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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-288

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	21-288
Drug:	Trelstar LA (Triptorelin pamoate lyophilized, 11.25 mg)
Sponsor:	Debio R.P.
Date of Submission:	06/29/00, 09/05/00, 10/04/00, 06/27/01, and 06/28/01
Type of Submission:	Original NDA
Reviewer:	Venkateswar R. Jarugula, Ph.D.

EXECUTIVE SUMMARY

Triptorelin pamoate is a synthetic decapeptide agonist anolog of naturally occurring lutenizing hormone releasing hormone (LHRH). Trelstar LA is a long acting suspension containing triptorelin pamoate intended to be administered as an intramuscular injection every 84 days as a palliative treatment of advanced prostate cancer. Trelstar Depot, a one-month (administered every 28 days) formulation of triptorelin palmoate (NDA 20-715) was approved by FDA on 06/15/00, also as a palliative treatment of prostate cancer.

Three clinical pharmacokinetic studies with the to be marketed formulation of Trelstar LA in men with advanced prostate cancer were submitted in the current NDA. In brief, the following are pharmacokinetic and pharmacodynamic characteristics of Trelstar LA.

Following the administration of Trelstar LA, serum concentrations of triptorelin reach peak levels in about 2 to 6 hours and declined slowly to levels below limit of quantitation by Day 29. As expected, since the dose is 3 times higher, peak serum concentrations of triptorelin were higher for the 3-month formulation than for the approved 1-month formulation. The 3-month formulation (Trelstar LA) has similar bioavailability (based on AUC values) of triptorelin compared to 1-month approved formulation. It should be noted the serum levels of triptorelin were below LOQ for substantial latter portion of 3-months dosing period. There is no significant accumulation of triptorelin upon multiple dosing of Trelstar LA.

As expected with LHRH agonists, the serum testosterone levels initially surged up to reach peak levels in about 2 to 4 days following administration of Trelstar LA. By Day 29, serum testosterone levels were suppressed below castration levels (1.735nmol/l). The

peak serum T levels, initially were slightly higher with Trelstar LA compared to Trelstar 1-month formulation, consistent with higher peak concentration of triptorelin. The 3-month formulation (Trelstar-LA) was shown to be as effective as the approved 1-month formulation (Trelstar) in suppressing serum T levels below castration.

In a retrospective analysis of the serum T concentration data in a subset of patients, 2 out of 15, who received Trelstar LA, showed rise in T levels above the castration limit whereas none of the 15 patients on 1-month Trelstar escaped castration. Since this effect was monitored only for a small sample size (15 patients), the clinical division is recommending a Phase IV study to evaluate the acute-on-chronic surge effect of Trelstar LA.

Sponsor's proposed in vitro dissolution method and specifications are acceptable. Due to lack of adequate validation, the IVIVC submitted by the sponsor can not be used to support any formulation changes that may take place in future.

The comments outlined in the Labeling section should be communicated to the sponsor as appropriate.

RECOMMENDATION

The human pharmacokinetics and bioavailability (section 6) of NDA 21288 for Trelstar LA is acceptable from Clinical Pharmacology and Biopharmaceutics perspective.

/S/

Venkateswar R. Jarugula, Ph.D.

/S/

RD initialed by Ameeta Parekh, Ph.D. , Team Leader _____

FT signed by Ameeta Parekh, Ph.D., Team Leader /S/

cc: NDA 21288, HFD-580 (Monroe, Best), HFD-870 (Malinowski, Parekh), CDR (B.Murphy for Drug).
CPB Briefing Attendees: Drs. Malinowski, Hunt, Parekh, and Monroe.

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CLINIAL PHARMACOLGY AND BIOPHARMACEUTICS SUMMARY

What is Trelstar LA (Triptorelin)? What is its mechanism of action?

Background

Triptorelin is a synthetic decapeptide agonist analog of the naturally occurring luteinizing hormone-releasing hormone (LHRH), also called gonadotropin releasing hormone (GnRH). Chemically triptorelin is similar in structure to LHRH except for the substitution of the 6th aminoacid Glycin in LHRH by D-Tryptophan. LHRH is synthesized by the hypothalamus and it selectively stimulates gonadotropin cells to synthesize and release the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In turn, LH and FSH stimulate the gonadal production of sex steroid hormones and gametogenesis. Hypothalamic release of LHRH and its action on the pituitary are controlled by bio-feedback mechanisms based on the amount of sex steroid hormones in the circulation. An acute injection of LHRH agonist induces a marked and prolonged release of LH and FSH. However, continuous stimulation of pituitary by either repeated administration of immediate release or single administration of long-acting LHRH agonists leads to suppression of LH and FSH secretion and consequently suppression of testicular (or ovarian) steroid production. Thus, chronic administration of LHRH agonists leads to suppression of testosterone in men.

