8.4.2 Primary Efficacy Assessment and Endpoints

8.4.2.1 Serum Testosterone Concentrations during Treatment with Triptorelin

Serum concentrations of testosterone for the ITT population from screening through the end of the treatment period (Study Day 253) are summarized in Table 11. Mean (±SD) serum testosterone concentrations declined from 11.57 nmol/L (±5.19) and 12.03 nmol/L (±5.32) in the 84-day and 28-day groups, respectively, on Day 1 to 0.28 nmol/L (±0.88) and 0.54 nmol/L (±1.41) on Day 29. In the 84-day formulation group, mean (±SD) serum testosterone concentrations ranged from 0.16 (±0.19) to 0.43 (±1.48) during the period from Day 57 through Day 253. In the 28-day formulation group, mean (±SD) serum testosterone concentrations ranged from 0.19 (±0.22) to 0.38 (±2.04) during the same period.

Table 11. Serum Testosterone Concentrations [nmol/L] in the ITT Population

Statistic	Scrn	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253
84-Day Formulation											
N	170	171	171	167	165	158	158	156	148	147	149
Mean	**11.24**	**11.57**	**0.28**	**0.18**	**0.34**	**0.16**	**0.21**	**0.27**	**0.21**	**0.27**	**0.43**
SD	4.60	5.19	0.88	0.50	1.19	0.19	0.29	0.86	0.25	0.49	1.48
Min											
Median	**10.50**	**10.70**	**0.10**	**0.10**	**0.10**	**0.10**	**0.10**	**0.10**	**0.10**	**0.10**	**0.10**
Max											
28-Day Formulation											
N	163	164	164	158	156	151	153	149	147	145	142
Mean	**12.31**	**12.03**	**0.54**	**0.24**	**0.24**	**0.27**	**0.36**	**0.19**	**0.35**	**0.20**	**0.38**
SD	4.70	5.32	1.41	0.55	0.66	0.91	1.49	0.22	1.99	0.26	2.04
Min											
Median	**11.60**	**11.50**	**0.10**	**0.10**	**0.10**	**0.10**	**0.10**	**0.10**	**0.10**	**0.10**	**0.10**
Max											

Source: Table 14.2.1.1, pg. 185, Vol. 29 of original submission.

The number and percent of patients with castration levels of testosterone (≤ 1.735 nmol/L) at each assessment in the ITT population are listed in Table 12. On Study Day 29, 167 of 171 (98%) patients receiving the 84-day formulation and 152 of 164 (93%) patients receiving the 24-day formulation had serum testosterone levels within the castrate range (testosterone ≤ 1.735 nmol/L). In the 84-day formulation group, the percentage of patients with castrate levels of serum testosterone concentrations ranged from during the period from Day 57 through Day 253. In the 28-day formulation group, the percentage of patients with castrate levels of serum testosterone concentrations ranged from during the same period.

Table 12. Number and Percentage of Medically Castrate Patients (Testosterone≤ 1.735 nmol/L) at Each Assessment

Statistic	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253
84-day Formulation										
Total No. of patients	171	171	167	165	158	158	156	148	147	149
No. of castrate patients	1	167	165	161	158	157	153	148	145	144
Percent castrate patients	1	98	99	98	100	99	98	100	99	97
28-Day Formulation										
Total No. of patients	164	164	158	156	151	153	149	147	145	142
No. of castrate patients	1	152	156	155	149	150	149	146	144	140
Percent castrate patients	1	93	99	99	99	98	100	99	99	99

Source: Table 14.2.1.1, pg. 185, Vol. 29 of original submission.

8.4.2.2 Achievement of Medical Castration by Day 29

The percentage of patients who achieved medical castration (testosterone ≤ 1.735 nmol/L) by Study Day 29 in each treatment group in the ITT and PP populations is listed in Table 13. In the ITT population, 167 out of 171 patients (97.7%) in the 84-day formulation group had serum testosterone levels within the castrate level on Day 29, while 152 out of 164 patients (92.7%) in the 28-day formulation group had testosterone levels within the castrate range. Similar results were obtained for the PP population with 97.6% of the patients in the 84-day formulation group and 92.5% of patients in the 28-day formulation group having serum testosterone levels within the castrate range. The point estimate of the difference in castration rates (84-day formulation minus 28-day formulation) was 5.0% in the ITT population and 5.1% in the PP population. The exact two-sided 95% CI for the difference was (-1.1%; 13.4%) for the ITT population and (-1.1%; 13.8%) for the PP population.

Table 13. Percentage of Patients Who Achieved Medical Castration (Testosterone ≤ 1.735 nmol/L) by Study Day 29

	Treatment Group					
	84-Day Formulation		28-Day Formulation		Percent Difference	
Population	N [1]	Percent [2]	N [1]	Percent [2]	Value [3]	95% CI [4]
Intent to Treat	171	97.7	164	92.7	5.0	(-1.1, 13.4)
Per Protocol	166	97.6	159	92.5	5.1	(-1.1, 13.8)

[1] Total number of patients in the respective population.
[2] Percentage of patients represented in Column "N" with castrate levels of testosterone.
[3] Percent difference in achievement of medical castration (84-day formulation minus 28-day formulation).
[4] 95% two-sided confidence interval for the difference between groups.
Source: Table 14.2.1.3, pg. 189, and Table 14.2.1.4, pg. 190, Vol. 29 of original submission.

Medical Officer's Comments

- *The criteria agreed to by both the Sponsor and DRUDP for non-inferiority was that the lower bound of the 95% CI for the point estimate of the difference (84-day formulation minus 28-day formulation) would be greater than –10%.*

- *Based on this criteria, the analysis summarized in Table 13 indicates that the 84-day formulation of triptorelin was not inferior to the 28-day formulation in terms of reducing serum testosterone concentrations to ≤ 1.735 nmol/L by Study Day 29.*
- *Several patients in both the 84-day formulation and 28-day formulation groups had serum testosterone levels of < 5 nmol/L on Study Day 1 prior to first dosing with Study Drug. These patients were not excluded by the Sponsor from either the ITT population or the PP population. Based on a separate analysis by the FDA statistician, exclusion of these patients has no significant effect on the analyses and findings represented in Table 13 and Table 14.*

8.4.2.3 Maintenance of Medical Castration

The maintenance of medical castration from Study Day 59 through Day 253, assessed by both (1) observed average maintenance and (2) cumulative maintenance (Kaplan Meier analysis) is summarized in Table 14.

Average monthly maintenance of castration levels of testosterone. The average maintenance of castration levels of testosterone in the ITT population was slightly higher in patients treated with the 84-day formulation (96.5%) compared to that in patients treated with the 28-day formulation (95.2%). Conversely, by the Sponsor's calculation, the average maintenance of castration levels of testosterone in the PP population was slightly higher in patients treated with the 28-day formulation (96.8%) compared to that in the 84-day formulation group (95.8%).

Cumulative maintenance of castration levels of testosterone (Kaplan-Meier analysis). In the ITT population the cumulative maintenance of castration from Day 57 through Day 253 was 94.4% for the 84-day formulation group and 94.2% for the 28-day formulation group. The point estimate for the difference in maintenance rates (84-day formulation minus 28-day formulation) was 0.2% (95% CI: [-4.9%; 5.3%]). In the PP population. the cumulative maintenance of castration from Day 57 through Day 253 was slightly lower in the 84-day formulation group (94.1%) compared to that in the 28-day formulation group (95.3%). The point estimate for the difference in maintenance rates was -1.2% (95% CI: [-6.3%; 3.9%]).

Table 14. Average and Cumulative Maintenance of Medical Castration (Testosterone ≤ 1.735 nmol/L) from Study Day 57 Through Study Day 253

	Treatment					
	84-Day Formulation		28-Day Formulation		Percent Difference	
Population (Analysis)	N [1]	Percent Success	N	Percent Success	Value	95% CI [4]
Intent-to-treat						
Average Maintenance [2]	171	96.5	164	95.2	1.3	NC [5]
Cumulative Maintenance [3]	171	94.4	164	94.2	0.2	(-4.9, 5.3)
Per Protocol						
Average Maintenance	166	95.8	159	96.8	-1.0	NC [5]
Cumulative Maintenance	166	94.1	159	95.3	-1.2	(-6.3, 3.9)

[1] Total number of patients in group.
[2] Calculated as [the sum of the number of testosterone measurements below castration levels] divided by [total number of testosterone measurements] from Day 57 to Day 253.
[3] Kaplan Meier estimate.
[4] 2-sided 95% confidence interval for the difference (84-day formulation minus 28-day formulation).
[5] Not calculated.
Source: Tables 14.2.1.3 (pg. 189), 14.2.1.4 (pg. 190), 14.2.1.6 (pg. 193), and 14.2.1.7 (pg. 194), Vol. 29 of original submission.

Medical Officer's Comments

- *Based on the sponsor's criteria of non-inferiority, the 84-day formulation of triptorelin was not inferior to the 28-day formulation in terms of maintaining serum testosterone ≤ 1.735 nmol/L from Day 57 through Day 253.*
- *The period that is generally considered by DRUDP for assessing the maintenance of suppression of testosterone commences on Study Day 29 and continues through 3 treatment cycles. If the Sponsor had used the interval from Day 29 through Day 253, the outcome of the statistical analysis also would have indicated that the 84-day formulation was not inferior to the 28-day formulation.*

8.4.2.4 Acute Increases in Serum Testosterone Levels following Repeat Dosing

In a subset of 30 patients (15 in each treatment group) at Center 1, blood samples were obtained per protocol through 48 hours after dosing on Study Days 85 and 169 for the measurement of serum triptorelin concentrations. At the request of the Medical Reviewer, the sponsor was asked to measure testosterone concentrations in these postdosing blood specimens. These measurements provided information on possible postdosing increases in serum testosterone levels in patients with otherwise suppressed serum testosterone levels. The number and percentage of patients who had a postdosing serum testosterone > 1.735 nmol/L or an LH increase of > 1.0 U/L through 48 hours after dosing on Days 85 and 169 are summarized in Table 15.

In the 84-day formulation group, there were no postdosing increase to or above these levels after dosing on Day 85. After dosing on Day 169, however, 2 patients had serum testosterone levels > 1.735 nmol/L (maximum values of 1.79 nmol/L and 2.65 nmol/L), and 2 other patients had LH increases of > 1.0 U/L (maximum increases of 1.15 and 2.3 IU/L). In the 28-day formulation group, there were no observed testosterone values above, or increases in LH to, these values.

Table 15. Acute Postdosing Increases in Serum Levels of Testosterone and LH

Formulation	Increased Testosterone [1]			Increased LH [2]		
Study Day	N [3]	n [4]	Per cent [4]	N	n	Per cent
84-Day Formulation						
Study Day 85	15	0	0%	15	0	0%
Study Day 169	15	2 [5]	13%	15	2 [6]	13%
28-Day Formulation						
Study Day 85	15	0	0%	15	0	0%
Study Day 169	14	0	0%	14	0	0%

[1] Testosterone > 1.735 nmol/L.
[2] LH increase of > 1.0 IU/L from predosing value.
[3] Total number of patients evaluated.
[4] Number or percent of patients with increased value.
[5] Testosterone values were 1.79 nmol/L and 2.65 nmol/L, respectively. Neither patient had an LH increase of > 1.0 IU/L.
[6] LH increases were 1.15 and 2.3 IU/L. Neither patient had a testosterone value of > 1.735 nmol/L.
Source: Prepared by Medical Officer from data in Supplemental Submission of October 24, 2000.

