of serum testosterone (≤ 1.735 nmol/L; equivalent to 50 ng/dL) were achieved at Day 29 in 97.5% (117 of 120) patients treated with TRELSTAR 22.5 mg. Castration was maintained in 93.3% of patients in the period from Day 57 to Day 337.
>
> Cumulative maintenance of castration levels of serum testosterone from Day 57 through Day 253 was found in 94.1% of patients treated with TRELSTAR 22.5 mg.
>
> A summary of the clinical studies for TRELSTAR is provided in Table 7.

Table 7. Summary of TRELSTAR Clinical Studies

Product Strength	3.75 mg	11.25 mg	22.5 mg
Number of Patients	137	171	120
Treatment Schedule	every 4 weeks	every 12 weeks	every 24 weeks
Duration of Study	253 days	253 days	337 days
Castration Rate [a] on Day 29, % (n/N)	91.2% (125/137)	97.7% (167/171)	97.5% (117/120)
Rate of Castration Maintenance[b] from Days 57 – 253, %	96.4%	94.4%	94.1%
Rate of Castration Maintenance from Days 57 – 337, % (n/N)	not applicable	not applicable	93.3% (112/120)[c]

[a] Maintenance of castration was calculated using a frequency distribution.

[b] Cumulative maintenance of castration was calculated using a survival analysis (Kaplan-Meier) technique.

[c] Calculation includes 5 patients who discontinued the study but who had castrate levels of testosterone prior to discontinuation.

The combined Clinical and Statistical Review made the following recommendation on regulatory action.

> Watson Pharmaceuticals submitted the TRELSTAR (triptorelin 22.5 mg) application, NDA 22-437, on September 12th, 2008, and requested marketing approval of this new formulation for the treatment of patients with advanced prostate cancer.
>
> Based on the data submitted and the analysis results obtained from our review, we found that the application has provided adequate evidence to support the efficacy and safety of the new triptorelin 22.5 mg formulation for use in the intended patient population at the proposed dosing schedule. Therefore, the reviewers recommend regular approval of the new formulation for the treatment of patients with advanced prostate cancer, provided that all issues raised by the other review disciplines have been addressed satisfactorily.
>
> It is necessary to point out that approximately 28% of patients in the key study supporting this NDA had biochemical relapse only disease with no evidence of metastasis. Since the disease setting generally is not recognized as advanced disease and since androgen deprivation in this setting has not been proven beneficial, the inclusion of these patients in the developmental study does not constitute a basis for or implied use of the new formulation in patients with biochemical relapse only disease in routine practice.

The Cross-Discipline Team Leader Review summarized the clinical issues with this application in the following excerpt from the Risk Benefit Assessment.

> This product will provide increased patient and physician convenience by extending the interval between treatments. Its adverse event profile is consistent with that seen in previous studies of GnRH agonists in prostate cancer. The risks of this product are primarily related to its efficacy. Using the analyses specified in the Statistical Analysis Plan, castrate testosterone levels were achieved in 93% (86.8%; 97.0%) of patients using the LC/MS testosterone levels. This is consistent with previous GnRH approvals. However, castrate testosterone levels were achieved in 80.2% (72.0%; 87.0%) using the immunoassay testosterone levels. Other approved products are available for use at 24
>
> week intervals for this indication. In order to not subject patients to a less efficacious product, it will be important to establish that this product provides comparable efficacy prior to its approval.

The review recommended that the following comments be sent to the applicant.

> 1. For Study DEB-TRI6M-301, you have provided testosterone levels using two difference assay methods, immunoassay and liquid chromatography/tandem mass spectroscopy (LC/MS). The result of the analysis of the co-primary endpoint, maintenance of castrate testosterone levels from Day 57 to Day 337, using testosterone levels derived from the immunoassay differs markedly from the result using testosterone levels derived from the assay using LC/MS. It is unclear whether the co-primary endpoints should be analyzed using the results of the immunoassay or of LC/MS.
>
>   a. Please provide your rationale for the use of testosterone levels from the LC/MS assay in your primary analyses. Please compare the testosterone assay used in your primary analysis to the methods used to assay testosterone levels in your own licensure applications, in the licensure applications of others and in published articles.
>   b. Please provide references to support your contention that the LC/MS method is preferred for the assay of hypogonadal testosterone levels. This should include a comparison of the intra-assay and inter-assay coefficient of variation using both of these assay methods.
>   c. Please provide information concerning the storage and shipment conditions used for the testosterone serum samples.

I concur that the inferior results with the testosterone immunoassay are of concern and agree with the comments/deficiencies in the CDTL Review.

8. Safety

The treatment-emergent adverse events reported in ≥ 1% of patients are shown in Table 4.

Table 1. TRELSTAR 22.5 mg: Treatment-Emergent Adverse Events Reported by ≥ 1% of Patients During Treatment

Adverse Events[1]	TRELSTAR 22.5 mg N = 120	
	N	%
Blood and lymphatic system disorders		
Anaemia	4	3.3%
Cardiac disorders		
Myocardial Infarction	2	1.7%
Endocrine disorders		
Diabetes mellitus	4	3.3%
Gastrointestinal disorders		
Constipation	5	4.2%
Diarrhoea	4	3.3%
Dyspepsia	4	3.3%
Nausea	2	1.7%
Vomiting	2	1.7%
General disorders and administration site conditions		
Oedema peripheral	6	5.0%
Fatigue	5	4.2%
Asthenia	2	1.7%
Gait disturbance	2	1.7%
Injection site bruising	2	1.7%
Injection site induration	2	1.7%
Injection site pain	2	1.7%
Malaise/Lethargy	3	2.5%
Pain	2	1.7%
Infections and infestations		
Influenza[2]	22	18.3%
Bronchitis	7	5.8%
Sinusitis	3	2.5%
Cystitis	2	1.7%
Pharyngitis	2	1.7%
Injury, poisoning and procedural complications		
Joint injury	2	1.7%
Post procedural nausea	2	1.7%
Investigations		
Prostatic specific antigen increased	4	3.3%
Metabolism and nutrition disorders		
Anorexia/Cachexia	3	2.5%
Fluid retention	2	1.7%
Musculoskeletal and connective tissue		

disorders		
Back pain	13	10.8%
Arthralgia	9	7.5%
Pain in extremity	9	7.5%
Bone pain	4	3.3%
Arthritis/Osteoarthritis	7	5.8%
Muscle spasms	3	2.5%
Myalgia	2	1.7%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Metastases to bone	2	1.7%
Nervous system disorders		
Dizziness	5	4.2%
Headache	9	7.5%
Hypoaesthesia	2	1.7%
Psychiatric disorders		
Depression	5	4.2%
Insomnia	6	5.0%
Renal and urinary disorders		
Urinary tract infection	14	11.7%
Urinary retention	6	5.0%
Hypertonic bladder/Bladder spasm	5	4.2%
Urinary incontinence	4	3.3%
Haematuria	3	2.5%
Dysuria	2	1.7%
Nocturia	2	1.7%
Reproductive system and breast disorders		
Erectile dysfunction	12	10.0%
Testicular atrophy	9	7.5%
Libido decreased	2	1.7%
Respiratory, thoracic and mediastinal disorders		
Cough	2	1.7%
Skin and subcutaneous tissue disorders		
Skin reaction	2	1.7%
Vascular disorders		
Hot flush*	87	72.5%
Hypertension	17	14.2%
Epistaxis	3	2.5%

[1] Adverse events for TRELSTAR 22.5 mg are coded using the Medical Dictionary for Regulatory Activities (MedDRA)

[2]Includes the preferred terms influenza, nasopharyngitis, and upper respiratory tract infection

Severe treatment-emergent adverse reactions in ≥ 1% of patients during treatment with TRELSTAR 22.5 mg include myocardial infarction and metastases to bone.

The proposed label has a contraindication for use in pregnancy and warnings and precautions regarding hypersensitivity reactions and potential worsening of symptoms or onset of new symptoms such as bone pain, neuropathy, hematuria, or urethral or bladder outlet obstruction due to an initial transient increase in testosterone.

The size of the safety database and the safety profile is similar to that of other GnRH agonists that have been approved.

9. Advisory Committee Meeting

This application was not taken to an Advisory Committee.

10. Pediatrics

A pediatric waiver was granted by PeRC.

11. Other Relevant Regulatory Issues

The DSI Clinical Inspection Summary stated the following.

> Two clinical site audits were conducted. Based on preliminary communication with the field investigator, there do not appear to be any significant issues of concern with respect to data integrity. The data generated from each study site appear to be valid and can be used in support of the application.

Based on their prior experience with GnRH agonists, a consult was obtained from the Division of Reproductive and Urologic Products. The DRUP responses to two questions and an additional comment are quoted below.

1. **Relevant to the medical castration rates demonstrated by the two approved Trelstar products, are the medical castration rates demonstrated in the Trelstar 22.5mg application sufficient for approval?**

Response: For the Trelstar 22.5mg analyses shown, the testosterone values used were those obtained with the LCMS method of the central laboratory in the [(b) (4)] [(b) (4)] not those obtained with the automated [(b) (4)] immunoassay used in the local central laboratory in the [(b) (4)] If one considers just the [(b) (4)] testosterone values, then the percentages of successful "achievers" and "maintainers" in the current Trelstar NDA are comparable to those

reported in the previous Trelstar applications as well as those reported for other approved products. See our Additional Comment below.

2. **The medical reviewer does not think that one isolated testosterone escape with a magnitude of > 1.735 but < 3.5 nM during the 48 week study period is clinically meaningful, since the magnitude is still considerably low as compared to the level for a confirmation of hypogonadism (< 6.9 nM or 200ng/dL). Technically, the castration cut-off of <1.735 nM or 50 ng/dL is relatively arbitrary, not well evidenced with large studies. Based on the Pub-med literature, not all patients who had successful orchiectomy had testosterone levels below 1.735 nM or 50 ng/dL. In addition, there might be other reasons for the blip observed in the patients. In the current case, the timing of the escape did not appear to relate to any incidence of adverse reactions or disease worsening in the patients. Therefore, the reviewer considers the sensitivity analysis may represent an acceptable castration rate of the new formulation, appropriate for consideration in regulatory decision-making for the product. Please comment on the phenomenon of minimum isolated testosterone escape and its clinical and regulatory relevancies.**

Response: Using the testosterone values obtained from (b) (4) there are 6 individual "non-maintainers" who had single isolated T levels > 1.735 nmol/L and two additional "non-maintainers" who had more than one T level >1.735 nmol/L. Four of these patients show an isolated "low grade" escape (T level between 1.735 nmol/L and 3.5 nmol/L). We agree that it is reasonable for clinical judgment to play a role in the assessment of these cases.

3. Additional Comment

We note that the submission contains two complete sets of testosterone data, one from (b) (4) (b) (4) immunoassay method) and one from (b) (4) (b) (4) LCMS method). On page 29 of 378 of the Clinical Study Report (CSR) for DEB the Sponsor states:

> *"Serum testosterone levels were measured in two central laboratories* (b) (4) (b) (4) (b) (4)
>
> *The local central laboratory on the* (b) (4) *[automated immunoassay,* (b) (4) *from Aug 2006, LOQ 0.35 nmol/L]) provided the Investigators with values for the daily follow-up of the patients, and these local laboratory values were also used to assess the eligibility of the patients for the study.*

However, it is known that the routine assays particularly in the hypogonadal testosterone range have poor precision. The [(b) (4)] method used by [(b) (4)] although validated, has shown a positive bias (overestimation of the testosterone values) when compared with the reference method, the liquid chromatography/tanden mass spectrometry [LC/MS], which has been validated especially for the low hypogonadal range [Reference 6]. Therefore, Debiopharm decided to have back-up samples for each testosterone sample analyzed with the more cumbersome but also more accurate LC/MS method to double-check the [(b) (4)] values. In all the analyses other than those regarding the inclusion of the patients, testosterone values obtained with the LC/MS of the central labeloratory in the [(b) (4)] were used [(b) (4)] and LC-MS/MS analyses, LOQ 0.1 nmol/L (30 pg/ml), section 16.1.10]."

While this reasonable explanation was provided in the CSR, we find nothing in the protocol or protocol amendments to this end. The Sponsor states that the [(b) (4)] assay was prone to higher T levels (due to "overestimation"), and it appears true that the T levels were higher for the [(b) (4)] data compared to the [(b) (4)] data. It is clear that an analysis of the [(b) (4)] data would show lower percentages of success for both "achieve" (perhaps 93%) and "maintain" (perhaps 82%) compared to the same analysis of the [(b) (4)] data. This issue raises several questions, but in our view, the key question is: Which assay methodology more accurately reflects a castrate T level (≤ 1.735 nmol/L)?

12. Labeling

- Proprietary name: In their consultation of 3/19/09 DMEPA objected to changing the names Trelstar Depot and Trelstar LA to Trelstar because of the potential for medication errors. In a telecon with the applicant on 4/22/09, it was agreed that the applicant could submit a revised integrated package insert that reflects information on all three strengths. The carton and container labels would also need to be revised.

- Physician labeling

  Negotiations on the physician labeling are ongoing but not complete because of the complete response action.

- Carton and immediate container labels: see issue under proprietary name.

- Patient labeling/Medication guide: none.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Complete response because of chemistry and clinical deficiencies

- Risk Benefit Assessment

Although the safety profile of this product is similar to other GnRH agonists, the risk benefit assessment is uncertain at the present time because of the inferior efficacy results with the immunoassay.

- Recommendation for Postmarketing Risk Management Activities

  None

- Recommendation for other Postmarketing Study Commitments

  None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice
7/10/2009 08:13:58 PM
MEDICAL OFFICER

Cross-Discipline Team Leader Review

Date	
From	V. Ellen Maher, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22-437
Applicant	Watson Laboratories
Date of Submission	9/12/2008
PDUFA Goal Date	7/10/2009
Proprietary Name / Established (USAN) names	Triptorelin pamoate
Dosage forms / Strength	Intramuscular sustained release/22.5 mg
Proposed Indication(s)	1. Advanced, (b) (4) Prostate Cancer
Recommended:	Complete Response

1. Introduction

Watson Laboratories submitted NDA 22-437 on September 12, 2008. The application requested approval of a new formulation and dose of triptorelin administered every 24 weeks. The application is supported by a single arm study, DEB-TRI6M-301. This study was submitted in April of 2006 and conducted from July 2006 to August 2007. The final statistical analysis plan was submitted in March 2007. There are currently two approved triptorelin formulations, one contains 3.75 mg of triptorelin and is administered every 4 week and the second contains 11.25 mg of triptorelin and is administered every 12 weeks.

This application will receive a complete response letter asking them to address the following deficiencies.

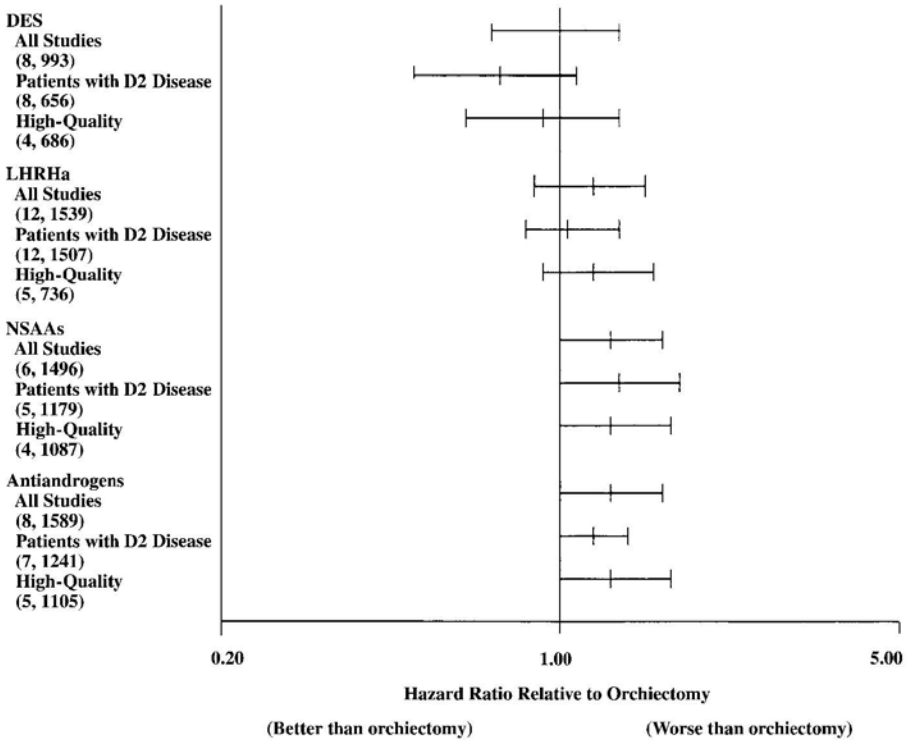
- Deficiencies were found in several Drug Master Files. Further, Debiopharm, the drug product manufacturer, has failed GMP inspection and on inspection, the responsibilities of the various contract laboratories are unclear. Additional sites may require inspection.
- The co-primary endpoints of DEB-TRI6M-301 are based on testosterone levels. The applicant has used two assay methods to measure serum testosterone. Analysis of the co-primary endpoints using the testosterone levels from the first assay results in a markedly different conclusion than the use of testosterone levels from the second assay. The difference is enough to affect the approvability of this product. It is unclear which assay results should be used in the primary analysis.

