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*APPLICATION NUMBER:*  
**22-437**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**BIOPHARMACEUTICS REVIEW**  
**Office of New Drugs Quality Assessment**

<b>Application No.:</b>	NDA 22-437	<b>Reviewer:</b> Houda Mahayni, Ph.D.	
<b>Submission Date:</b>	09/10/2009		
<b>Division:</b>	DDOP	<b>Team Leader:</b> Angelica Dorantes, Ph.D.	
<b>Sponsor:</b>	Watson Laboratories, Inc	<b>Supervisor:</b> Patrick J. Marroum, Ph.D.	
<b>Trade Name:</b>	Trelstar® (b) (4)	<b>Date Assigned:</b>	12/04/2009
<b>Generic Name:</b>	Triptorelin Pamoate	<b>Date of Review:</b>	02/05/2010
<b>Indication:</b>	The palliative treatment of advanced prostate cancer	<b>Type of Submission:</b> Resubmission: Responses to FDA "Complete Response" Letter	
<b>Formulation/strength</b>	Injectable Suspension/22.5 mg		
<b>Route of Administration</b>	Intramuscular Injection		

**SUBMISSION:**

Reference is made to the original New Drug Application for TRELSTAR 22.5 mg (triptorelin pamoate for injectable suspension), NDA 22-437, submitted on September 11, 2008. Reference is also made to the Division's Complete Response letter dated July 10, 2009. This resubmission provides Watson's responses to the Division's letter dated July 10, 2009. Watson considers this resubmission to be a complete response to the deficiencies outlined in the complete response letter from the Division.

The Division's deficiencies from the July 10, 2009 Complete Response letter relevant to biopharmaceutics are provided below, followed by Watson's response and FDA's response to Watson's response.

**11. Division's Request: Revise the proposed in-vitro dissolution method and acceptance criteria as follow:**

**a. Add a sampling point between 1 and 24 hours.**

**Watson's Response:** An 8 hour sampling point has been added to the proposed in-vitro dissolution method and acceptance criteria.

**FDA's Response:** Watson satisfied our request.

**b. Eliminate the (b) (4) sampling point, and replace with a sampling point at 96 hours.**

**Watson's Response:** The (b) (4) sampling point has been replaced by a 96-hour sampling point.

**FDA's Response:** Watson satisfied our request.

**12. Division's Request: Revise the dissolution sampling points and acceptance criteria as follow: 1 hr (b) (4), 12 hr (b) (4), 24 hr (b) (4), 96 hr (b) (4), and 168 hr (b) (4). Note that the 12-hour and 96-hour timepoints and acceptance criteria reflect interpolation, as no data were provided for the 12-hour and 96-hour sampling points.**

**Watson's Response:** As noted by the Division in the Complete Response, FDA's requested specifications were based on an interpolation of the dissolution data provided in the NDA, as no dissolution data were provided for the suggested timepoints. In order to assess the requested specification change against observed dissolution data, Watson performed additional dissolution experiments to support the new timepoints and acceptance criteria as seen in Table 1 below.

**Table 1: Dissolution Profiles for Triptorelin Pamoate 22.5 mg Batches to Date**

Lot Number [Use]	Storage	Percent Peptide Released, mean (range)				
		1 hour	8 hour	24 hours	96 hours	7 days
4126M0503 [study DEB- TRI6M-201]	release test	(b) (4)				
	3 mo 25°C					
	6 mo 25°C					
	9 mo 25°C					
	12 mo 25°C					
	18 mo 25°C					
	24 mo 25°C					
	36 mo 25°C					
55 mo 4°C						
4126M0605 [study DEB- TRI6M-301]	release test	(b) (4)				
	3 mo 25°C					
	6 mo 25°C					
	9 mo 25°C					
	12 mo 25°C					
	18 mo 25°C					
	24 mo 25°C					
	36 mo 25°C					
4126M0606 [study DEB- TRI6M-301]	release test	(b) (4)				
	3 mo 25°C					
	6 mo 25°C					
	9 mo 25°C					
	12 mo 25°C					
	18 mo 25°C					
	24 mo 25°C					
34 mo 4°C						
D306I02C8 [process consistency]	release test	(b) (4)				
	3 mo 25°C					
	16 mo 4°C					
D306I03D8 [process consistency]	release test	(b) (4)				
	3 mo 25°C					
	16 mo 4°C					
D306I04D8 [process consistency]	release test	(b) (4)				
	3 mo 25°C					
	16 mo 4°C					
4126M0707 [high viscosity]	release test	(b) (4)				
	3 mo 25°C					
	6 mo 25°C					
	9 mo 25°C					
	12 mo 25°C					
	18 mo 25°C					
29 mo 4°C						

Lot Number [Use]	Storage	Percent Peptide Released, mean (range)				
		1 hour	8 hour	24 hours	96 hours	7 days
4126M0708 [low viscosity]	release test	(b) (4)				
	3 mo 25°C					
	6 mo 25°C					
	9 mo 25°C					
	12 mo 25°C					
	18 mo 25°C					
	29 mo 4°C					
D306D05F8 [low core loading]	release test	(b) (4)				
	13 mo 4°C					
D306D06F8 [high core loading]	release test	(b) (4)				
	13 mo 4°C					
3126M048 [high particle size]	release test	(b) (4)				
	17 mo 4°C					
3126M049 [low particle size]	release test	(b) (4)				
	17 mo 4°C					
mean		(b) (4)				
proposed specification						

<sup>a</sup> Proposed specification limits set at mean (b) (4) (absolute)

<sup>b</sup> Proposed specification of (b) (4) in accordance with USP <1092>, and ICH

<sup>c</sup> Dissolution testing performed in support of the new 8 hour and 96 hour dissolution sampling points are presented in italics. Data are within proposed acceptance criteria.

Based on the dissolution data from above, Watson is proposing the following sampling timepoints and acceptance criteria:

Watson's proposed sampling timepoints and acceptance criteria are as follows

Time (hr)	% Released
1	(b) (4)
8	(b) (4)
24	(b) (4)
96	(b) (4)
168	(b) (4)

**FDA's Response:** Watson's proposed acceptance criteria are acceptable.

**13. Division's Request:** The IVIVR is not acceptable because the formulations used to develop the relationships did not have different release rates, and the IVIVR did not predict the entire profile for the two phases of drug release. Additionally, the IVIVR did not meet the criteria for internal and external predictability. Therefore, this IVIVR can not be used to support any post-approval changes.

**Watson Response:** Watson acknowledges FDA's comments on the IVIVR.

**FDA's Response:** We have no further comment.

**BIOPHARMACEUTIC INFORMATION:**

In the original NDA submitted on September 11, 2008, Watson proposed the following in-vitro dissolution test conditions and acceptance criteria :

**Watson's Proposed In-Vitro Dissolution Test Conditions:**

**Dissolution Apparatus:** USP Type 2 Paddle  
**Dissolution Medium:** 50 mL of methanol to 950 mL of water  
**Stirring Speed:** 75 rpm  
**Temperature:** Gradient from 37 to 61°C over 48 hours, followed by continuous heating at 61°C  
**Test Duration:** 10 days  
**Sampling Points:** 1, 24<sup>(b) (4)</sup> and 168 hours  
**Dissolution Analysis:** HPLC

<b>Watson's Proposed Sampling Points and Acceptance Criteria</b>	
<b>Time (hr)</b>	<b>% Release</b>
1	(b) (4)
24	(b) (4)
(b) (4)	(b) (4)
168	(b) (4)

In the Complete Response Letter from the Division dated July 10, 2009, FDA recommended that Watson revise the proposed in-vitro dissolution method and acceptance criteria as follows:

- To add a sampling point between 1 and 24 hour
- To eliminate the (b) (4) hour sampling point
- To add instead a sampling point at 96 hour.

FDA recommended the following sampling timepoints and acceptance criteria:

<b>FDA Recommended Sampling Timepoints and Acceptance Criteria</b>	
<b>Time (hr)</b>	<b>% Release</b>
1	(b) (4)
12	(b) (4) *
24	(b) (4)
96	(b) (4) *
168	(b) (4)

\*Interpolated sampling time points and specifications as no data is provided in this application on the 12 and 96 hours sampling points

Watson added FDA's recommended sampling timepoints at 8 hour and 96 hour, and eliminated two sampling timepoints at 12 hour and (b) (4). Because FDA's recommended acceptance criteria at the two sampling timepoints (12 and 96 hours) were based on interpolation, Watson submitted Table 1 above providing stability data on FDA's recommended two sampling timepoints (8 and 96 hours).

**RECOMMENDATION:**

**Watson's proposed in-vitro dissolution test conditions and acceptance criteria are acceptable.**

**The in-vitro dissolution test conditions, the sampling timepoints, and acceptance criteria are as follows:**

**The In-Vitro Dissolution Test Conditions:**

**Dissolution Apparatus:** USP Type 2 Paddle  
**Dissolution Medium:** 50 mL of methanol to 950 mL of water  
**Stirring Speed:** 75 rpm  
**Temperature:** Gradient from 37 to 61°C over 48 hours, followed by continuous

**Test Duration:** heating at 61°C  
10 days  
**Sampling Points:** 1, 8, 24, 96, and 168 hours  
**Dissolution Analysis:** HPLC

**The sampling timepoints and acceptance criteria:**

Time (hr)	% Released
1	(b) (4)
8	(b) (4)
24	(b) (4)
96	(b) (4)
168	(b) (4)

**Signature**  
**Houda Mahayni, Ph.D.**  
Biopharmaceutics Reviewer  
Office of New Drugs Quality Assessment

**Signature**  
**Patrick J. Marroum, Ph.D.**  
Biopharmaceutics Expert  
Office of New Drugs Quality Assessment

cc: Adorantes, Dmesmer, Wadams

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22437

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ORIG-1

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WATSON  
LABORATORIES  
INC

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TRELSTAR (b) (4)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HOUDA MAHAYNI  
02/17/2010

PATRICK J MARROUM  
02/17/2010

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## Memorandum

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<b>NDA</b>	22-437/SN15
<b>Submission Date:</b>	10 September 2009
<b>Brand Name:</b>	TRELSTAR®
<b>Generic Name:</b>	Triptorelin pamoate
<b>Formulation:</b>	22.5 mg injectable suspension
<b>OCP Reviewers:</b>	Bahru A Habtemariam, Pharm.D.
<b>OCP Team Leader:</b>	Brian Booth, Ph.D.
<b>OCP Division:</b>	Division of Clinical Pharmacology V
<b>ORM Division:</b>	Division of Drug Oncology Products
<b>Sponsor:</b>	(b) (4)
<b>Submission Type; Code:</b>	Original/000; 4F
<b>Dosing regimen:</b>	Single-Dose Vial Injected Intramuscularly every 6 Months
<b>Indications</b>	Palliative Treatment of Advanced Prostate Cancer

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The NDA (22-437) for Triptorelin was submitted on 09/15/2007 and the clinical pharmacology review was completed and uploaded onto DARRTS (S Abraham, 6/18/2009). The NDA was not approved following initial submission; instead, a complete response was issued on 07/10/2009.

The sponsor re-submitted NDA 22-437 on 9/10/2009 addressing deficiencies and comments conveyed at the time of the complete response. No additional clinical pharmacology data or information were provided upon resubmission. Therefore, a detailed clinical pharmacology review was not performed for the resubmitted NDA. Minor updates were made to the label (see attachment).