Medical Officer's Comments

- *A superactive GnRH agonist, in contrast to a true GnRH antagonist, has the potential to increase serum testosterone concentrations on repeat dosing, even in the face of apparent prior suppression of testosterone to ≤ 1.735 nmol/L. Such increases may be of potential harm to a patient with prostate cancer undergoing androgen deprivation therapy.*

- *Unfortunately, the sponsor did not follow the strong and continued recommendation of DRUDP that all, or at least a meaningful number of patients be monitored for acute on chronic changes in serum testosterone levels. Two (2) of 15 patients (13%) receiving the 84-day formulation in this study exhibited a small (1.79 nmol/L) or moderate (2.65 nmol/L) increase, respectively, in their serum testosterone concentrations after their third dose of Study Drug. Neither, however, exhibited an LH increase of > 1.0 IU/L, the Sponsor's criteria for identifying patients who were likely to have had a postdosing increase in serum testosterone to > 1.735 nmol/L.*
- *Of some concern is the observation that these increases in testosterone occurred after the third, but not the second dose of the 84-day formulation. This may indicate that the percentage of patients exhibiting such changes may be increasing over time.*
- *The Sponsor should conduct a Phase IV pharmacology study designed to obtain addition clinical data regarding increases in serum testosterone to levels > 1.735 nmol/L between 48 to 72 hours after repeat dosing.*

8.4.2.5 Comparative Efficacy in Black and Caucasian Patients

Secondary analyses for the co-primary efficacy endpoints of attainment of medical castration (testosterone ≤ 1.735 nmol/L) by Day 29 and maintenance of medical castration from Day 57 through Day 253 are summarized in Table 16. The proportion of patients who had castrate levels of testosterone on Day 29 was similar in Black and Caucasian patients (98.4% and 97.5%, respectively). However, the average maintenance of medical castration was lower in Black patients (92.1%) compared to Caucasian patients (98.8%). Similarly, the cumulative maintenance of medical castration was lower in Black patients (91.5%) compared to that in Caucasian patients (94.9%).

Table 16. Attainment and Maintenance of Medical Castration in Black and Caucasian Patients Treated with the 84-Day Formulation of Triptorelin (ITT Populations)

Endpoint	Black Patients N = 64	Caucasian Patients N = 80
Testosterone ≤ 1.735 nmol/L by Day 29		
Number of successes	63	78
Proportion of successes (percent)	98.4%	97.5%
Average maintenance of castration (Day 57 to Day 253) [1]		
Percent of months with testosterone ≤ 1.735 nmol/L	92.1%	98.8%
Cumulative maintenance of medical castration (Day 57 to Day 253)		
Number of patients who failed	5	4
Number of censored patients	59	76
Product limit survival estimate at Month 9 [2]	91.5%	94.9%

[1] Calculated as [the sum of the number of testosterone measurements below castration levels] divided by [total number of testosterone measurements] from Day 57 to Day 253.
[2] Kaplan Meier estimate.
Source: Submission of April 27, 2001; Tables 14.2.1.3 (pg. 276) and 14.2.1.7 (pg. 279).

Medical Officer's Comment

- *Although the percentages for average and cumulative maintenance of medical castration were lower in Black patients, they were acceptable as the point estimates for both were > 90%.*

8.4.3 Other Efficacy Assessments

8.4.3.1 Changes in Serum LH and FSH Concentrations

Long-term changes in serum LH and FSH concentrations. Mean serum concentrations of LH and FSH immediately prior to the first dose of Study Drug on Day 1 and every 28 days thereafter are listed in Table 17. Mean baseline LH concentrations on Day 1 were 7.13 IU/L and 6.87 IU/L for the 84-day and 28-day formulation groups, respectively, in the ITT population. These values had decreased markedly by Day 29, with mean LH concentrations of 0.49 IU/L and 0.79 IU/L, respectively. LH levels were then maintained at lower or similar levels during the remaining visits. Similar results were recorded for the PP population. Mean baseline FSH concentrations on Day 1 were 10.96 IU/L and 9.91 IU/L for the 84-day and 28-day formulation groups, respectively, in the ITT population. These values had decreased by Day 29 to mean values of 3.08 IU/L and 2.80 IU/L for the 84-day and 28-day formulation groups, respectively. Over the remaining visits, serum FSH concentrations in both treatment groups remained lower than on Day 1 but increased gradually throughout the treatment period. By Day 253, mean FSH values had increased from their nadirs on Day 29 to 6.05 IU/L and 5.92 IU/L for the 84-day and 28-day formulation groups, respectively. Similar results were observed in the PP population.

Table 17. Serum Concentrations of LH and FSH

Treatment Gp (Statistic)	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253
LH (IU/L)										
84-day formulation										
N	171	171	167	165	158	158	156	148	147	149
Mean	7.13	0.49	0.35	0.39	0.31	0.31	0.37	0.37	0.36	0.52
28-day formulation										
N	164	164	158	156	151	153	149	147	145	143
Mean	6.87	0.79	0.34	0.39	0.34	0.45	0.78	0.35	0.36	0.36
FSH (IU/L)										
84-day formulation										
N	171	171	167	165	158	158	156	148	147	149
Mean	10.96	3.08	4.31	5.40	5.70	5.64	6.06	5.79	5.88	6.05
28-day formulation										
N	164	164	158	156	151	153	149	147	145	143
Mean	9.91	2.80	4.12	4.85	4.99	5.52	5.71	5.63	5.90	5.92

Source: Tables 14.2.1.9, 14.2.1.10, 14.2.1.13, 14.2.1.14, Vol. 29 of original submission.

Medical Officer's Comments

- *These changes are similar to those reported following long-term administration of other superactive GnRH agonists. For reasons that are not known, superactive agonistic GnRH analogs appear to suppress serum LH concentrations to a greater degree than serum FSH concentrations.*

Acute (2 hour) postdosing changes in serum LH concentrations. The percentages of patients with serum LH ≤ 1.0 IU/L above predosing values at 2 hours after dosing are summarized in Table 18. On Study Day 1, virtually no patient in either treatment group exhibited an LH increase of ≤ 1.0 IU/L above his predosing value. On Days 85 and 169, more than 90% of patients in both treatment groups had LH increases of ≤ 1.0 IU/L at 2 hours after dosing compared to their predosing values. However, the percentages of patients with increases of ≤ 1.0 IU/L were greater in the 28-day formulation group. In the ITT population, the point

estimates (and 2-sided 95% CIs) for the differences between the 2 treatment groups (84-day formulation minus 28-day formulation) were –4.7% (-13.3; 1.5) on Day 85 and –6.3% (-15.0; 0.0) on Day 169, both showing numerically better suppression in the 28-day formulation group. Similar changes were observed in the PP population.

Table 18. Percentage of Patients with Serum LH ≤ 1.0 IU/L Above Predosing Values 2 Hours After Dosing

	Treatment					
	84-Day Formulation		28-Day Formulation		Percent Difference	
Population (Analysis)	N[1]	Percent ≤1.0 IU/L[2]	N[1]	Percent ≤1.0 IU/L[2]	Value[3]	95% CI[4]
Intent-to-treat						
Day 1	171	1.8	164	0.6	NC[5]	NC
Day 85	165	92.7	156	97.4	-4.7	(-13.3; 1.5)
Day 169	156	91.7	149	98.0	-6.3	(-15.0; 0.0)
Per Protocol						
Day 1	166	1.8	159	0.6	NC	NC
Day 85	159	92.5	152	97.4	-4.9	(-13.6; 1.4)
Day 169	145	92.4	143	98.6	-6.2	(-15.3; -0.1)

[1] Number of patients studied.
[2] Percentage of patients with an increase in serum LH ≤ 1.0 IU/L 2 hours after dosing compared to their predosing values.
[3] Difference for percentage of patients with an LH increase ≤ 1.0 IU/L (84-day formulation minus 28-day formulation).
[4] 2-sided 95% confidence interval.
[5] Not calculated.
Source: Tables 14.2.1.11 and 14.2.1.12, Vol. 29 of original submission.

Medical Officer's Comments

- *A numerically (and perhaps statistically) lower proportion of patients receiving the 84-day formulation had an LH increase of ≤ 1.0 IU/L above baseline compared to patients in the 28-day formulation group on Days 85 and 169.*
- *This difference in LH response is most likely a result of 2 factors: (a) less complete suppression of pituitary gonadotropes at the time of repeat dosing in patients receiving the 84-day formulation and (b) a greater stimulus to release LH since serum concentrations of triptorelin are greater immediately after administration of the 84-day formulation compared to levels observed after dosing with the 28-day formulation.*
- *These data, based on the sponsor's contention that the absence of an acute increase in serum LH indicates that there is no ensuing increase in serum testosterone, would indicate that a greater proportion of patients receiving the 84-day formulation have an acute and transient increase in serum testosterone levels. However, the data obtained from the subset of 30 patients at Center 1 indicate that there is not a good correlation between an LH increase of ≤ 1.0 IU/L and a subsequent serum testosterone ≤ 1.735 nmol/L.*
- *Using the absence of an increase in serum LH as a surrogate endpoint for the absence of a subsequent increase in serum testosterone is conceptually sound. However, the immunoassay employed to measure LH concentrations in this Study was not sufficiently sensitive to reliably identify LH changes of greater than 1.0 IU/L in patients with low baseline LH values.*
- *The issue of acute increases in serum testosterone levels after repeat dosing with the 84-day formulation will need to be investigated further by the Sponsor as part of a Phase IV commitment as discussed in Section 8.4.2.4.*

8.4.3.2 Serum PSA Concentrations

In the ITT population on Day 1 (baseline), the median PSA value was 53.3 µg/L in the 84-day formulation group and 70.5 µg/L in the 28-day formulation group (Table 19). Median PSA levels decreased markedly in both groups after the start of treatment and remained suppressed throughout the treatment period. The median PSA levels on Day 253 were 1.7 µg/L in the 84-day formulation group and 1.6 µg/L in the 28-day formulation group. The median changes from baseline at Day 253 were –37.6 µg/L and -60.9 µg/L for the 84-day and 28-day formulation groups, respectively. The two-sided 95% CIs of the median difference of the changes from baseline (3-month formulation- 1-month formulation) were (-8.90µg/L; 18.07µg/L) on Day 85, (-10.8µg/L ; 16.12µg/L) on Day 169 and (-4.81µg/L ; 23.90µg/L) on Day 253.

The percent changes in serum PSA from baseline also were similar in both treatment groups. The 84-day formulation group had a median percent change of -93.9% on Day 85, -95.8% on Day 169 and -96.8% on Day 253. The 28-day formulation group had a median percent change in PSA of -94.6% on Day 85, -97.0% on Day 169 and -97.6% on Day 253.