The clinical review has focused on the percentage of patients achieving and maintaining medical castration and the standards and methods used to assess this endpoint.

2. Background

GnRH (gonadotropic releasing hormone) agonists initially cause a transient surge in luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone. This surge desensitizes the LH and FSH receptors and is followed by a sustained decrease in testosterone to levels comparable to orchiectomy. Prostate cancer is a hormone responsive disease and testosterone withdrawal results in tumor shrinkage. However, patients who cannot tolerate the initial surge in testosterone (and resultant increase in tumor mass) should not receive a GnRH agonist. This includes patients at risk of spinal cord compression or ureteral obstruction. Over time, tumors can become hormone independent and they no longer respond to testosterone withdrawal. Nonetheless, portions of the tumor remain hormone sensitive and GnRH agonists are typically continued in these patients.

Because GnRH agonists act by causing a decrease in serum testosterone, the ability to induce castrate levels of testosterone has been used as a surrogate endpoint for the approval of both GnRH agonists and antagonists. Early studies compared GnRH agonists to orchiectomy or DES. Seidenfeld et al have conducted a thorough meta-analysis of these early trials (Ann Intern Med 2000 132(7):566).



They were able to show that when GnRH agonists (as a class) are compared to orchiectomy, the hazard ratio for overall survival is 1.262 (95% CI 0.915, 1.386) in favor of orchiectomy. Given this overlap in confidence intervals and increased patient acceptability, GnRH agonists have become the standard of care for the first line treatment of metastatic prostate cancer.

Several early studies also compared testosterone levels following orchiectomy to those following the administration of a GnRH agonist. In a study of leuprolide versus DES, testosterone levels fell more slowly following use of a GnRH agonist, but were actually lower than the levels detected after orchiectomy (NEJM 1984 311:1281). This is also true in studies of orchiectomy versus a GnRH agonist (Lancet 1985 2:1201). These early observations have resulted in the use of testosterone levels as a surrogate endpoint for studies on GnRH agonists and antagonists. From these early studies, the testosterone cutoff value (castrate level, non-castrate level) has been determined to be 50 ng/dL or 1.735 nM. Also from these early studies, some variability was seen in the number of patients who attained castrate testosterone levels using orchiectomy or DES. This is in part related to the use of pulpectomy rather than orchiectomy and to the inaccuracy of the assay. Therefore, in the previous approvals of GnRH agonists and antagonists have permitted a small percentage of patients to have non-castrate testosterone levels at a limited number of time points.

The pivotal study in this application DEB-TRI6M-301 used two methods to measure testosterone levels, an immunoassay and liquid chromatography/tandem mass spectroscopy (LC/MS). The protocol stated that levels would be measured centrally, but did not state what method would be used. It is unclear whether the co-primary endpoints should be calculated using the immunoassay or LC/MS. The immunoassay has a lower limit of quantitation (LLQ) of 0.35 nM (10.1 ng/dL) while the LC/MS method has a lower limit of 0.105 nM (3.0 ng/dL). The coefficient of variation of these two methods is similar. Approved GnRH agonists have used assays with a LLQ of 3 ng/dL. Eligard used a protein extraction followed by a radioimmunoassay. This method had a 15% inter and intra-assay variability and a lower limit of quantitation of 3 ng/dL. Lupron used chromatography followed by a radioimmunoassay. The LLQ was 3 ng/dL and the coefficient of variation is not available. Previous Trelstar approvals have used a ^{125}I-radioimmunoassay with a LLQ of 0.2 nM (5.8 mg/dL). The coefficient of variation is not available for this assay.

3. CMC/Device

A complete response letter will be issued for this application due to unresolved CMC issues. Major deficiencies include the following.

1. Deficiencies were found in Drug Master Files (b) (4) (drug substance), 8084 (water for injection syringe), and (b) (4) (release polymer).
2. Debiopharm, the drug product manufacturer, has failed GMP inspection.
3. The responsibilities of the proposed manufacturing and control sites and the various contract laboratories were found to be unclear or incorrect by the inspectors. Additional sites may require inspection.

Please see the CMC review for additional information concerning these deficiencies. Please see the DSI Review for complete information concerning the facilities inspections.

Triptorelin pamoate is a synthetic decapeptide agonist of GnRH. Triptorelin substitutes a different D amino acid at position 6, increasing resistance to cleavage by proteolytic enzymes and prolonging the half life when compared to native GnRH. Triptorelin is formed into

microgranules (b) (4) The 24 week formulation administers (b) (4) To administer the investigational product, lyophilized powder is dissolved in 2 mL water for injection and the product is administered intramuscularly every 24 weeks. The product may be administered using the Mixject device (K963583). The composition of Trelstar 22.5 mg is shown below.

Commercial Formulation-per vial

Triptorelin pamoate		(b) (4)
Poly(d,l lactide-co-glycolide)	(b) (4)	
Poly(d,l-lactide co-glycolide)	(b) (4)	
Mannitol		
Carboxymethylcellulose sodium		
Polysorbate 80		

4. Nonclinical Pharmacology/Toxicology

Limited nonclinical pharmacology/toxicology studies were conducted with the 24 week formulation of triptorelin pamoate. This included PK/PD studies of various 24 week formulations of triptorelin pamoate. Local toxicity with the 24 week formulation was not assessed.

Studies of acute and chronic toxicity, genotoxicity, mutagenicity, reproductive toxicity, and local tolerance were included in NDA 20-715, triptorelin 3.75 mg/monthly. Briefly, triptorelin pamoate was not mutagenic in the Ames assay or in CHO cells. However, pituitary tumors and sarcomas were found following long term animal exposure. Further, triptorelin is considered Pregnancy Category X. Male fertility has not been assessed in an animal model.

5. Clinical Pharmacology/Biopharmaceutics

The effect of triptorelin on drug metabolizing enzymes is unknown. Triptorelin is metabolized in the tissues and plasma and is eliminated by both the kidneys and liver. Exposure is increased in patients with moderate to severe renal disease and in those with liver disease. Elimination is delayed in the elderly. This is thought to be due to the decrease in creatinine clearance that occurs with age. In an elderly population with prostate cancer, the Cmax of the 24 week formulation is 44.1 ng/mL and the AUC 112 ng·h/mL. A QT study has not been performed and an increase in arrhythmias (beyond that expected in an elderly population) has not been seen.

6. Clinical Microbiology

See the CMC review.

7. Clinical/Statistical- Efficacy

This application is supported by a single clinical trial, DEB0TRI6M-301, in which patients received 2 doses of triptorelin 22.5 mg every 24 weeks. This study was submitted in April of 2006 and completed at 13 centers in the Republic of South Africa from July 2006 to August 2007. Prior to this, the applicant conducted a study (N=10) using a different formulation of triptorelin intended for administration every 24 weeks. This study failed to meet its endpoint. The applicant then conducted a second study (N=24; 8 per formulation) using 3 different formulations of triptorelin. One of these formulations was chosen for use in DEB-TRI6M-301. DEB-TRI6M-301 recruited patients with pathologically confirmed adenocarcinoma of the prostate who had locally advanced disease, metastatic disease, or a rising PSA after primary therapy. Patients entering this study had a baseline testosterone level > 5 nM. Patients could not receive hormonal therapy for prostate cancer within 6 months of entry, 5-α-reductase inhibitors within 2 months of entry, and medications which could affect the metabolism and/or secretion of androgenic hormones (ketoconazole, etc.) at the time of entry. Triptorelin 22.5 mg was administered intra-muscularly on Days 1 and 169. Testosterone levels were obtained monthly and PSA was collected every 3 months.

Patient Disposition

Patient Disposition[1]	
Patient Disposition	Triptorelin 22.5 mg N = 120
Patients Enrolled	120
Patients Who Received Study Drug	120
Completed the Study	115
Discontinued	5
Death	3
Lost to Follow Up 01602	1
Patient Decision 13606	1

[1]This table is derived from the primary review.

Triptorelin 22.5 mg was administered IM to 120 patients on Day 1. One patient died on Day 85 and triptorelin 22.5 mg was administered to 119 patients on Day 169. The 3 patients who died on study and the 2 who discontinued are discussed in the safety section. All had castrate testosterone levels at their last assessment.

Disease Characteristics

The table below provides the baseline disease characteristics of the 120 patients enrolled in DEB-TRI6M-301. The median age of these patients was 69.9 years and 64.2% were white, 22.5% black, and 13.3% colored.

Baseline Disease Characteristics[1]	
Baseline Characteristic	N = 120
Disease Stage	
Metastatic Disease	10 (8%)
Locally Advanced Disease	76 (63%)
Rising PSA After Definitive Therapy	34 (28%)
Median PSA (25-75)	20.1 ng/dL (5.8-59.2)
Prior Therapy	
Surgery	57 (47.5%)
Radiation Therapy	20 (16.7%)
Hormonal Therapy	27 (22.5%)

[1]This table is derived from the primary review.

Note that only 8% of patients had metastatic disease. Also note that 23 patients had a normal PSA (primarily patients with locally advanced disease) at study entry. While these findings should not affect the primary endpoints, castrate testosterone levels, it is clear that the study was not conducted in the indicated population.

Primary Endpoint

The study was designed with two co-primary endpoints. These are the percentage of patients achieving castrate levels of testosterone ($\leq$ 1.735 nM) at Day 29 and the percentage maintaining castrate levels of testosterone from Day 57 to Day 337. The protocol planned to perform an exact binomial estimate at Day 29 and to use a survival analysis to estimate the percentage of patients maintaining castrate testosterone levels from Day 57 to Day 337. The statistical analysis plan stated that an exact binomial estimate would be performed at Day 29 and that the percentage of patients maintaining castrate levels of testosterone would be determined in assessable patients. Assessable patients were defined as "the total number of all patients having values at all visits and all patients having missing data according to the criteria a), c), d), and e) mentioned previously." Criteria a-e for the handling of missing data are as follows.

a) In patients escaping castration level at a certain visit, subsequent missing data is irrelevant.
b) Patients maintaining castration level up to a certain visit with missing data afterwards (drop out due to non-drug related reasons) will be excluded from the analysis.
c) Patients maintaining castration level up to a certain visit with missing data afterwards (dropout due to drug related reasons) will be treated as having escaped the castration level (failure).

d) Missing data between 2 visits where castration levels were maintained will be handled as missing for that particular visit, and considered as maintaining the castration level.
e) Two consecutive missing data points between two visits where castration levels were maintained will be handled as missing and the patient will be considered as having escaped the castration level at those visits.

Both the original protocol and the statistical analysis plan stated that the primary analysis would be performed on the intent-to-treat and the per protocol population (one was not considered primary). In the protocol the intent to treat population was defined as all patients with laboratory values on Day 29. In the statistical analysis plan, the intent to treat population was defined as all patients assigned to treatment. The per protocol population excluded patients with major protocol violations.

The applicant used two different assay methods to assess testosterone levels. Study samples were centrifuged at the site and shipped to (b) (4) at ambient temperature. Samples could be held at ambient temperature for up to 5 days. Samples were then aliquoted into a 6 mL transfer tube and a 1.8 mL back up tube which was stored at -70^0 C. Testosterone was considered stable at -20^0 or -70^0 C for 6 months. Testosterone levels were run at (b) (4) and reported to the site. In the (b) (4) assay, testosterone was first released from endogenous binding proteins and then a competitive immunoassay was performed in which serum testosterone competed with acridinium ester labeled testosterone for polyclonal rabbit anti-testosterone antibody. The analytic range of this assay was 0.35-52.1 nmol/L with a lower limit of quantitation of 0.35 nmol/L. The within run coefficient of variation (CV) varied from 2.3-6.2% and the between run CV from 1.4-4.7%. The applicant also used a second method to quantitate serum testosterone. These assays were run by (b) (4) We have no information on shipping conditions, but at (b) (4) the samples were stored at -20^0 C. This assay involved protein precipitation and solid phase extraction followed by liquid chromatography and tandem mass spectroscopy (LC/MS). With this method, the lower limit of quantitation was 0.105 nmol/L and the CV was 8.58% and 8.81%. The assays at (b) (4) were performed over the entire period of study conduct. The applicant has based their final study report on the results of the (b) (4) assay. There is evidence to support their statements that the LC/MS method is more accurate at low levels of testosterone (Clin Chim Act 2007 386 (1-2):12, J Clin Endocrinol Metab 2004 89(2):534).

The table below presents the number of patients achieving castrate testosterone levels on Day 29 using the results of the [redacted] immunoassay and the [redacted] LC/MS assay. The protocol pre-defined a castrate testosterone level as < 1.735 nM.

Day 29

Testosterone Levels on Day 29	
Testosterone	Triptorelin 22.5 mg N = 120
Percent with Testosterone Levels ≤ 1.735 nM (50 ng/dL)	
LC/MS Assay	117/120 (97.5%)
Immunoassay	112/120 (93.3%)
Median Testosterone (25-75)	
LC/MS Assay	0.570 nM (0.428-0.791)
Immunoassay	0.97 nM (0.80-1.35)

Three patients did not achieve castrate levels of testosterone at Day 29. This includes two patients (02601, 03606) who did not have castrate levels on Day 29, but had castrate levels at the next assessment (Day 57) and all subsequent assessments. It also includes patient 11613 who did not achieve castrate levels of testosterone until after the second injection on Day 197.

Day 57-337

The tables below presents the number of patients maintaining castrate testosterone levels from Day 57 to Day 337. The first table uses a Kaplan-Meier method as specified in the original study protocol. The second table uses the exact binomial method specified in the Statistical Analysis Plan.

Five patients did not complete the study and their data can be handled in a variety of ways. These include patients 01602, 05612, 05614, 11615, and 13606. Eight patients did not maintain castrate testosterone levels using the LC/MS assay and 23 patients did not maintain castrate testosterone levels using the immunoassay.

In this analysis, the 5 patients who did not complete the study maintained castrate testosterone levels in the LC/MS assay and 4 patients (except 11615) maintained castrate levels in the immunoassay. The per protocol population, N = 115, removes a further 5 patients with major protocol violations (06609, 07602, 08609, 09607, and 10602).

This table uses the Kaplan-Meier method as specified in the original protocol.

Kaplan-Meier Estimate: Maintenance of Testosterone Levels Day 57 to Day 337		
Percent Maintaining Castrate Testosterone Levels	Triptorelin 22.5 mg ITT, N = 120	Triptorelin 22.5 mg PP, N = 115
LC/MS Method (95% CI)	93.3% (88.7%; 97.8%)	93.0% (88.3%; 97.7%)
Immunoassay (95% CI)	91.6% (84.9%; 95.4%)	97.4% (94.5%; 100%)

In the table below, the 5 patients who did not complete the study are removed from the analyses using the LC/MS method. In the analyses using the immunoassay, 4 of the 5 patients are removed since patient 11615 had a non-castrate testosterone level using the immunoassay. The per protocol analyses remove a further 5 patients who had major protocol violations.

This table estimates the percentage of patients who maintained castrate testosterone levels using the method outlined in the statistical analysis plan, as interpreted by the sponsor.

Binomial Estimate: Maintenance of Testosterone Levels Day 57 to Day 337		
Percent Maintaining Castrate Testosterone Levels	Triptorelin 22.5 mg N = 115	Triptorelin 22.5 mg N = 110
LC/MS Method (95% CI)	93.0% (86.8%; 97.0%)	92.7% (86.2%; 96.8%)
	Triptorelin 22.5 mg N = 116	Triptorelin 22.5 mg N = 111
Immunoassay (95% CI)	80.2% (72.0%; 87.0%)	79.3% (71.0%; 86.0%)

The table below provides exact binomial estimates using a variety of imputation methods. Given the large number of non-castrate testosterone levels with the immunoassay, the sensitivity analyses, which involved the data handling for the 5 patients who discontinued, were not conducted using the results of the immunoassay.

Sensitivity Analyses: Maintenance of Testosterone Levels Day 57 to Day 337				
	S1 N = 120	S2 N = 115	S3 N = 120	S4 N = 120
Percent Maintaining Testosterone Levels $\leq$ 1.735 nM				
LC/MS	112/120 (93.3%)	107/115 (93.0%)	115/120 (95.8%)	107/120 (89.2%)

- S1-This population uses the last observation carried forward to account for the 5 patients who discontinued prior to Day 337.
- S2-This population removes the 5 patients who discontinued prior to Day 337 from the analysis. GnRH agonists have, typically, been analyzed in this way.
- S3-This is a best case analysis in which the 5 patients who discontinued prior to Day 337 are considered a success and patients 11606, 06608, and 13613 who had an isolated elevation in testosterone are also considered a success.
- S4-This is a worst case analysis in which the 5 patients who discontinued are considered failures.