### **Recommendation:**

The resubmitted NDA is acceptable from clinical pharmacology perspective.

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Reviewer: Bahru A Habtemariam,  
Pharm.D.  
Division of Clinical Pharmacology 5

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Team Leader: Brian Booth, Ph.D.  
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **K Robertson**; MTL - **E Maher**; MO - **M Ning**  
DOP-5: Reviewers - **B Habtemariam**, TL - **B Booth**, DDD - **B Booth**,  
DD - **A Rahman**

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

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22437

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ORIG-1

-----  
WATSON  
LABORATORIES  
INC

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TRELSTAR (b) (4)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BAHRU A HABTEMARIAM  
03/04/2010

BRIAN P BOOTH  
03/05/2010

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## Clinical Pharmacology Review

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<b>NDA</b>	22-437
<b>Brand Name:</b>	TRELSTAR (b) (4)
<b>Generic Name:</b>	Triptorelin Pamoate Injectable Suspension
<b>Dosage Form/Strength:</b>	22.5 mg of Triptorelin (Free Base) in Single-Dose Vial
<b>Dosing regimen:</b>	A Single-Dose Vial Injected Intramuscularly every 6 Months
<b>Indication</b>	Palliative Treatment of Advanced Prostate Cancer
<b>Submission Date:</b>	September 12, 2008
<b>Submission Type:</b>	Original NDA; 000
<b>Applicant:</b>	Watson Laboratories Inc.
<b>OCP Reviewer:</b>	Sophia Abraham., Ph.D.
<b>OCP Team Leader:</b>	Brian Booth, Ph.D.
<b>OCP Division:</b>	Division of Clinical Pharmacology 5
<b>ODDP Division:</b>	Division of Drug Oncology Products

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## 1 EXECUTIVE SUMMARY

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  $\leq 0.5$  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  $\leq 0.5$  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.

### Labeling Recommendations

Please refer to Section 3 - OCP Labeling Recommendations.

## 1.2 PHASE IV COMMITMENTS

[None]

## 1.3 CLINICAL PHARMACOLOGY SUMMARY

Triptorelin is a synthetic decapeptide agonist analogue of naturally occurring luteinizing hormone-releasing hormone (LHRH). LHRH is also known as gonadotropin releasing hormone (GnRH). It acts as a potent inhibitor of gonadotropin secretion, initially producing a transient rise in LH, FSH, and testosterone levels. Continuous triptorelin pamoate administration desensitizes pituitary LHRH receptors and inhibits LH and FSH secretion, resulting in chemical castration within ~ 2-4 weeks.

Triptorelin, like other GnRH agonists, has a short half-life *in vivo* ( $t_{1/2}$ =5 hours). Therefore, sustained-release dosage forms for intramuscular administration (**IM**) have been developed by combining triptorelin with a (b) (4). Triptorelin 1-month (**3.75 mg**) and 3-month (**11.25 mg**) sustained-release IM formulations have been approved for marketing in the United States on 15-Jun-2000 under NDA #20-715 and 29-Jun-2001 under NDA #21-288, respectively, as a palliative treatment of advanced prostate cancer.

In the current NDA 22-437 submission, the Applicant proposes to market a **new** formulation for Trelstar® (Viz., **6-Month 22.5 mg** triptorelin sustained-release formulation), which has the same indication (advanced prostate cancer), dosage form (injection), and route of administration (IM) as for the **approved** Trelstar® **1-Month 3.75 mg** and **3-Month 11.25 mg** sustained-release formulations.

In the pivotal Phase 3 **Study 301**, more than 90% of 120 patients had castration serum testosterone levels of  $\leq 0.5$  ng/mL in the first month of the study and maintained these levels over the study period.

At **Day 29**, the mean percentage of patients who had castration serum testosterone levels of  $\leq 0.5$  ng/mL after the **6-Month** formulation in **Study 301** was roughly comparable to that obtained after the

**3-Month** and **1-Month** formulations in **Study TRI-01** (previous NDA 21-288 submission) ( mean %=97.5%, 98%, and 93%, respectively). At **Day 169**, the mean percentage of patients was 98%, 98%, and 100%, respectively. This suggests that the 6-Month formulation of triptorelin is at least as effective as the approved 1-month and the 3-Month formulations in achieving and maintaining castration level of testosterone.

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**.

After the **first injection** of the **6-month** triptorelin formulation, the mean  $C_{max}$  and  $AUC_{1-169 \text{ days}}$  for triptorelin were  $44.1 \pm 20.2$  ng/mL and  $111.5 \pm 43.3$  ng.d/mL, respectively. The median  $T_{max}$  was 3 days (range=2-12 days).

The PK parameters for triptorelin following the **second injection** of the **6-month** formulation averaged  $39.2 \pm 19.2$  ng/mL,  $115.2 \pm 31.9$  ng.d/mL, and  $0.19 \pm 0.26$  ng/mL for  $C_{max}$ ,  $AUC_{1-169 \text{ days}}$ , and  $C_o$ , respectively. The median  $T_{max}$  was 4 hours (range=1-24 hours). No accumulation was observed between the first and second injection. The accumulation ratio calculated as  $AUC_{1-169 \text{ days}}$  (second injection/first injection) averaged  $1.13 \pm 0.26$ .

Fourteen patients (14/15, 93%) achieved castration **testosterone** serum levels of  $\leq 0.5$  ng/mL at **Day 29** and maintained these levels at **Days 57-337**. One patient (Patient #12603) did not maintain castration testosterone levels during this period (testosterone serum levels ranged from 0.52-0.82 ng/mL).

The **6-Month** formulation proposed for marketing was used in the pivotal Phase 3 **Study 301**. The mean  $C_{max}$  and  $AUC_{1-169 \text{ days}}$  for **testosterone** after **this formulation** were  $7.9 \pm 2.9$  ng/mL and  $76.9 \pm 26.7$  ng.d/mL, respectively in the 15 patients. The median  $T_{max}$  and time to castration ( $T_{cast}$ ) were 3 days (range=2-5 days) 19 days (range=13-25 days).

The following issues have **not** been addressed in the current NDA 22-437 submission or previous NDA 20-715 and 21-288 submissions for Triptorelin:

- **No *in vitro*** screening CYP450 isozyme studies for triptorelin have been performed. However, published data indicate that triptorelin is degraded by **peptidases** into inactive fragments and **not likely** to be metabolized by CYP450 isozymes [Barron *et al.*, *Metabolic clearance and plasma half-disappearance time of D-Trp6 and exogenous luteinizing-hormone releasing hormone. J Clin Endocrinol Metab* 54:1169-1173, 1982]. No additional metabolism studies should be required.
- **No *in vitro*** CYP450 isozyme studies for inhibition or induction by triptorelin for have been performed for triptorelin. There is no need to conduct such studies as the post marketing data for the approved triptorelin 1- and 3-Month formulations since 22 years did not report any clinically significant interactions of triptorelin with any other coadministered medication.
- **No *in vitro*** studies for interactions with P-glycoprotein (P-gp) have been performed for triptorelin. However, it was reported that no active efflux transport by Pglycoprotein was demonstrated in Caco-2 for another GnRH peptide agonist (leuprolide) [Guo *et al.*, *Transport of leuprolide across rat intestine, rabbit intestine and Caco-2 cell monolayer. Int J of Pharmaceutics.* 278:415-422, 2004).

## 2 QUESTION BASED REVIEW

### 2.1 GENERAL ATTRIBUTES

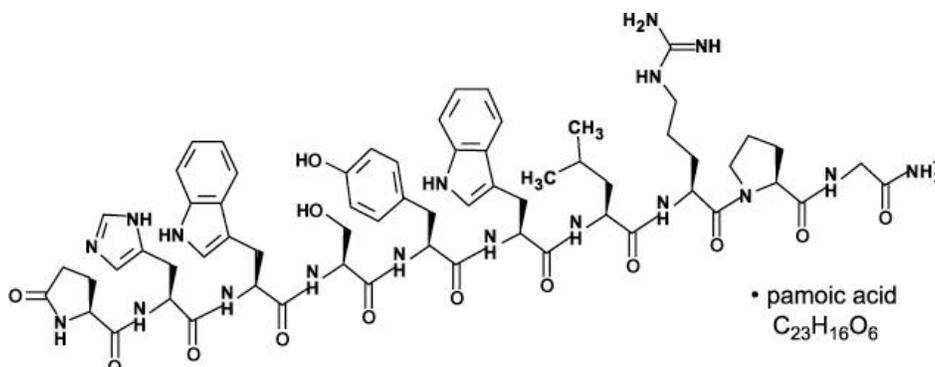
#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Triptorelin is a synthetic decapeptide agonist analogue of the naturally occurring gonadotropin-releasing hormone (GnRH), also called luteinizing hormone-releasing hormone (LHRH). As shown in the [amino acid sequences](#) below, the major structural difference between the native decapeptide (GnRH) and triptorelin is the substitution of the D-amino acid at position six, which is the hinge between the two active portions of the peptide. Triptorelin retains those parts of the native decapeptide responsible for its biological activity. GnRH has an L-glycine at position six, whereas triptorelin has a D-tryptophan.

	1	2	3	4	5	6	7	8	9	10
<b>GnRH (pyro)</b>	Glu	-His	-Trp	-Ser	-Tyr	-Gly	-Leu	-Arg	-Pro	-Gly-NH <sub>2</sub>
<b>Triptorelin</b>	(pyro) Glu	-His	-Trp	-Ser	-Tyr	-D-Trp	-Leu	-Arg	-Pro	-Gly-NH <sub>2</sub>

#### Physico-chemical properties

1. Structural formula:



2. Established name: triptorelin pamoate

3. Molecular Weight: 1699.9 g/mol = 1311.5 (triptorelin) + 388.4 (pamoate)

4. Molecular Formula:  $C_{64}H_{82}N_{18}O_{13} \cdot C_{23}H_{16}O_6$

5. Chemical Name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tryosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycine amide (pamoate salt).

It is a yellowish powder soluble in N,N-dimethylformamide (DMF) and pyridine; practically insoluble in water.

TRELSTAR <sup>(b) (4)</sup> is a sterile, lyophilized, biodegradable microparticle parenteral controlled-release poly(*d,l*-lactide-co-glycolide) (PLG)-based formulation designed to deliver a dose of 22.5 mg triptorelin (3.75 mg per month over 24 weeks). It is supplied as a single-dose vial, containing **22.5 mg** triptorelin pamoate (as free base). When 2-mL Sterile Water for Injection is added to the vial and mixed, a suspension is formed which is intended for intramuscular (IM) administration every 6 months. The drug substance used for manufacture of triptorelin pamoate 22.5 mg was identical to that used for manufacture of the FDA approved Trelstar Depot **3.75 mg** (1-month sustained release) and Trelstar LA **11.25 mg** (3-month sustained release) formulations [NDA 20-715 and NDA 21-288, respectively].

## 2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Triptorelin acts as a potent inhibitor of gonadotropin secretion, initially producing a transient rise in LH, FSH, and testosterone levels. Continuous triptorelin pamoate administration desensitizes pituitary LHRH receptors and inhibits LH and FSH secretion, resulting in chemical castration within ~ 2-4 weeks. In men, a reduction of serum testosterone concentration to a level typically seen in surgically castrated men is obtained.