Medical Officer's Comment

- *Treatment with both formulations of triptorelin produced a marked and similar decrease in serum concentrations of PSA.*

Table 19. Changes in Serum PSA Concentrations (µg/L) (ITT Population)

	Day 1	Day 85		Day 169		Day 253	
Statistic	Value	Value	Change [1]	Value	Change	Value	Change
84-day formulation							
N	170	164		155		147	
Mean	469.9	28.8		26.5		37.1	
Median	53.3	3.2		2.2		1.7	
Absolute change [2]			-38.4		-40.2		-37.6
Percent change [2]			-93.9%		-95.8%		-96.8%
28-day formulation							
N	165	156		148		142	
Mean	480.5	29.8		34.0		18.7	
Median	70.5	3.3		1.7		1.6	
Absolute change			-58.7		-59.4		-60.9
Percent change			-94.6%		-97.0%		-97.6%

[1] Change from Day 1 (baseline) value; [2] based on median values.
Source: Tables 14.2.1.27 and 14.2.1.29, pg 234 and 236, Vol. 29 of original submission.

8.4.3.3 Changes in Bone Pain Assessed by VAS and Analgesic Usage

Bone pain evaluated by Visual Analog Scale (VAS). The 84-day formulation group (ITT population) had a median pain value at baseline of 7 mm VAS (mm), while the 28-day formulation group had a median pain value at baseline of 4 mm VAS . Pain ratings generally remained low, with median values over the visits ranging The changes over time were small, with no distinctive trend in bone pain evident over time in either the ITT or PP populations in either treatment group.

Bone pain as evaluated by use of analgesics. In the ITT population, 64.9% of patients and 67.7% of patients in the 84-day and 28-day formulation groups, respectively, said that they had

used analgesics on Day 1. The mean and median percentages of days that a patient reported the use of analgesics during the 28-day period preceding each clinical visit are listed in Table 20. The percentages of reported analgesic use during treatment declined in a similar fashion in both treatment groups. The PP population showed similar results.

Table 20. Percentage of Days on Which Analgesics Were Used in the 28-Day Interval Preceding the Respective Clinical Visit (ITT Population)

	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253
84-Day Formulation									
N [1]	142	140	137	134	135	132	127	128	128
Mean (%)	40.5	34.4	32.6	29.7	28.9	23.9	25.4	17.0	15.9
Median (%)	12.3	3.6	3.6	0	0	0	0	0	0
28-Day Formulation									
N [1]	140	138	136	132	132	131	128	127	126
Mean (%)	37.7	36.4	31.6	32.9	27.6	23.0	24.7	23.4	15.4
Median (%)	7.1	3.6	0	0	0	0	0	0	0

[1] Number of patients for whom data were available at the respective clinical visit.
Source: Table 14.2.1.25, Vol. 29.

8.5 Conclusions Regarding Demonstrated Efficacy

8.5.1 Achievement of Protocol-Defined Primary Efficacy Endpoints

The primary efficacy endpoints of the principal efficacy Study, DEB-96-TRI-01-Phase 1 were:

1. The proportion of patients achieving castrate levels of serum testosterone (testosterone ≤ 1.735 nmol/L) on Study Day 29 and
2. The proportion of patients maintaining castrate levels of serum testosterone from Study Day 57 through Study Day 253 during treatment with Study Drug.

The results of the Sponsor's analysis indicated that the 84-day formulation of triptorelin pamoate was not inferior to the approved 28-day formulation of triptorelin pamoate in terms of both of the primary efficacy endpoints.

Achievement of testosterone ≤ 1.735 nmol/L by Day 29. In the ITT population, 167 out of 171 patients (97.7%) in the 84-day formulation group had serum testosterone levels within the castrate level on Day 29, while 152 out of 164 patients (92.7%) in the 28-day formulation group had testosterone levels within the castrate range. The point estimate of the difference in castration rates (84-day formulation minus the 28-day formulation) was 5.0% (95% CI: [-1.1%; 13.4%]). Similar results were obtained for the PP population.

Maintenance of medical castration. In the ITT population, the cumulative maintenance of castration (Kaplan Meier Analysis) from Day 57 through Day 253 was 94.4% for the 84-day formulation group and 94.2% for the 1-month formulation group. The point estimate for the difference in maintenance rates (84-day formulation minus the 28-day formulation) was 0.2% (95% CI: [-4.9%; 5.3%]). Similar results were obtained for the PP population.

8.5.2 Achievement of Principal Secondary Efficacy Endpoint

Absence of testosterone surges following repeated dosing with a superactive GnRH agonist (acute on chronic testosterone response), although not a primary efficacy endpoint, has been a required secondary efficacy endpoint in other applications in which suppression of serum testosterone has been used as the primary efficacy endpoint. The Sponsor provided testosterone data regarding

this assessment from only 15 of the 171 ITT patients who received the 84-day formulation. Two of the 15 patients had serum testosterone levels > 1.735 nmol/L (maximum values of 1.79 nmol/L and 2.65 nmol/L, respectively) within 48 hours after their third dose of Study Drug. Although this response rate would be acceptable, the sample size was too small to make any meaningful estimates of the true acute on chronic testosterone response rate. Therefore, the Sponsor will be requested to conduct a Phase IV pharmacology study to obtain a better estimate of the response rate in patients treated with the 84-day formulation of triptorelin pamoate (Trelstar™ LA).

8.5.3 Support of Label Efficacy Claim

The results of Study DEB-96-TRI-01-Phase 1 indicated that the 84-day formulation of triptorelin pamoate suppressed testosterone to ≤ 1.735 nmol/L within 29 days of first dosing and maintained testosterone at ≤ 1.735 nmol/L through 3 dosing cycles (253 days) in greater than 90% of patients. This finding, along with the limited data provided by the Sponsor regarding the acute on chronic testosterone response, is sufficient to support the Sponsor's label claim that "Trelstar™ LA is indicated in the palliative treatment of advanced prostate cancer. It offers an alternative treatment for prostate cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient."

8.6 Supportive Efficacy Studies

Complete Description of DEB-95-TRI-01

The capacity of the to-be-marketed 84-day formulation of triptorelin pamoate to suppress serum testosterone to ≤ 1.735 nmol/L also was evaluated in 2 small Phase II studies.

DEB-95-TRI-01. This was a single center, open label comparative Phase II study conducted in Bulgaria. Twenty (20) men with prostate cancer each received a single IM dose of one of two 84-day formulations of triptorelin pamoate (10 patients per formulation). Although both formulations were able to induce medical castration in all patients, the mean plasma triptorelin AUC value was somewhat greater and the mean serum testosterone concentrations were slightly lower in the patients who received formulation DLGSD-3-95-21; consequently, this formulation was selected was further clinical evaluation and subsequently became the to-be marketed 84-day formulation of triptorelin pamoate.

DEB-99-TRI-01. This was an open, non-comparative pharmacokinetic and pharmacodynamic study of the to-be-marketed 84-day formulation of triptorelin pamoate. Twelve men in South Africa with histologically proven advanced prostate cancer (Stage C or D) each received a single IM injection of triptorelin pamoate on Study Day 1. No subject achieved castration levels of testosterone (≤1.735 nmol/L) on Days 1 through 8. By Days 15 and 22, however, 5 of 12 subjects (42%) and 12 of 12 subjects (100%), respectively, were medically castrate. Thereafter, serum testosterone levels were maintained at ≤1.735 nmol/L through Day 85 in all subjects.

8.7 Statistician's Assessment of Efficacy (Protocol-Defined Primary Endpoint)

Dr. Hoberman, FDA statistician, analyzed the testosterone data submitted in NDA 21-288 from Study DEB-96-TRI-01-Phase 1 in two ways in order to confirm the sponsor's results concerning the cumulative maintenance of testosterone suppression. The first analysis followed that of the sponsor in that failure was defined as any testosterone value > 1.735 nmol/L from Day 57 through Day 253. The second analysis was a modification of the Sponsor's analysis in that failure was defined as any testosterone value > 1.735 nmol/L from Day 29 through Day 253. In the first analysis, the Kaplan-Meier estimates for success (castration by Day 57 that is maintained throughout the trial) were 95% for the 28-day formulation and 96% for the 84-day formulation. The 95% confidence interval for the difference (84-day regimen minus 28-day regimen) was (-3.8%, 5.8%). In the second analysis, the Kaplan-Meier estimates of success (castration by Day

29 that is maintained throughout the trial) were 89% for the 28-day formulation and 95% for the 84-day formulation. The 95% confidence interval for the difference (84-day regimen minus 28-day regimen) was (0%, 12%).

Medical Officer's Comments

- *DRUDP prefers that the analysis for the cumulative maintenance of testosterone suppression cover the interval beginning on Day 29 and extending through 3 dosing cycles. The Sponsor's primary analysis for this endpoint, however, considered the interval from Day 57 through 3 dosing cycles (Day 253).*
- *The second of Dr Hoberman's analyses evaluated maintenance of testosterone suppression in the interval from Day 29 through Day 253.*
- *His reanalysis and modified analysis support the conclusion that the 84-day formulation is not inferior to the 28-day formulation in terms of attainment of testosterone suppression by Day 29 and maintenance of suppression from either Day 29 or Day 75 through Day 253.*

8.8 Medical Officer's Overall Assessment of Efficacy (Statistical and Clinical Significance)

The results of Study DEB-96-TRI-01-Phase 1 indicated that treatment with the 84-day formulation of triptorelin pamoate (1) successfully achieved the clinical and statistical efficacy objectives of the trial and (2) successfully achieved the principal criteria that DRUDP has used to evaluate the efficacy of superactive GnRH analogs in the palliative management of prostate cancer.

- The 84-day formulation of triptorelin suppressed serum testosterone to ≤ 1.735 nmol/L within 29 days of first dosing and maintained testosterone at ≤ 1.735 nmol/L through 3 dosing cycles (253 days) in greater than 90% of patients.
- The 84-day formulation was not statistically inferior to the approved 28-day formulation in that the lower bounds of the 2-sided 95% CIs were greater than –10% for the differences between the proportion of patients who (a) had a serum testosterone value ≤ 1.735 nmol/L by Day 29 of treatment (84-day formulation minus 28-day formulation) and (b) maintained serum testosterone values ≤ 1.735 nmol/L from Day 57 through Day 253.

The clinical data provided by the Sponsor, however, may not have been sufficient to provide a meaningful estimate of the actual incidence of transient postdosing increases in serum testosterone to levels > 1.735 nmol/L after repeat dosing. Therefore, the Sponsor will be requested to conduct a limited Phase IV pharmacology study to obtain addition clinical data regarding serum testosterone levels 48-72 hours following the second and third dosing with the 84-day formulation of triptorelin pamoate (Trelstar™ LA).

9 INTEGRATED REVIEW OF SAFETY

9.1 Safety Studies

The sponsor submitted data from 5 clinical studies that were conducted using an 84-day formulation of triptorelin pamoate. Four of the studies were conducted in men with cancer of the prostate, and 1 study was conducted in women with gynecologic disorders. An overview of each of these Studies is provided in Table 5. All of the studies were conducted outside of the United States. Study DEB-96-TRI-01-Phase 1 provided almost all of the data in this submission supporting the safety of the to-be-marketed 84-day formulation of triptorelin pamoate for the palliative treatment of advanced prostate cancer. The other studies that were conducted in men with prostate cancer (Studies UK DCP 94-090, DEB-95-TRI-01, and DEB-99-TRI-01) were supportive safety or pharmacology studies. In each of these latter studies, subjects received only a single dose of an 84-day formulation of triptorelin. In addition, none of the patients in Study UK DCP 94-090 and only 10 of the 20 patients in Study DEB-95-TRI-01 received the to-be-marketed formation. The sponsor made no effort to integrate the safety findings from these studies, stating that each study was conducted under very different protocols and, in some instances, with different 84-day formulations of triptorelin.