Finally, testosterone levels, using both the immunoassay and the LC/MS methods, are shown below. The first portion of the table shows the patients whose testosterone levels were elevated using the LC/MS method. In all but 2 cases, the testosterone level is also elevated using the immunoassay. The table includes only monthly testosterone levels and does not include the additional levels drawn in patients who participated in the pharmacokinetics studies. Note that patient 08604 had a castrate LC/MS testosterone level on Day 169, but an elevated level on Day 171 (after triptorelin 22.5 mg on Day 169). Day 171 levels were only drawn in patients participating in the pharmacokinetic studies.

The second portion of the table shows the patients whose testosterone levels were only elevated using the immunoassay. Note that patient 11611 participated in the pharmacokinetics studies and had a castrate testosterone level on Day 169, but an elevated level on Day 171. While the patients in this portion on the table only had elevated levels using 1 of the 2 assay methods, elevations tended to cluster at Day 169 and Day 337.

Testosterone Levels Using the (b) (4) Immunoassay and the (b) (4) Liquid Chromatography/Mass Spectroscopy Methods																										
Patient #	Day 1		Day 29		Day 57		Day 85		Day 113		Day 141		Day 169		Day 197		Day 225		Day 253		Day 281		Day 309		Day 337	
	I[1]	MS[1]	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS
Elevated by the (b) (4) Method																										
04602	26.19	22.423	1.76	1.19	1.38	.624	1.49	.841	1.63	.663	1.42	.546	2.08	.374	1.73	.902	1.76	.797	1.49	.656	1.04	.769	1.8	.836	41.8	42.047
06604	11.8	13.112	1.28	.774	.69	.398	.83	.339	.87	.385		.393	1.49	1.938	.66	.176	.76	.219	.66	.338	.83	.471	.97	.338	.97	.382
06608	13.42	14.195	1.11	.668	.45	.333	.8	.451	4.5	6.119	.52	.252	1.04	.373	.8	.456	1.07	.272	.62	.442	.69	.724	.76	.275	1.11	.388
08604	15.5	18.867	.97	.828	.87	.611	1.21	.59	1	.365	.59	.307	1.63	.753	.66	.377	.62	.613	1.14	.49	.8	.664	1.31	.683	1.25	.801
10601	18.44	18.446	.87	.559		.233		.295	.76	.256	.73		.9	.282	.66	.201	1.14	.61	3.46	5.201	8.48	8.98	8.82	8.311	13.22	11.436
11606	11.56	18.522	1.63	1.30	2.77	2.333	.83	.447	1.45	.756	1	.316	1.76	.551	1.04	.629	1.35	.699	1.38	.658	1.07	.894	1.73	.652	1.73	1.077
11613	22.21	17.545	12.77	14.6	15.5		13.74	6.745	14.53	11.028	12.978	7.091	14.22	7.242	1.8	.763	2.25	.862	1.8	.55	1.9	.984	1.7	.649	1.94	.679
13613	27.26	27.553	1.73	1.11	1.25	.706	1.35	.46	3.25	3.354	1	.469	1.31	.648	.93	.522	1.73	.653	1.11	.463	1.59	1.553	.59	.486	1.63	.792
Elevated by the (b) (4) Method																										
01604	16.71	16.811	1.18	.77	.93	.352	1.11	.464	1.35	.998	1.59	.347	1.11	.464	1.59	.493	1.31	.262	1.49	.621	.66	.349	1.38	.886	1.76	.415
05606	9.58	7.978	2.53	.739	2.32	.614	2.04	.573	2.08	.874	2.35	.801	1.87	.233	1.66	.46	1.49	.338	2.01	.589	1.52	.442	1.94	1.245	1	.244
08602	9.24	13.86	.9	.484	1	.512	1.56	.576	1.11	.61	1.04	.245	1.49	.503	.52	.283	1.35	.504	1.7	.487	1.42	.83	1.94	.377	1.59	.685
08605	24.6	25.852	2.46	1.22	1.35	.558	1.56	.416	1.11	.536	1.7	.208	3.18	1.33	.83	.169	1.38	.554	1.49	.752	2.01	1.347	.87	.658	1.66	.602
10603	16.68	15.739	1.14	.557	1.14	.312	1.31	.292	1	.209	1.25	.228	1..25	.392	1	.195	1.13	.387	.83	.513	.69	.167	2.11	.315	1.28	.271
11609	13.74	17.412	1.28	.543	.8	.341	.8	.304	.76	.345	1.14	.214	1.76	.354	.83	.293	1.11	.299	.97	.202	1.04	.602	1.18	.298	.8	.526
11611	27.61	22.481	.8	.892	.55	.284	1.11	.435	1.07	.892	.59	.226	.76	.393	.83	.394	.93	.262	.73	.429	.8	.433	.62	.377	1.18	.527
11614	19.65	16.305	1.49	.568	1.21	.456	1.52	.417	1.35	.586	1.04	.22	1.76	.391	1.31	.392	1.52	.268	1	.289	.97	.539	.87	.582	1.35	.64
12603	17.51	16.34	1.28	.671	1.28	.748	1.56	.689	1.63	1.029	2.84	.674	1.8	.791	2.25	.845	2.25	.945	1.66	1.075	1.66	.952	1.87	1.414	2.15	.875
13601	20.03	25.369	1.52	.97	1.49	.666	.73	.46	1.45	.48	1.28	.646	1.94	.512	1.21	.616	.8	.446	1.73	.575	1.42	.762	1.56	.67	1.56	.505
13602	11.63	14.418	1.45	.75	1.11	.479	.69	.477	1.28	.67	.8	.456	1.8	.683	.97	.383	1.04	.916	1.11	.441	.66	.818	1.42	.663	.83	.698
13609	12.39	20.382	1.63	.855	1	.437	1.11	.186	1.45	.624	1.42	.751	1.87	.396	.69	.336	1.18	.511	1.31	.429	1.45	1.059	1.25	.426	1.11	.66
13612	16.57	20.484	1.21	.498	1.21	.559	1.18	.439	1.25	.722	1.87	.414	1.7	.391	1.14	.577	1.25	.485	1.38	.501	1.25	.726	1.63	.257	1.7	.499
13616	15.78	16.539	1.66	.875	.73	.344	1.31	.239	1.28	.585	1.63	.447	1.56	.726	1.18	.712	.76	.489	1.42	.998	1.76	1.34	1.11	1.118	1.59	.734
13618	17.92	19.017	1.49	.705	1.31	.464	1.31	.421	1.28	.305	1.45	.305	1.56	.401	.8	.286	.87	.276	1.45	.504	1.8	1.074	1.35	.331	1.35	.436

[1]I-Immunoassay; MS-Liquid Chromatography Tandem Mass Spectroscopy

Secondary Endpoints

The findings above should be considered in terms of the effect of these non-castrate testosterone levels had on the underlying disease. However, the only estimate of disease burden recorded by the applicant was the PSA. The 2 patients who discontinued due to progressive disease, but with castrate testosterone levels using the LC/MS assay had an elevated PSA prior to discontinuation. Among the 8 patients with non-castrate testosterone levels from Day 57 to Day 337 using the LC/MS assay, 2 had an elevated PSA (04602, 10601) at Day 337. In both patients this occurred after an initial decrease in PSA. Among the 23 patients who had at least 1 testosterone level > 1.735 nM using the immunoassay, 4 had an elevated PSA. Two achieved a PSA < 4 ng/mL, but later PSAs were > 4 ng/mL and 2 never achieved a PSA < 4 ng/mL (although PSA was trending downward).

Conclusion

Using the (b) (4) LC/MS assay, the co-primary endpoints are in the range of previous approvals for GnRH agonists. However, using the results of the (b) (4) immunoassay, the co-primary endpoints are well below the range of previous approvals for GnRH agonists. The LC/MS assay is better able to detect hypogonadal testosterone levels and its ability to detect hypogonadal testosterone levels is in the range of previous approvals. The applicant should be asked to address the use of the two different assays and to provide a compelling rationale for the use of the LC/MS results (as used in their final study report).

8. Safety

The triptorelin 22.5 mg safety database includes only 128 patients. One hundred and twenty patients were treated on DEB-TRI6M-301. Eight patients on DEB-TRI6M-201 received the formulation taken forward into study 301. The analyses below focus on the 120 patients treated under DEB-TRI6M-301. While this database is small, the adverse events seen with triptorelin 22.5 mg are consistent with those seen with the 4 week (3.75 mg) and 12 week (11.25 mg) formulations and no new safety signals were seen. This database was, therefore, considered acceptable.

Deaths

There were 3 deaths on study. Patient 11615 died on Day 85 due to a cardiac arrest. He had an extensive history of cardiovascular disease and castrate testosterone levels at the time of his death.

Patients 05612 and 05614 are very similar. Both had newly diagnosed prostate cancer and both died of progressive disease 8 and 9 months after diagnosis. Their short course is unusual. Both patients were diagnosed with T3NXMX disease in June 2006 and underwent radical prostatectomy. Both entered the study in August 2006. At the time of entry, both had markedly elevated PSAs (684 μg/L-05612, 446 μg/L-05614). This suggests that both patients

had widely metastatic disease at the time of entry. Both attained castrate testosterone levels that were initially accompanied by a decrease in PSA. However, both presented on approximately Day 169 with an increase in bone pain, castrate testosterone levels, and a rising PSA. Both died at their homes.

No adverse events led to discontinuation.

Serious Adverse Events

Fourteen patients had a serious adverse event on study. Serious adverse events related to the patient's prostate cancer and to their response to triptorelin 22.5 mg include hematuria (1), obstructive uropathy (1), and bone metastases/metastatic prostate cancer (2).

- Patient 03606 had obstructive uropathy at the time of study entry. He did not achieve castrate testosterone levels until Day 57 and required a TURP for the treatment of obstruction.
- Patient 11605 developed hematuria after replacement of his supra pubic catheter.
- Patient 08609 developed worsening pain despite castrate testosterone levels and underwent a bilateral orchiectomy and radiation therapy.
- Patient 11621 had castrate testosterone levels but developed bone pain and a worsening bone scan.

Adverse Events

Grade 3 Adverse Events

Events were graded as mild, moderate, or severe by the investigator. Twenty-four grade 3 events were reported in 17 patients. These are listed in the table below. These events are consistent with the known effect on androgen deprivation therapy as well as the general condition of elderly patients with prostate cancer.

Grade 3 Adverse Events	
Adverse Event	Triptorelin 22.5 mg N = 120
Cardiac Disorders	
Myocardial Infarction	2
Atrial Flutter	1
Infections	
Herpes Zoster	1
Pneumonia	1
Injury, Poisoning and Procedural Complications	
Soft Tissue Injury	1
Metabolism and Nutrition Disorders	
Anorexia	1
Dehydration	1
Musculo-Skeletal and Connective Tissue Disorders	
Arthritis	1
Back Pain	1
Bone Pain	1
Neoplasms	
Prostate Cancer	3
Metastases to Bone	2
Penis Carcinoma	1
Nervous System Disorders	
Diabetic Neuropathy	1
Psychiatric Disorders	
Loss of Libido	1
Renal and Urinary Disorders	
Obstructive Uropathy	1
Urinary Retention	1
Reproductive System and Breast Disorders	
Erectile Dysfunction	1
Vascular Disorders	
Hot Flush	1

All Adverse Events

Adverse events which occurred in $\geq$ 10% of patients are shown in the table below. These events are consistent with the known effects of androgen deprivation therapy. Further information on elevated transaminases is included under the analysis of laboratory events below.

Adverse Events in ≥ 10% of Patients[1]	
Adverse Reaction	Triptorelin 22.5 mg N = 120
Hot Flush	87 (72.5%)
Weight Gain	41 (36.3%)
Increase in Hepatic Transaminase	23 (19.2%)
Influenza	20 (16.0%)
Hypertension	17 (14.2%)
Back pain	13 (10.8%)
Erectile Dysfunction	12 (10.0%)
Urinary Tract Infection	11 (10.0%)

[1]Derived from the primary review

Local Reactions

Patients were seen on the day of injection and observed for 4 hours after each injection. During the 4 hour observation period redness (1), local pain (4), swelling (4), bruising (2) and induration (2) were reported. Patients were then seen 28 days after injection. Examining adverse events over the entire reporting period, the following injection site reactions were reported; bruising (2), erythema (1), induration (2), pain (2), pruritus (1), and swelling (1). The gap between injection and the next study visit may have resulted in under reporting of local reactions.

Laboratories

A CBC and chemistries were obtained at baseline, the day of injection, and at the last study visit. The laboratory values were graded by the primary reviewer using the NCI CTCAE v 3.0 and the values in the table include all laboratories with a grade shift on study. Although an increase in hepatic transaminases is listed as a common adverse event, only one patient had a documented grade 2 ALT. This value later returned to baseline.

On Study Laboratories with a Grade Shift[1]				
Laboratory (%)	Triptorelin 22.5 mg N=120			
	All Grades	Grade 1/2	Grade 3	Grade 4
Increase in ALT/AST	23 (19%)	23* (19%)	0	0
Decrease in Hemoglobin	25 (21%)	23 (19%)	2 (2%)	0
Hyperglycemia	30 (25%)	27 (23%)	3 (3%)	0
Increase in Creatinine	11 (9%)	11 (9%)	0	0

[1]Derived from the primary review

Post-Marketing Safety Reports

The applicant provided an update on the adverse events voluntarily submitted for the approved product. These events are difficult to interpret since the reporting requirements are not specified and since the number of treated patients is unknown. Anaphylaxis was reported in 3 patients receiving triptorelin. This should be added to the product label.

9. Advisory Committee Meeting

An Advisory Committee meeting will not be held to discuss the 24 week formulation of triptorelin pamoate 22.5 mg. A large number of GnRH agonists and antagonists have been previously approved and the standards set for their approval.

10. Pediatrics

A pediatric waiver was granted for this indication, advanced prostate cancer.

11. Other Relevant Regulatory Issues

No irregularities were found during the clinical inspections of two sites in South Africa. The financial disclosures were evaluated by the primary reviewer and found acceptable.

12. Labeling

Please see primary clinical review for an overview of the package insert and the CMC review for information on carton and container labeling.

13. Recommendations/Risk Benefit Assessment

- Recommendation

Both CMC and clinical deficiencies were identified during application review and a complete response letter will be sent to the sponsor asking them to address these issues.

- Risk Benefit Assessment

This product will provide increased patient and physician convenience by extending the interval between treatments. Its adverse event profile is consistent with that seen in previous studies of GnRH agonists in prostate cancer. The risks of this product are primarily related to its efficacy. Using the analyses specified in the Statistical Analysis Plan, castrate testosterone levels were achieved in 93% (86.8%; 97.0%) of patients using the LC/MS testosterone levels. This is consistent with previous GnRH approvals. However, castrate testosterone levels were achieved in 80.2% (72.0%; 87.0%) using the immunoassay testosterone levels. Other approved products are available for use at 24

week intervals for this indication. In order to not subject patients to a less efficacious product, it will be important to establish that this product provides comparable efficacy prior to its approval.

- Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are planned at this time. Additional consideration will be given to postmarketing risk management activities following the applicant's response to our Complete Response Letter.

- Recommendation for other Postmarketing Study Commitments

No post-marketing commitments or requirements are recommended at this time.

- Recommended Comments to Applicant

1. For Study DEB-TRI6M-301, you have provided testosterone levels using two difference assay methods, immunoassay and liquid chromatography/tandem mass spectroscopy (LC/MS). The result of the analysis of the co-primary endpoint, maintenance of castrate testosterone levels from Day 57 to Day 337, using testosterone levels derived from the immunoassay differs markedly from the result using testosterone levels derived from the assay using LC/MS. It is unclear whether the co-primary endpoints should be analyzed using the results of the immunoassay or of LC/MS.

    a. Please provide your rationale for the use of testosterone levels from the LC/MS assay in your primary analyses. Please compare the testosterone assay used in your primary analysis to the methods used to assay testosterone levels in your own licensure applications, in the licensure applications of others and in published articles.
    b. Please provide references to support your contention that the LC/MS method is preferred for the assay of hypogonadal testosterone levels. This should include a comparison of the intra-assay and inter-assay coefficient of variation using both of these assay methods.
    c. Please provide information concerning the storage and shipment conditions used for the testosterone serum samples.