## 2.1.3 What are the proposed dosage and route of administration?

For advanced prostate cancer, the proposed dosage for **TRELSTAR** (b) (4) is 22.5 mg (6 x 3.75 mg) triptorelin pamoate (as free base) administered every 6 months as a single intramuscular injection in either buttock.

## 2.2 GENERAL CLINICAL PHARMACOLOGY

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The pharmacokinetics (PK: serum triptorelin) and pharmacodynamics (PD: serum testosterone) were evaluated after the **6-month formulation** in **15 patients** in the pivotal **Study 301** and in **24 patients** in **Study 201**. The PK and PD of triptorelin were also evaluated for the **1-month formulation** (N=14) and for the **3-month formulation** (N=13) in **Study TRI-01**. **Study TRI-01** was previously submitted and reviewed under NDA #21-288 on 29-Jun-2000. A description of these clinical studies is shown in Table 1.

**Table 1 A List of Clinical Studies of Trelstar®** (b) (4)

Study Ref. No, (Country)	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects for PK/PD No. M/F Type
DEB-TRI6M-201 (Bulgaria)	Assess achievement of castration ( $\leq 1.735$ nmol/L) on Day 29 and maintenance of castration over Days 57-169 (pilot study)	Single center; Randomized (1 of 3 test formulations); Open-label	22.5 mg q24w x1 6-mo depot intramuscular Batch 4126M0503	8 / 0 Advanced prostate cancer
DEB-TRI6M-301 (South Africa)	Assess achievement of castration ( $\leq 1.735$ nmol/L) on Day 29 and maintenance of castration over Days 57-337 (pivotal study)	Multicenter; Open-label; Non-comparative	22.5 mg q24w x 2 6-mo depot intramuscular Batches 4126M0605 4126M0606	15 / 0 Advanced prostate cancer
DEB-96-TRI-01, 1 <sup>st</sup> phase (South Africa)	Assess achievement of castration ( $\leq 1.735$ nmol/L) on Day 29 and maintenance of castration over Months 2-9 (pivotal study)	Multicenter; Randomized; Parallel group; Active-controlled; Open-label	11.25 mg q12w x3 3-mo depot intramuscular	13 / 0 Advanced prostate cancer
			3.75 mg q4w x9 1-mo depot intramuscular	14 / 0 Advanced prostate cancer

#### ▪ Pivotal Study 301:

This was a **Phase 3**, multi-center, open-label, non-comparative, repeated-dose study in **120 patients** with advanced prostate cancer. All patients received two IM injections of triptorelin pamoate 22.5 mg, one on Day 1 and the other on Day 169. The **primary efficacy endpoint** was to determine the percentage of patients who achieved castration levels of testosterone of  $\leq 1.735$  nmol/L ( $\leq 0.5$  ng/mL, **MW of testosterone=288**) after the first injection of study drug (**Day 29**) and the percentage of

patients who maintained castration serum testosterone levels of  $\leq 1.735$  nmol/L ( $\leq 0.5$  ng/mL) throughout the duration of study treatment (Days 57-337). The sample size of the study was set to assess achievement and maintenance of testosterone castration levels in 95% of patients. According to the Applicant, for the intent-to-treat (ITT) population, the percentage of patients who achieved castration levels of testosterone of  $\leq 0.5$  ng/mL on **Day 29** was 97.5% (95% confidence interval (CI): 93%- 99%) (N=117/120) and the percentage of patients who maintained these castration levels throughout study treatment (**Days 57-337**) was 93% (95% CI: 87%-97%) (N=107/115). In the ITT population, 3 patients did not achieve castration testosterone levels on Day 29: Patient 02601 (0.51 ng/mL), Patient 03606 (0.67 ng/mL) and Patient 11613 (14.21 ng/mL). All three patients remained in the study. Five patients who discontinued the study due to non-drug-related reasons were excluded from the maintenance analysis).

▪ **Pilot Study 201:**

The primary objective of this study was to assess the efficacy of 3 different triptorelin pamoate 6-month formulations in achieving castration levels of testosterone ( $\leq 1.735$  nmol/L, 0.5 ng/mL) at Day 29 after study drug injection and in maintaining the castration levels of serum testosterone from Day 57 to Day 169 in patients with advanced prostate cancer. This was a **Phase 2**, randomized, single-blind, parallel-group, single dose study in **24 patients**. Three different triptorelin pamoate 6-month formulations were tested in **8 patients each**. For each patient, the duration of the treatment period was 169 days (~ 6 months), with a **single IM injection** of study drug given on **Day 1** and the final laboratory testing on Day 169. The composition of these three formulations was as follows:

**Table 2 Composition of the 6-Month Trelstar Formulations Used in Study 201**

Component	Formulation A (batch 4126M0503)	Formulation B (batch 4216M0501)	Formulation C (batch 4126M0502)
triptorelin (peptide base)*	22.5 mg	22.5 mg	22.5 mg
poly (dl-lactide-co-glycolide) (b) (4)	(b) (4)		
(b) (4)			
mannitol	68 mg	68 mg	68 mg
Carboxymethyl-cellulose sodium	24 mg	24 mg	24 mg
polysorbate 80	1.6 mg	1.6 mg	1.6 mg

The primary efficacy endpoint was to determine the percentage of patients who achieved castration levels of serum testosterone ( $\leq 1.735$  nmol/L or 0.5 ng/mL) on Day 29 and the percentage of patients who maintained these levels from month 2 (Day 57) through end of month 6 (Day 169). According to the Applicant, the percentage of patients who achieved castration levels of testosterone of  $\leq 0.5$  ng/mL on **Day 29** and throughout study treatment (**Days 57-337**) are presented in the Tables 3 and 4.

**Table 3 Percentage of Patients Achieving Castration Testosterone Level of  $\leq 0.5$  ng/mL on Day 29**

	A		B		C	
	N	%	N	%	N	%
	8	100.00	8	100.00	8	100.00
<b>95% binomial CI</b>		(63.06 ;1)		(63.06 ;1)		(63.06 ;1)

**Table 4 Percentage of Patients Maintaining Castration Testosterone Level of < or = 0.5ng/mL from Day 57 Till Day 169**

	A		B		C	
	N	%	N	%	N	%
	8	100.00	7	100.00*	6	75.00
<b>95% binomial CI</b>		(63.06 ;1)		(59.04 ;1)		(34.91;96.81)

\*Patient 0146, in the formulation B, died on Day 74; therefore he is not assessable for this criterion.

The following Table summarizes the serum testosterone levels observed during the study.

**Table 5 Descriptive Statistics for Testosterone Serum Levels (ng/mL) during Study 201**

	Formulation A	Formulation B	Formulation C
N	8	8	8
Mean	4.28	4.56	4.39
Std Dev	1.65	0.98	1.24

There was no statistically significant difference among the three formulations in terms of mean testosterone levels ( $p > 0.05$ ). A similar formulation to **Formulation A** was used in the pivotal Phase 3 Study 301 and is the to-be-marketed product (see Section 2.5.3. of this review).

▪ **Study DEB-96-TRI-01:**

The Applicant has also submitted the key **efficacy** data for the **approved Trelstar® 1-month and 3-month** sustained release formulations (**Study DEB-96-TRI-01, first phase**), as agreed upon during the pre-NDA meeting on 17-Mar-2008. This study was submitted and reviewed under NDA #21-288 on 29-Jun-2000.

This was a parallel-group, randomized, multi-center study of two depot formulations of triptorelin pamoate in patients with histologically proven advanced prostate cancer. The study was conducted in two phases. The first phase involved the assessment of the comparative testosterone pharmacodynamics and efficacy of 1-month and 3-month formulations of triptorelin pamoate. Patients in the **first phase** of the study were randomized to receive either three IM injections of triptorelin pamoate 3-month formulation every 84 days or nine IM injections of triptorelin pamoate 1-month formulation every 28 days. The second phase of the study, which was not included in the current NDA 22-437 submission, involved the assessment of the comparative safety and efficacy of 1-month formulations of triptorelin pamoate and leuprolide acetate microspheres.

According to the Applicant, for the ITT population, the percentage of patients who achieved castration levels of testosterone of  $\leq 0.5$  ng/mL at **Day 29** was 97.7% (N=167/171) and 92.7% (N=152/164) for Trelstar® **3-** and **1-month** sustained release formulations, respectively. By Day 85, these levels were maintained in 96.5% of the patients (N=164/177) for the 3-month formulation and in 95.2% of the patients (N=156/164) for the 1-month formulation.

**2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?**

Triptorelin is a potent inhibitor of gonadotropin secretion when given in therapeutic doses. It causes rapid reduction in the circulating levels of androgens (e.g., luteinizing hormone (LH), follicle-stimulating hormone (FSH), **testosterone**, and estradiol). Therefore, the **suppression of testosterone** serum levels was used as the **primary biomarker** in clinical studies. The primary clinical endpoint in the pivotal **Phase 3 Study 301** was to determine:

1. Percentage of patients achieving castration levels of serum testosterone ( $\leq 1.735$  nmol/L or 0.5 ng/mL) on Day 29 calculated as the number of patients with castration levels at the visit, divided by the total number of patients in the considered population (ITT, Per Protocol).
2. Percentage of patients maintaining castration levels of serum testosterone ( $\leq 1.735$  nmol/L or 0.5 ng/mL) from Month 2 to end of Month 12 (Days 57-337) calculated as the number of

patients with castration levels at all visits from Day 29 to Day 337 divided by the total number of patients in the considered population (ITT, Per Protocol).

Serum testosterone level of  $\leq 1.735$  nmol/L (0.5 ng/mL) is currently the most commonly recognized limit of castration and known efficacy criterion to be used in clinical studies for testing new agents in patients suffering from advanced prostate cancer [Lepor, H., "Comparison of Single-Agent Androgen Suppression for Advanced Prostate Cancer", *Reviews in Urology* 7( Suppl. 5): S3-S12, 2005].