Currently, leuprolide and goserelin are available in this chemical class for prostate cancer indication. Trelstar Depot, a 1-month formulation, has been approved by FDA for the palliative treatment of advanced prostate cancer in men. In this NDA, sponsor is seeking approval for a new controlled release formulation of triptorelin (11.25 mg dose) in microgranules for 3-month (every 84 days) administration.

What is the formulation of Trelstar -LA?
What are the differences between the to be marketed Vs clinical trial formulation?

Formulation

Trelstar LA is a lyophilized powder which contains triptorelin palmoate incorporated in to microgranules of poly (d,l lactide-glycolide), along with the stabilizers carboxymethyl cellulose sodium (CMC): a thickening agent that slows the sedimentation of microgranules, and polysorbate 80 (Tween 80) to improve dispersion of microgranules both during lyophilization and subsequent reconstitution, and mannitol as an excipient. The ratio of lactide to glycolide in the ploymer

Composition of Trelstar LA:

Triptorelin (free base units)	11.25 mg
Triptorelin pamoate	
Poly(d,l-lactide-co-gycolide)	145 mg
Mannitol, USP	85 mg
Carboxymethylcellulose sodium, USP	30 mg
Polysorbate 80, NF (Tween 80)	2 mg
Sterile water for irrigation, USP	qs

The to be marketed formulation described above was used in the pivotal phase III clinical trial as well as the pivotal pharmacokinetic studies. There were no changes in the site of manufacturing and scale-up.

Are the analytical methods for measuring triptorelin, testosterone and other pharmacodynamic endpoints adequate?

Analytical Methods

Radioimmuno assay methods were used to determine serum triptorelin and testosterone concentrations. The following table summarizes the validation parameters of the assay methodology used in different studies of the NDA.

Study	Analyte	Assay variability (%CV)		LOQ
		Intra-assay	Inter-assay	
DEB-96-TRI-01	Triptorelin	1.7-10.8%	3.6 – 9.7%	ng/ml
	Testosterone	6.2-8.6%	6.9-13.6%	nmol/l
DEB-95-TRI-01	Triptorelin	<14%	<18%	ng/ml
	Testosterone	<8%	<8.5%	nmol/L
DEB-99-TRI-01	Triptorelin	2.3 – 5.3%	3.5 – 12.7%	ng/ml
	Testosterone	6.2-8.6%	9.1 – 19.2%	9 ng/ml

The cross reactivity of RIA method for triptorelin assay was <0.1% with D-Trp^{6} des Gly^{10}GnRH-EA; <0.001% with LH, FSH, somastatin, and TRH. The cross reactivity of 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, sponsor stated that this is not a problem. No assay validation and cross reactivity data are reported for the RIA method used for Study DEB-95-TRI-01. Only assay variability and LOQ are reported in the summary section. The RIA method for this study used different antibody compared to the RIA method used in the other two studies. Upon FDA's request, sponsor provided validation information for this assay method. Validation information for this method is acceptable.

The assay methodology for testosterone measurements (primary efficacy endpoint) is acceptable. However, the triptorelin serum concentrations following Trelstar administration were found below LOQ after 2 weeks following dosing in studies DEB-96-TRI-01 and DEB-99-TRI-01. Although the LOQ is low (ng/ml), the assay method is not adequate to determine the entire serum concentration profile for the dosing period. For Study DEB-95-TRI-01, plasma levels of triptorelin could be measured for the entire dosing period of 3 months due to more sensitive RIA method. The mean AUC

value following the administration of Trelstar LA in this study is similar to that reported in the other two studies where sponsor assumed ½ LOQ values when the drug levels could not be measured.

Pharmacokinetics and Pharmacodynamics

Are there any dose-response/dose finding studies conducted for Trelstar LA?

Dose/Formulation finding (Study DEB-95-TRI-01)

Trelstar Depot, one-month formulation (3.75 mg) was approved for the same indication. Sponsor investigated two 11.25mg (3 x 3.75 mg) 3-month formulations for 84 day duration. No other dose was investigated for this duration of treatment. Therefore, it is unknown whether a lower dose would work as well for 84 days period of duration. It is also not known if this dose will work for more than 84 days duration.