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/s/

Virginia E Maher
7/2/2009 11:59:20 AM
MEDICAL OFFICER

Robert Justice
7/7/2009 06:32:29 PM
MEDICAL OFFICER

Clinical and Statistical Reviews

Application Type	NDA
Submission Number	22-437
Submission Code	None
Letter Date	Sep. 12, 2008
Stamp Date	Sep. 29, 2008
PDUFA Goal Date	July 12, 2009
Clinical Reviewer Name	Yangmin M Ning M.D., Ph.D.
Clinical Team Leader Name	Virginia Ellen Maher, M.D.
Statistical Reviewer Name	Yu-Ling Chang, Ph.D.
Statistical Supervisor Name	Shenghui Tang, Ph.D.
Review Completion Date	June 26, 2009
Established Name	Triptorelin
Proposed Trade Name	TRELSTAR® 22.5 mg
Therapeutic Class	Gonadotropin releasing hormone receptor agonist
Applicant	Watson Pharmaceuticals
Priority Designation	Standard Review

Formulation:	Suspension for intramuscular injection
Dosing Regimen:	The suspension of 22.5 mg is recommended to be administered intramuscularly every 24 weeks
Proposed Indication:	For palliative treatment of advanced prostate cancer
Intended Population:	Adult patients with prostate cancer in whom orchiectomy or estrogen administration is either not indicated or unacceptable

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Commonly Used Abbreviations in the Review

Abbreviation	**Full Term**
ADT	Androgen Deprivation Therapy
AR	Adverse Reaction
CRF	Case Report Form
DRAR	Drug-Related Adverse Reaction
EKG	Electrocardiogram
PP	Per Protocol
GnRH	Gonadotropin Releasing Hormone
ITT	Intent-to-Treat
LH	Luteinizing Hormone
MedDRA	Medical Dictionary for Regulatory Activities
PSA	Prostate Specific Antigen
PK	Pharmacokinetics
SAE	Serious Adverse Event
TEAE	Treatment-Emergent Adverse Event

1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Watson Pharmaceuticals submitted the TRELSTAR (triptorelin 22.5 mg) application, NDA 22-437, on September 12th, 2008, and requested marketing approval of this new formulation for the treatment of patients with advanced prostate cancer.

Based on the data submitted and the analysis results obtained from our review, we found that the application has provided adequate evidence to support the efficacy and safety of the new triptorelin 22.5 mg formulation for use in the intended patient population at the proposed dosing schedule. Therefore, the reviewers recommend regular approval of the new formulation for the treatment of patients with advanced prostate cancer, provided that all issues raised by the other review disciplines have been addressed satisfactorily.

It is necessary to point out that approximately 28% of patients in the key study supporting this NDA had biochemical relapse only disease with no evidence of metastasis. Since the disease setting generally is not recognized as advanced disease and since androgen deprivation in this setting has not been proven beneficial, the inclusion of these patients in the developmental study does not constitute a basis for or implied use of the new formulation in patients with biochemical relapse only disease in routine practice.

1.2 Risk Benefit Analysis

The risk benefit analysis for the new formulation of triptorelin 22.5 mg administered every 24 weeks is based on the safety and efficacy of the formulation demonstrated in Study DEB-TRI6M-301. This was an open-label, single-arm, multicenter phase 3 trial of the triptorelin pamoate 22.5 mg formulation in patients with advanced prostate cancer. Treatment was administered intramuscularly on Days 1 and 169 and patients were monitored every 28 days, for both efficacy and safety, until Day 337. One hundred twenty (120) patients were enrolled in the study. Seventy-two percent (72%) of patients had metastatic or locally advanced disease and 28% had elevated PSA with no evidence of metastases following primary curative therapy.

The primary endpoints were the percentages of patients achieving (by Day 29) and maintaining (Day 57 to 337) castrate testosterone levels ≤ 1.735 nM. The results demonstrated that 97.5% (95% CI: 92.9% - 99.5%) of patients achieved medical castration by Day 29 and that 93.3% (95% CI: 88.1% - 97.3%) of the patients were able to maintain castrate levels of testosterone during the Day 57-337 period, indicating that

the triptorelin 22.5 mg formulation was efficacious in achieving and maintaining castrate levels of testosterone.

The key secondary efficacy endpoints included 1) the percentage of patients with an increase of serum ≤ LH 1.0 IU/L 2 hours after study drug injection on Days 1 and 169, 2) the percentage of patients (in a subset of 60 patients) who had testosterone levels above 1.735 nM within 48 hours after the second injection on Day 169 (known as the "acute-on-chronic" phenomenon), and 3) changes in PSA from baseline throughout treatment. LH analysis showed that 98.3% of patients had an LH increase of ≤ 1.0 IU/L after the 2nd injection on Day 169, but no patients had an increase of such low magnitudes on Day 1. This reflects the changes in pituitary sensitivity known to result from repeat dosing with a GnRH agonist. The percentage of patients with testosterone levels > 1.735 nM after the 2nd dose was 3.33% (2/60) in the subset of 60 patients. Both patients returned to castrate levels of testosterone in follow-up monitoring. Decreases in PSA were observed in the majority of patients with mean declines, compared to baseline, ranging between 82.3% and 90.0% at various time points, consistent with the expected responsiveness of the disease to castration in the studied patients.

The safety analysis shows that the commonly observed adverse reactions with a frequency of ≥ 10%, regardless of causality, included hot flushes, weight increases, influenza, hypertension, back pain, and erectile dysfunction. The commonly detected laboratory abnormalities with a frequency of ≥ 10% were anemia, hyperglycemia, and increases in hepatic transaminases. The majority of these laboratory abnormalities were mild to moderate and reversible. In addition, 7% of patients had injection site reactions (e.g. bruising, erythema, swelling or induration).

Overall, the new formulation appears well tolerated. No new safety signals were revealed when the adverse event profile of the new formulation was examined against that of the two approved triptorelin formulations. The majority of the observed or detected adverse reactions are consistent with the known toxicities of androgen deprivation. Notably, three patients had cardiac ischemic events during the study and one of them died of myocardial infarct. Although attribution to the study product cannot be excluded, the interpretation of causality is confounded by the single-arm design of the study and the preexisting cardiovascular conditions in these patients. With the recent retrospective evidence that suggests an increased risk of cardiovascular mortality with androgen deprivation (see Section 2.4), the three cases do not necessarily represent a safety signal for triptorelin per se, but may represent a class effect of GnRH analogs. This highlights the necessity of appropriate use of GnRH-based androgen deprivation agents, including triptorelin, for the treatment of prostate cancer.

Taken together, the safety and efficacy results demonstrated in the study are adequate to support regular clinical use of the new formulation for palliative treatment of

advanced prostate cancer. Different from the two approved triptorelin formulations, the new formulation will be administered every 24 weeks, thereby reducing the number of injections for the convenience of both the patients and health care providers.

1.3 Recommendations for Risk Evaluation and Mitigation Strategies

None

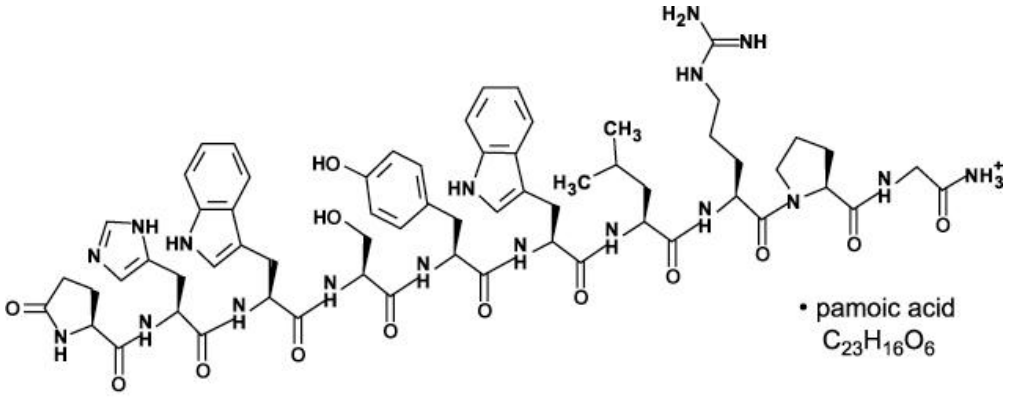
1.4 Recommendations on Post Marketing Requirements/Phase 4 Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

The active ingredient of TRELSTAR is triptorelin, a synthetic decapeptide GnRH receptor agonist analog with greater potency than the naturally occurring GnRH.
The chemical name of triptorelin pamoate is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycine amide (pamoate salt).
The empirical formula is $C_{64}H_{82}N_{18}O_{13} \cdot C_{23}H_{16}O_6$ and the molecular weight is 1699.9.
Its structural formula is shown below.



The 22.5 mg TRELSTAR product is a sterile, lyophilized biodegradable microgranule formulation supplied as a single dose vial. Its composition is shown in Table 1. To make a suspension suitable for injection, 2 mL of sterile water is added to the vial and mixed as instructed in the product labeling.

Table 1: TRESLTAR (Triptorelin 22.5 mg) Composition

Ingredients	TRELSTAR 22.5 mg
triptorelin pamoate (base units)	22.5 mg
poly-*d*,*l*-lactide-co-glycolide	182 mg
mannitol, USP	68 mg
carboxymethylcellulose sodium, USP	24 mg
polysorbate 80, NF	1.6 mg

The proposed dosing schedule for the product is TRELSTAR 22.5 mg administered as a single intramuscular injection every 24 weeks.

2.2 Tables of Currently Available Treatments for Proposed Indications

The new formulation of triptorelin 22.5 mg every 24 weeks was proposed to treat patients with advance prostate cancer. Triptorelin has been approved for the same indication in two other formulations since 2000. It works by inducing testosterone levels similar to those achieved with orchiectomy (medical castration). Between the 1940s and 1980s, castration for the treatment of prostate cancer was generally achieved by orchiectomy or by the use of synthetic estrogens. After the first GnRH agonist (leuprolide) was approved in 1985,[1] the use of GnRH analogs has become the most common approach for patients who require androgen deprivation therapy. The analogs approved for the same indication are summarized in Table 2, which includes both agonists and antagonists. Although both GnRH agonists and GnRH antagonists can lead to medical castration, they act differently within the first few weeks after initial dosing. In general, GnRH agonists induce an initial surge in serum testosterone before attaining suppression; whereas GnRH antagonists produce testosterone suppression without causing an early testosterone flare. The testosterone surge may be harmful to patients with symptomatic disease and may precipitate spinal cord compression or urinary obstruction. To minimize clinical complications associated with the surge, anti-androgen receptor drugs are used along with a GnRH agonist for the first few weeks at the beginning of treatment. In contrast, use of a GnRH antagonist would not require anti-androgen receptor drugs to prevent tumor flare phenomenon because of the lack of a testosterone surge.

Table 2: FDA-Approved GnRH Analogs for Treatment of Advanced Prostate Cancer

Class	Product Name	Year of Initial Approval
GnRH Agonist*	Leuprolide**	1985
	Goserelin	1987
	Triptorelin	2000
	Histrelin	2004
GnRH Antagonist	Abarelix	2003
	Degarelix	2008
* Products may have different formulations or delivery systems for longer drug action (up to 12 month with one administration) that were approved after their initial marketing application. ** Other leuprolide products approved after Lupron include Viadur and Eligard.		

2.3 Availability of Proposed Active Ingredient in the United States

Triptorelin 3.75 mg in a formulation administered every 4 weeks and triptorelin 11.25 mg in a formulation administered every 12 weeks have been available in the United States since 2000 and 2001, respectively.

2.4 Important Safety Issues with Consideration to Related Drugs

Adverse reactions related to GnRH analogs are generally secondary to androgen deprivation that disrupts the physiologic function of androgens. The commonly known short-term reactions are hot flushes, erectile dysfunction, increases in weight, and mild anemia. With long-term use, there is an increased risk for the development of osteoporosis and related fragility fractures.[6-7] In addition, profound changes in the metabolism of lipids and glucose may occur. This can aggravate the pathological processes of other diseases frequently seen in patients with prostate cancer and may precipitate cardiovascular morbidity.[6] Indeed, several retrospective studies, based on the different study patient populations in the US, suggest that continuous androgen deprivation therapy may be associated with an increased risk of diabetes and cardiovascular diseases such as myocardial infarction.[8-10] On the other hand, a similar study using a linked administrative database, conducted in Canada, found that 6 months of androgen deprivation was not associated with acute myocardial infarction or hypercholesterolemia, but rather associated with an increased risk of diabetes and fragility fractures.[11] Similarly, the analysis of cardiovascular mortality in the patients enrolled in RTOG 85-31, a study that compared adjuvant gorserelin plus radiation *vs.* radiation alone for locally advanced prostate cancer showed no increase in cardiovascular-related deaths after a median follow-up of 8.1 years.[12] Despite the

differences in these study results, the findings highlight the importance of appropriate use of androgen deprivation therapy. Inappropriate use in early disease settings of prostate cancer, e.g. use as primary therapy in patients with localized prostate cancer with favorable prognostic factors or in patients with PSA recurrence (without evidence of metastasis) after initial definitive primary therapy, may not benefit patients, [3-5] but conversely may increase the possibility of developing serious adverse reactions to long-term androgen deprivation, especially with the long natural history of prostate cancer from diagnosis to distant metastasis and death secondary to the disease.[13] Therefore, the safety of these products largely relates to appropriate use of GnRH analogs in patients with prostate cancer. Overall, to reduce the unnecessary toxicity of GnRH analogs, one has to examine whether androgen deprivation's benefits outweigh its risks before initiating GnRH based therapy.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The pre-submission regulatory activities with the FDA are summarized in Table 3.

Table 3: Key Regulatory Activities in Trelstar's Clinical Development

Milestone	Date	Comments related to clinical perspectives
TRELSTAR DEPOT (Triptorelin 3.75 mg)-NDA 20-715	6/15/2000	The first triptorelin formulation, administered every 4 weeks, was approved in the United States for treatment of advanced prostate cancer.
TRELSTAR LA (Triptorelin 11.25 mg)-NDA 21-288	06/29/2001	The second triptorelin formulation, administered every 12 weeks, was approved in the United States for treatment of advanced prostate cancer.
[redacted] (b) (4)		
Pre-NDA Meeting for the triptorelin 22.5 mg formulation	03/17/2008	Advice and agreements reached on the submission of the NDA supporting the new formulation.
NDA-submission for the triptorelin 22.5 mg	09/12/2008	Regular review designation was made after submission.

2.6 Other Relevant Background Information

Endpoint for Evaluation and Approval of Androgen Deprivation Products

The first GnRH agonist, leuprolide, was approved in 1985.[1] This was based on improvements in patient symptoms (e.g., pain) and tumor response as well as on biochemical evidence of leuprolide-induced medical castration in patients with symptomatic advanced prostate cancer. Since the improvements in symptoms and the tumor responses were related to the achievement of biochemical castration, it was agreed and accepted that demonstration of (achieving and maintaining) medical castration can serve as the primary endpoint for similar studies in the same patient population. Since then, other formulations of leuprolide and other GnRH analogs have been approved using the surrogate endpoint of suppression of testosterone levels to ≤50 ng/dL or 1.735 nM. The cut-off criteria reflect testosterone levels in the majority of castrated patients, but do not represent an absolute value that definitively demonstrates castration. Few patients post-orchiectomy [2] were found to have serum testosterone levels between 50 ng/dL and 200 ng/dL (the cut off for the diagnosis of hypogonodism in males). Nevertheless, sustained suppression of testosterone to the defined levels has been accepted as the established surrogate for the evaluation of products intended to treat prostate cancer through medical castration.

For the majority of approved products, medical castration was achieved and maintained in more than 90% of the patients studied. For the two approved triptorelin formulations, the castration rates that led to their approval are summarized in Table 4.

Table 4: **Medical Castration Rates Related to the Two Approved Triptorelin Products**

	Trelstar Depot* (3.75 mg) Q 4 Weeks	**Trelstar LA* (11.25 mg) Q 12 Weeks**
Castration Rate on Day 29 (95% CI)**	91.2% (125/137) (85.2%; 95.4%)	97.7% (167/171) (94.1%; 99.4%)
Castration Maintenance Rate (Day 57-253) (95% CI)	96.4% (132/137) (91.7%; 98.8%)	96.5% (165/171) (92.5%; 98.7%)

*Both products were requested to be renamed in the current application (See Section 4.3).
** No 95% intervals were found in their original reviews or labels. The numbers shown in red are calculated for discussion purpose only.