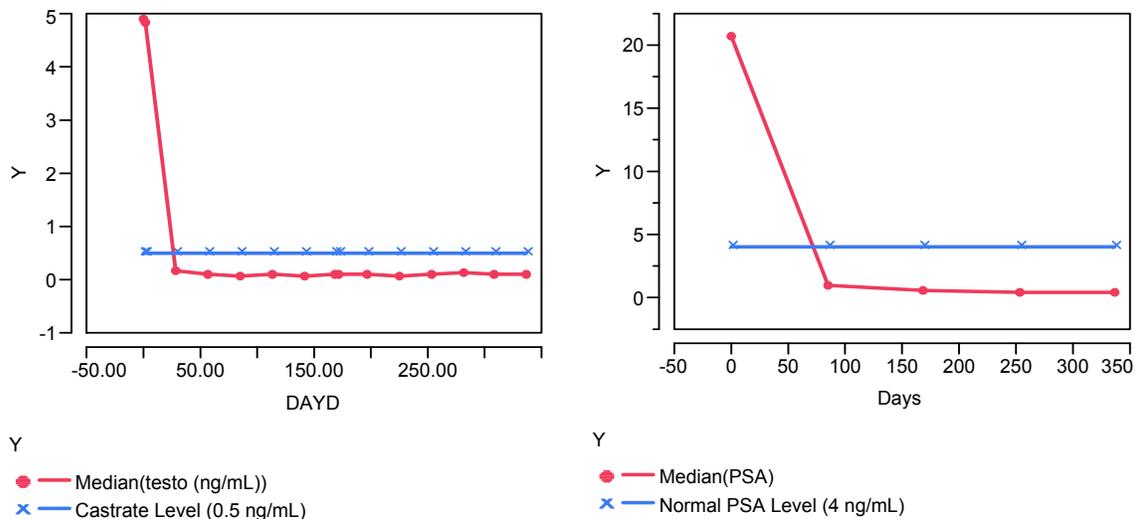
### 2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In **Studies 301** and **201**, human serum samples were analyzed for **triptorelin** using a liquid phase, competitive double antibody radioimmunoassay (RIA) assay method. Human serum samples were analyzed for **testosterone** using a validated LC-MS/MS assay method in **Study 301** and using an RIA assay method in **Study 201**. [See Section 2.6 of this review for the assay validation of these methods]

### 2.2.4 Exposure-response

The primary biomarker used in clinical studies was testosterone serum levels. As a secondary biomarker, the serum level of prostate specific antigen (PSA) was also assessed in Study 301. The following Figure shows the median testosterone and PSA values measured during the study. Table 6 and 7 show the descriptive statistics of testosterone and PSA serum levels measured in the **120 patients** who participated in the pivotal Phase 3 **Study 301** at **Day 29**, at **Days 57-337** and over the **entire period** of the study (**Days 0-337**).

**FIGURE 1:** Testosterone and PSA Serum Levels during Study 301 (N=120)



[Blood samples for testosterone assessments were collected from all patients prior to injections on Days 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337.]

[Blood samples for PSA assessments were collected from all patients prior to injections on Days 1, 85, 253, and 337.]

**Table 6 Descriptive Statistics for Testosterone Serum Levels (ng/mL) during Study 301 (N=120)**

	Day 0 (Baseline)	Day 29	Day 57	Day 169	Day 337
Mean	5.07	0.22	0.13	0.34	0.83
Std Dev	2.05	0.38	0.39	0.38	1.9
Median	3.8	0.28	0.21	0.30	0.27
Range	1.45-10.24	0.13-3.67	0.10-4.46	0.11-4.09	0.10-12.04

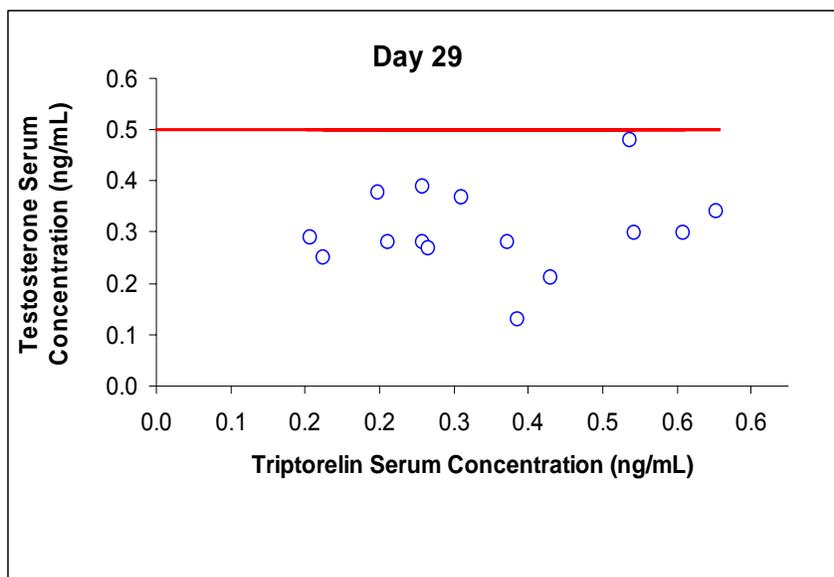
**Table 7 Descriptive Statistics for PSA Serum Levels (ng/mL) during Study 301 (N=120)**

	Day 0 (Baseline)	Day 85	169	253	Day 337
N	120	120	119	116	115
Mean	104.4	6.3	12.6	10.6	24.2
Std Dev	247.1	17.3	66.6	51.8	115.7
Median	19.1	0.95	0.5	0.4	0.4
Range	0.05-1630	0.05-105	0.05-674	0.05-310	0.05-936

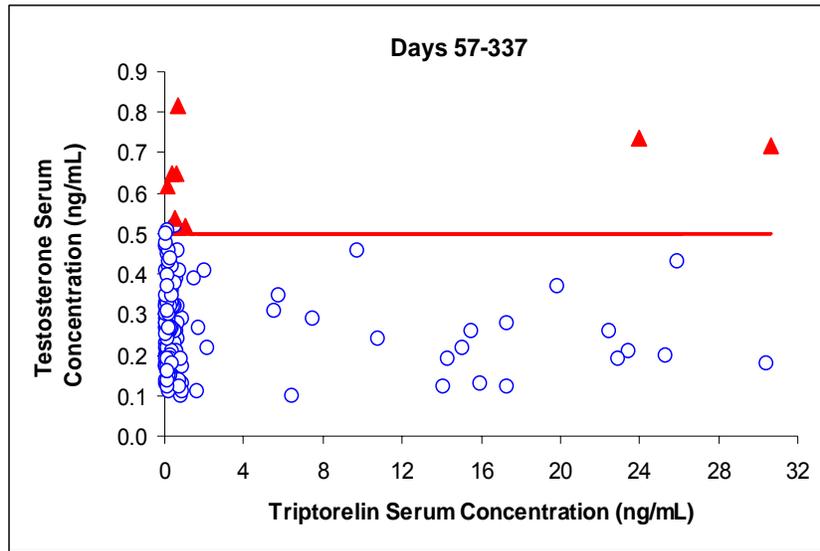
**2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?**

In the pivotal Phase 3 Study 301, **15** out of the **120** patients had their **triptorelin** serum concentrations measured over the study period of 1-337 days. The relationship between testosterone serum levels and **triptorelin** serum concentrations in **15 patients** over the study period is shown in Figures 2 and 3. From Figures 3 and 4 below, 14 out of the 15 patients who had their serum **triptorelin** levels measured **achieved** and **maintained** castration testosterone serum levels of  $\leq 0.5$  ng/mL at **Day 29** and at **Days 57-337, respectively**. Patient #12603 did not maintain castration testosterone levels during Days 57-337. Testosterone and triptorelin serum levels for this patient are presented in Table 8.

**FIGURE 2:** Testosterone Serum Concentrations versus Triptorelin Serum Concentrations at Day 29 from Study 301



**FIGURE 3:** Testosterone Serum Concentrations versus Triptorelin Serum Concentrations on Days 57-337 from Study 301



**Table 8 Testosterone and Triptorelin Serum Levels in Patient # 12603**

Days	Testosterone Serum Concentration (ng/mL)	Triptoreline Serum concentration (ng/mL)
0	5.270	0
1	5.043	0.1
2	7.445	40.39
3	9.677	16.57
5	9.009	2.79
8	5.700	1.098
15	0.507	0.613
29	0.369	0.328
57	0.369	0.402
85	0.449	0.305
113	0.469	0.1
141	0.818	0.685
169	0.518	1.03
170	0.717	30.63
171	0.737	23.96
197	0.648	0.567
225	0.648	0.492
253	0.478	0.355
281	0.748	0.1
309	0.539	0.501
337	0.619	0.169

**2.2.4.2** What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

**Table 9 Treatment-Emergent Adverse Events (TEAEs) Occurred in  $\geq$  2% of Patients in Studies 301 and TRI-01**

MedDRA Preferred Term	Patients Experiencing Events, n (%)		
	6-Month Study 301 N=120	3-Month Study TRI-01 N=174	1-Month Study TRI-01 N=172
Any TEAE	115 (95.8%)	171 (98.3%)	163 (94.8%)
Arthralgia	9 (7.5%)	17 (10%)	21 (12%)
Back pain	13 (11%)	31 (18%)	29 (17%)
Bone pain	4 (3%)	40 (23%)	39 (23%)
Constipation	5 (4%)	32 (18%)	32 (19%)
Cough	2 (1.7%)	18 (10%)	18 (10.5%)
Diarrhea	4 (3%)	16 (9%)	13 (8%)
Edema peripheral	6 (5%)	23 (13%)	22 (13%)
Erectile dysfunction	12 (10%)	4 (2%)	7 (4%)
Headache	9 (7.5%)	45 (26%)	35 (20%)
Hot flush	87 (72.5%)	127 (73%)	115 (67%)
Hypertension	17 (14.2%)	22 (12.6%)	22 (12.8%)
Influenza	19 (16%)	30 (17%)	34 (20%)
Insomnia	6 (5%)	17 (10%)	16 (9%)
Nausea	2 (1.7%)	15 (8%)	16 (9%)
Pain	2 (1.7%)	23 (13%)	24 (14%)
Urinary tract infection	11 (9%)	17 (10%)	21 (12%)

The majority of treatment emergent adverse events (TEAEs) occurred in the pivotal **Study 301** were mild or moderate in severity: 104/120 (87%) patients reported mild TEAEs, 57/120 (47.5%) patients reported moderate TEAEs, and 17/120 (14%) patients reported severe TEAEs. The most frequently reported TEAEs, occurring in  $\geq$ 2% of patients, were hot flushes (72.5%), influenza (16%), hypertension (14%), back pain (11%), and erectile dysfunction (10%) (see Table 9 above). These TEAEs were roughly comparable among the 6-Month, 3-Month, and 1-Month triptorelin formulations.

There were 3 (2.5%) deaths during the pivotal Study 301 of the 6-month formulation. Two patients died due to disease progression at Months 7 and 8. A third patient, who had been at high risk for coronary occlusion and had a history of myocardial bypass and stent placement, died at Month 4 due to a myocardial infarction.