In study DEB-95-TRI-01, the pharmacokinetics and pharmacodynamics of two formulations of Trelstar LA were compared in twenty patients with advanced prostate cancer. The two formulations differ in the polymer composition as show below:

Batch DLGSD-3-95-021: 1/1: polymer lactide 75: gycollide 25 (=11.25 mg)

Batch DLGSD-3-95-22: 1/3: polymer lactide 50: glycolide 50 (=3.75 mg)
2/3: polymer lactide 75: gylcolyde 25 (=7.5 mg)

Following the intramuscular injection of triptorelin pamoate 11.25 mg, plasma concentrations of triptorelin reached peak levels rapidly within 4-10 hrs for formulation DLGSD-3-95-21 and 2-8 hours for formulation DLGSD-3-95-22. The plasma levels declined progressively during first two weeks and remained at steady-state at around 200 pg/ml for the next 8 weeks and then decreased progressively during the last 2 to 4 weeks with both the formulations. The mean pharmacokinetic parameters are listed in Table 1.

Table 1. Mean (±SD) pharmacokinetic parameters of triptorelin following a single IM injection of Trelstar LA

Formulation	DLGSD-3-95-21	DLGSD-3-95-22
Cmax (ng/ml)	74.3	59.0
SD	24.9	23.4
Median Tmax (hours) (range)	4	6
$AUC_{0\text{-}84d}$ (day.pg/ml)	2316	1961
SD	611	639

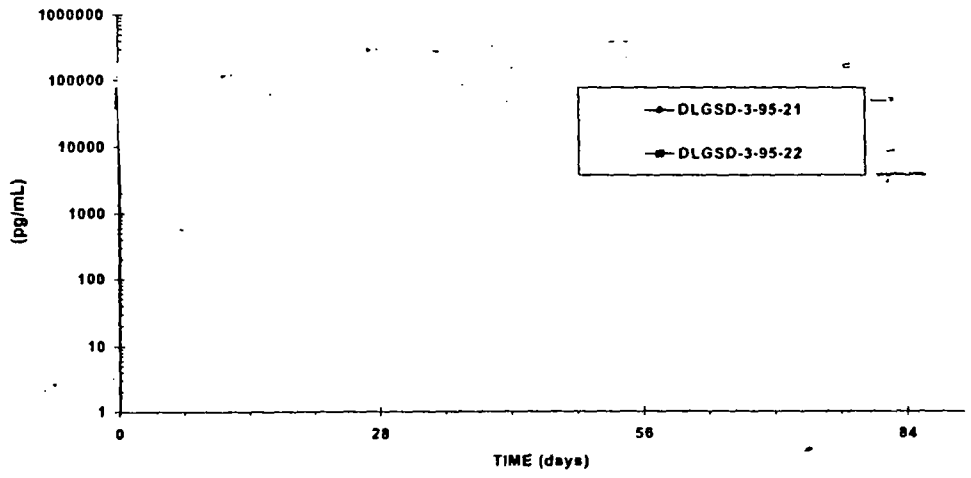

Figure 1. Serum concentration profiles of triptorelin following single 3-month IM injection of Trelstar formulations

The total systemic exposure to triptorelin (based on Cmax and AUC values) is higher following administration of formulation DLGSD-3-95-21. Plasma levels for this formulation were always higher than lower limit of detection (LOD) compared to formulation DLGSD-3-95-22 with which there were 15 observation times with levels below LOQ (When the plasma levels were below LOQ, sponsor assumed ½ LOQ value). This indicates that DLGSD-3-95-21 formulation was able to maintain continuous and steady state levels over 3-month period more effectively than the other formulation.

Testosterone levels following IM injection of triptorelin pamoate have increased rapidly as expected for a GnRH agonist and reached peak concentrations at 2 days after dosing with both formulations. The plasma T levels then declined rapidly during the next 2 to 3 weeks and reached castration levels (T_{cast} = 1.735 nmol/L) between 3 to 4 weeks post-injection. Thereafter T levels remained below T_{cast} until 84 days post-injection.

Both the formulations were effective in suppressing patients' T levels to castration levels although formulation DLGSD-3-95-21 appeared to achieve castration levels slightly earlier than the other formulation. There were three patients in each formulation for which T levels were above castration limit on or after Day 28. The total AUC of T levels was lower with GLSD-3-95-21 and T levels in the castration range tend to be lower with this formulation. It should be noted that neither of the formulations was investigated beyond 84 days following single injection to see if the suppression of T levels continued.