Medical Officer's Comment

- *The supportive safety studies conducted in men with prostate cancer, as well as Study E5452014 099 that was conducted in women with gynecologic disorders, were reviewed primarily for the occurrence of deaths, serious drug-related adverse events, and allergic reactions.*

9.1.1 Extent of Exposure to Any 84-Day Formulation of Triptorelin Pamoate

The number of subjects exposure to any 84-day formulation of triptorelin pamoate and the maximum duration of exposure, based on the number of doses received, are summarized in Table 21. Each dose of Study Drug is assumed to provide 84 days of exposure to triptorelin pamoate. A total of 196 patients received one or more doses of the to-be-marketed 84-day formulation of triptorelin pamoate. Of these patients, 174 were in the principal safety and efficacy study, DEB-96-TRI-01-Phase 1. Of these patients 174 patients, 165 and 156 received 2 and 3 doses, respectively, of the 84-day formulation.

Medical Officer's Comments

- *Although the number of subjects treated with the to-be-marketed 84-day formulation of triptorelin is small, triptorelin acetate or triptorelin pamoate in 28-day formulations has been marketed worldwide for many years (see Section 3.4.2). The exposure to triptorelin (based on mean plasma AUC values) after a single dose of the 84-day formulation containing 11.25 mg is similar to that after 3 does of the 28-day formulation of triptorelin pamoate, each dose containing 3.75 mg of triptorelin (see Section 5.1).*
- *The number of patients exposed to the 84-day formulation and their duration of exposure, in conjunction with the submitted safety data and overall safety experience with the 28-day formulations, are adequate to assess the general safety of the 84-day formulation of triptorelin pamoate for the indication of management of advanced prostate cancer.*

Table 21. Number of Subjects Exposed to Any 84-Day Formulations of Triptorelin

Maximum duration of exposure [1]	Number of Subjects Receiving 1 to 3 Doses of Study Drug [2]				
	DEB-96-TRI-01-first phase (Prostate Ca)	UK DCP 94-090 Part 2 (Prostate Ca)	DEB-95-TRI-01 (Prostate Ca)	DEB-99-TRI-01 (Prostate Ca)	E545201-099 (Gynecologic Disorders)
84 days	174	53 [3]	20 [4]	12	14 [3]
168 days	165	---	---	---	---
252 days	156	---	---	---	---

[1] Duration of exposure based on number of doses of the 84-day formulation administered.
[2] Numbers represent the number of subjects that received 1 (84 days), 2 (168 days), or 3 (252 days) doses of Study Drug. Not all subjects in each category were monitored for the entire maximum duration of exposure.
[3] Patients did not receive the to-be-marketed formulation.
[4] Ten (10) of the 20 patients received the to-be-marketed formulation.
Source: Modified from Table 4, pg. 16, Vol. 40 of original submission.

9.2 Protocol Defined Safety Assessments in the Primary Safety Study

Safety assessments in Study DEB-96-TRI-01-Phase 1 (the primary safety study in this application) included monitoring and recording of treatment emergent adverse events and measurements of serum chemistries and hematology parameters. Table 6 lists the times at which the protocol-required safety assessments were to be performed.

9.2.1 Adverse Events and Other Safety Assessments

Collection of adverse event and other safety data. At each clinical visit (scheduled at 28-day intervals throughout the study), patients were to be assessed for potential adverse events. At each visit, adverse events were recorded on a visit-specific adverse event case report form. The severity of the adverse event was to be graded in accordance with the World Health Organization (WHO) toxicity scales as provided in the Study Protocol. Additional information about serious adverse events was provided to the Sponsor on a separate Serious Adverse Event (SAE) Form.

Local tolerance to the Study Drugs (assessed as "swelling", "redness", "bruising", "pain" and "induration") was recorded 2 hours after dosing on Study Days 1, 85 and 169.

Analysis and reporting of adverse event data. Adverse events were classified into body system categories. Adverse events were coded into preferred terms using the World Health Organization (WHO) Adverse Reaction Dictionary (ARD). The preferred coded terms were used in the statistical analyses. Adverse events were summarized by the number of patients reporting an event, the number of mentions of that event, and the percentage of patients with that event.
Clinical Laboratory Tests

Blood samples for hematology, coagulation, and blood chemistry measurements were collected at screening and on Study Days 1, 85, 169, and 253 or at termination if before Day 253. The specific laboratory measurements were:

- Hematology
  - hemoglobin, red blood cell count, and total leukocytes
- Coagulation
  - prothrombin time
- Blood chemistry
  - Glucose, BUN, creatinine, SGOT/AST, SGPT/ALT, alkaline phosphatase, and bilirubin

Analysis and reporting of laboratory data. Individual laboratory values were listed by patient and visit. Laboratory parameters before treatment, at each visit, and the change from pretreatment values to each on-treatment assessment were presented as summary statistics. The values for each laboratory test were compared across treatment groups using an analysis of variance (ANOVA) for continuous variables. Shift tables (change from baseline value to on-treatment values) based on laboratory normal ranges were presented for each laboratory measurement and each assessment time. Incidence rates of new on-treatment abnormal laboratory values, based on the shift tables, were calculated and listed by laboratory test and visit.

9.3 Patient Disposition (Principal Safety Study)

A total of 348 patients were enrolled in Study DEB-96-TRI-01-Phase 1. Two patients, one in each treatment group, did not receive any injections of Study Drug. The safety population therefore consisted of 346 patients (174 and 172 patients in the 84-day formulation and 28-day formulation treatment groups, respectively). Fifty-four (54) of the patients in the safety population did not complete the study (26 in the 84-day formulation group and 28 in the 28-day formulation group). The reasons for withdrawal are summarized in Table 22. Twenty-four (24) of the premature withdrawals were due to death (12 in each treatment group). Twenty-five (25) of the withdrawals were due to "lost to follow-up."

Medical Officer's Comment

- *The percentage of patients "lost to follow up" was high, but comparable in both treatment groups. The reason for these high rates of lost to follow up was not provided in the Study Report. It is possible that some of these patients may have experienced unreported adverse events and withdrew from the study because of them.*

Table 22. Patient Enrollment and Disposition in Study DEB-96-TRI-01-Phase 1

	Treatment Group	
	84-Day Formulation N = 175 n (%)	28-Day Formulation N = 173 n (%)
Received Study Drug (Safety Population	174 (100%)	172 (100%)
Terminated Prematurely	26 (14.9%)	28 (16.3%)
Drug-related adverse event	1 (0.6%) [1]	1 (0.6%) [2]
Non-drug related adverse event	12 (6.9%) [3]	12 (7.0%) [4]
Patient lost to follow-up	12 (6.9%)	13 (7.6%)
Other [5]	1 (0.6%)	2 (1.2%)
Completed Study	148 (85.1%)	144 (83.7%)

[1] A single death (pulmonary embolus) that was assessed as "unlikely" to be related to Study Drug.
[2] A single death (cardiac arrest) that was assessed as "unlikely" to be related to Study Drug
[3] All terminations due to death of patient with one exception (a case of bladder cancer).
[4] All terminations due to death of patient with one exception (repair of inguinal hernia and surgical orchiectomy).
[5] All terminations due to inappropriate enrollment or a significant protocol violation.
Source: Modified from Table (not numbered) on pg. 51, Vol. 29 of original submission.

9.4 Demographics and Other Baseline Characteristics (Principal Safety Study)

Baseline demographic characteristics are listed in Table 9. The mean age of the patients in the safety population was 70.0 years (range:) in the 84-day group and 71.0 years (range) in the 28-day group. The mean weight of the patients in the safety population was 72.8 kg (range:) in the 84-day group and 72.9 kg (range) in the 28-day group. Just under 50% of the patients were Caucasian (47% in the in the 84-day group

and 49% in the 28-day group). Thirty eight (38) percent and 37% of the patients in the 84-day and 28-day groups, respectively, were Black.

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

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9.5 Adverse Events

9.5.1 Overview of Adverse Events (Principal Safety Study)

Three hundred thirty-four (334) of 346 patients (96.5%) reported a total of 2720 adverse events during the clinical trial. In the 3-month formulation group, 171 of 174 patients (98.3%) reported 1409 adverse events compared with 163 of 172 patients (94.8%) reporting 1311 adverse events in the 1-month formulation group (Table 23).

In the 84-day formulation group, 147 of 174 patients (84.5%) reported a total of 423 adverse events that were at least possibly related to treatment. In the 28-day formulation group, 134 of 172 patients (77.9%) reported a total of 417 adverse that were at least possibly treatment related. Approximately 30% of the adverse events reported in each of the treatment groups were considered to be at least possibly related to the study medications.

In both treatment groups, the majority of adverse events were mild or moderate in severity. In the 3-month formulation group, 161 patients (92.5%) reported 834 mild adverse events, 125 patients (71.8%) reported 407 adverse events of moderate severity, and 64 patients (36.8%) reported 168 severe adverse events. In the 1-month formulation group, 149 patients (86.6%) reported 773 mild adverse events, 123 patients (71.5%) reported 372 adverse events of moderate severity, and 64 patients (37.2%) reported 166 severe adverse events.

In the 84-day formulation group, 30 patients (17.2%) experienced a total of 39 serious adverse events. In the 28-day formulation group, 39 patients (22.7%) experienced a total of 45 serious adverse events.

Twelve (12) patients in each treatment group died during the study, and one patient in each group died after completing their participation in the study. One patient in each group was withdrawn for an unrelated-to-treatment, nonfatal serious adverse (a bladder neoplasm in the 84-day group and an inguinal hernia in the 28-day group).

Table 23. Number and Percentage of Patients Reporting Adverse Events

	84-Day Formulation N = 174			28-Day Formulation N = 172		
	n[1]	%	(m)[2]	n	%	(m)
Any Adverse Event	171	98.3	(1409)	163	94.8	(1311)
Relationship of adverse event						
Related	147	84.5	(423)	134	77.9	(417)
Not related	156	89.7	(986)	144	83.7	(894)
Intensity of adverse event						
Mild	161	92.5	(834)	149	86.6	(773)
Moderate	125	71.8	(407)	123	71.5	(372)
Severe	64	36.8	(168)	64	37.2	(166)
Serious adverse events (including deaths)	30	17.2	(39)	39	22.7	(45)
Deaths						
During study	12	6.9		12	7.0	
After study	1	0.6		1	0.6	

[1] Number of patients reporting an adverse event in the category.
[2] Number of mentions of an adverse event in the category.
Source: Modified from Tables 14.3.1.1, 14.3.1.3, 14.3.1.4, and 14.3.2.1, Vol. 29 of original submission.

9.5.2 Adverse Events (All Intensities and All Relationships to Study Drug)

In the 3-month formulation group, 171 of 174 patients (98.3%) reported one or more adverse events compared with 163 of 172 patients (94.8%) in the 1-month formulation group. The incidence of adverse events by body system category is shown in Table 24. There were no statistically significant differences between the treatment groups in the percentage of patients experiencing adverse events in any of the body system categories.