Indication for the Use of Androgen Deprivation Therapy in Different Disease Stages in Patients with Prostate Cancer

Another important issue is the use of androgen deprivation therapy to treat patients with localized prostate cancer or PSA recurrence following definitive therapy (without evidence of metastasis). This trend has been reflected in clinical studies that have supported some of the approved GnRH analogs or that were intended to develop similar products, in which patients with these early disease settings were included in the trial population. However, the participation of these patients in clinical trials does not justify use of GnRH analogs in these early disease settings. Evidence has shown no benefit in retrospective analyses; in contrast, evidence has suggested that use of androgen deprivation therapy in these settings may be harmful for most patients.[3-5] Therefore, the inclusion of patients with PSA recurrence but no evidence of metastases in the key study supporting this NDA should not be interpreted as endorsement of the treatment of patients in that disease setting.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the submitted data are found to be sufficient. Limited by the single arm design of the key study, assessment of the attribution of some adverse reactions may not be reliable. Also, two methods were used to evaluate efficacy. These methods were not pre-specified in the original protocol. This might introduce bias into the interpretation and integrity of the results (see Sections 6.1.1; 6.1.4). These limitations introduce variability in the analysis, but do not alter the overall results of the application.

3.2 Compliance with Good Clinical Practices

Two study sites, as listed in Table 5, were selected for inspection by the Division of Scientific Investigation (DSI). Both sites are located in the Republic of South Africa. The study was conducted entirely in South Africa. These sites enrolled large numbers of patients and had few patients with 2 or more elevated testosterone levels. The results of the inspection are pending as of June 26, 2009.

Table 5: Sites Selected for Compliance Inspection.

Site # (Name, Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Center # 11: Dr Johann.H. van Wyk, Suite 207, Wilmedpark Hospital, C/o Ametis and Marmer Street, Wilkoppies, Klerksdorp, 2570 Republic of South Africa	DEB-TRI6M-301	23 patients received Trelstar (b) (4) (b) (4) 22.5 mg	Palliative treatment of patients with advanced prostate cancer
Center # 05: Dr Johann. Bahlmann, 20 Varing Avenue, George, 6529 Republic of South Africa	DEB-TRI6M-301	16 patients received Trelstar (b) (4) (b) (4) 22.5 mg	Palliative treatment of patients with advanced prostate cancer

3.3 Financial Disclosures

Disclosure of the financial interests of the investigators who conducted the clinical studies supporting this NDA was submitted to the FDA using form 3454. The disclosure was certified by Kevin Barber, Ph.D, Executive Director of Regulatory Affairs for the applicant. All of the investigators disclosed no financial conflict of interest, either a proprietary interest or a significant equity in the applicant.

The efficacy claims for the study were determined by central laboratory analysis of serum testosterone. This would minimize the effects of financial conflicts of interest, if any, on the outcome of the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC reviewers found that three of the Drug Master Files (b) (4), 8084 and (b) (4)) for the triptorelin 22.5 mg formulation are deficient. A letter detailing the deficiencies has been sent to the designated agents for each DMF holder. The reviewers recommend that the current application not be approved until these deficiencies have been addressed satisfactorily. See CMC review for the details of the deficiencies.

4.2 Review of Product Proprietary Name

The applicant has proposed a change to the proprietary names of the three triptorelin formulations. These will be changed to one proprietary name, Trelstar with the strength of the formulations to be used as a modifier with the addition of the frequency of use in weeks to container labels and carton labeling. All three formulations will be integrated into one product label. The applicant has also developed marketing and communication plans to targeted parties of interest (healthcare providers, pharmacists, patients, etc) to make them aware of the name changes to the current Trelstar Depot and Trelstar LA products, in conjunction with the introduction of the 24 week formulation that is the subject of this application. The labeling review for this NDA is based on the integrated label for all three formulations submitted by the applicant. As a result, the product in the current NDA should be labeled "TRELSTAR (triptorelin) 22.5 mg Every 24 Weeks".

4.3 Clinical Pharmacology

The clinical pharmacology reviewers considered the NDA submission acceptable based on their analyses of the PK/PD data submitted. No Phase 4 commitments are recommended by the clinical pharmacology reviewer. Please see details in their review.

The following summarizes the important clinical pharmacology information about triptorelin and provides specific information on the formulation that is the subject of this NDA.

4.3.1 Mechanism of Action

Triptorelin is a GnRH receptor agonist.

4.3.2 Pharmacodynamics

Following the first administration, there is a transient surge in circulating levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and estradiol. After chronic and continuous administration, usually 2 to 4 weeks after initiation of therapy, a sustained decrease in LH and FSH secretion and a marked reduction of testicular steroidogenesis is observed. A reduction in serum testosterone concentration to a level typically seen in surgically castrated men is obtained.

For triptorelin 22.5 mg, serum testosterone levels increased, peaking on Day 3, and declined thereafter to low levels by Weeks 3 – 4 in men with advanced prostate cancer.

4.3.3 Pharmacokinetics

Absorption: Following a single intramuscular injection of TRELSTAR to patients with prostate cancer, peak serum concentrations were reached in 1 to 3 hours with mean concentrations of 28.4 ng/mL, 38.5 ng/mL, and 44.1 ng/mL with the 3.75 mg, 11.25 mg, and 22.5 mg formulations, respectively. Triptorelin did not accumulate over 9 (3.75 mg and 11.25 mg) or 12 months (22.5 mg) of treatment.

Distribution: The distribution volume following a single IV bolus dose of 0.5 mg of triptorelin peptide was 30 – 33 L in healthy male volunteers. There is no evidence that triptorelin, at clinically relevant concentrations, binds to plasma proteins.

Metabolism: The metabolism of triptorelin in humans is unknown, but is unlikely to involve hepatic microsomal enzymes (cytochrome P-450). The effect of triptorelin on the activity of other drug metabolizing enzymes is also unknown. Thus far, no metabolites of triptorelin have been identified. Pharmacokinetic data suggest that C-terminal fragments produced by tissue degradation are completely degraded in the tissues, rapidly degraded in plasma, or cleared by the kidneys.

Excretion: Triptorelin is eliminated by both the liver and the kidneys. Following IV administration of 0.5 mg triptorelin peptide to six healthy male volunteers with a normal creatinine clearance, 41.7% of the dose was excreted in urine as intact peptide with a total triptorelin clearance of 211.9 mL/min. This percentage increased to 62.3% in patients with liver disease who had a lower creatinine clearance (89.9 mL/min). It has also been observed that the nonrenal clearance of triptorelin (patient anuric, CI_{creat} = 0) was 76.2 mL/min, thus indicating that the nonrenal elimination of triptorelin is mainly dependent on the liver.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Table 6: Clinical Studies for Development of the Triptorelin 22.5 mg Dosing Formulation in Patients with Prostate Cancer

Phase	Study ID (time period)	Number of Patients	Key Objectives	Key Design Elements	Major Findings
Phase 2	DEB-99-TRI-03 (01/2000-09/2000)	N=10	Efficacy evaluation of a triptorelin 22.5 mg formulation in inducing and	Open-label, single dose study	Only 70% of patients were able to maintain castrate testosterone levels to Day 169. The formulation was not

			maintaining castrate testosterone levels to Day 169		developed further.
	DEB-TRI6M-201 (05/2005-02/2006)	N=24	Estimating the efficacy of 3 different triptorelin 22.5 mg formulations (A, B, & C) in achieving castrate testosterone levels by Day 29 and maintaining these levels from Day 57 to 169.	Randomized, single blind, parallel group study of one does of each formulation. 8 patients per formulation.	The two formulations (A & B) containing (b) (4) in addition to (b) (4) appeared to maintain castrate testosterone levels to the end of the study. Having considered the manufacturing advantages of formulation A, it was selected for the phase 3 study shown below.
Phase 3	DEB-TRI6M-301* (03/2006-09/2007)	N=120	Proportions of patients with castrate levels of testosterone by Day 29 and from Day 57 to 337; Safety profile.	Open-label, single arm study: Two doses of the test formulation administered on Day 1 and Day 169.	97.5% (95% CI: 92.9% - 99.5%) of patients achieved medical castration by Day 29 and 93.3% (95% CI: 88.1% - 97.3%) of the patients were able to maintain castrate testosterone levels from Day 57-337.
* The key study supporting the efficacy and safety claims for the formulation in NDA 22-437.					

5.2 Review Strategy

The reviewers examined the submitted data by comparing information in different relevant datasets, investigating information listed in datasets against information recorded in case report forms, and conducting independent analyses of efficacy and safety. In addition, the reviewers scrutinized the applicant's study reports and applied sound medical judgment for addressing discrepancies revealed during the review. Special attention was paid to differences in defining the ITT population, managing patients with an isolated medically insignificant testosterone escape, and tabulating certain safety parameters, particularly adverse reactions known to be secondary to androgen deprivation.

5.3 Discussion of Individual Studies

The three studies submitted to the application were summarized in Table 6 along with the key findings from each study. Clearly, the key study supporting this NDA is the Phase 3 study DEB-TRI6M-301. Review of this study, as described in Sections 6 and 7, constitutes the basis for the regulatory recommendation on this product.

The first Phase 2 study of a triptorelin 22.5 mg formulation was DEB-99-TRI-03 (N=10), which was conducted to explore the feasibility of the formulation intended for dosing every 24 weeks. The results were suboptimal and its development was stopped. The applicant then conducted another Phase 2 study (DEB-TRI6M-201) of three triptorelin 22.5 mg formulations (A, B, and C). This study randomized 24 patients into three groups, 8 patients in each group received one of the three formulations. Patients were blinded as to which formulation they received until study completion. All the patients enrolled completed the study as planned. Castrate levels of testosterone were maintained from Day 57-169 in 100% of patients with both formulations A and B while only 75% of patients maintained castrate levels with formulation C. The key difference between A, B, and C was that (b) (4) The results suggested that combination of the microparticles of (b) (4) may sustain triptorelin release for approximately 6 months. Having considered the manufacturing differences between formulations A and B, formulation A was chosen for further development in the Phase 3 study, DEB-TRI6M-301. The detailed analyses of this Phase 3 study are described in the following 2 sections.

6 Review of Efficacy

6.1 Indication

The proposed indication for the triptorelin 22.5 mg formulation is for the treatment of patients with advanced prostate cancer (b) (4)

6.1.1 Methods

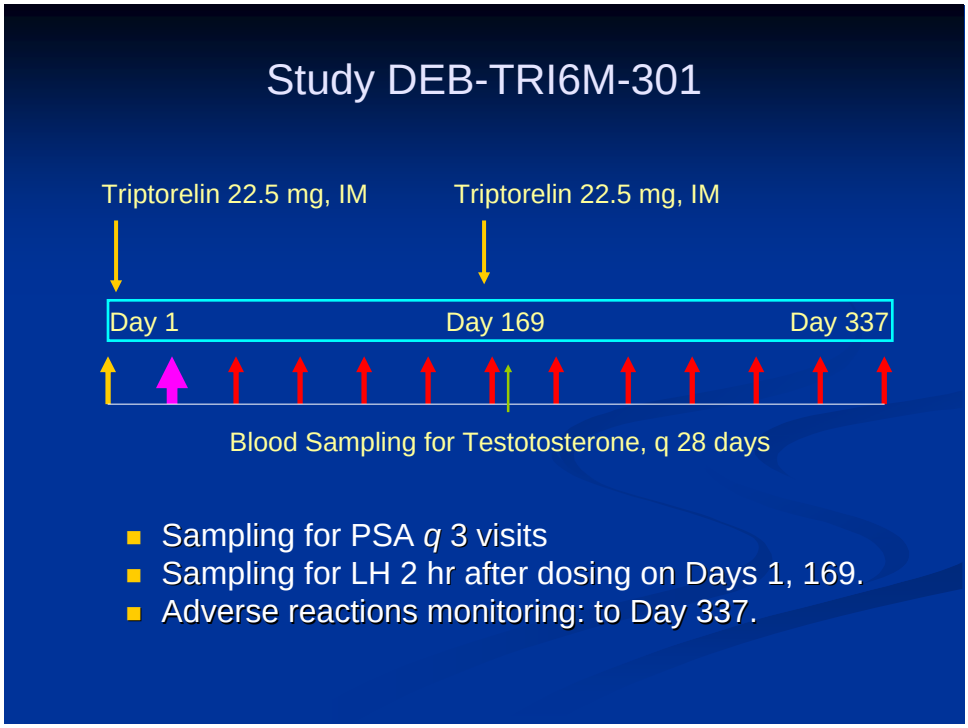
Since the clinical efficacy and safety claims for the new formulation are based on Study DEB-TRI6M-301, the reviewers evaluated its original protocol and follow-up amendments. These were evaluated in relation to the FDA recommendations during its development. Since efficacy endpoints were based on laboratory measurements of testosterone levels, all potential factors that may affect the results, from patient eligibility to final laboratory assay process, were considered in the review. Analysis results were generated independently from the raw data submitted and verified by comparison to the applicant's report. Discrepancies were investigated carefully with consultation, as necessary, to reviewers in other disciplines. Sensitivity analyses were conducted, whenever indicated, to assess the reliability of the results and conclusions. The importance and implications of the results are addressed accordingly.

Protocol Review for Study DEB-TRI6M-301

Study Design

Study DEB-TRI6M-301 was an open-label, single-arm, multicenter phase 3 trial of two injections of triptorelin pamoate 22.5 mg formulation in patients with advanced prostate cancer. Eligible patients received the treatment on Days 1 and 169 and were monitored with pre-specified clinical visits up to Day 337. The design can be summarized in the schema shown in Figure 1. Efficacy of the formulation was evaluated as the percentage of patients achieving (by Day 29) and maintaining (Days 57-337) castrate testosterone levels (≤ 1.735 nM).

Figure 1: Schematic Illustration of Study DEB-TRI6M-301



Protocol Amendments

The original protocol was developed in March 2006. The trial started in July 2006 and the NDA based on the results of the trial was submitted in September 2008. During the study, one protocol revision was submitted. The applicant conducted an interim analysis of efficacy after the first 6 months of treatment. This analysis was performed to determine whether a new formulation of triptorelin pamoate would be necessary. There were no plans to stop the study or to change the efficacy endpoints or conduct of the study. The plan was evaluated by the FDA reviewers and the sponsor was advised to consider recalculating the sample size and power if the additional interim analysis is to be conducted". Major protocol events are summarized in Table 7. It is important to point out that there was no special protocol assessment performed for this protocol.

Table 7: Protocol Milestones of Study DEB-TRI6M-301

Milestone	Date	Comments or Major Changes
Original Protocol	03/2006	
Initiation of Protocol	07/2006	First patient enrolled.
Last Enrollment	09/2006	
Amendment 1	03/2007	An interim analysis proposed for administrative purpose. See text for details.
Data Review and Analyses	09/2007	
NDA-submission	09/2008	Designated for regular review

Objectives

Primary:

- To evaluate the efficacy of triptorelin pamoate 22.5 mg formulation in achieving castrate levels of serum testosterone (≤ 1.735 nmol/L) by Day 29 and in maintaining castrate levels of serum testosterone (≤ 1.735 nmol/L) from Month 2 (Day 57) to end of Month 12 (Day 337) in patients with advanced prostate cancer

Secondary:

- To assess the absence of LH stimulation 2 hours after the second injection of triptorelin pamoate 22.5 mg formulation in patients with advanced prostate cancer
- To assess the absence of a testosterone increase (in a subset of 60 patients only) above 1.735 nmol/L 48 hours after the second injection of triptorelin pamoate 22.5 mg in patients with advanced prostate cancer
- To assess the safety and tolerability of the formulation in patients with advanced prostate cancer
- To assess the efficacy of the formulation by changes in PSA from baseline throughout treatment in patients with advanced prostate cancer
- To assess the testosterone pharmacodynamic response to triptorelin pamoate 22.5 mg formulation in a subset of 15 patients with advanced prostate cancer
- To assess the pharmacokinetics of triptorelin pamoate 22.5 mg formulation in the same subset of 15 patients with advanced prostate cancer.

Inclusion criteria

- Patients with a pathologically confirmed adenocarcinoma of the prostate
- Locally advanced disease, metastatic disease, or a rising PSA after primary therapy
- Serum testosterone at screening > 5.0 nM
- Karnofsky Performance index of 40% or more
- Age 18 years or older
- Signed informed consent before entry in the study

Exclusion criteria

- Hormonal treatment of prostate cancer within 6 months prior to enrollment
- Use of any 5-α-reductase inhibitors within 2 months prior to study initiation
- Current use or use within 6 months prior to study initiation of any medications that are known to affect the metabolism and/or secretion of androgenic hormones, such as ketoconazole, aminoglutethimide, estrogens, and progesterone.
- Use of systemic or inhaled corticosteroids (topical application permitted)
- Use of anticoagulants: heparin and coumarin derivatives (acetylsalicylic acid permitted)
- Presence of another neoplastic lesion or brain metastasis
- Prior hypophysectomy or adrenalectomy
- Known or suspected vertebral metastases with a risk of spinal cord compression
- Known hypersensitivity to any component of the investigational product or related products
- Severe kidney or liver failure (creatinine > 2 times the upper normal limit, AST and ALT > 3 times the upper normal limit)
- Any concomitant disorder or resulting therapy that is likely to interfere with patient compliance or with the study in the opinion of the Investigator
- Participation in another study with an experimental drug within 3 months prior to study initiation

Reviewer's Comments:
The eligibility criteria are acceptable. However, the intention to recruit patients with a rising PSA after primary therapy (either prostatectomy or radiotherapy) may not be appropriate. No evidence has shown that patients with biochemical failure in the absence of metastatic disease benefit from early initiation of androgen deprivation therapy. In contrast, it may increase the risks of metabolic dysfunction and cardiac morbidity and mortality. Therefore, inclusion of patients with the biochemical failure only in the research setting does not justify routine use of androgen deprivation therapy in this disease setting.