Sponsor has chosen formulation DLGSD-3-95-21 for the phase III study because AUC of triptorelin was higher and the suppression of T was better for this formulation.

What are the pharmacokinetics and pharmacodynamics of Trelstar LA in the Phase III safety and efficacy trial?

Safety and Efficacy Study (DEB-96-Tri-01)

A phase III study was conducted to compare the safety and efficacy of Trelstar LA (3-month) with Trelstar one month formulation. This study was conducted in two phases. The first phase compared the testosterone pharmacodynamics and efficacy of 3-month and 1-month formulations. The second phase included the assessment of comparative safety and efficacy of 1-month formulation of triptorelin versus leuprolide. The second phase results are not discussed here.

The primary objectives of this study were to demonstrate that the 3-month formulation was at least as effective as 1-month formulation in terms of percentage of patients achieving castration levels of serum testosterone (≤1.735 nmol/L) on Day 29 following initial IM injection and percentage of patients maintaining castration levels of serum T from months 2 through 9 of treatment.

Blood samples for measurement of triptorelin levels were taken on Days 1, 29, 57, 85, 113, 141, 169, 197, 225, and 253. Triptorelin levels were also measured over a period of 48 hours following injections on Days 1, 85 and 169 in a subset of 30 patients (15 per treatment group).

Serum testosterone, LH, and FSH levels were determined prestudy and on Days 1, 29, 57, 85, 113, 141, 169, 197, 225, and 253 for all the patients in the study. In addition, serum T levels were also compared for first 7 days in the subset of patients whose triptorelin levels were determined following the injection of each formulation.

Table 2. Geometric mean (range) pharmacokinetic parameters of Triptorelin:

Treatment	$C_{max(1\text{-}85d)}$ (ng/ml)	$C_{max\ (85\text{-}169d)}$ (ng/ml)	$C_{max\ (169\text{-}253d)}$ (ng/ml)
3-month formulation	37.1 (22.4-57.4)	44.0 (23.9-61.4)	48.5 (32.1-88.1)
1-month formulation	15.2 (9.1-25.2)	19.5 (13.6-36.0)	21.3 (14.1-31.1)

Treatment	$AUC_{(1\text{-}85d)}$(ng.h/ml)	$AUC_{(85\text{-}169d)}$(ng.h/ml)	$AUC_{(169\text{-}253d)}$(ng.h/ml)
3-month formulation	2226 (1469-3098)	2153 (1532-4501)	2428 (1412-3903)
1-month formulation	NA	NA	2375 (1221-5431)