#### 2.2.4.3 Does this drug prolong the QT or QTc interval?

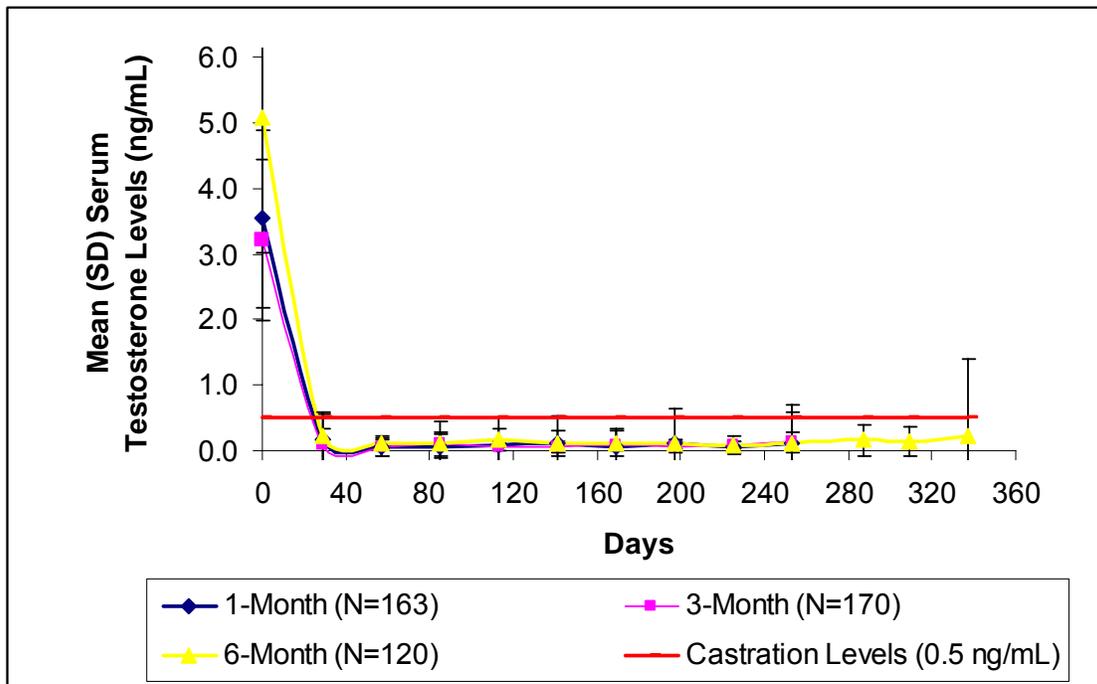
The Applicant has not formally assessed the effect of triptorelin on the QTc interval prolongation. It is well known that hormonal therapies that produced androgen deficiency in men were associated with significant prolongation of the QT interval in patients with prostate cancer.

#### 2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The triptorelin 22.5 mg dose for the 6-month formulation is equivalent to the 3.75 mg triptorelin per one month (i.e., 22.5 mg for the 6-month formulation is 6 x 3.75 mg for the 1-month formulation). The selection of the 3.75 mg dose for the 1-month sustained-release formulation was supported by two small dose-response studies (NDA #20-715). Results of these studies showed that a single intramuscular injection of 1.9 mg to 7.5 mg triptorelin lowered serum testosterone levels to or near castration levels by 28 days post-injection. However, a high proportion of patients receiving 1.9 mg **escaped** castration within 28 days and most patients receiving 7.5 mg **maintained** castration levels >60 days.

A comparison of serum testosterone levels obtained after the three formulations (1-, 3-, and 6-Month) in the Intent-To-Treat (ITT) populations is shown in the Figure below:

**FIGURE 4:** Mean (SD) Testosterone Serum Concentration versus Time Profiles Following IM Injection of TRELSTAR 1-Month (N=163), 3-Month (N=170), and 6-Month (N=120) Sustained Release Formulations



## 2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

### 2.2.5.1 What are the single dose and multiple dose PK parameters?

The pharmacokinetics (PK: **triptorelin**) and pharmacodynamics (PD: **serum testosterone**) were evaluated in the following clinical Studies:

**Table 10** Number of Patients Participated in Clinical Studies 301, 201, and TRI-01

Study	Formulation	N	N with PK Sampling
301	6-Month	120	15
201	6-Month	24	24
*TRI-01	1-Month	164	14
	3-Month	171	13

\*Study TRI-01 was submitted and reviewed under NDA #21-288 on 29-Jun-2000.

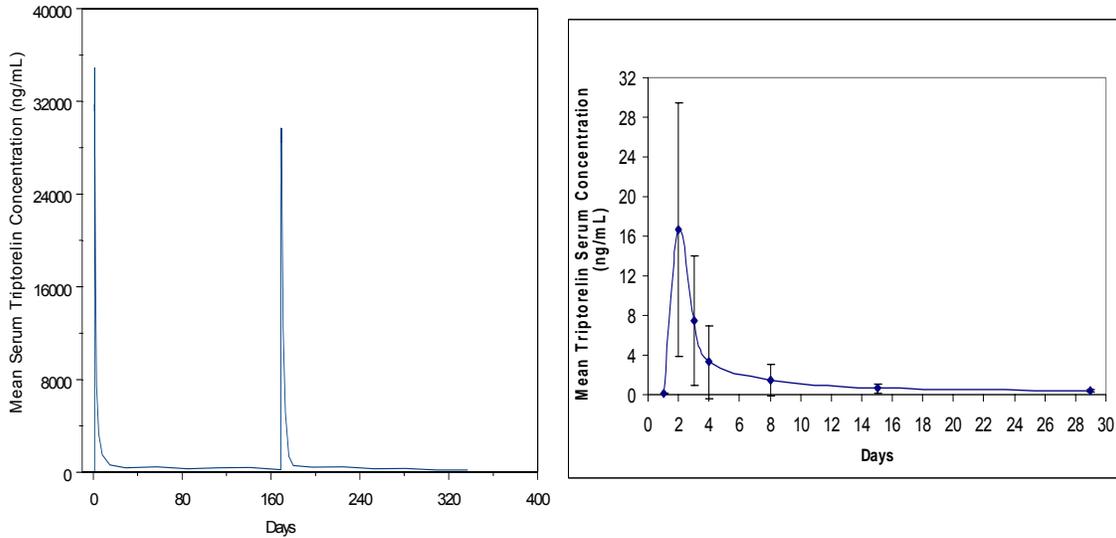
#### ▪ Study 301

This was a Phase 3, multi-center, open-label, non-comparative, repeated-dose study in 120 patients with advanced prostate cancer. All patients received two IM injections of triptorelin 22.5 mg, one on Day 1 and the other on Day 169. In this study, the pharmaco-kinetics (PK) of triptorelin and testosterone were assessed in a subset of 15 patients. Blood samples for triptorelin PK were drawn just prior to the first injection (time 0) and at 1, 2, 3, 4, 6, 8, and 12 hours after the injection on Day 1, then on Days 2, 3, 5, 8, 15, 29, 57, 85, 113, 141, just prior to the second injection (time 0) and at 1, 2, 3, 4, 6, 8, and 12 hours after the injection on Day 169, then on Days 170, 171, 173, 176, 183, 191, 197, 225, 253, 281, 309, and 337. Triptorelin serum levels were measured using a validated radioimmunoassay method. Blood samples for testosterone levels were drawn prior to the first

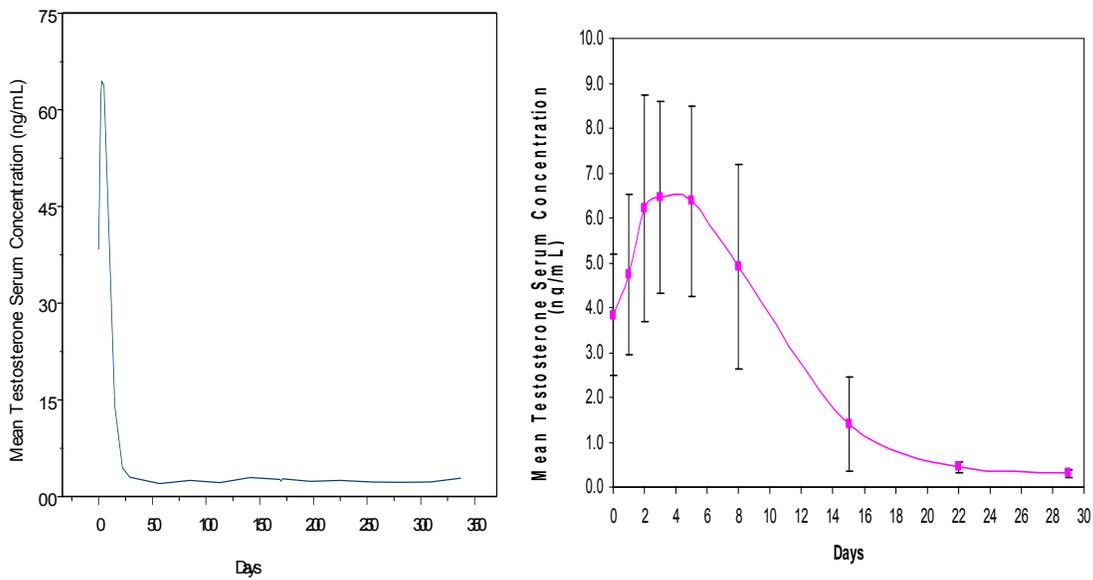
injection (time 0) and on Days 1, 2, 3, 5, 8, 15, 22, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337. Testosterone serum levels were measured using a validated LC-MS/MS method. Figures 7 and 8 below show the mean concentration-time profiles for triptorelin and testosterone, respectively, from PK sampling obtained from the 15 patients.

As seen from Figure 6, during the first month of therapy, testosterone serum levels dropped to castration level of  $\leq 0.5$  ng/mL in these 15 patients.

**FIGURE 5:** Mean (SD) Triptorelin Serum Concentration versus Time Profiles in 15 Patients from Study 301



**FIGURE 6:** Mean (SD) Testosterone Serum Concentration versus Time Profiles in 15 Patients from Study 301



Mean **PK parameters** obtained in **Studies 301** and **TRI-01** for both triptorelin and testosterone are listed in Table 11.

In Study TRI-01, mean  $C_{max}$  values were determined following the injection at the beginning of each 84-day period (~ 3 months). Mean  $AUC_{1-85d}$ ,  $AUC_{85-169d}$  values were only determined for the 3-month formulation and  $AUC_{169-253d}$  for both formulations. Each of these 84-day periods represented one injection of the 3-month formulation or 3 injections of the 1-month formulation.

**Table 11 Mean±SD (%CV) PK Parameters of Triptorelin and Testosterone after the First Injection Following the IM Injection of the current 6-Month and approved 3-Month and 1-Month Formulations**

PK Parameters	Study 301	Study TRI-01*	
	6-Month, 22.5 mg (N=15)	3-Month, 11.25 mg (N=13)	1-Month, 3.75 mg (N=14)
	<b>Triptorelin</b>		
$C_{max}$ (ng/mL)	44.1±20.2 (46%)	38.5±10.5 (27%)	15.8±4.9 (31%)
** $AUC_{1-T}$ (ng*d/mL)	112±43.3 (49%)	105±30.2 (27%)	105±43.2 (41%)
*** $T_{max}$ (days)	3.0 (2.0-12)	2.0 (2.0-6.0)	2.0 (2.0-4.0)
	<b>Testosterone</b>		
$C_{max}$ (ng/mL)	7.9±2.9 (37%)	7.8±2.3 (30%)	6.7±2.3 (34%)
& $AUC_{1-T}$ (ng*days/mL)	76.9±26.7 (35%)	37.2±11.7 (32%)	32.9±11.2 (34%)
*** $T_{max}$ (days)	3.0 (2.0-5.0)	2.0 (1.0-4.0)	4.0 (1.0-6.0)
*** $T_{cast}$ (days)	19.6 (12.8-24.9)	ND	ND

\*Original NDA 21-288

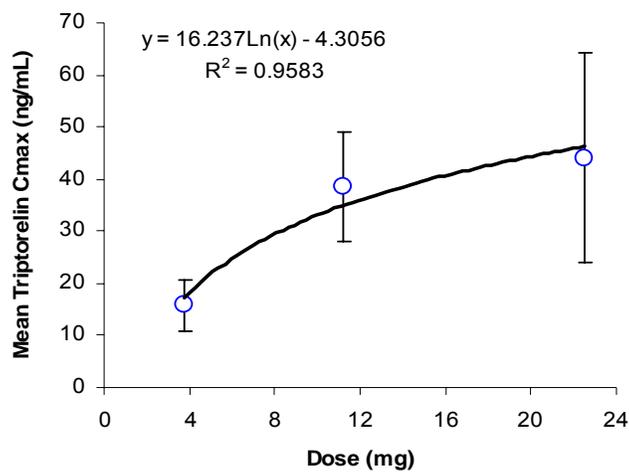
\*\* $AUC_{1-169\text{ days}}$  for the 6-Month formulation and  $AUC_{169-253d}$  for the 3- and 1-Month formulations