In addition, the protocol did not clearly specify "prior hormone treatment". Nevertheless, the majority of available hormonal agents do not have prolonged effects (> 6 months) on serum testosterone levels. Few agents are known to act more than 6 month. If used, these agents would induce castrate levels of testosterone, which would make the patient ineligible for the study.

Treatment Plan

After registration, eligible patients received study medication (triptorelin pamoate 22.5 mg) intramuscularly in the upper outer quadrant of either the right or left buttock. The injection was administered on Days 1 and 169, preferably between 7:00 and 9:00 am. The use of the study drug was documented on the drug accountability form.

Concomitant Therapy: During the study period, all drugs mentioned in the exclusion criteria remained prohibited. This included hormonal treatment for prostate cancer, finasteride, dutasteride, and any drug known to affect the metabolism and/or secretion of androgenic hormones. Administration of treatments or procedures with an effect on androgenic hormones during the study was considered a protocol violation.

Analgesics and other concomitant medications were permitted at the discretion of the Investigator. Administration of all concomitant medications was reported in the appropriate section of the Case Report Forms (CRFs).

Reviewer's Comments: *The protocol did not discuss the use of antiandrogen receptor agents in the first weeks of the study. Their use should not affect the serum testosterone levels, the primary endpoint of the study.*

Efficacy Assessments and Safety Monitoring

Primary Endpoints (for the primary objectives)

- To determine the percentage of patients achieving castrate levels of serum testosterone (≤ 1.735 nmol/L) by Day 29
- To determine the percentage of patients maintaining castrate levels of serum testosterone (≤ 1.735 nmol/L) from Month 2 (Day 57) to the end of Month 12 (Day 337).

Testosterone blood samples were collected, as shown in Figure 2. They were collected on Day 1 prior to injection and on Days 29, 57, 85, 113, 141, 169 (prior to injection), 171 (in a subset of 60 patients), 197, 225, 253, 281, 309 and 337. If testosterone levels were > 1.735 nM on Day 171 they were repeated at 48-72 hours intervals until castrate testosterone levels were reached or for a maximum of two weeks post-dosing. For the efficacy assessment, testosterone levels were measured using a validated Liquid Chromatography/tandem Mass Spectrometry (LC/MS) method in a central laboratory in the (b) (4). To determine patient eligibility and for subsequent follow-up, a local central laboratory measured testosterone levels using an automated immunoassay (b) (4)

Figure 2: Study Flow Chart (adopted from the protocol)

Best Available Copy

All patients except subset of 15 patients

End of week			4	8	12	16	20	24		28	32	36	40	44	48
Day	Pre-study	1	29	57	85	113	141	169	171	197	225	253	281	309	337
Eligibility/Informed consent	X														
Medical history & Physical examination	X														X[2]
Injection of triptorelin 6-month form.		X						X							
Blood sampling for testosterone	X	X[1]	X	X	X	X	X	X[1]	X[8]	X	X	X	X	X	X
Blood sampling for LH		X[5]						X[5]							
Blood sampling for Prostate Specific Antigen		X[1]			X			X[1]				X			X
Blood[3] and urine[4] safety parameters	X[6]	X[1]						X[1]							X
Vital signs (supine blood pressure, supine heart rate)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local tolerance[7]		X						X							
Body weight	X							X[1]							X
Adverse event		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Karnofsky index	X														

1. To be performed prior to study drug injection.
2. Physical examination only
3. Hematology (RBC, WBC, Platelet count, Hb) Blood Chemistry (Creatinine, Glucose, ALAT, AST, Alkaline Phosphatase) and Prothrombin time
4. Urinalysis (dipstick). Urine microscopy if urinalysis abnormal
5. Sampling on Day 1 and 169 at 0 hr and 2 hours post study drug injection.
6. Only blood safety parameters will be measured at the pre-study visit.
7. Local tolerance on Day 1 and 169 at 2hr and 4hr after study drug injection.
8. If testosterone levels are > 1.735 nmol/L on Day 171 the assessments should be repeated at an interval of 48-72 hours until castrate testosterone levels are reached again or for a maximum of two weeks post-dosing (assessed in 60 patients).

Reviewer's Comments:

The original protocol did not specify how the two assay methods for testosterone would be used to evaluate efficacy. Since the LC/MS method is the most sensitive one at present for measuring testosterone under hypogonadal conditions, the sponsor used it for the final efficacy determination. This is acceptable to the reviewer. However, it would be much better if the sponsor specified the application of the two methods at the beginning of the protocol. The key question should always be what methodology of assay reflects castrated testosterone levels more accurately. In general, laboratory values based on a sensitive, reliable method reduce both bias and variations.

In addition, the protocol did not recommend that sample collection for testosterone be within the same time period of the day at each visit to mitigate the diurnal variation in testosterone. For patients with testosterone suppression levels around 1.735 nM, differences in timing of collection might cause some variations in their results. Furthermore, the protocol did not specify if the samples were measured in triplicate or duplicate. A single assay of a sample can generate considerable deviations from the real concentration of testosterone in the sample.

Secondary Endpoints (for secondary objectives)

Key secondary efficacy endpoints included assessment of the proportion of patients with an increase in serum LH $\leq$ 1.0 IU/L 2 hours after study drug injection on Days 1 and 169, the percentage changes in PSA from baseline throughout treatment, and the percentage of patients (in a subset of 60 patients) that had testosterone levels above 1.735 nM after the second injection on Day 169.

Blood samples for PSA and LH were collected as shown in Figure 1. Their levels were measured in a local central laboratory in the [redacted] (b) (4) by validated methods.

To evaluate the safety of the formulation, patients were evaluated and adverse events collected at each visit as shown in Figure 2. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and graded as mild, moderate, or severe according to the following definitions:

Mild: causing no limitation of usual activities, the subject may experience slight discomfort
Moderate: causing some limitation of usual activities, the subject may experience annoying discomfort
Severe: causing inability to carry out usual activities, the subject may experience intolerable discomfort or pain

The relationship of an adverse event to study drug was assessed in three categories: reasonable causal relationship, no reasonable causal relationship, or unassessable.

A Serious Adverse Event (SAE) was defined as any untoward medical occurrence that at any dose results in death, is life threatening (i.e., puts the patient at immediate risk of death), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or any event that jeopardizes the patient or requires intervention to prevent one of the events listed above.

Statistical Methods

There were two co-primary efficacy endpoints evaluated in this study. The study estimated the proportion of patients achieving castrate levels of serum testosterone (≤ 1.735 nmol/L) by Day 29 and the proportion of patients maintaining castrate levels of serum testosterone (≤ 1.735 nmol/L) from Month 2 to end of Month 12 (Week 48). The 95% confidence intervals (exact binomial) were presented for both co-primary efficacy endpoints. The probability of maintaining castrate levels of testosterone from Month 2 to end of Month 12 (Week 48) was also analyzed using the Kaplan-Meier method.

Analyses of the two co-primary endpoints were conducted in both the Intention-to-Treat (ITT) and the Per Protocol (PP) populations. The ITT analysis was considered primary. The ITT population consisted of all enrolled patients, regardless of protocol deviations. The PP analysis set consisted of all ITT patients who did not have a major protocol violation/deviation and who had completed the study as planned.

For the secondary endpoints, the proportion of patients with a ≤ 1.0 IU/L increase in serum LH from 0 to 2 h after the first and second injection of study drug, the percentage change in PSA from baseline throughout treatment as well as the percentage of patients (in a subset of 60 patients) who had testosterone levels above 1.735 nmol/L within 48 hours after the second injection were to be summarized.

In Amendment 1, the applicant modified the protocol to include an interim analysis of efficacy. No changes to the study could be made as a result of the interim analysis. This analysis was used by the applicant to determine whether another formulation should be developed.

Reviewers' comments:

1. *In February 2008, FDA sent the following comments in response to the sponsor's interim analysis in the revised statistical analysis plan: "If the additional interim analysis is to be conducted in study DEB-TRI6M-301, the sample size and power calculation should be re-evaluated with consideration of such addition. However, the application for marketing approval should be submitted only after the final analysis." The applicant decided to conduct one interim analysis after 6 months on study. The protocol could not be altered as a result of this analysis and, therefore, no alpha adjustment was needed. A subset of 60 patients was included in this interim analysis and the estimated proportion of patients maintaining castrate levels of serum testosterone from Day 57 to Day 169 or to Day 171 was 94.96% (95% CI:89.4%, 98.1%).*

2. *The statistical plan, which was developed in December 2007, was based on the assumption that 95% of patients would achieve the primary endpoints with a two sided 95% confidence interval of 88.7%. Recently, FDA has requested that the lower bound of the confidence interval be no less than* (b) (4)*. If this criterion was applied to the current study, with a point estimate for the primary endpoints of 93%, the sample size would be 278. However, there were only 120 subjects in this study.*

3. (b) (4)

6.1.2 Demographics

A total of 120 patients were enrolled in Study DEB-TRI6M-301. All of them were from the Republic of South Africa, and were enrolled from 13 study centers. The distribution of the patients by center is summarized in Table 8.

Table 8: Center Distribution of the Patients in Study DEB-TRI6M-301

Center #	Number of Patients
01	8
02	4
03	10
04	2
05	16
06	10
07	2
08	10
09	8
10	3
11	23
12	5
13	19

Demographic and baseline disease characteristics of the patients were examined and the results are shown by the treatment arm in Tables 9 and 10.

Table 9: Basic Demographics of the Patients in Study DEB-TRI6M-301

	Triptorelin 22.5 mg N=120
Age Median (Range)	69.9 (51-93)
Race (%) White Black Other	 77 (64%) 27 (22%) 16 (13%)
BMI (kg/m^2) (Range)	27.6 (18.7-40.8)

Table 10: Disease Characteristics of the Patients in Study DEB-TRI6M-301

	Triptorelin 22.5 mg N=120
Disease Stage (%)	
Metastatic	**10 (8%)**
Locally advanced	**76 (63%)**
Other*	**34 (28%)**
PSA (ng/mL) Median (Range)	**20.1 (0.1-1630)**
Testosterone (nM) Median (Range)	**13.2 (5.1-35.6)**
*Patients with PSA recurrence after primary curative therapy.	

All of the 120 patients received the first triptorelin 22.5 mg injection on Day 1 and are included in the ITT population of the study for both efficacy and safety analyses.

Reviewer Comments:
The key purpose of this study was to evaluate the effectiveness of triptorelin 22.5 mg on the suppression of serum testosterone levels in patients with prostate cancer. Baseline and disease characteristics, except for baseline testosterone levels, should not have important effects on laboratory based measurement of testosterone levels. All enrolled patients had a baseline testosterone value > 5 nM (required for enrollment). Approximately 34% of patients enrolled had PSA-only disease with no evidence of metastases. The clinical benefit of early castration in this population has not been demonstrated.

Patient Disposition

Of the 120 patients enrolled, 5 did not complete the study as planned. The reasons for their discontinuation and the time of their discontinuation are shown in Table 11.

Table 11: Patients Disposition in Study DEB-TRI6M-301

	Triptorelin 22.5 mg N=120	***Time of Discontinuation***
Completed (%)	115 (96%)	*n/a*
Not Completed (%)	5 (4%)	
Lost to Follow-up	1	Day 176
Voluntary Withdrawal	1	Day 281
Death	3	
Disease Progression*	2	Days 169, 197
Adverse Event**	1	Day 85
*Both patients had castrate levels of testosterone. **Patient 11615 died of a myocardial infarction.		

In addition, 5 patients who completed the study were found to have major protocol violations or deviations, which may affect the assessment of the primary endpoints. The violations are summarized in Table 12. As such, the per-protocol (PP) population had 115 patients. The efficacy of study agent in the PP population will be examined in the review for the purpose of examining the sensitivity of the results generated from the ITT population.

Table 12: Major Protocol Violations/Deviations that May Impact on the Assessment of the Primary Endpoints

	Triptorelin 22.5 mg N=120
Use of prohibited hormonal agents during the study period*	3
Orchiectomy	1
Prolonged delay in visit	1
Total	5
* Use of ketoconazole, aminoglutethimide, estrogens, and progesterone	

Reviewer Comments:
Since 5 patients discontinued the study during the maintenance phase of the protocol, it is important to evaluate their testosterone levels prior to discontinuation. All 5 patients were found to have castration levels of testosterone prior to discontinuation.

6.1.3 Analysis of Primary Endpoint(s)

Analysis of Primary Endpoints

The primary endpoints were the percentage of patients achieving castrate levels of serum testosterone (≤ 1.735 nmol/L) on Day 29 and the percentage of patients maintaining castrate levels of serum testosterone (≤ 1.735 nmol/L) from Month 2 to the end of Month 12 (Day 57 to Day 337). These percentages including the 95% confidence intervals (exact binomial) are shown below.

Three (Study IDs 02601, 03606 and 11613) of the 120 enrolled patients did not achieve castrate testosterone levels on Day 29. In the ITT population, the estimated percentage of patients achieving castrate levels of serum testosterone (≤ 1.735 nmol/L) on Day 29 was 97.5% (95% CI: 92.87%; 99.48%). In the PP population that excluded 5 patients with identified protocol violations, the estimated percentage of patients achieving castrate levels of serum testosterone (≤ 1.735 nmol/L) on Day 29 was 97.39% (95% CI: 92.57% - 99.46%). The results are shown in Table 13.

Table 13: Proportion of Patients Who Achieved Castration Levels of Testosterone on Day 29

	ITT (N = 120)	PP (N = 115)
N (%)	117 (97.50)%	112 (97.39)%
95% exact binomial CI	(92.87% ; 99.48%)	(92.57% ; 99.46%)

Source: Table 10 in the sponsor's clinical study report, results verified

In the maintenance phase, the 8 patients below did not maintain castrate testosterone levels from Day 57 to Day 337. Their testosterone levels are listed in Table 14.

- Patients 06608, 08604, 11606, and 13613 had isolated elevations in their testosterone levels.
- Patient 06604 had an elevated testosterone level on Day 169 on the day of the second dosing. Patient 10601 had elevated testosterone levels on Day 253. Patient 04602 had an elevated level on Day 337.
- Patient 11613 did not achieve castrate testosterone levels after the 1st injection. This patient achieved castrate levels on Day 197 following the 2nd injection of triptorelin on Day 169.

Table 14: Time Course of Testosterone Levels (nM) in Patients with Elevated Testosterone Levels (≥ 1.735 nmol/L) During the Maintenance Phase (Days 57-337)

	Patient Identification Number							
Day of Study	***06608***	***08604***	***11606***	***13613***	***06604***	***10601***	***04602***	***11613***
0	9.381	28.201	23.36	40.591	14.113	18.367	35.581	16.62
1*	14.195	18.867	18.522	27.553	14.112	18.446	22.423	17.545
29	0.668	0.828	1.303	1.108	0.774	0.559	1.19	14.63
57	0.333	0.611	2.333	0.706	0.398	0.233	0.625	.
85	0.451	0.59	0.447	0.46	0.339	0.295	0.841	6.745
113	6.119	0.365	0.756	3.354	0.385	0.256	0.663	11.028
141	0.252	0.307	0.316	0.469	0.393	0.052	0.546	7.091
169*	0.373	0.753	0.551	0.648	1.938	0.282	0.374	7.242
171	1.625	1.966	1.231	.	0.328	.	0.787	12.239
197	0.456	0.377	0.629	0.522	0.176	0.201	0.902	0.763
225	0.272	0.613	0.699	0.653	0.219	0.61	0.797	0.862
253	0.442	0.49	0.658	0.463	0.338	5.201	0.656	0.55
281	0.724	0.664	0.894	1.553	0.471	8.98	0.769	0.984
309	0.275	0.683	0.652	0.486	0.338	8.311	0.836	0.649
337	0.388	0.801	1.077	0.792	0.382	11.436	42.047	0.679

*Day of dosing
Isolated elevations in testosterone levels are shown in pick.
Multiple escapes or an escape at the end of a dosing interval are shown in red.

In the ITT population, the estimated percentage of patients maintaining castrate levels of serum testosterone (≤ 1.735 nmol/L) from Day 57 to Day 337 was 93.33% (95% CI: 88.06% - 97.26%). In the PP population, the estimated percentage of patients maintaining castrate levels of serum testosterone (≤ 1.735 nmol/L) from Day 57 to Day 337 was 93.04% (95% CI: 86.75% - 96.95%). The results are shown in Table 15.