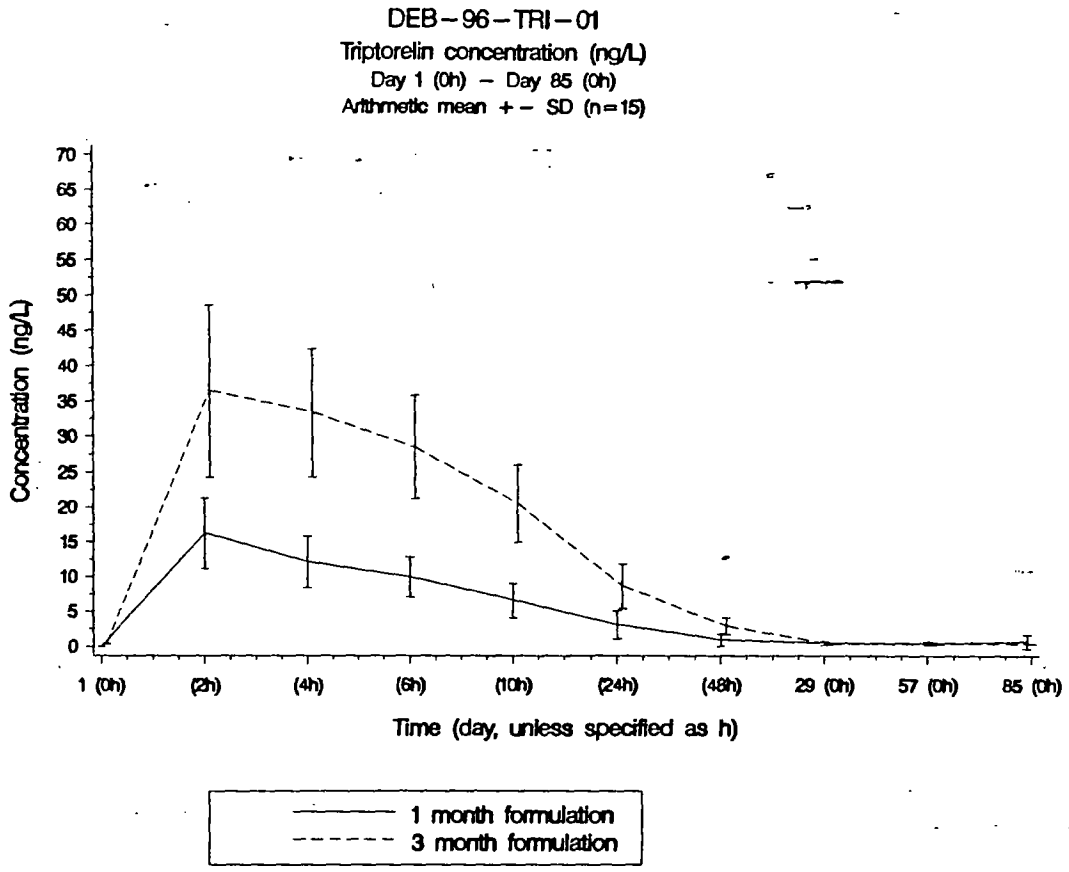

Fig 2. Comparison of serum triptorelin concentrations following first IM injection of 1-month vs 3-month formulations

Serum concentrations of triptorelin reached peak levels within 2-6 hours following intramuscular injection of either formulation. As expected the peak serum levels of triptorelin were higher with the 3-month formulation. The point estimate (two-sided 95% CI) of the "3-month formulation/1-month formulation" ratio of the geometric means for the $AUC_{(169\text{-}253d)}$ of triptorelin was 102.2% (82.4%-126.8%) indicating the systemic exposure following one 3-month injection is similar to 3 injections of 1-month formulations over 3-month period.

Based on the AUC and C_{max} values, there does not seem to be an accumulation of triptorelin in serum following multiple injections with both the formulations.

It should be noted that serum concentrations of triptorelin were below limit of quantitation (LOQ = . ng/ml) in almost all the patients (in subset of 30) for a substantial latter portion of the dosing period for both 1-month and 3-month formulations. If the assay value was below LOQ, it was replaced with ½ LOQ. If the triptorelin concentration at 0 hours on Day 1 was missing or below LOQ, it was replaced with zero. Thus the assay method used in this study was not adequate for measuring triptorelin blood levels through the entire dosing period of 84 days for Trelstar LA.

It should be noted that triptorelin concentrations following Trelstar LA administration were measured for entire dosing period of 84 days in Study DEB-95-TRI-01 using more sensitive RIA method (LOQ=(ng/ml). The mean AUC value from Study DEB-96-TRI-01 (which is reported in the pharmacokinetics section of the label) is similar to the value obtained in Study DEB-95-TRI-01, which used more sensitive assay method.

Pharmacodynamics of testosterone:

The serum testosterone levels in a subset of 30 patients are summarized in Table 3 and Figure 2.

Table 3. Serum Testosterone levels during 144 h following the first injection

	Cmax (nmol/L)	tmax (h)	AUC 0-144h (nmol.h/L)
3-month formulation	26.0 (17-41)	48 (24-96)	2964 (1865-5215)
1-month formulation	21.4 (5.5-37.5)	96 (24-144)	2489 (536-4622)

Cmax and AUC are expressed as geometric mean and range; Tmax is expressed as median and range.