Medical Officer's Comment

- *Although not statistically different, the percentage of patients reporting "application site disorders" was more than 2-fold greater in the 84-day formulation group. This difference was due largely to greater percentage of patients reporting "injection site pain" in the 84-day group (4.6% of patients) than in the 28-day formulation group (1.2% of patients).*

Table 24. Number of Patients with Adverse Events Classified by Body System Category

	84-Day Formulation N = 174			28-Day-Formulation N = 172			
	n[1]	%	(m)[2]	n[1]	%	(m)[2]	p[3]
All Body Systems	171	98.3	(1409)	163	94.8	(1311)	
Application site disorders	12	6.9	(12)	5	2.9	(5)	0.086
Body as a whole – general disorders	146	83.9	(347)	133	77.3	(339)	0.121
Cardiovascular disorders, general	28	16.1	(41)	28	16.3	(38)	0.962
Nervous system disorders	58	33.3	(188)	50	29.1	(137)	0.392
Endocrine disorders	9	5.2	(12)	5	2.9	(6)	0.285
Gastrointestinal system disorders	72	41.4	(130)	71	41.3	(142)	0.985
Hearing and vestibular disorders	4	2.3	(5)	3	1.7	(4)	1.000
Heart rate and rhythm disorders	1	0.6	(1)	4	2.3	(7)	0.213
Liver and biliary system disorders	8	4.6	(12)	7	4.1	(7)	0.809
Metabolic and nutritional disorders	40	23.0	(59)	39	22.7	(62)	0.945
Musculoskeletal system disorders	70	40.2	(151)	66	38.4	(121)	0.724
Cardiac disorders	3	1.7	(3)	6	3.5	(8)	0.335
Neoplasms	7	4.0	(9)	8	4.7	(8)	0.774
Platelet, bleeding and clotting disorders	1	0.6	(1)	5	2.9	(6)	0.120
Psychiatric disorders	46	26.4	(76)	33	19.2	(55)	0.108
Red blood cell disorders	3	1.7	(4)	7	4.1	(9)	0.218
Reproductive disorders, male	7	4.0	(9)	15	8.7	(18)	0.073
Resistance mechanism disorders	40	23.0	(55)	38	22.1	(54)	0.842
Respiratory system disorders	49	28.2	(105)	49	28.5	(90)	0.946
Skin and appendages disorders	19	10.9	(32)	19	11.0	(28)	0.970
Urinary system disorders	68	39.1	(124)	56	32.6	(133)	0.206
Vascular (extra-cardiac) disorders	3	1.7	(3)	4	2.3	(10)	0.723
Vision disorders	12	6.9	(14)	5	2.9	(6)	0.086
White cell and residual disorders	1	0.6	(1)	1	0.6	(1)	1.000

[1] Number of patients reporting an adverse event in the category.
[2] Number of mentions of an adverse event in the category.
[3] Chi Square Test
Source: From table 14.3.1.1, Vol. 29 of original submission.

Adverse events that occurred in 5% or more of the patients in the 84-day formulation group are listed by decreasing incidence in Table 25. The most common adverse events (events that

occurred in ≥ 10% of these patients) in order of decreasing frequency were hot flushes, headache, skeletal pain, back pain, constipation, viral infection, dysuria, arthralgia, pain, hypertension, coughing. leg pain, and urinary tract infection.

Medical Officer's Comments

- *The percentages of patients reporting each of the respective adverse events listed in Table 24 were similar across the 2 treatment groups.*
- *Hot flushes, the most frequently reported adverse event in each of the treatment groups, is an expected physiologic response to rapid suppression of serum androgens levels.*
- *The types of adverse events reported and their frequencies are not unexpected considering the study population, namely, elderly men (mean age of 70 years) with advanced prostate cancer. Skeletal pain and back pain, the third and fourth most frequently reported adverse events in the 84-day formulation group, were likely to have been a result of metastatic prostate cancer in many, if not most instances.*

Table 25. Adverse Events (All Treatment Relationships) Occurring in ≥ 5% of Patients

	Treatment Groups			
	84-day formulation N=174		28-day formulation N=172	
Adverse Event	n [1]	%	n [1]	%
Hot flushes	127	73.0	115	66.9
Headache	45	25.9	35	20.3
Skeletal pain	43	24.7	40	23.3
Back pain	36	20.7	31	18.0
Constipation	32	18.4	32	18.6
Viral infection	29	16.7	34	19.8
Dysuria	27	15.5	13	7.6
Arthralgia	27	15.5	26	15.1
Pain	26	14.9	31	18.0
Hypertension	22	12.6	22	12.8
Coughing	19	10.9	20	11.6
Leg pain	19	10.9	19	11.0
Urinary tract infection	18	10.3	22	12.8
Insomnia	17	9.8	16	9.3
Nausea	16	9.2	16	9.3
Diarrhea	16	9.2	13	7.6
Leg edema	15	8.6	17	9.9
Abdominal pain	14	8.0	11	6.4
Urinary retention	14	8.0	17	9.9
Upper respiratory tract infection	13	7.5	15	8.7
Dizziness	12	6.9	7	4.1
Fatigue	9	5.2	8	4.7
Cystitis	9	5.2	13	7.6

[1] Number of patients reporting the respective adverse event.
Source: From Table 14.3.1.1, Vol. 29 of original submission.

9.5.3 Treatment-Related Adverse Events

Treatment-related adverse events, events classified as possibly or probably related to treatment with Study Drug, were reported for 147 of 174 patients (84.5%) in the 84-day formulation group and 134 of 172 patients (77.9%) in the 28-day formulation group. Treatment-related adverse events that occurred in > 1% of patients in the 84-day formulation group are listed in order of decreasing frequency in Table 26.

9.5.3.1 Local Tolerance to Study Drugs

Local tolerance to the Study Drugs (assessed as "swelling", "redness", "bruising", "pain" and "induration") was recorded 2 hours after dosing on Study Days 1, 85 and 169. No patients in either treatment group reported induration and only one patient (0.6%) in the 84-day formulation group reported redness. Swelling was reported by one patient (0.6%) at two different visits in the 84-day formulation group and by no patient in the 28-day formulation group. On Day 1, 21 (12.1%) patients in the 84-day formulation group and 13 (7.6%) patients in the 28-day formulation group reported pain. The percentage of patients reporting pain decreased in both treatment groups on Study Days 85 and 169 but continued to be somewhat higher in the 84-day formulation group.

Medical Officer's Comments

- *Hot flashes, an expected response to rapid suppression of serum androgen levels, occurred in 73% and 66% of patients in the 84-day and 28-day formulation groups, respectively. In some patients, treatment-related skeletal pain may have been a consequence of the surge of testosterone that occurs during the first 2 weeks of treatment with any superactive GnRH agonist.*
- *Adverse events at the injections site were generally recorded on the case report form (CRF) specifically designated to assess local tolerance although in some instances such events were recorded on the standard Adverse Event CRF. Regardless of which source is used to assess local tolerance, a numerically higher percentage of patients in the 84-day formulation group reported pain within 2 hours after dosing. In other respects, tolerance to the 2 formations was similar. The reason for the higher incidence of pain in the 84-day formulation group is not obvious since both formulations are administered in a 2 mL volume of sterile water. In general, both formulations appeared to be well tolerated.*
- *Although a higher proportion of patients treated with the 84-day formulation reported postdosing injection site pain, this formulation is administered only one-third as frequently as the 28-day formulation.*

Table 26. Treatment-Related Adverse Events Occurring in ≥ 1% of Patients

	Treatment Groups			
	84-Day Formulation N=174		28-Day Formulation N=172	
Adverse Event	n [1]	%	n [1]	%
Hot flushes*	127	73.0	114	66.3
Skeletal pain	23	13.2	20	11.6
Headache	12	6.9	7	4.1
Edema in legs	11	6.3	14	8.1
Leg pain	9	5.2	5	2.9
Dysuria	8	4.6	3	1.7
Injection site pain	7	4.0	2	1.2
Hypertension	7	4.0	8	4.7
Pain	6	3.4	10	5.8
Back pain	5	2.9	6	3.5
Dizziness	5	2.9	5	2.9
Nausea	5	2.9	7	4.1
Fatigue	4	2.3	5	2.9
Dependent edema	4	2.3	0	0
Breast pain	4	2.3	5	2.9
Arthralgia	4	2.3	4	2.3
Decreased libido*	4	2.3	1	0.6
Impotence*	4	2.3	7	4.1
Chest pain	3	1.7	0	0
Leg cramps	3	1.7	1	0.6
Gynecomastia	3	1.7	0	0
Constipation	3	1.7	4	2.3
Dyspepsia	3	1.7	2	1.2
Increased alkaline phosphatase	3	1.7	1	0.6
Insomnia	3	1.7	2	1.2
Anorexia	3	1.7	1	0.6
Coughing	3	1.7	1	0.6
Rash	3	1.7	1	0.6
Asthenia	2	1.1	2	1.2
Peripheral edema	2	1.1	3	1.7
Diarrhea	2	1.1	4	2.3
Abdominal pain	2	1.1	1	0.6
Abnormal hepatic function	2	1.1	0	0
Myalgia	2	1.1	1	0.6
Dyspnea	2	1.1	3	1.7
Pharyngitis	2	1.1	0	0
Urinary retention	2	1.1	0	0
Eye pain	2	1.1	1	0.6
Conjunctivitis	2	1.1	0	0

[1] Number of patients reporting the event.
* Possible pharmacologic consequences of testosterone suppression to castrate levels.
Source: From Table 14.3.1.4, Vol. 29 of original submission.

9.5.4 Nonfatal Adverse Events Resulting in Patient Withdrawal

One patient in each group was withdrawn because of a nonfatal adverse event that was unrelated to treatment (i.e., a bladder neoplasm in a patient in the 84-day group and an inguinal hernia in a patient in the 28-day group). In the latter patient, a bilateral orchiectomy was performed at the time of repair of the hernia, thus eliminating the need for further medical suppression of testicular androgens.

9.5.5 Serious or Life-Threatening Adverse Events

All reported serious or life-threatening adverse events are listed in Table 27 (84-day formulation group) and Table 28 (28-day formulation group). In the 84-day formulation group, 39 serious adverse events involving 30 of 174 patients (17.2%) were reported. In the 28-day formulation group, 45 serious adverse events involving 39 of 172 patients (22.7%) were reported. In the 84-day formulation group, 2 adverse (motor weakness of legs in Patient No. 1017 and skeletal pain in Patient No. 3035) were considered as probably related to treatment with Study Drug by the Investigators. All other serious adverse events were considered to have either an unlikely relationship (n = 8) or no relationship (n = 29) to Study Drug. In the 28-day formulation group, all serious adverse events were considered to have either an unlikely relationship (n = 4) or no relationship (n = 41) to Study Drug.

Only 2 patients with nonfatal serious adverse events (bladder neoplasm and inguinal hernia, respectively) withdrawn from the study as described previous in Section 9.5.4.