Table 15: Proportion of Patients Maintaining Castrate Levels During Days 57-337

	ITT (N=120)	PP (N=115)
N (%) 95% exact binomial CI	112 (93.33)% (88.06%, 97.26%)	107 (93.04)% (86.75%, 96.95%)

To further validate the analysis results of the primary endpoint in the maintenance phase from Day 57 to Day 337, we conducted three sensitivity analyses. The first sensitivity analysis did not include the 5 patients who discontinued the study from Day

57 to Day 337. These patients were eliminated from the ITT and PP populations. As shown in Table 16, the estimated proportion of patients and its 95% CI were similar to the results shown in Table 15.

Table 16 Sensitivity Analysis of the Primary Endpoint, Removing Patients Who Discontinued from Day 57 to Day 337

	S1-ITT* (N=115)	S1-PP* (N=110)
n (%) 95% exact binomial CI	107 (93.04)% (86.75%, 96.95%)	105 (92.73)% (86.17%, 96.81%)

*The populations used in the sensitivity analyses are described above.

The second sensitivity analysis excluded 15 patients who had any missing testosterone values from Days 57 to 337. The results, shown in Table 17, are similar to the results in Table 15.

Table 17 Sensitivity Analysis of the Primary Endpoint: Excluding 15 Patients with Missing Testosterone Values from Days 57 -337

	S2-ITT (N=105)	S2-PP (N=101)
N (%) 95% exact binomial CI	98 (93.33)% (86.75%, 97.28%)	94 (93.07)% (86.24%, 97.17%)

*The populations used in the sensitivity analyses are described above.

The third sensitivity analysis was to consider the 4 patients (ID# 06608, 08604, 11606, and 13613) with isolated testosterone elevations from Day 57 to Day 337 as having achieved successful medical castration. Detailed testosterone levels for these patients are shown in Table 14. Such levels of blip were likely from laboratory error and do not appear to be clinically important or to cause any changes in patients' symptoms. Therefore, it is reasonable to consider these patients as having achieved successful medical castration. After inclusion of the 4 patients as successfully medically castrate, the estimated proportions and 95% CIs in both the ITT and PP populations are shown in Table 18. These are increased, approximately 2 to 3 percents, compared to the results in Table 15.

Table 18: Sensitivity Analysis of the Primary Endpoint: Including Patients with Isolated Elevations in Testosterone Levels (> 1.735 but < 3.5 nM) from Day 57 to Day 337

	S3-ITT* (N=120)	S3-PP* (N=115)
N (%) 95% exact binomial CI	116 (96.67)% (91.69%, 99.08%)	111 (96.52)% (91.33%, 99.04%)

*The populations used in the sensitivity analyses are described above.

The results of the three sensitivity analyses suggest that the triptorelin 22.5 mg formulation is efficacious in maintaining clinical meaningful castration from Day 57 to Day 337.

Furthermore, the cumulative probability of maintenance of medical castration from Day 57 to Day 337 was estimated using the Kaplan-Meier method. The results are shown in Table 19. These probabilities and their 95% confidence intervals are similar to the observed percentages in Table 15.

Table 19: Cumulative Probability of Castration from Day 57 to Day 337 (Kaplan-Meier Estimates)

Population	Product Limit Survival Estimate at Day 337	
ITT (N = 120)	Maintenance rate	93.25%
	95% CI for the maintenance rate	(88.72%; 97.78%)
PP (N = 115)	Maintenance rate	92.95%
	95% CI for the maintenance rate	(88.25%; 97.65%)

(Adopted from the study report after verification)

Reviewer's Comments
The evaluation of the primary endpoints indicates that the triptorelin 22.5 mg formulation dosed every 24 weeks is efficacious in achieving and maintaining medical castration in 93-97% of patients. These results are comparable to the efficacies demonstrated with the two approved triptorelin formulations, 3.75 mg and 11.25 mg. To ensure the objectiveness of our assessment of the efficacy results, we sent a consult to Division of Urological and Reproductive Products for comments. The consultants agreed that the results, based on the levels of testosterone assayed with the liquid chromatography/tandem mass spectrometry [LC/MS] method, are comparable to those reported in the previous Trelstar applications. The LC/MS method is the most sensitive method for measuring hypogonadal ranges of testosterone. Regarding the four patients with one elevated testosterone level among the 12 measurements after the first dose, the consultants also agreed that it is reasonable for clinical judgment to play a role in the assessment of these cases. Overall, the efficacy results demonstrate that the 22.5 mg formulation is adequate for use in patients with prostate cancer whose disease requires androgen deprivation therapy.

The two patients (IDs 10601 and 11613) had multiple escapes, one after the 2nd dosing, and the other after the first dosing, respectively. This might be related to an inappropriate method of administrating the product since both achieved castration in the rest of study, which at least suggested that the drug worked in them. Therefore, appropriate administration procedures for the product should be described and/or illustrated clearly in its label.

6.1.4 Analysis of Secondary Endpoints(s)

The key secondary efficacy endpoints as specified in the protocol were to assess the proportion of patients with an increase of serum LH ≤ 1.0 IU/L within 2 hours of study drug injection on Days 1 and 169, the percentage of patients (in a subset of 60 patients) that had testosterone levels above 1.735 nM within 48 hours after the second injection on Day 169, and the percent change in PSA from baseline throughout treatment. Other secondary endpoints included the evaluation of the safety of the formulation in all patients treated and pharmacokinetic and pharmacodynamic parameters in a subset of patients. The following discussion will focus on the three key secondary endpoints as listed above. The PK-PD metrics have been reviewed by the clinical pharmacology reviewers and can be found in the approval document package.

Changes in the levels of LH reflect the sensitivity of the pituitary gland to the GnRH agonists. On Day 1, all the patients had more than a 1.0 IU/L increase in LH level. This is an appropriate response by the GnRH receptor. In contrast, on Day 169, 117 of the 120 patients as shown in Table 20 had a ≤ 1.0 IU/L increases in LH, suggesting the GnRH receptor's sensitivity was minimal to the re-dosing of the agonist (receptor desensitization). The three patients not satisfying the specified cut-off included one with an increase of 1.1 IU/L, one (ID 11613) with an increase of 15.2 IU/L who achieved medical castration after the 2nd dose, and one who did not have a LH values on Day 169 because of his death on Day 85.

Table 20: Percentage of Patients Showing a ≤ 1.0 IU/L Increases in Serum LH Levels 2 Hours After Injection on Days 1 and 169

	Triptorelin 22.5 ITT (N=120)
N (%) on Day1 95% CI	0 (0.0%; 3.1%)
N (%) on Day 169 95% CI	117 (98.3%) (94.1%; 99.8%)

Increases in testosterone levels above the medical castration criteria can occur with repeat doses of GnRH agonists. This is known as the "acute-on-chronic" phenomenon. This was studied in a subset of patients whose testosterone levels were monitored 48 hours after the 2nd dosing. Of the 60 patients studied, 2 had > 1.735 nM increases in

testosterone. Their testosterone time courses are shown in Fig 3. The proportion of patients with the phenomenon was approximately 3% in the study (Table 21). Stringently speaking, only one patient had the phenomenon as the other patient did not achieve the "chronic" status by achieving medical castration prior to dosing.

Figure 3: Time Courses of Testosterone Levels in Two Patients with the Acute-on Chronic Phenomenon.

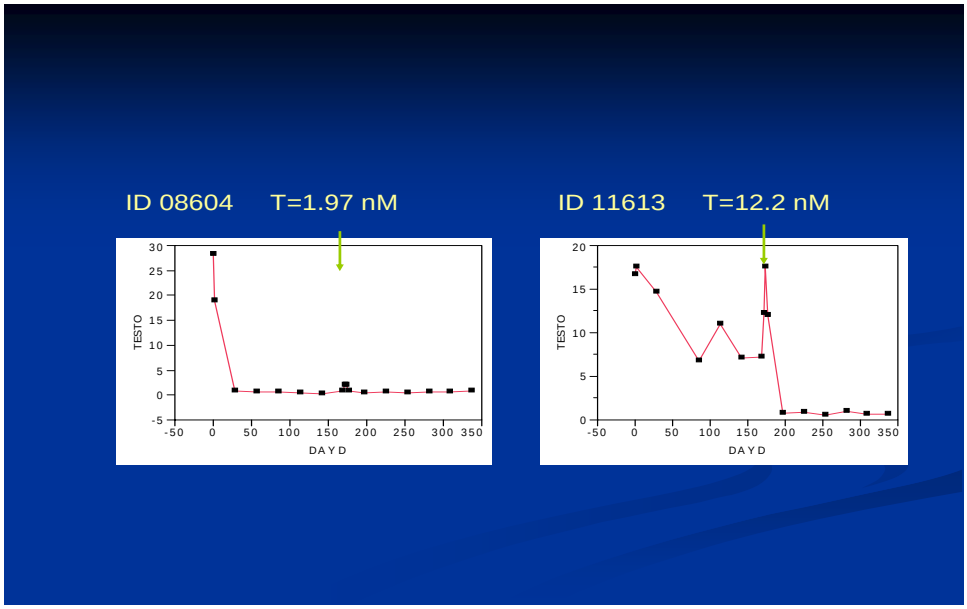


Table 21: Percentage of Patients with Elevated Testosterone Levels (>1.735 nM) Within 2 Days of the 2nd Injection (Day 169)

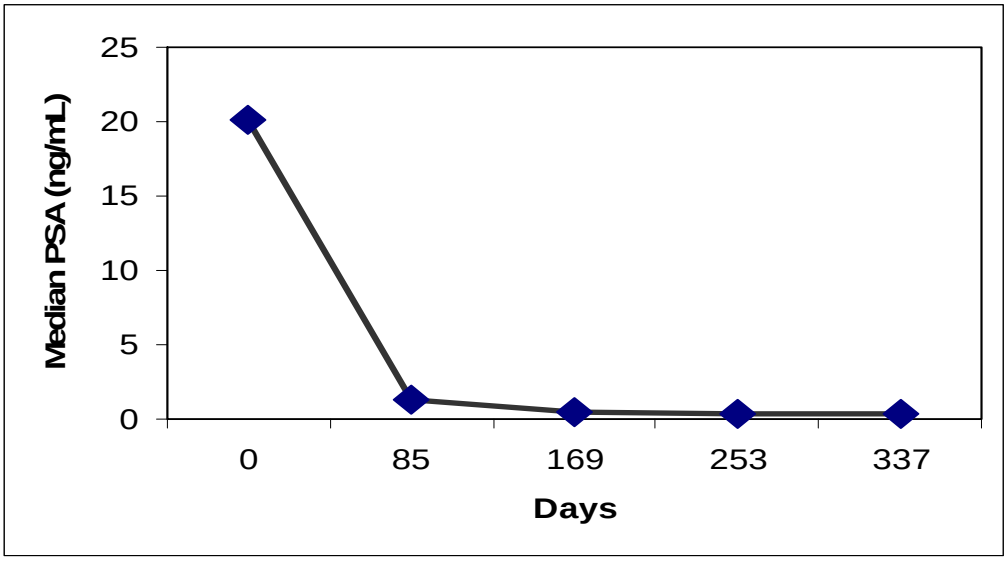
	Subset Patients **(N=60)**
Escape from Medical Castration (%) 95% CI	3.33% (0.4%; 11.5%)

Percent changes in PSA in the ITT population were estimated on Days 85, 169, 253, and 337. The results, on average, are shown in Table 22. Changes in median PSA levels in the ITT population were also analyzed for general observation of the trend with treatment and the results are shown in Fig 4. These results are consistent with the known PSA responsiveness to androgen deprivation in patients with hormone ablation naïve prostate cancer.

Table 22: Percent Changes in PSA at Four Time Points in the Study

	Day 85 (N=116)	Day 169 (N=117)	Day 253 (N=110)	Day 337 (N=113)
% of Decrease Mean (SD) (range)	-89.5% (17.6%) (-99.8%; -28.6%)	-90.2% (21.6%) (-99.9%; -51.2%)	-90.1% (20.7%) (-99.9%; -57.8%)	-82.3% (66.7%) (-99.9%; -54.5%)

Figure 4: Changes in Median PSA Level during the Study



Reviewer's Comments
The results of the analyses of the key secondary endpoints as discussed above are consistent with the analysis of the primary endpoint and support the efficacy claim for the triptorelin 22.5 mg formulation. The testosterone flare observed after the 2nd dosing, due to the intrinsic nature of GnRH agonists, may need to be assessed in patients whose clinical symptoms worsen with repeated dosing.

6.1.5 Subpopulations

Relevant to the primary endpoints of the study, efficacy differences between patients ≥ 72 years old and those < 72 were evaluated. Since serum testosterone levels may go down with aging, there is a possibility that patients at advanced ages may more easily

achieve medical castration than younger patients. The age cutoff selected for the analysis was because of the median age of 69.9 years in the study. The results, as shown in Table 23, suggest similar castration effects of the formulation between the two age groups. In addition, castration rates were estimated between White and non-White (Black and Other) patients. Their rates were 91% (70/77) in White and 98% (42/43) in non-White, respectively. The results suggest the effectiveness of the triptorelin formulation was comparable regardless of races.

Table 23: Castration Rates in Two Different Age Groups

	Age <72 (N=66)	Age ≥72 (N=54)
N (%)	62 (93.9%)	50 (92.6%)

6.1.6 Analysis of Clinical Information Relevant to Dosing Recommendations

There was only one dosing schedule studied for the new formulation. Based on the study results, the proposed dosing schedule for the planned indication is triptorelin 22.5 mg every 24 weeks, with no dosing modifications. This is similar to the two approved triptorelin formulations administered either every 4 weeks (triptorelin 3.75 mg formulation) or every 12 weeks (triptorelin 11.25 mg formulation).

6.1.7 Discussion of Persistence of Efficacy and/or Tolerance Effects

The key study supporting this NDA monitored testosterone levels every 28 days for approximately one year. The efficacy results, as discussed above, do not provide data to support an efficacy claim of more than one year. However, repeat dosing of triptorelin in the two approved formulations mentioned above has not been known to result in efficacy attenuation or to induce tolerance over time. Therefore, it is unlikely, with the same active ingredient, triptorelin that the new formulation would not demonstrate sustained efficacy. As the product exerts its antitumor activity indirectly through suppression of testosterone, monitoring testosterone levels during treatment with the product should be considered in patients whose disease shows signs of progression.

6.1.8 Additional Efficacy Issues/Analyses

None

7 Review of Safety

7.1 Methods

The safety of the triptorelin 22.5 mg formulation in patients with prostate cancer was evaluated based on the submitted datasets, case report forms (CRFs), and the sponsor's study reports. Internal consistency between the datasets and CRFs was checked and compared in selected patients who had important adverse reactions or events. Narratives for SAEs were also checked against the datasets and analyzed for causality to study product. Patients who died during the study were examined closely for the cause of death and for possible involvement of study product.
Special attention was paid to the known adverse reactions of GnRH analogs and the long-term adverse reactions related to androgen deprivation therapy.

Adverse events or reactions were coded with Medical Dictionary for Regulatory Activities (MedDRA)-preferred terms and were analyzed based on the submitted datasets. A treatment-emergent adverse event (TEAE) was defined as any new adverse events during the study; whereas a drug-related adverse reaction (DRAR) was defined as any adverse event considered to be related to the drug, classified by investigators as "reasonable causal relationship" in the datasets. Adverse events designated as ""no reasonable causal relationship" or "unassessable" in causality were not considered to be drug-related.

7.1.1 Clinical Studies Used to Evaluate Safety

The evaluation of safety and tolerability was mainly based on the Phase 3 study DEB-TRI6M-301. In addition, two small studies that pioneered the initial test of the formulation for the Phase 3 trial and of other formulations had a total of 34 patients who received one dose of triptorelin 22.5 mg and who were observed for the study period of 24 weeks. These studies along with the number of participants are shown in Table 24. The safety data from the Phase 2 studies were used for an exploratory analysis of pooled data.

Table 24: Clinical Studies of Triptorelin 22.5 mg

Phase	Study Name	Number of patients	Dosing Schedule
Phase 3	DEB-TRI6M-301	120	Triptorelin 22.5 mg in pamoate microgranules q24wks x 2
Phase 2	DEB-99-TRI-03	10	Triptorelin 22.5 mg in pamoate microgranules x 1
	DEB-TRI6M-201	24*	Triptorelin 22.5 mg pamoate microgranules x 1
* All the 24 patients received one injection of triptorelin 22.5 mg. Three different formulations were used in which the amount of (b) (4) varied.			