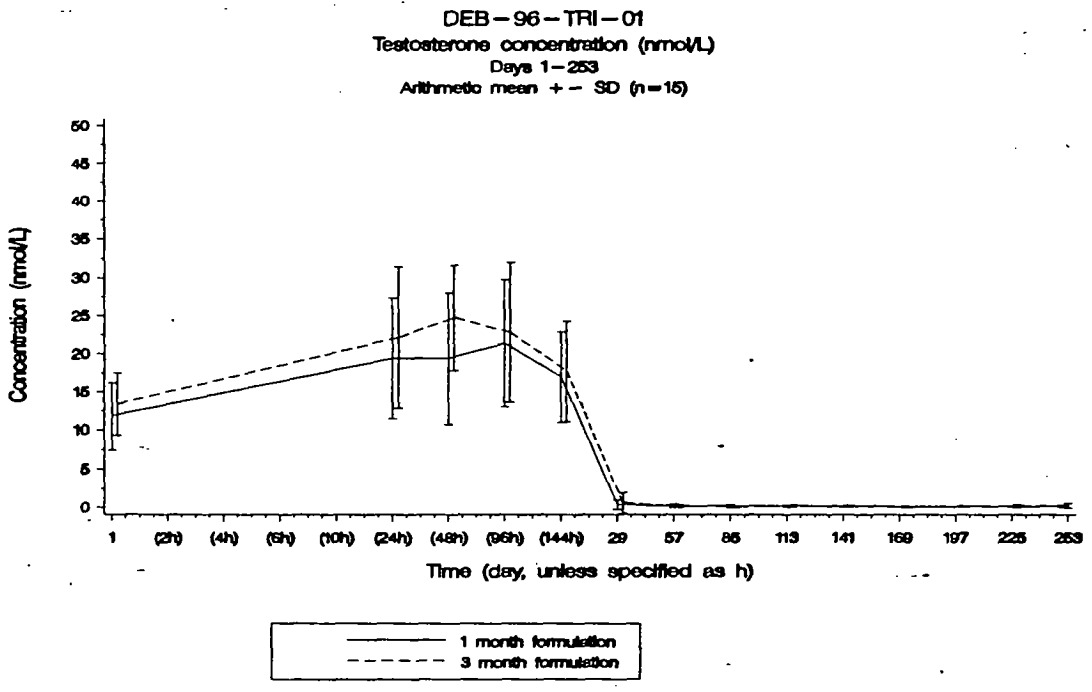

Fig 2. Mean serum testosterone concentrations following first injection in subset of 30 patients from study DEB-96-TRI-01

Based on the data presented above, the 3-month formulation appears to induce higher testosterone surge/flare up (20% higher), possibly because of higher triptorelin levels with this formulation compared to 1-month formulation. Serum testosterone reached peak concentrations in 1 to 4 days for 3-month formulation and in 1 to 7 days for 1-month formulations following injection and reached castrate levels by Day 29 and remained low up to Day 253.

Achievement and maintenance of castration data from the Phase III study results are presented in Table 4 and Table 5, respectively. Please refer to Medical Officer's review regarding details of safety and efficacy evaluation of this study.

Table 4. Achievement of Castration (T<1.73 nmol/L)

	3-month formulation (84 days)			1-month formulation (28 days)		
	Day 29	Day 57	Day 85	Day 29	-Day 57	Day 85
PP population						
Proportion	162/166	159/161	155/159	147/159	153/155	151/152
Percentage	97.6%	98.8%	97.5%	92.5%	98.7%	99.3%
ITT population						
Proportion	167/171	165/167	161/165	152/164	156/158	155/156
Percentage	97.7%	98.8%	97.6%	92.7%	98.7%	99.4%

PP: per protocol; ITT: intent to treat

Both formulations (3-month and 1-month) are effective in suppressing serum T under castration levels. The 3- month formulation appears to be slightly more effective on Day 29 with 97.6% castrated patients as opposed to 92.5% for 1-month formulations. But this difference diminished by day 57. By Day 85, 3-month formulation is slightly (about 2%) lower on proportion of castrated patients. Overall this study showed that 3-month formulation is as effective as 1-month formulation in suppressing serum T levels below castration.

Table 5. Maintenance of castration

	3-Month formulation		1-month formulation	
	PP	ITT	PP	ITT
Average maintenance[a]	158.96/166	164.96/177	153.83/159	156.19/164
Percentage	95.8%	96.5%	96.7%	95.2%
Cumulative maintenance[b]				
Maintenance rate	94.1%	94.4%	95.3%	94.2%
p-value			0.6615	0.9234
Point estimate			-1.2%	0.2%
Two-sided 95% CI			(-6.3%; 3.9%)	(-4.9%;5.3%)

[a] number of scheduled testosterone measurements below castration level, over total number of scheduled testosterone measurements from month 2 to month 9, summed up for all patients.
[b] based on survival analysis

The maintenance of castration was compared for the two formulations in the above table. The estimated rate of maintenance of castration over nine months was similar for the two treatments.