Medical Officer's Comments

- *Withdrawal of only 2 patients for nonfatal adverse events in a 253-day study involving approximately 350 patients is unusual. However, the lost-to-follow rate was higher than in many studies of this duration – 7.5% and 7.6% of patient in the 2 treatment groups.*
- *The proportion of patients reporting serious adverse events was high in both treatment groups but to be expected considering the age of the patients (mean age of 70-71 years) and the fact that all had advanced prostate cancer. The percentage of patients experiencing a serious adverse event was slightly lower (17.2%) in the 84-day formulation group compared to that (22.7%) in the 28-day formulation group.*
- *The types of reported serious adverse events were generally similar across the 2 treatment groups and were compatible with the advanced age of the patients and the advanced stage of their prostate cancer disease.*
- *Two patients in the 84-day formulation group experienced serious adverse events that were probably a result of the initial surge of testosterone at the onset of treatment with Study Drug (Investigators' assessments). Patient No. 1017 developed weakness of his legs thought by the Investigator to be due to pressure on the spinal cord from adjacent metastatic disease. Patient No. 3035 reported increased skeletal pain. No patient in the 28-day formulation group was reported to have experienced similar serious adverse events.*

Table 27. Listing of Serious or Life-Threatening Adverse Events (84-Day Formulation)

Pt ID	Adverse Event	Severity	Relation to Study Drug
1003	Deep thrombophlebitis	Moderate	Unlikely
1003	Urinary retention	Moderate	Not related
1003	Pulmonary embolism	Fatal	Unlikely
1007	Atrial fibrillation/CHF	Fatal	Not related
1017	Motor weakness of legs 2nd to testosterone surge	Moderate	Probably
2011	Chronic Obstructive Respiratory Disease	Fatal	Not related
2016	Pulmonary mass (metastatic vs. primary neoplasm)	Fatal	Not related
2022	Back pain	Severe	Unlikely
2022	Hyperglycemia	Severe	Unlikely
2022	Hepatitis cholestatic (obstructive jaundice)	Severe	Unlikely
2025	Cancer of bladder	Severe	Not related
3009	Cerebrovascular disorder (stroke)	Mild	Not related
3020	Urinary retention	Mild	Not related
3031	Urinary retention	Moderate	Not related
3035	Skeletal pain (flare up syndrome)	Moderate	Probably
3037	Cataract	Mild	Not related
3041	Abscess (sacroiliac)	Severe	Not related
3043	Prostate cancer (progression)	Fatal	Not related
3045	Fever	Severe	Not related
3055	Cataract	Mild	Not related
3061	Lung abscess	Fatal	Not related
4008	Urinary tract infection (HIV+)	Fatal	Not related
4009	Prostate cancer (progression)	Fatal	Not related
4013	Abdominal pain	Severe	Unlikely
4013	Pneumonia	Fatal	Not related
4025	Prostate cancer (progression)	Fatal	Not related
5004	Convulsions	Moderate	Not related
5004	Cystitis	Moderate	Not related
7010	Cardiopulmonary failure	Fatal	Not related
7017	Prostate cancer (progression)	Fatal	Not related
9017	Pain	Severe	Not related
10004	Pneumonia	Severe	Not related
10004	Severe weakness	Severe	Unlikely
15012	Mastitis	Severe	Unlikely
16019	Renal failure	Fatal	Not related
16019	Syndrome of inappropriate ADH secretion	Fatal	Not related
16019	Urinary tract infection	Severe	Not related
16021	Urinary tract infection	Severe	Not related
19002	Hyperglycemia	Severe	Not related

Source: From Table 14.3.2.1, Vol. 29 and selected patients narratives, Appendix B, Vol. 40 of original submission.

Table 28. Listing of Serious or Life-Threatening Adverse Events (28-Day Formulation)

Pt ID	Adverse Event	Severity	Relation to Study Drug
1001	Inguinal hernia	Moderate	Not related
1008	Angina	Severe	Not related
2007	Urinary retention	Moderate	Not related
2009	Hemoptysis	Moderate	Not related
2015	Weakness in legs	Severe	Unlikely
3002	Pain in back and legs	Severe	Not related
3002	Prostate cancer (progression)	Fatal	Not related
3005	Prostate cancer (progression)	Fatal	Not related
3010	Convulsions	Severe	Unlikely
3019	Myocardial infarction	Fatal	Not related
3021	Prostate cancer (progression)	Fatal	Not related
3027	Back pain	Moderate	Not related
3036	Prostate cancer (progression)	Fatal	Not related
3036	Pelvic lymphocele	Mod	Not related
3038	Cardiac arrest	Fatal	Unlikely
3059	Cataract	Mild	Not related
4002	Ischemic heart disease (unstable angina)	Fatal	Not related
4012	Paralysis	Severe	Not related
4016	Chronic obstructive respiratory disease	Fatal	Not related
4016	Paralysis of right leg	Severe	Not related
4022	Urinary retention	Moderate	Not related
6011	Cataract	Mild	Not related
7011	Anemia	Severe	Not related
7018	Dehydration	Severe	Not related
8004	Bladder outlet obstruction	Severe	Not related
8004	Urethral stricture	Severe	Not related
9002	Pleural effusion	Severe	Not related
9005	Congestive heart failure & hemorrhage 2nd to cardiac cath	Fatal	Not related
9005	Bladder tumor	Severe	Not related
9007	Myocardial infarction	Fatal	Not related
9015	Sepsis of right knee	Severe	Not related
9020	Angina	Moderate	Not related
9025	Swelling right side of face	Severe	Not related
9030	Bladder tumor	Severe	Not related
12001	Inguinal hernia	Severe	Not related
14001	Choking	Severe	Not related
16003	Knee injury	Severe	Not related
16004	Pleural fibrosis	Moderate	Not related
16007	Renal failure/acute pylonephritis	Fatal	Not related
16024	Prostate cancer (progression)	Fatal	Not related
16024	Skeletal pain 2nd to metastatic disease	Severe	Not related
16027	Edema of legs	Severe	Not related
17002	Abdominal aortic aneurysm	Fatal	Not related
19003	Urinary retention	Severe	Not related
21001	Cerebrovascular accident (stroke)	Severe	Unlikely

Source: From Table 14.3.2.1, Vol. 29 and selected patients narratives, Appendix B, Vol. 40 of original submission.

9.5.6 Comparison of Adverse Events in Black and Caucasian Patients

The Sponsor, at the request of the Medical Officer, also performed subset analyses based on race for the safety assessments of adverse events and deaths for principal Study DEB-96-TRI-01-Phase 1. The percentages of Black and Caucasian patients in the 84-day formulation treatment group reporting adverse events are summarized in Table 29. The percentages of patients reporting any adverse event and treatment-related adverse events were similar in Black and Caucasian patients. A numerically higher percentage of Caucasian patients experienced severe adverse events (44.4% versus 33.3%) while a higher percentage of Black patients experienced serious adverse events (16.7% versus 12.3%). Deaths were reported for 7 of 66 Black patients (10.6%) and 4 of 81 Caucasian patients (4.9%) in the 84-day formulation group.

Table 29. Number and Percentage of Black and Caucasian Patients Reporting Adverse Events (84-Day Formulation Treatment Group)

	Black Patients N = 66			Caucasian Patients N = 81		
	n [1]	%	(m)[2]	n	%	(m)
Any Adverse Event	64	97.0	(441)	80	98.8	(828)
Relationship of adverse event						
Related	59	89.4	(177)	69	85.2	(204)
Not related	52	78.8	(264)	78	96.3	(624)
Intensity of adverse event						
Mild	58	87.9	(295)	78	96.3	(444)
Moderate	44	66.7	(107)	65	80.2	(263)
Severe	22	33.3	(39)	36	44.4	(121)
Serious adverse events (including deaths)	11	16.7	(14)	10	12.3	(14)
Deaths	7	10.6		4	4.9	

[1] Number of patients reporting an adverse event in the category.
[2] Number of mentions of an adverse event in the category.
Source: Submission of 27 April 2001, pg. 321-322.

The number and percentages of Black and Caucasian patients with adverse events classified by body system category in the 84-day formulation treatment group are listed in Table 30. Although the percentage of patients reporting one or more adverse events was similar in the Black and Caucasian groups, the percentages of patients experiencing adverse events in specific body system categories varied across the 2 racial groups. A higher percentage of Black patients experienced adverse events classified as cardiovascular disorders (primarily hypertension), metabolic and nutritional disorders (primarily increased peripheral edema and alkaline phosphatase levels), red blood cell disorders (anemia), and urinary tract disorders (primarily urinary tract infections and urinary retention) ($p < 0.1$, comparison across groups for respective category). A higher percentage of Caucasian patients experienced adverse events classified as general disorders or body as a whole (primarily increased pain), nervous disorders (primarily headaches), endocrine disorders (primarily breast pain and gynecomastia), psychiatric disorders (primarily insomnia, anxiety, nervousness, and depression), resistance mechanism disorders (primarily viral infections), and respiratory system disorders (primarily upper respiratory infections and sinusitis) ($p < 0.1$, comparison across groups for respective category).

Medical Officer's Comment

- *Although these differences may be related in some way to treatment with triptorelin, this reviewer believes that they are more likely related to other factors.*

Table 30. Number and Percentage of Black and Caucasian Patients with Adverse Events Classified by Body System Category (84-Day Formulation Group)

	Black N = 66		Caucasian N = 81		
	n [1]	%	n	%	p [2]
All body systems	64	(97)	80	(99)	.588
Application site disorders	8	(12)	4	(5)	.114
Body as a whole – general disorders	53	(80)	74	(91)	.052
Cardiovascular disorders, general	20	(30)	8	(10)	.002
Nervous system disorders	11	(17)	40	(49)	.001
Endocrine disorders	1	(2)	7	(9)	.058
Gastrointestinal system disorders	23	(35)	36	(44)	.238
Hearing and vestibular disorders	0	(0)	3	(4)	.253
Heart rate and rhythm disorders	0	(0)	1	(1)	1.0
Liver and biliary system disorders	4	(6)	3	(4)	.701
Metabolic and nutritional disorders	23	(35)	13	(16)	.008
Musculoskeletal disorders	28	(42)	39	(48)	.488
Cardiac disorders	0	(0)	3	(4)	.253
Neoplasms	3	(5)	3	(4)	1.0
Platelet, bleeding and clotting disorders	0	(0)	1	(1)	1.0
Psychiatric disorders	9	(14)	33	(41)	.001
Red blood cell disorders	3	(5)	0	(0)	.053
Reproductive disorders, male	1	(2)	5	(6)	.224
Resistance mechanism disorders	6	(9)	27	(33)	.001
Respiratory system disorders	13	(20)	27	(33)	.065
Skin and appendages disorders	7	(11)	8	(10)	.884
Urinary system disorders	32	(49)	28	(35)	.088
Vascular (extra-cardiac) disorders	0	(0)	2	(3)	.502
Vision disorders	3	(5)	5	(6)	.731
White cell disorders	1	(2)	0	(0)	.449

[1] Number of patients reporting an adverse event in the respective category
[2] Chi square or Fisher exact test.
Source: Modified from Table 14.3.1.1, pg 310-319 of submission of 27 April 2001.