& $AUC_{1-169\text{ days}}$  for the 6-Month formulation and  $AUC_{1-144\text{ days}}$  for the 6-Month formulation

\*\*\*Median (range)

After the **first injection** of the **6-month** triptorelin formulation, the mean  $C_{max}$  and  $AUC_{1-169\text{ days}}$  for triptorelin were 44.1±20.2 ng/mL and 111.5±43.3 ng.d/mL, respectively. The median  $T_{max}$  was 3 days (range=2-12 days). A non-linear relationship was noted between each of mean  $C_{max}$  and **triptorelin** dose

**FIGURE 7:** Relationship between Mean  $C_{max}$  and Dose of Triptorelin



The PK parameters for triptorelin following the **second injection** of the **6-month** formulation averaged  $39.2 \pm 19.2$  ng/mL,  $115.2 \pm 31.9$  ng.d/mL, and  $0.19 \pm 0.26$  ng/mL for  $C_{max}$ ,  $AUC_{1-169 \text{ days}}$ , and  $Co$ , respectively. The median  $T_{max}$  was 4 (range=1-24 hours). No accumulation was observed between the first and second injection. The accumulation ratio calculated as  $AUC_{1-169 \text{ days}} \text{ (second injection/first injection)}$  averaged  $1.13 \pm 0.26$ . In general, the variability in PK parameters was moderate,  $< 50\%$ .

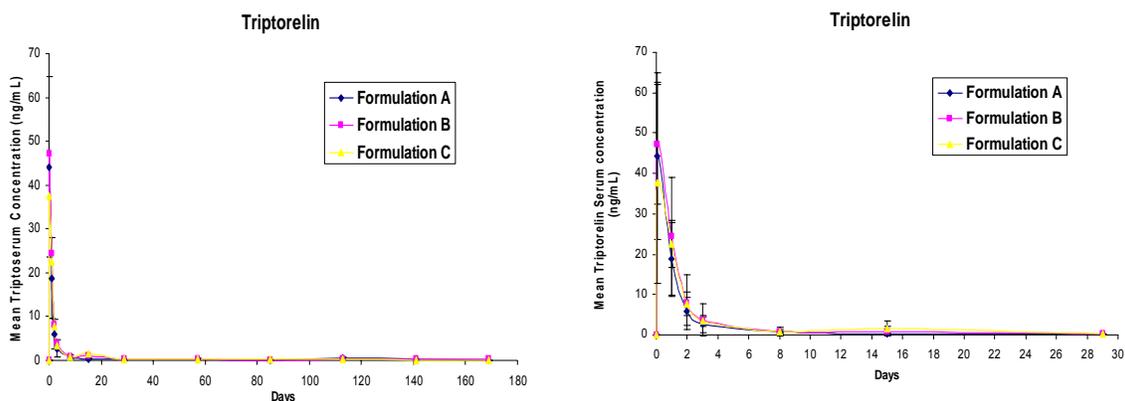
The mean  $C_{max}$  and  $AUC_{1-169 \text{ days}}$  for **testosterone** after the **6-month** formulation were  $7.9 \pm 2.9$  ng/mL and  $76.9 \pm 26.7$  ng.d/mL, respectively. The median  $T_{max}$  and time to castration ( $T_{cast}$ ) were 3 days (range=2-5 days) 19 days (range=13-25 days). Comparable  $C_{max}$  values for serum **testosterone** were between the 6- and 3-Month formulations.  $C_{max}$  was 14% lower after the 1-Month formulation than after the other formulations.

▪ **Study 201**

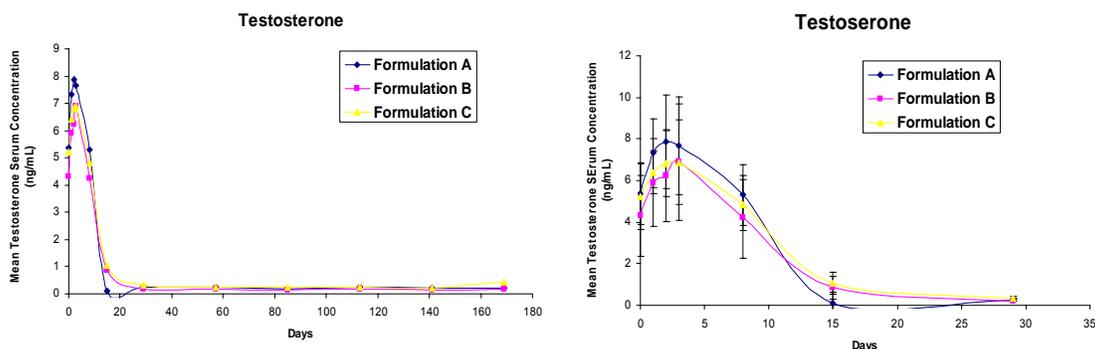
This was a **Phase 2**, randomized, single-blind, parallel-group, single dose, study in **24 patients**. Three different triptorelin pamoate 6-month formulations were tested in **8 patients each**. For each patient, the duration of the treatment period was 169 days (~ 6 months), with a **single IM injection** of study drug given on **Day 1** and the final laboratory testing on Day 169. Blood samples for **triptorelin** PK were drawn just prior to injection (time 0) and at 1, 2, 3, 4, 6, 8, and 10 hours after the injection on Day 1, then on Days 2, 3, 4, 8, 15, 29, 57, 85, 113, 141, and 169. Triptorelin serum levels were measured using a validated radioimmunoassay method. Testosterone levels were measured at t0 (prior to injection) on Day 1 and on Days 2, 3, 4, 8, 15, 29, 57, 85, 113, 141 and 169. Serum testosterone levels were measured using a validated radioimmunoassay method.

The mean concentration-time profiles for triptorelin and testosterone from **Study 201** following IM injection of three different formulation are presented in Figures 10 and 11, respectively. Mean percent of patients achieved castration testosterone levels of  $\leq 0.5$  ng/mL over the study period is shown in Figure 12. The PK parameters are summarized in Table 11.

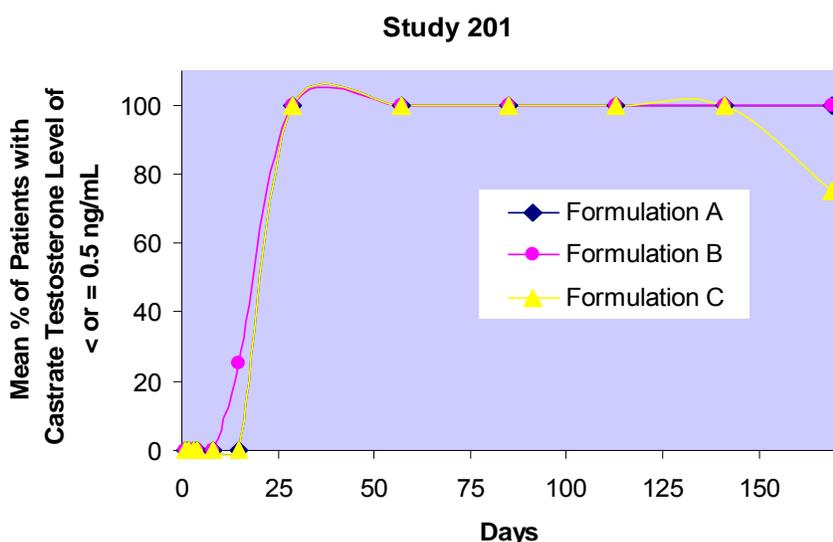
**FIGURE 8:** Mean (SD) Triptorelin serum Concentration versus Time (N=8/Formulation) from Study 201



**FIGURE 9:** Mean (SD) Testosterone Concentration versus Time (N=8/Formulation) from Study 201



**FIGURE 10:** Mean Percent of Patients with Castration Testosterone Serum Levels of  $\geq$  or  $\leq$  0.5 ng/mL (Study 201)



**Table 12** Mean SD (%CV) PK Parameters after IM Injection of Triptorelin and Testosterone (Study 201)

PK Parameters	Formulation		
	A (N=8)	B (N=8)	C (N=8)
<b>Triptorelin</b>			
$C_{max}$ (ng/mL)	81.1±17.1 (21%)	77.1±12.6 (16%)	67.3±19.1 (28%)
$AUC_{1-169 \text{ days}}$ (ng*d/mL)	98.2±30.9 (31%)	105±38.3 (36%)	108±22.9 (21%)
* $T_{max}$ (days)	3.5 (3.0-10)	3.5 (3.0-6.0)	4.0 (3.0-6.0)
<b>Testosterone</b>			
$C_{max}$ (ng/mL)	8.25±2.2 (27%)	7.17±2.8 (38%)	7.48±2.0 (26%)
$AUC_{1-169 \text{ days}}$ (ng*days/mL)	106±21.0 (20%)	82.5±32.8 (40%)	105±25.2 (24%)
* $T_{max}$ (days)	2.0	3.0	2.0

PK Parameters	Formulation		
	A (N=8)	B (N=8)	C (N=8)
	(1.0-3.0)	(1.0-3.0)	(1.0-3.0)
*T <sub>cast</sub> (days)	24 (16-26)	20 (9.0-26)	24.5 (20-26)

\*Median (range)

As seen in the Table and Figures above, the formulations tested in the pilot **Study 201** showed comparable serum triptorelin and serum testosterone profiles. However, because 2 of the 8 patients who received **Formulation C** had testosterone levels above castration levels at Day 169, the Applicant discarded **Formulation C** for further development. Another formulation similar to Formulation A was developed and was used in the pivotal Phase 3 **Study 301**. This formulation was also proposed for marketing (see Section 2.5.3. of this review). Bioequivalence testing was performed on Formulations A, B, and C (see Section 2.5.2. of this review).

There was no need to perform any bioequivalence testing between **Formulation A** and the one used in **Study 301**. The formulation used in Study 301 was also the one proposed for marketing. From Tables 10 and 11, it is noted that the mean AUC<sub>1-269</sub> values were comparable between the two formulations. However, mean C<sub>max</sub> was 1.8-fold higher after **Formulation A** than after the proposed for marketing formulation. Mean C<sub>max</sub> for serum **testosterone** was comparable between the two formulations, 7.9 ng/mL and 8.25 ng/mL, respectively.