Race effect

For the analysis of effect of race on the efficacy of Trelstar LA, please refer to medical review. The results of this analysis are briefly presented here. Achievement of castration by Day 29 was found to be similar for Caucasians (n=78) and black/colored (n=63) patients. However, the average maintenance of castration was 99% and for blacks it was 92%. This difference may not be statistically significant and the study itself is not powered to find the race differences.

Acute on chronic phenomenon

Sponsor did not provide any data regarding T levels immediately following the second or subsequent injections to evaluate any acute-on-chronic effect of Trelstar. Upon FDA's request, sponsor reanalyzed the frozen samples in subset of 30 patients (15 for 1month formulation 15 for 3- month formulation) for T levels and other secondary PD endpoints such as LH and submitted to FDA on 10/4/00.

These results show that all 15 patients who received the 1-month injection remained castrated during 48 hours following the fourth and seventh injections. Two patients out of 15 who received the 3-month formulation showed transient T levels slightly above the castration levels. One patient had a T level of 1.79 nmol/L 48 hours after the third injection and another patient had a T level of as high as 2.65 nmol/L within 48 hours after the third injection of 3-month formulation. However, both these patients were fully castrated at one, two and three months following this third injection of 3-month formulation. Since this effect was monitored only for a small sample size (15 patients), the clinical division is recommending a Phase IV study to evaluate the acute-on-chronic surge/flare effect of Trelstar LA.

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Effect on LH and FSH

Table 6. Comparison of geometric mean (range) of serum LH pharmacodynamic variables in a subset of 30 patients

	C_{max} (IU/L)	t_{max} (h)	AUC_{0-10h} (IU.h/L)
3-month (n=15)			
Day 1	46.9 (15.9 –99.0)	4 (2-10)	363 (126 – 723)
Day 85	0.4 (0.3 – 1.3)	0 (0-10)	3.4 (2.5-10.7)
Day 169	0.5 (0.3 –4.0)	0 (0-10)	3.91 (2.5-14.6)
1-month (n=15)			
Day 1	45.4 (12.2 – 92.2)	4 (2-10)	365 (95-753)
Day 85	0.4 (0.3 –1 .3)	0 (0-10)	3.87 (2.5 –57.4)
Day 169	0.6 (0.3 – 7.9)	0 (0-10)	4.26 (2.5 – 54.0)

Serum levels of LH were measured for 10 h after each injection. As expected from triptorelin pharmacological activity, LH levels initially surged to reach peak levels at about 4h following first injection. However, following subsequent injections, the rise in LH levels is much lower on Days 85 and 169. These results are consistent with initial testosterone surge following first injection and lack of significant surge following subsequent injections of Trelstar LA. Similar results were noted for FSH also.

It should be noted that the number of LH surges >1.0 IU/L are greater for 3-month formulation compared to 1-month formulation based on all patients data in the Phase III trial (refer to medical review). Since LH is surrogate for testosterone surge, there may be a concern of higher escapes from castration for 3-month formulation when compared to 1-month formulation. In this context, please note that 2 out of 15 patients escaped castration (one patient with marginal rise above castration level). Because of these concerns, Clinical division is recommending a Phase IV study to evaluate the acute-on-chronic effect of Trelstar LA in prostate cancer patients.

Single dose PK/PD study (DEB-99-TRI-01)

Sponsor conducted a single dose pharmacokinetic study (DEB-99-TRI-01) of 3-month formulation with slightly higher dissolution values to establish in vitro/ in vivo correlation. The formulation used in this study is same as that one used in the pivotal Phase III study, but this is a different batch. This study was an open, non-comparative study of triptorelin 3-month formulation in 12 patients with histologically proven advanced prostate cancer. All patients in the study were black. Mean serum triptorelin concentrations are illustrated in Figure 3.