9.6 Deaths

The number and percentage of patient deaths in each treatment group and each racial group in Study DEB-96-TRI-01-Phase 1 are listed in Table 31. Twenty-four (24) patients (12 in each treatment group) died during their participation in the Study. Two (2) additional patients (1 in each group) died within 90 days of completing the Study. In the 84-day formulation group, 7 of 66 Black patients (10.6%) and 4 of 81 Caucasian patients (4.9%) died. In the 28-day formulation group, 3 of 62 black patients (4.7%) and 9 of 84 Caucasian patients (10.7%) died. Overall, the percentages of Black and Caucasian patients who died in Study DEB-96-TRI-01-Phase 1 were similar (10 of 130 black patients [7.7%] and 13 of 165 Caucasian patients [7.9%]).

Table 31. Number and Percentage of Deaths in Each Treatment Group and in Each Race

	84-DAY FORMULATION			28-DAY FORMULATION			TOTAL		
Race	N [1]	n [2]	Percent	N [1]	n [2]	Percent	N [1]	n [2]	Percent
All	174	13	7.5	172	13	7.6	346	26	7.5
Black	66	7	10.6	64	3	4.7	130	10	7.7
Caucasian	81	4	4.9	84	9	10.7	165	13	7.9
Colored	27	2	7.4	24	1	4.2	51	3	5.9

[1] N = total number of patients.
[2] n = number of patients who died.
Source: Table 14.3.1.6, pg 325, Submission of 27 April, 2001.

All deaths with 2 exceptions were considered by the Investigators as being *Not Related* to treatment with Study Drugs (Table 32). The causes of death in the 2 exceptions were believed to have had an *Unlikely Relationship* to Study Drug. These latter 2 deaths were due to a fatal pulmonary embolus in Patient No. 1003 (84-day formulation group) and a cardiac arrest in Patient No. 3038 (28-day formulation group).

In the 84-day formulation group, the 13 causes of death were progression of prostate cancer (n=5), cardiac or thromboembolic disease (n=3), sepsis other than that involving the urinary tract (n=2), syndrome of inappropriate ADH secretion (n=1), chronic obstructive airway disease (n=1), and a pulmonary mass (n=1, metastatic prostate cancer or primary lung tumor). In the 28-day formulation group, the 13 causes of death were progression of prostate cancer (n=6), cardiac disease (n=4), chronic obstructive airway disease (n=1), aortic aneurysm (n=1), and stroke (n=1).

Medical Officer's Comments

- *All of the deaths in both treatment groups, with one exception, appeared to be due to progression of prostate cancer or a condition or disease that is a common cause of death in an elderly population of men. The exception was Patient No. 16019 who developed the syndrome of inappropriate ADH secretion and died of complications resulting from this disorder. It is unlikely that treatment with Study Drug was responsible for the development of this disorder or the death of any patient in the clinical trial.*
- *There is no reason to believe that the higher percentage of Black-patient deaths in the 84-day formulation group and the higher percentage of Caucasian-patient deaths in the 28-day formulation group were related to treatment with the respective formulations. Rather, the numerical differences are likely to be a result of the small number of events. Overall, the percentages of Black and Caucasian patients who died in Study DEB-96-TRI-01-Phase 1 were similar (10 of 130 black patients [7.7%] and 13 of 165 Caucasian patients [7.9%]).*
- *All patients with on-treatment serum testosterone values who died of progressive disease, were medically castrate (testosterone ≤ 1.735 nmol/L) prior to their death.*

Table 32. Listing of Patient Deaths

Patient Number	Last Dose (Study Day)	Death (Study Day)	Cause of death	Relationship to Study Drug	Testosterone Suppressed
84 Day Formulation					
1003	176	190	Pulmonary embolism	Unlikely	Yes
1007	169	195	Atrial fibrillation/CHF	Not related	Yes
2011	85	120	Chronic obstructive airway disease	Not related	Yes
2016	85	183	Pulmonary mass (neoplasm)	Not related	Yes
3043	85	141	Progression of prostate cancer	Not related	Yes
3061	88	158	Lung abscess/?septicemia	Not related	Yes
4008	169	226	Progression of prostate cancer/urinary tract infection	Not related	Yes
4009	1	70	Progression of prostate cancer	Not related	Yes
4013	1	48	Pneumonia	Not related	Yes
4025	169	274 [1]	Progression of prostate cancer	Not related	Yes
7010	1	35	Cardiopulmonary failure	Not related	Yes
7017	85	87	Progression of prostate cancer	Not related	Yes
16019	171	186	Inappropriate ADH Secretion Syndrome	Not related	Yes
28 Day Formulation					
3002	169	193	Progression of prostate cancer	Not related	Yes
3005	86	100	Progression of prostate cancer	Not related	Yes
3019	29	50	Myocardial infarction	Not related	Yes
3021	30	49	Progression of prostate cancer/pulmonary metastases	Not related	Yes
3036	202	229	Progression of prostate cancer	Not related	Yes
3038	57	62	Cardiac arrest	Unlikely	Yes
4002	141	144	Ischemic heart disease/CHF	Not related	By D85
4016	225	346 [1]	Chronic obstructive airway disease	Not related	Yes
9005	169	189	CHF/hemorrhage 2nd to cardiac catheterization	Not related	Yes
9007	1	28	Myocardial infarction	Not related	Died <D29
16007	85	103	Renal failure/acute pylonephritis	Not related	Yes
16024	226	230	Progression of prostate cancer	Not related	Yes
17002	39	57	Abdominal aortic aneurysm	Not related	Yes

[1] Occurred after termination from the Study.
Source: Data Listing 16.2.8.2 from Jan 26, 2001 Submission and Table/Listing 14.3.2.1, Vol. 29 of original submission.

9.7 Laboratory Assessments

9.7.1 Mean Hematology and Chemistry Values and Absolute Changes from Baseline

Table 33 lists the following values for each laboratory measurement: (1) baseline and last measurement mean values, (2) mean of the absolute changes from baseline to last measurement, and (3) the p-value (based on ANOVA) for the change from base compared across the 2 treatment groups. In the 84-day formulation group, mean changes from baseline that represented a change of at least 10% of the baseline value were observed for 6 of the 11 laboratory measurements. Mean increases of 10% or more above the baseline value were observed for BUN, SGOT, SGPT, and alkaline phosphatase (median change). Mean decreases of 10% or more below the baseline value were observed for the measurements of leukocytes and prothrombin time. There were no statistically significant differences between the 84-day formulation and the 28-day formulation treatment groups in terms of the change from baseline for any of the laboratory measurements.

Table 33, Mean Baseline and Last Hematology and Serum Chemistry Values

Laboratory Procedure	Unit	Formulation	Baseline Value	Last Measurement Value	Last Measurement Change from Baseline	p-Value[1]
Hemoglobin	g/dL	84-Day	14.04	13.57	-0.52	0.349
		28-Day	13.84	13.22	-0.74	
RBCs	10^{12}/L	84-Day	4.61	4.43	-0.20	0.261
		28-Day	4.66	4.42	-0.28	
Leukocytes	10^{9}/L	84-Day	7.45	6.28	-1.16	0.254
		28-Day	6.87	6.37	-0.46	
Prothrombin Time	Sec	84-Day	14.00	12.17	-1.82	0.456
		28-Day	13.70	12.11	-1.49	
Glucose	mg/dL	84-Day	109.14	113.43	3.99	0.407
		28-Day	108.28	117.30	8.97	
Creatinine	mg/dL	84-Day	1.17	1.23	0.06	0.294
		28-Day	1.21	1.19	0.00	
BUN	mg/dL	84-Day	18.16	20.27	1.98	0.766
		28-Day	17.60	19.35	2.36	
SGOT/AST	U/L	84-Day	23.48	27.22	4.19	0.915
		28-Day	21.55	26.22	4.46	
SGPT/ALT	U/L	84-Day	19.11	24.83	5.81	0.890
		28-Day	17.41	22.74	5.42	
Alkaline Phosphatase	U/L	84-Day	135.07	136.41	8.13	0.099
		28-Day	183.20	137.42	-50.69	
Alkaline Phosphatase[2]	U/L	84-Day	80.00	93.00	10.00	ND
		28-Day	81.50	96.00	14.50	
Bilirubin	mg/dL	84-Day	0.49	0.47	-0.02	0.211
		28-Day	0.49	0.38	-0.12	

[1] Difference between the 2 treatment groups in the change from Baseline to Last Measurement, calculated by ANOVA.
[2] Median values
Source: Table 14.3.4.2 of April 27, 2001 submission.

Medical Officer's Comment

- *The magnitude of the mean change from baseline for the parameters that were measured in the 84-day formulation group exceeded 20% for only one assessment. Mean SGPT concentrations increased from 19.11 U/L at baseline to 24.83 U/L at the last measurement, representing an increase of approximately 30%. Mean SGOT concentrations increased to a lesser degree (~18%), and there was no increase in mean total bilirubin levels.*

9.7.2 Incidence of Shifts to Low or High Hematology and Chemistry Values

The incidence rates of patients with shifts in laboratory values to (a) values below the lower limit of the normal range (shift to low) or (b) to values above the upper limit of the normal range (shift to high) are listed in Table 34. For 7 of the 11 laboratory measurements, more than 10% of patients shifted into the low or high range. In the 84-day formulation group, measurements for which > 10% of patients had shifted to below the normal range by Study Day 253 were hemoglobin (21% of patients) and red blood cell count (27% of patients). Measurements for which > 10% of patients had shifted to above the normal range by Study Day 253 were glucose (27% of patients), BUN (17% of patients), SGOT (12% of patients), SGPT (13% of patients), and alkaline phosphatase (16% of patients). Similar changes were observed in the 28-day formulation group.

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Table 34. Incidence Rates (%) of Patients with Shift to Low or High Laboratory Values

Laboratory Procedure		Shift to LOW Percentage of Patients			Shift to HIGH Percentage of Patients		
	Formulation	Day 85	Day 169	Day 253	Day 85	Day 169	Day 253
Hemoglobin	84-Day	17	20	21	0	1	1
	28-Day	16	19	26	0	0	0
RBCs	84-Day	19	24	27	1	1	1
	28-Day	20	29	31	0	0	0
Leukocytes	84-Day	6	6	4	3	1	1
	28-Day	5	7	8	3	3	2
Prothrombin Time	84-Day	1	0	1	5	7	1
	28-Day	1	1	1	2	3	1
Glucose	84-Day	2	3	3	26	33	27
	28-Day	3	0	1	21	26	19
Creatinine	84-Day	7	6	5	8	7	8
	28-Day	9	8	5	4	7	5
BUN	84-Day	1	1	1	16	17	17
	28-Day	1	0	1	14	19	13
SGOT/AST	84-Day	0	1	0	11	9	12
	28-Day	0	0	0	12	10	7
SGPT/ALT	84-Day	0	1	1	13	11	13
	28-Day	0	1	0	17	11	12
Alkaline Phosphatase	84-Day	0	0	1	12	15	16
	28-Day	1	0	0	15	17	28
Bilirubin	84-Day	5	10	7	1	2	0
	28-Day	9	8	7	1	0	1

INCIDENCE RATE = (Number of patients reporting the abnormality at the respective on-treatment assessment) divided by (the number of patients without missing data who did not report the abnormality at the baseline assessment).
Source: Tables 14.3.4.4 and 14.3.4.5 of April 27, 2001 submission.