**Please refer to the original NDA 20-715 and 21-288 submissions for the following issues**

- 2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?
- 2.2.5.3 What are the characteristics of drug absorption?
- 2.2.5.4 What are the characteristics of drug distribution?
- 2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?
- 2.2.5.6 What are the characteristics of drug metabolism?
- 2.2.5.7 What are the characteristics of drug excretion?
- 2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?
- 2.2.5.9 How do the PK parameters change with time following chronic dosing?
- 2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

## 2.3 INTRINSIC FACTORS

- 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

**2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

## **2.4 EXTRINSIC FACTORS**

**2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?**

### **2.4.2 Drug-drug interactions**

**2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?**

**2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?**

**2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?**

**2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?**

**2.4.2.5 Are there other metabolic/transporter pathways that may be important?**

**2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?**

**2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

## **2.5 GENERAL BIOPHARMACEUTICS**

**2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**

**2.5.2 What is the composition of the to-be-marketed formulation?**

The Applicant proposes to market **TRELSTAR** (b) (4) as sterile, lyophilized, biodegradable microgranules in single-dose vial containing triptorelin pamoate (22.5 mg as the peptide base). When 2-mL sterile Water for Injection is added to the vial and mixed, a suspension is formed which is intended as an intramuscular administration every 6 months. The quantitative composition of the drug product is provided in the Table 13.

**Table 13 Composition of Triptorelin Pamoate 6-Month Formulations**

Component* (includes (b) (4) overfill)	Formulation A (batch 4126M0503)	Formulation B (batch 4126M0501)	Formulation C (batch 4126M0502)	Proposed Commercial Formulation
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
triptorelin (peptide base)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
PLG (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
mannitol	(b) (4)	85 mg	85 mg	(b) (4)
carboxymethylcellulose sodium	(b) (4)	30 mg	30 mg	(b) (4)
polysorbate 80	(b) (4)	2 mg	2 mg	(b) (4)
water for injection	qsad	qsad	qsad	qsad

Formulations A, B, and C were used in the pilot Phase 2 **Study 201**. There was no statistically significant difference between the three formulations in terms of log-transformed AUC and C<sub>max</sub> of either **triptorelin** or **testosterone** (see Tables 14-16).

**Table 14 Geometric Means, Geometric Mean Ratios, and 90% Confidence Intervals (CI) for Log-Transformed C<sub>max</sub> of Triptorelin**

Formulation	Geometric Mean C <sub>max</sub> (ng/mL)	Test/ Reference	Ratio (%)	90% CI	p-value
A	81.1	A/B	104	88-124	0.666
B	77.1	A/C	1.23	98-154	0.137
C	67.3	B/C	117	95-145	0.197

**Table 15 Geometric Mean, Geometric Mean Ratios, and 90% Confidence Intervals (CI) for Log-Transformed AUC<sub>1-169 days</sub> of Triptorelin**

Formulation	Geometric Mean AUC <sub>1-169 days</sub> (ng.d/mL)	Test/ Reference	Ratio (%)	90% CI	p-value
A	94.4	A/B	95	70-128	0.753
B	99.7	A/C	89	71-111	0.368
C	106.3	B/C	94	72-122	0.672

**Table 16 Geometric Means, Geometric Mean Ratios, and 90% Confidence Intervals for Log-Transformed C<sub>max</sub> of Testosterone**

Formulation	Geometric Mean C <sub>max</sub> (ng/mL)	Test/ Reference	Ratio (%)	90% CI	p-value
A	7.97	A/B	123	84-184	0.354
B	6.45	A/C	110	87-138	0.491
C	7.28	B/C	89	60-130	0.586

**Table 17 Geometric Means, Geometric Mean Ratios, and 90% Confidence Intervals for Log-Transformed C<sub>max</sub> of Testosterone**

Formulation	Geometric Mean AUC <sub>1-169 days</sub> (ng.d/mL)	Test/Reference	Ratio (%)	90% CI	p-value
A	104.25	A/B	95	70-128	0.753
B	75.17	A/C	89	71-111	0.368
C	102.53	B/C	94	72-122	0.672

Formulation C was discarded from further development. **Formulation A** was selected over **Formulation B** for further development because it uses a manufacturing process that is common to the approved **1-month** and **3-month** formulations. A formulation similar to Formulation A was used in the pivotal Phase 3 Study 301 and also was proposed for marketing (see Table 18 below).

**2.5.3 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?**

The **commercial formulation** was used in the pivotal Phase 3 Study 301 (Batch No.: for the First Injection = **Batch 4126M0605**; for the Second Injection = **Batch 4126M0606**), therefore, there was no need to conduct a formal bioequivalence study to compare between the product used in the clinical study and the one proposed for marketing. The Composition of commercial 6-Month formulation compared to the approved 1-Month and 3-Month formulation is as follows:

**Table 18 Composition of the TRELSTAR 6-Month Formulation Compared to the Approved 1-Month and 3-Month Formulations**

Ingredient	Quantity per Dose		
	1-Month	3-Month	6-Month
Triptorelin Pamoate (base)	3.75 mg	11.25 mg	22.5 mg
Poly-d-l-lactide co-glycolide (b) (4)	170 mg	145 mg	(b) (4)
(b) (4)	--	--	(b) (4)
(b) (4)	--	--	(b) (4)
Mannitol	85 mg	85 mg	68 mg
Carboxymethylcellulose sodium	30 mg	30 mg	24 mg
Polysorbate 80	2 mg	2 mg	1.6 mg
Water for Injection	q.s	q.s.	q.s.

**2.5.4 What moieties should be assessed in bioequivalence studies?**

**2.5.5 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

**2.5.6 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?**

**2.6 ANALYTICAL SECTION**

**2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology studies?**

No relevant metabolites were measured in human serum samples for either triptorelin or testosterone in the clinical pharmacology Studies 301 and 201.

**2.6.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?**

Serum samples from **Studies 201 and 301** were assayed for **triptorelin** using a liquid phase, competitive double antibody radioimmunoassay (RIA) with untreated human serum samples. To avoid a matrix effect the serum samples were subjected to a (b) (4) process

prior to the execution of the immunoassay. The primary antibody was rabbit D-Trp6-GnRH antiserum. The tracer was radioiodinated D-Trp6-GnRH. Separation was done by goat anti-rabbit IgG and Normal Rabbit Serum.

Serum samples from **Study 301** were assayed for **testosterone** using LC method with MS/MS detection (**LC-MS/MS**). The analytical procedure involved extraction of testosterone from human serum by a (b) (4) method.

Serum samples from **Study 201** were assayed for **testosterone** using an **RIA** method. This assay method is based on a competitive test principle using an antiserum specifically directed against testosterone.

The cross reactivity of RIA method for **triptorelin** assay was >0.1% with D-Trp6.desgly10GnrH-EA and <0.001% with LH, FSH, somastatin, and TRH.

The cross reactivity of RIA method for **testosterone** assay was 3.8% with dihydrotestosterone, 3.7% with methyltestosterone, 10.2% with nortestosterone, and <1% with other steroids.

Cross reactivity with endogenous GnRH is 100%. Since the endogenous GnRH levels in males are below the sensitivity of the assay method; this was not a problem.

These assays were validated with regard to selectivity, sensitivity, accuracy, precision, and stability. Serum samples were diluted 10-fold to cover the linear range of the assay. The analytical parameters are given in the following table.

**Table 19 Summary of Bioanalytical Methods Used for Triptoreon and Testosterone in the Clinical Pharmacology Studies**

Studies	Pilot Study 201		Pivotal Study 301	
	Triptorelin	Testosterone	Triptorelin	Testosterone
Method	RIA	RIA	RIA	LC-MS/MS
LLOQ	0.75 ng/mL	0.1 ng/mL	0.05 ng/mL	0.03 ng/mL
Standard Curve	0.017 to 2.0 ng/mL	0.1-14 ng/mL	0.05-15 ng/mL	0.03-3.0 ng/mL
<b>Precision (%CV) of QC Samples</b>				
Intra-Assay	4.2-9.7%	4.2-8.8%	7.3-13.4%	4.8-14%
Inter-Assay	2.4-6.8%	5.5-9.4%	5.5-20.6%	0.6-3.2%
<b>Accuracy (%) of QC samples</b>				
	85-117%	79-109%	85-115%	100-113%

### 3 OCP LABELING RECOMMENDATIONS

Changes which were sent to the sponsor are below. Only relevant clinical pharmacology sections are included.



(b) (4)

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

## **4.2 APPENDIX 2 – INDIVIDUAL STUDY REPORTS**

Available upon Request

### 4.3 APPENDIX 3 – OCP FILING REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics				
NEW DRUG APPLICATION FILING AND REVIEW FORM				
4.3.1.1.1 General Information About the Submission				
	Information		Information	
NDA Number	22-437	Brand Name	Trelstar (b) (4)	
OCP Division (1,2,3,4,5)	DCP5	Generic Name	Triptorelin pamoate	
Medical Division	DDOP	Drug Class	Leutinizing hormone releasing hormone (LHRH) agonist	
OCP Reviewer	Sophia Abraham	Indication(s)	Palliative treatment of advanced prostate cancer	
OCP Team Leader	Brian Booth	Dosage Form	22.5 mg as a single intramuscular injection	
Date of Submission	12-Sep-2008	Dosing Regimen	Once every 6 months	
Estimated Due Date of OCP Review	12-May-2009	Route of Administration	Intramuscular	
PDUFA Due Date	12-Jul-2009	Sponsor	Watson Laboratories, Inc.	
Division Due Date	02-Jun-2009	Priority Classification		
Clin. Pharm. and Biopharm. Information				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	3	3	
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)				
<b>4.4 HEALTHY VOLUNTEERS-</b>				
single dose:				
multiple dose:				
<b>4.4.1 Patients-</b>				
single dose:				
multiple dose:	x	2	2	
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		<b>5</b>	<b>5</b>	

<b>Filability and QBR comments</b>				
	<b>“X” if yes</b>	<b>Comments</b>		
<b>Application filable ?</b>	<b>x</b>	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
<b>Comments sent to firm ?</b>		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
<b>QBR questions (key issues to be considered)</b>				
<b>Other comments or information not included above</b>				
<b>Primary reviewer Signature and Date</b>				
<b>Secondary reviewer Signature and Date</b>				

CC: NDA 22-437, DDOP (Robertson), DCP5 (Booth, Rahman), CDR (Biopharm)

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6/18/2009 01:49:05 PM  
BIOPHARMACEUTICS

Brian Booth  
6/30/2009 07:44:20 AM  
BIOPHARMACEUTICS

## Biopharmaceutics Review

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<b>NDA:</b>	<b>22-437</b>
<b>Submission Date:</b>	<b>September 12, 2008</b>
<b>Type of Submission:</b>	<b>Original Application</b>
<b>Product name</b>	<b>Trelstar® (b) (4) (Triptorelin Pamoate)</b>
<b>Dosage Form:</b>	<b>Injectable Suspension</b>
<b>Dosage Strengths:</b>	<b>22.5 mg</b>
<b>Sponsor:</b>	<b>Watson</b>

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### Recommendation

The test conditions and specifications of the *in vitro* dissolution method of triptorelin pamoate 22.5 mg formulation proposed by the sponsor are summarized below.

<b>Dissolution Apparatus:</b>	USP Type 2 Paddle
<b>Dissolution Medium:</b>	50 mL of methanol to 950 mL of water
<b>Stirring Speed:</b>	75 rpm
<b>Temperature:</b>	Gradient from 37 to 61°C over 48 hours, followed by continuous heating at 61°C
<b>Test Duration:</b>	10 days
<b>Sampling Points:</b>	1, 24, (b) (4), and 168 hours
<b>Dissolution Analysis:</b>	HPLC

The Sponsor Proposed Sampling Points and Dissolution Specifications	
Time (hr)	% Release
1	(b) (4)
24	(b) (4)
(b) (4)	(b) (4)
168	(b) (4)

The sponsor's proposed *in vitro* dissolution method and specifications are acceptable pending the implementation of the following recommendations:

- To add a sampling point between 1 and 24 hour
- To eliminate the (b) (4) hour sampling point
- To add instead a sampling point at 96 hour.