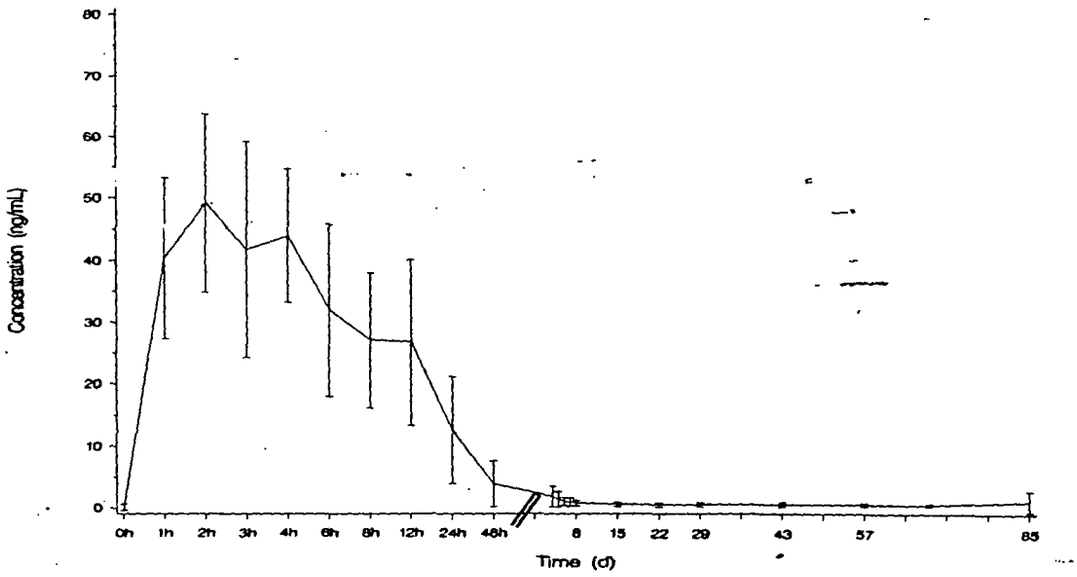

Fig 3. Mean serum triptorelin concentration following single IM administration of Trelstar LA

Table 7. Triptorelin pharmacokinetic parameters

	$AUC_{(1\text{-}85\ d)}$ (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)
Geometric mean	2040	55.09	2*
Min	1311	40.39	1
Max	3440	76.26	6

*Median

Systemic exposure of triptorelin is similar to that reported in subset of patients in the pivotal clinical study DEB-96-01. The mean Cmax in this study is higher than that reported in Study DEB-96-01 (mean 37.1 ng/ml, range . [1]).

Majority of the patients in this study had plasma concentrations of triptorelin that were below the limit of quantitation from Day 15 onwards. In study DEB-96-01, serum levels of triptorelin measured were above LOQ for only 48 hours and fell below LOQ from the next sampling time of Day 29 onwards. Thus the AUC information from current study is more realistic than study DEB-96-01.

Pharmacodynamic results of this study showed by Day 15, 41.7% of patients were castrated and all patients were castrated on Days 22, 29, 43, 57, 71 and 85.

In Vitro Dissolution

The following dissolution method and specifications were proposed by the sponsor.

Apparatus Type:	USP Type II glass (500 ml)
Medium:	Water : Methanol
Volume:	500 ml
Speed of Rotation:	200 rpm
Sampling times:	1 h ± 1min; 48 h ± 50 min; 72 h ± 80 min
Proposed specifications:	1 h ± 1min: 48 h ± 50 min: 72 h ± 80 min:

The proposed dissolution method is the same as the current approved method for the 1-month formulation. Specifications for the dissolution method were proposed based on the mean ± absolute 10% of the release test results for the biobatches.

Sponsor submitted *in vitro/in vivo* correlation (IVIVC) analysis to validate the *in vitro* dissolution test. For IVIVC, clinical pharmacokinetic data over days 1-85 after injection (Protocols DEB-96-Tri-01 for batch DLGSD3-96-24 and DEB-99-Tri-01 for batch 4123A9901) were compared point-by-point with **in vitro** dissolution data over a period of 74 to 79 days, changing the dissolution media once weekly after the first 72 hours..
For IVIVC, the *in vitro* time (hrs) necessary for certain % of release is correlated with *in vivo* time necessary to obtain *in vivo* release (based on cumulative AUC values). This method of correlating in vitro release time with in vivo release time is not a common one. Usually in Level A correlations, *in vitro* release is correlated with *in vivo* release (exposure).

The *in vitro* hours versus *in vivo* hours data was fitted to a third order polynomial equation.

(for batch #DLGSD3-96-24)
(for batch #4123A9901)

The IVIVC plots for the above equations are included in Attachment.
It should be noted that the same *in vitro* dissolution method with same time points was approved for 1-month formulation of Trelstar. Based on the *in vitro* release data for clinical and biobatches, sponsor's proposed dissolution specifications are found to be acceptable. Thus for purpose of setting dissolution/release specs, the IVIVC discussed above was not utilized.
It should be noted that due to lack of adequate validation, this IVIVC could not be used to support any formulation changes that may take place in future.

10 pages redacted from this section of the approval package consisted of draft labeling