Medical Officer's Comments

- *The decrease in mean hemoglobin and RBC count values and relatively high percentage (~25%) of patients who shifted to low for these assessments is not unexpected in patients with prostate cancer who are treated by reducing their serum testosterone to castrate levels. These were the only laboratory assessments that showed a consistent trend toward a higher percentage of patients shifting to outside of the normal range as the treatment period increased.*
- *The laboratory data represented in Table 33 and Table 34 do not indicate that there are any significant differences in end-of-treatment laboratory values or changes in laboratory values in patients treated with the 84-day formulation as compared to those treated with the 28-day formulation.*
- *There were isolated instances of extreme changes in one or more laboratory measurements in some patients. In some instances, these could be explained by other disease processes. In other instances there were no obviously explanations for the changes. Some were likely to have reflected data transfer or data entry errors (see Medical Officer's Comments in Sections 7.2.2 and 7.3). The magnitude of the mean changes and the percentage of patients shifting*

either to above or below the normal range is consistent with the changes that might be expected in the study population. Overall, the laboratory data from Study DEB-96-TRI-01-Phase 1 do not raise concerns about significant drug-induced toxicity associated with the use of the 84-day formulation of triptorelin for the treatment of advanced prostate cancer.

9.8 Safety Issues of Special Concern

There are no safety issues of special concern. Triptorelin, either as the acetate or pamoate salt, has been marketed in a 28-day formulation for more than a decade and was approved for marketing by the FDA in June 2000. As a class, superactive agonists of GnRH have been found to be safe and well tolerated and are approved not only for the treatment of prostate cancer but also for benign estrogen-dependent gynecologic disorders and precocious puberty.

9.9 Postmarketing Safety Issues and Safety Update

The Sponsor's Safety Update submitted on October 24, 2000 covered the period from September 6, 1999 through September 29, 2000. According to the Sponsor, the update "summarized all the safety information pertaining to the triptorelin pamoate 11.25 mg formulation arising from clinical trials and post-marketing surveillance collected by Debio from its licensee Beaufour-Ipsen during the reporting period."

Clinical trials sponsored by Debio and Beaufour-Ipsen. Limited safety data from 3 clinical trials sponsored by Beaufour-Ipsen (1 trial conducted in women with benign gynecologic disorders (Study E54.52014.099) and 2 trials conducted in men with prostate cancer) were presented and reviewed. No safety issues of concern were identified in the 2 clinical trials conducted in men with prostate cancer. However, in Study E54.52014.099, a 30 year old women developed life threatening dyspnea lasting for 1 hour 2 days after receiving the 84-day formulation of triptorelin. Further information about this reaction was not provided. In a clinical trial sponsored by Debio (DEB-99-TRI-04), a patient with prostate cancer experienced an anaphylactic reaction (including "anaphylactic shock") 4.5 hours after his second injection of the 28-day formulation of triptorelin acetate. This latter formulation of triptorelin contains dextran, a possible cause of the reaction, according to the Sponsor. The formulation under review in this NDA does not contain dextran.

Post marketing spontaneous safety reports. Beaufour-Ipsen stated in their Periodic Safety Update Report (PSUR) covering the period March 5, 1999 to March 5, 2000 that the overall reporting rate for adverse events in France was 77 spontaneous reports among 338,081 treatment month equivalents or 1 event per 4000 treatment months. Among the 77 reports of serious adverse events were a single case of severe angioedema, a single case of rash associated with facial edema, and several cases of cutaneous hypersensitivity reactions. An estimate of the incidence of hypersensitivity reactions (all types of reactions) reported to Beaufour-Ipsen over the most recent 3 year period was included in the PSUR and is summarized in Table 35.

Table 35.- Incidence Estimates of Triptorelin Hypersensitivity Reactions in France

Exposure	1997	1998	1999-2000
Exposure treatment months [1]	306,817	309,951	337,043
Number of ADRs	11	15	14
Incidence [2]	< 4/100,000	< 5/100,000	<5/100,000

[1] All formulations of triptorelin
[2] Hypersensitivity ADRs per 100,000 treatment months
Source: Table 4, pg. 53, Safety Update and Periodic Safety Update Report, Beaufour-Ipsen Group, July 2000.

Medical Officer's Comments

- *To obtain more information about the types of hypersensitivity reactions reported in patients treated with triptorelin, the Sponsor was asked to provide line-listings for the data represented in Table 35. Among the reactions were 3 cases of anaphylaxis and 12 cases of angioedema or facial edema.*
- *Based on information in the FDA database for spontaneous reporting of postmarketing adverse events, the incidence of allergic reactions reported in Table 35 does not appear to be significantly different than that for other superactive GnRH agonists.*
- *No cases of serious systemic allergic reactions were reported in the principal safety study with either the 84-day or 28-day formulations of triptorelin (Study DEB-96-TRI-01-Phase 1) in NDA 21-288.*
- *The Sponsor estimates that since the launch of the 28-day formulation of triptorelin in 1986 and the 84-day formulation in 1997, and treatment months of product, respectively, have been sold world-wide by its Licensees' Beaufour-Ipsen and Ferring.*

9.10 Safety Consultations

No safety consultations were obtained.

9.11 Adequacy of Patient Exposure and Safety Assessments

A total of 196 patients represented in NDA 21-288 received one or more doses of the to-be-marketed 84-day formulation of triptorelin pamoate. Of these patients, 174 were in the principal safety and efficacy study (DEB-96-TRI-01-Phase 1). Of these patients, 165 and 156 received 2 and 3 doses, respectively, of the 84-day formulation (Table 21).

Although the number of subjects treated with the 84-day formulation of triptorelin described in this NDA is small, triptorelin acetate or triptorelin pamoate in 28-day formulations and triptorelin pamoate in a 84-day formulation are presently marketed in many countries. The total exposure to triptorelin (based on plasma triptorelin AUC values) after a single dose of the 84-day formulation containing 11.25 mg of active drug substance is similar to that after 3 doses of the approved 28-day formulation (3.75 mg of triptorelin per dose x 3 doses). Consequently, the 172 patients (Phase 1) and 140 patients (Phase 2) who were treated for up 253 days with the 28-day formulation of triptorelin in Study DEB-96-TRI-01 provide additional supportive safety data.

Based on the data from Study DEB-96-TRI-01 Phase 1, no drug-induced toxicity unique to the 84-day formulation is likely to occur. Therefore, the number of patients exposed to the 84-day formulation and the duration of exposures are adequate to assess the general safety of the 84-day formulation for the proposed indication of palliative treatment of advanced prostate cancer.

9.12 Safety Findings and Proposed Labeling

The safety findings that were (1) observed in the primary safety study (DEB-96-TRI-01-Phase 1) and (2) reported in the Safety Updates are adequately and appropriately represented in the proposed labeling with the exception of those specific items listed below in Section 11 (Package Insert).

10 USE IN SPECIAL POPULATIONS

10.1 Women and Children

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

10.2 Subjects with Renal or Hepatic Impairment

Data on the pharmacokinetics of triptorelin in subjects with impaired renal or hepatic function was previously submitted and reviewed under NDA 21-715. Administration of a single IV bolus dose of 0.5 mg triptorelin to subjects with renal or hepatic insufficiency indicated that these subjects had a decrease in total triptorelin clearance compared to healthy volunteers (Table 4). The decrease in triptorelin clearance was most pronounced in subjects with liver insufficiency. In subjects with renal disease, the increase was proportional to the decrease in creatinine clearance. Subjects with renal or hepatic impairment had a 2- to 4-fold higher exposure to triptorelin (higher AUC values) than young healthy males.

Medical Officer's Comment

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

10.3 Racial Differences in Efficacy and Safety Findings

The sponsor, at the request of the medical officer, performed subset analyses based on race for efficacy (the co-primary efficacy endpoints of attainment and maintenance of medical castration) and safety (adverse events and deaths) for principal Study DEB-96-TRI-01-Phase 1. Results of these analyses are presented in Section 8.4.2.5 (efficacy), Section 9.5.6 (adverse events), and Section 9.6 (deaths).

11 PACKAGE INSERT

The proposed label submitted by the Sponsor requires some modification and additions. The most significant of these changes are listed below. Words and statements to be added are underlined. Words and statements to be deleted are lined-through.

All references to frequency of dosing with triptorelin pamoate 11.25 mg should be stated in terms of an interval of 84 days or 12 weeks and not in terms of an interval of 3 months. A 3-month interval may be interpreted as 13 weeks. In the principal efficacy and safety clinical trial, triptorelin pamoate 11.25 mg was administered every 84 days and *not* every 3 months.

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- Pg. 4 and 5: **CONTRAINDICATIONS**

- Pg. 5: **WARNINGS**

- Pg. 5:

- Pg. 9:

12 CONCLUSIONS AND RECOMMENDATIONS

12.1 Overall Risk/Benefit Assessment

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

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

dosing, are sufficient to support the efficacy of the 84-day formulation of triptorelin pamoate for the palliative treatment of advanced prostate cancer.

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

As a class, superactive agonists of GnRH have been found to be safe and well tolerated and are approved not only for the treatment of prostate cancer but also for benign estrogen-dependent gynecologic disorders and precocious puberty. Triptorelin, either as the acetate or pamoate salt, has been marketed outside of the United States in 28-day formulations for more than a decade for the treatment of advanced prostate cancer. In 1996, an 84-day formulation of triptorelin for the treatment of prostate cancer was approved in France and has subsequently received marketing approvals in a total of 10 countries. The Sponsor estimates that since the launch of a 28-day formulation of triptorelin in 1986 and the 84-day formulation in 1997, and treatment months of the 2 formulations, respectively, have been sold world-wide by its licensee's Beaufour-Ipsen and Ferring.

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

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

12.2 Major Issues with Regard to Sponsor's Proposed Labeling

There are no major labeling issues. The sponsor will be requested to make the labeling changes described above in Section 11. These changes are primarily to increase the clarity of the label and to provide some additional safety information.

12.3 Approvability

12.3.1 General Recommendations

It is recommended that the 84-day formulation of triptorelin (Trelstar™ LA) be approved for the proposed indication of "*palliative treatment for advanced prostate cancer*" conditional upon the Sponsor's agreeing to the specific recommendations described below in Section 12.3.2.

12.3.2 Specific Recommendations

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

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

/S/ 6/29/01

Scott E. Monroe MD

Medical Officer, DRUDP

Addendum to Review (June 25, 2000)

1. On June 22, 2001 the Sponsor committed to conduct a Phase IV pharmacology study to collect additional clinical data regarding changes in serum testosterone concentrations after repeat dosing with the 84-day formulation of triptorelin pamoate (Trelstar™ LA 11.25 mg). In this Study, 15-20 subjects will each receive 3 doses of Trelstar LA. Blood samples for the measurement of serum testosterone levels will be obtained at screening and immediately prior to and 48-72 hours after the second and third doses of Trelstar LA. Entry criteria will include a screening serum testosterone of > 5 nmol/L.

   The outline of the proposed Phase IV Study was reviewed and found to be acceptable.

2. On June 27, 2001 the Sponsor submitted a revised label in accordance with the recommendations of DRUDP. The revised label was reviewed and found to be acceptable.

There are no remaining outstanding clinical issues.