Overall, the recommended sampling points and specifications are listed below.

FDA Recommended Sampling Points and Dissolution Specifications	
Time (hr)	% Release
1	(b) (4)
12	(b) (4)
24	(b) (4)
96	(b) (4)
168	(b) (4)

\*Interpolated sampling time points and specifications as no data is provided in this application on the 12 and 96 hours sampling points

The IVIVR is not acceptable because the formulations used to develop the relationships did not have different release rates. The IVIVR did not predict the entire profile for the two phases of drug release. The IVIVR was able to predict only the AUC but not the Cmax. Additionally, the IVIVR did not meet the criteria for internal and external predictability. Therefore, this IVIVR can not be used to support any post-approval changes.

## Background

Triptorelin is a synthetic decapeptide agonist analogue of the naturally occurring gonadotropin-releasing hormone (GnRH). Triptorelin was originally developed as a soluble acetate salt, formulated as a conventional solution for immediate release (triptorelin acetate). Triptorelin was further developed as an insoluble pamoate salt, formulated as microgranules designed to deliver 3.75 mg of the active moiety over 28 days (1-month formulation), and then as microgranules to deliver 11.25 mg of the active moiety over 84 days (3-month formulation).

Triptorelin was approved for the first time in 1986 in France for the treatment of advanced prostate cancer. In 2000, a 1-month formulation (3.75 mg) of triptorelin (Trelstar® Depot) was approved in the United States for this indication under NDA 20-715. A 3-month formulation (Trelstar® LA) was subsequently approved in 2001 under NDA 21-288.

Watson is submitting NDA 22-437 for a new sustained release formulation (Trelstar® (b) (4)) designed to release 22.5 mg of triptorelin over a period of 168 days (6 months). This is achieved by (b) (4)

This (b) (4) is primarily responsible for maintaining the plasma concentration of triptorelin in the later months. Watson is seeking approval for the palliative treatment of advanced prostate cancer, (b) (4)

(b) (4) This indication is the same as the one approved for the 1- and 3-month formulations.

Triptorelin pamoate 22.5 mg is a sterile, lyophilized, biodegradable microgranule formulation supplied as a single-dose vial. When 2 mL Sterile Water for Injection is added to the vial containing the lyophilized microgranule formulation and mixed, a suspension is formed which is intended as an intramuscular injection to be administered every 168 days (i.e., every 24 weeks). The triptorelin pamoate salt is relatively insoluble in aqueous media (60µg/mL in water), which is critical for the prolonged release.

## Assessment of The In Vitro Dissolution Method

Triptorelin pamoate 22.5 mg formulation is a blend of (b) (4). The composition per vial of clinical batches and proposed commercial formulation are shown in Table 1.

Table 1: The composition per vial of clinical batches and proposed commercial formulation

Component* (includes (b) (4) overfill)	Formulation A (batch 4126M0503)	Formulation B (batch 4126M0501)	Formulation C (batch 4126M0502)	Proposed Commercial Formulation
(b) (4)	(b) (4)	(b) (4)		(b) (4)
triptorelin (peptide base)				
PLG (b) (4)				
(b) (4)				
mannitol		85 mg	85 mg	
carboxymethylcellulose sodium		30 mg	30 mg	
polysorbate 80		2 mg	2 mg	
water for injection	qsad	qsad	qsad	qsad

Source: [Module 3.2.P.2.2.2](#)

Note that Formulation A is identical to the proposed commercial formulation. However, formulations B and C differ from the proposed commercial formulation.

During formulation development, it was necessary to establish an accelerated in vitro dissolution test in order to characterize test formulations. The goal is for the accelerated test to satisfy the following criteria:

- Works under sink conditions;
- Achieves release of (b) (4) of the active substance incorporated into the formulation;
- Test duration of no more than 10 days in order to (b) (4);
- No need to change dissolution medium during the test (b) (4);
- Discriminative and able to be validated.

The conditions for the accelerated dissolution test for the triptorelin pamoate 22.5 mg formulation were based on the conditions developed and validated for the previously approved Trelstar LA 11.25 mg formulation. However, in order to meet the targeted test duration it was necessary to accelerate the degradation rate of the polymer by either acidifying the pH of the medium or heating it.

Since triptorelin is degraded in acid conditions, it was necessary to work at higher temperatures. A temperature gradient from 37 to 61°C over 48 hours, followed by continuous heating at 61°C was implemented.

The test conditions of in vitro dissolution of the Trelstar LA 11.25 mg formulation and the triptorelin pamoate 22.5 mg formulation are summarized in the table 2 below.

Table 2: In-Vitro Dissolution Test for Trelstar LA 11.25 mg and Triptorelin pamoate 22.5 mg Formulations.

Test Parameter	Trelstar LA 11.25 mg	Triptorelin pamoate 22.5 mg 22.5 mg
Dissolution system	USP type 2	USP type 2
Dissolution medium	water:methanol, 95:5	water:methanol, 95:5
Stirring speed	200 rpm	200 rpm*
Conditions	1 vial drug product in 500 mL dissolution medium	1 vial drug product in 1 L dissolution medium
Temperature	37°C	gradient from 37 to 61°C over 48 hours, followed by continuous heating at 61°C
Duration	3 days	10 days**
Sampling points	1h, 48h, 72h	1h, 24h, 48h, 72h, 6d, 7d, 10d*
Analysis of dissolution samples by	HPLC	HPLC

\* For release testing for commercial product the test is performed at 75 rpm, which has proved to be equivalent to 200 rpm, and over 7 days. Data on file.

\*\* During development tests were performed for up to 13 days.

The accelerated in vitro release is achieved by adding 50 mL of methanol to 950 mL of water as test medium, stirring at 75 rpm, and raising the water bath temperature from 37°C to 61°C during the first 48 hours and maintaining it at 61°C thereafter. The dissolution medium is sampled at 1 hour, 24 hours, (b) (4), and 7 days and tested for triptorelin content using a validated HPLC method. The in vitro dissolution profiles obtained for batches of Trelstar (b) (4) manufactured to date are summarized in Table 3 below.

Table 3: Summary of In Vitro Dissolution Studies of Triptorelin Pamoate 22.5 mg

Product ID/ Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean% Dissolved (range)			
				1 hr	24 hr	(b) (4)	7 days
4126M0503 <sup>A</sup>	Lyophilisate, resuspended in 2 mL Water for Injection	USP Type 2 vessel; 2 mL sample in methanol:water (50 mL:950 mL); Stirred at 75 rpm; 37°-61°C over 48 hr, then kept at 61°C	6	(b) (4)			
4126M0605 <sup>B</sup>			6				
4126M0606 <sup>B</sup>			6				
4126M0707 <sup>C</sup>			6				
4126M0708 <sup>C</sup>			6				
3126M011 <sup>D</sup>			6				
D306I01C8 <sup>D</sup>			6				
D306I02C8 <sup>E</sup>			6				
D306I03D8 <sup>E</sup>			6				
D306I04D8 <sup>E</sup>			6				
D306D05F8 <sup>F</sup>			6				
D306D06F8 <sup>F</sup>			6				
3126M048 <sup>G</sup>			6				
3126M049 <sup>G</sup>	6						
Proposed commercial specification limits**			6				

\* Results from batch release testing

\*\* Proposed specification limits set at mean (b) (4) absolute

A: Batch used for pilot clinical study DEB-TR16M-201

B: Batches used for pivotal clinical study DEB-TR16M-301

C: Batches to assess effects of PLGA polymer viscosity at the lower and upper specification limits

D: Batch irradiated at (b) (4)

E: Consistency batches

F: Batches to assess effects of the core loading at the lower and upper specification limits

G: Batches to assess effects of the particle size at the lower and upper specification limits

For the *in vitro* dissolution test, the sponsor proposed the specifications based on the *in vitro* dissolution profiles for 12 batches manufactured to date using the proposed commercial process (see table 4 below). For the 1 hour, 24 hour, and (b) (4) timepoints, a (b) (4) absolute range was added to the mean value for the 12 batches. For the 7 day timepoint, the proposed commercial specification was set at (b) (4)

Table 4: Dissolution Profiles for Triptorelin Pamoate 22.5 mg Batches to Date

Lot Number [Use]	Storage	Percent Peptide Released, mean (range)			
		1 hour	24 hours	(b) (4)	7 days (b) (4)
4126M0503 [study DEB-TRI6M-201]	release test				
	3 mo 25°C				
	6 mo 25°C				
	9 mo 25°C				
	12 mo 25°C				
	18 mo 25°C				
	24 mo 25°C				
	36 mo 25°C				
4126M0605 [study DEB-TRI6M-301]	release test				
	3 mo 25°C				
	6 mo 25°C				
	9 mo 25°C				
	12 mo 25°C				
	18 mo 25°C				
	24 mo 25°C				
4126M0606 [study DEB-TRI6M-301]	release test				
	3 mo 25°C				
	6 mo 25°C				
	9 mo 25°C				
	12 mo 25°C				
D306I02C8 [process consistency]	release test				
D306I03D8 [process consistency]	release test				
D306I04D8 [process consistency]	release test				
4126M0707 [high viscosity]	release test				
	3 mo 25°C				
	6 mo 25°C				
	9 mo 25°C				
	12 mo 25°C				
4126M0708 [low viscosity]	release test				
	3 mo 25°C				
	6 mo 25°C				
	9 mo 25°C				
	12 mo 25°C				
D306D05F8 [low core loading]	release test				
D306D06F8 [high core loading]	release test				
3126M048 [high particle size]	release test				
3126M049 [low particle size]	release test				
mean					
proposed specification					

\* Results from batch release testing

\*\* Proposed specification limits set at mean (b) (4) (absolute)

\*\*\* Proposed specification of (b) (4) in accordance with USP <1092>, and ICH

**Reviewer's Note:**

It is recommended that the sponsor add a sampling point between 1 and 24 hour, eliminate the (b) (4) sampling point, and add instead a sampling point at 96 hour. In total, the recommended sampling points are five: at 1 hour, 12 hour, 24 hour, 96 hour and 7 days as seen in Table 5 below.

Table 5: Sampling Points and Dissolution Specifications

Sponsor Proposed Sampling Points and Dissolution Specifications		FDA Recommended Sampling Points and Dissolution Specifications	
Time (hr)	% release	Time (hr)	% release
1	(b) (4)	1	(b) (4)
24	(b) (4)	12	(b) (4)
(b) (4)	(b) (4)	24	(b) (4)
168	(b) (4)	96	(b) (4)
		168	(b) (4)

\*Interpolated sampling time points and specifications as no data is provided in this application on the 12 and 96 hours sampling points

**Assessment of the In Vitro-In Vivo Relationship**



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/s/

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Houda Mahayni  
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Patrick Marroum  
6/25/2009 01:42:19 PM  
BIOPHARMACEUTICS