7.1.2 Adequacy of Data

Adequate safety information was found in the submitted datasets. Physical and laboratory information was correlated with clinical visits and adverse event reports. The submitted CRFs were found in agreement with the information documented in the relevant datasets.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

A pooled analysis of the safety of triptorelin 22.5 mg was conducted based on the three studies listed in Table 23. Pooling of this data is unsatisfactory for a variety of reasons. The triptorelin formulation used in DEB-99-TRI-03 is different that that used in the Phase 3 study. In DEB-TRI6M-201 the formulation used in the Phase 3 study was administered to only 8 of 24 patients. Further, both DEB-99-TRI-03 and DEB-TRI6M-201 provided only 24 weeks of follow up while the Phase 3 trial provided 48 weeks of follow up. However, all patients did receive triptorelin pamoate 22.5 mg.

TEAEs with an incidence ≥10% are tabulated in Table 25. Among these TEAEs, hot flush and weight gain are consistent with the known adverse reactions of androgen deprivation. The attribution of these AEs to study agent is difficult to assess because of the nature of these small single arm studies.

Table 25: Adverse Events or Reactions Reported in ≥ 10% of Patients who Received Triptorelin 22.5 mg (A Pooled Exploratory Analysis)

Adverse Reaction (%)	TEAE N=154	
	All Severities	Severe*
Hot Flush	96 (62%)	1 (<1%)
Weight Gain	41 (27%)	0
Hypertension	24 (16%)	0
Influenza	20 (13.0%)	0
Back pain	15 (10%)	1 (<1%)
*Causing inability to carry out usual activities, the subject may experience intolerable discomfort or pain		

7.2 Adequacy of Safety Assessments

Triptorelin has been used in clinical practice in the United States for nine years. For this NDA, a total of 154 patients were exposed to at least one dose of triptorelin 22.5 mg followed by a 24-week monitoring period. The key study, as stated above, had 120 patients who were exposed to study drug and monitored for 48 weeks. This would be adequate to assess the short-term toxicities of the new formulation. Toxicities related to long-term use of the formulation could not be gathered from the key study.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The exposure of patients to triptorelin in Study DEB-TRI6M-301 is summarized in Table 26. Since almost all of the patients received study agent and completed the study as planned, the duration of exposure was consistent with the study design.

Table 26: Extent of Exposure to the Triptorelin 22.5 mg in Study DEB-TRI6M-301

	Triptorelin 22.5 mg N=120
Duration of Exposure (weeks) Median (range)	48.0 (12.1-48.0)
Total dose/per patient (mg) Median (range)	45.0 (22.5-45.0)
Patient (%) =Median Dose <Median Dose*	119 (99.0%) 1 (1.0 %)
* One patient died prior to the 2nd dose.	

7.2.2 Explorations for Dose Response

Not applicable

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

All patients enrolled in the study had pre-study and post-study physical and laboratory examinations as shown in Figure 2. Local reactions to the two injections were evaluated on the day of injection. Every 4 weeks, vital signs and adverse events were assessed and blood was collected for testosterone measurement. The results of these tests appear to be adequate for use in determining the requirements for safe use of the product in regular practice.

7.2.5 Metabolic, Clearance, and Interaction Workup

No drug interaction studies were planned or conducted. Please see clinical pharmacology review for information on the metabolism and clearance of this formulation.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

All GnRH analogs act through androgen deprivation and are known to cause hot flushes, decreases in libido and erectile function, increases in weight, osteoporosis and related fractures, alterations in the metabolism of lipids and glucoses, and increased risk for cardiovascular morbidity and mortality. Some of these adverse reactions may be related to long-term administration of the analogs. The study supporting this NDA provided only 48 weeks of observation. Therefore, short term adverse reactions such as hot flushes, erectile dysfunction, and weight gain may be evident; whereas information about the known long-term adverse reactions would have a low likelihood to be detected. This is particularly true in a single arm design since many of these patients may have underlying conditions which place them at risk for diabetes, cardiovascular disease, etc and it will be difficult to differentiate a comorbid disease from a drug effect. Nevertheless, the reviewers have paid special attention to all known adverse reactions related to androgen deprivation.

7.3 Major Safety Results

Major safety results were evaluated based on the data from the 120 patients in Study DEB-TRI6M-301. All the patients except for one who died prior to the 2nd dose received two doses of study drug.

7.3.1 Deaths and Serious Adverse Events

Three patients died during the course of the study, two because of disease progression and one because of myocardial infarction. The two patients who died due to disease progression had castrate levels of testosterone. The incidence rates of SAEs along with the incidence of adverse reactions (TEAEs and TRARs) are shown in Table 27. With the increased concerns about cardiac toxicity with longer-term androgen deprivation, the patient who died of myocardial infarction and the patients who had a SAE of cardiac ischemia were examined closely. Although it is impossible to rule out the involvement of androgen deprivation in these events, it appears unlikely that the death due to myocardial infarction was related directly to triptorelin. This patient had a known history of cardiovascular ischemic events prior to the study.

Table 27: Overview of Adverse Reactions, Serious Adverse Events, and Death in DEB-TRI6M-301

	ITT N=120
All Grades TEAEs (%)	115 (95.8%)
All Grades TRARs (%)	97 (80.8%)
*SAEs (%)	17 (14.2%)

Death (%) Disease Other**	3 (2%) 2 1
*Three patients had cardiac ischemic events, two cases of myocardial infarction, and one case of angina pectoris. **Secondary to myocardial infarction	

7.3.2 Dropouts and/or Discontinuations

Dropouts and discontinuations can be seen in Section 6.1.3. No patients discontinued the study because of an adverse event.

7.3.3 Significant Adverse Events

Based on the known pattern of adverse reactions associated with GnRH analogs and an assessment of the commonly observed adverse events (≥ 10%), as shown in Section 7.4.1, the DRARs listed in Table 28 are considered important and/or significant. These DRARs were tabulated based on the investigators' assessment of causality of adverse events observed or reported. Hot flushes, erectile dysfunction, and testicular atrophy are the most common adverse reactions attributed to the treatment. No anaphylactic reactions were observed based on the data and study report.

Table 28: Important DRARs Observed in Study DEB-TRI6M-301

Adverse Reaction (%)	**ITT N=120**	
	All Severities	**Severe***
Hot Flush	86 (71.7%)	1 (<1%)
Erectile Dysfunction	12 (10.0%)	0
Testicular Atrophy	9 (7.5%)	0
Injection Site Reaction**	8 (6.7%)	0
Fatigue	5 (4.2%)	0
*Causing inability to carry out usual activities, the subject may experience intolerable discomfort or pain ** Including bruising, erythema, induration, swelling, pain, and pruritus		

Reviewer's Comments
It is difficult to assess the attribution of adverse events or severe adverse events in a single arm study. The three cardiac ischemic events had comorbidities (dyslipidemia and/or hypertension) that are well known to increase cardiac ischemic risk. However, the involvement of triptorelin cannot be ruled out in these events. Except for the known adverse events associated with androgen deprivation, no specific safety signals were discerned.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events or reactions reported in the key study DEB-TRI6M-301 with an incidence of ≥ 10% were tabulated regardless of causality and the results are shown in Table 29. Compared to the DRAR results shown in Table 28, the common TEAEs differ mostly in mild to moderate weight gain, hypertension, increased transaminases, influenza, back pain, and urinary tract infection. These differences reflect the investigators' assessment of their causality. Changes in transaminases will be discussed further in Section 7.4.2.

Table 29: Common TEAEs Observed in Study DEB-TRI6M-301

Adverse Reaction (%)	**Triptorelin 22.5 mg ITT N=120**	
	All Severities	**Severe***
Hot Flush	87 (72.5%)	1 (<1%)
Weight Gain	41 (36.3%)	0
Increase in Hepatic Transaminases	23 (19.2%)	0
Influenza	20 (16.0%)	0
Hypertension	17 (14.2%)	0
Back pain	13 (10.8%)	1 (<1%)
Erectile Dysfunction	12 (10.0%)	0
Urinary Tract Infection	11 (10.0%)	0
*Causing inability to carry out usual activities, the subject may experience intolerable discomfort or pain		

7.4.2 Laboratory Findings

Key laboratory parameters monitored in Study DEB-TRI6M-301 included CBC, glucose, hepatic transaminases, and creatinine. These were measured at screening, on each of the injection days (Day 1 and Day 169), and at the last visit (Day 337). The abnormalities detected after the first dose are summarized in Table 30. Since the initial protocol did not define how laboratory values would be graded, the reviewers used the NCI CTCAE v 3.0 criteria to classify their severity for better analysis. Among the parameters listed in the table, hyperglycemia and anemia may be clinically meaningful. Given the known adverse events associated with androgen deprivation, it will be important to monitor these values during treatment. On the other hand, almost all of the

changes in hepatic transaminases and creatinine were mild and reversible; suggesting that routine monitoring of hepatic and renal function is not needed for the formulation.

Table 30: Treatment Related Laboratory Changes

Laboratory Parameter (%)	Triptorelin 22.5 mg N=120			
	All Grades	**Grade 1/2**	**Grade 3**	**Grade 4**
Increase in ALT/AST	23 (19%)	23* (19%)	0	0
Decrease in Hemoglobin	25 (21%)	23 (19%)	2 (2%)	0
Hyperglycemia#	30 (25%)	27 (23%)	3 (3%)	0
Increase in Creatinine	11 (9%)	11**(9%)	0	0

* Only 1 patient had a grade 2 ALT elevation on Day 169. This resolved to Grade 1 (baseline in the patient) at the end of the study.
** Only 1 patient had a Grade 2 elevation of creatinine on Day 169. This resolved to Grade 1 (baseline in the patient) at the end of the study.
# Includes patients whose glucose worsened during treatment.
Note: patients with pre-existing protocol-allowed abnormalities are not excluded from this tabulation.

7.4.3 Vital Signs

Patients in Study DEB-TRI6M-301 had vital signs taken every 28 days and were weighed at screening, the time of the 2nd dose, and the last study visit. Changes in weight and blood pressure were analyzed. The percentage of patients with increases in their weight or blood pressures during study has been presented in Table 29.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed, per the protocol.

7.4.5 Special Safety Studies

None

7.4.6 Immunogenicity

Not monitored in the study.

Reviewer's Comments

The observed common TEAEs, including the laboratory abnormalities, represent both androgen deprivation-related known adverse reactions and non-specific adverse events likely associated with the underlying disease (prostate cancer). With the analysis results as shown and the known toxicity of androgen deprivation, periodic monitoring of glucose and hemoglobin should be considered during treatment with triptorelin 22.5 mg.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable with the one dose used in the study.

7.5.2 Time Dependency for Adverse Events

Not implicated with the evidence available

7.5.3 Drug-Demographic Interactions

The study enrolled only elderly men with a median age of 69.9 years. Differences in the incidence of major adverse events were examined between patients ≥ 72 years old and those < 72. The results are shown in Table 31. The incidences appear to be similar although urinary tract infection occurred more in patients ≥ 72 years old. However, the size of the sampling limits the interpretation of the results. Similarly, differences between White and non-White patients were examined and found to be comparable as shown in Table 32. Again, the size of the sampling limits the interpretation of the results.

Table 31: Adverse Reactions between Patients ≥ 72 and <72 Years Old

Adverse Reaction (%)	Age <72 (N=66)	Age ≥72 (N=54)
	All Severities	**All Severities**
Hot Flush	50 (76%)	37 (69%)
Influenza	12 (18%)	8 (15%)
Back pain	8 (12%)	5 (9%)
Erectile Dysfunction	10 (15%)	2 (4%)
Urinary Tract Infection	3 (5%)	8 (15%)

Table 32: Adverse Reactions between White and non-White Patients

Adverse Reaction (%)	White (N=77)	Non-White (N=43)
	All Severities	All Severities
Hot Flush	51 (66%)	36 (84%)
Influenza	13 (17%)	7 (16%)
Back pain	8 (10%)	5 (12%)
Erectile Dysfunction	6 (8%)	6 (14%)
Urinary Tract Infection	7 (9%)	4 (9%)

7.5.4 Drug-Disease Interactions

Not implicated with the evidence available.

7.5.5 Drug-Drug Interactions

Not planned in this study

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

No suggestion of potential carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

No reports of pregnancy in the female partners of the patients in the study.

7.6.3 Pediatrics and Effect on Growth

Not applicable for this NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdoses were reported in the study. The drug has no potential for being abused in the population intended.

8 Postmarketing Experience

Based on the sponsor's report submitted in the NDA, various triptorelin formulations using both acetate and pamoate salts have been marketed in 81 countries worldwide for a variety of indications including advanced prostate cancer, endometriosis, uterine fibromyoma, breast cancer, female infertility as part of an *in vitro* fertilization program, and precocious puberty. Post-marketing surveillance of various triptorelin formulations is available from sales in Western Europe, Israel, and North America, and started from first commercialization worldwide (January 1987) to March 2008. In the United States, triptorelin is only indicated for treatment of advanced prostate cancer.

There were 132 SAEs reported for patients with prostate cancer who received any triptorelin formulations. The SAEs reported in two or more patients included hepatitis (8), thrombocytopenia (4), anaphylactic shock (3), myalgia (3), injection site pain (3), hypertension (3), cerebrovascular accident (3), angioedema (3), cerebrovascular disorder (2), thrombosis (2), pain in extremity (2), hemolytic anemia (2), normochromic normocytic anemia (2), pulmonary edema (2), facial edema (2), allergic dermatitis (2), peripheral neuropathy (2), jaundice (2), interstitial lung disease (2), hot flush (2), prostate cancer (2), overdose (2), and drug ineffective (2).

Reviewer's Comments
Because these events were reported voluntarily from a population of uncertain size, it is difficult to estimate the frequency of these serious adverse reactions or to establish a causal relationship to triptorelin. In addition, no ECGs were obtained in the study. It is known that androgen deprivation therapy may prolong the QT interval in some patients. Therefore, patients with known QT prolongation or taking drugs with the potential for QT prolongation should be evaluated and the benefits and risks of androgen deprivation therapy discussed prior to use of GnRH analogs such as triptorelin.

9 Appendices

9.1 Literature Review/References

1. Fourcroy J. Regulatory history of hormone therapy for prostate cancer. Mol Urol 1998; 2:215-220
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european organisation for the research and treatment of cancer protocol 30846 after 13 years of follow-up (A randomized controlled trial) Eur Urol 2008; 55:14-22
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6. Isbarn H, et al. Androgen deprivation therapy for the treatment of prostate cancer: consider both benefits and risks. Euro Urology 2009; 55: 62-75
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8. Keating NL et al. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J. Clin. Oncol. 2006; 24: 4448-4456
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11. Alibi SM et al. Impact of androgen deprivation therapy (ADT) on bone, cardiovascular, and endocrine outcomes: A propensity-matched analysis of 20,000 patients. J Clin Oncol 26: 2008 (May 20 suppl; abstr 5012)
12. Efstathiou JA, et al. Cardiovascular mortality after androgen dperivation therapy for locally advanced prostate cancer RTOG 85-31. J. Clin. Oncol 2008; 27: 92-99.
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9.2 Labeling Recommendations

Considerable changes in the sponsor's proposed label were recommended in the highlights, safety, and efficacy sections. These recommendations are listed below with the original showing markup, changes, and comments. These snapshots may not represent the final version of the product label. In addition, information deleted from the original may not be shown well. In general, the changes were proposed to assure inclusion of the accurate validated information based on the review and to modify the label to the required formatting.

5 page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

9.3 Advisory Committee Meeting

This application was not referred to the Oncologic Drugs Advisory Committee. The evidence presented in the key study adequately demonstrated the clinical efficacy and safety of the triptorelin 22.5 mg formulation in the intended patient population. Further, the study used an established surrogate endpoint for efficacy. No significant efficacy or safety issues that could invalidate the conclusions of the study were identified in the review.

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/s/

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NDA Number: 22-437 **Applicant:** Watson Laboratories Inc. **Stamp Date: 9/18/08**

Drug Name: Trelstar **NDA Type:**

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comments
1	Is Index sufficient to locate necessary reports, tables, data, etc.?	x		
2	Are study reports including original protocols, subsequent amendments, etc. complete and available?	x		
3	Were safety and efficacy for gender, racial, and geriatric subgroups investigated (if applicable)?	x		
4	Are data sets in EDR accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets)?	x		
5	Were ISS and ISE submitted?	x		
6	Designs utilized appropriate for the indications requested	x		
7	Endpoints and methods of analysis spelled out in the protocols	x		
8	Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	x		
9	Appropriate references included for novel statistical methodology (if present)	x		
10	Sufficient data listings and intermediate analysis tables to permit a statistical review	x		
11	Intent-to-treat analyses	x		
12	Effects of dropouts on primary analyses investigated	x		

Any Additional Comments:

Yu-Ling Chang 03/17/09

Reviewing Statistician Date

Shenghui Tang 03/17/09

Supervisor/Team Leader Date

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/s/

Yu-Ling Chang
3/17/2009 10:44:23 AM
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