acceptable if the data could be validated (1/18/95). The sponsor was told that a meta-analysis could be used as supportive data (6/16/94). The Statistical review further elucidates the meta-analysis issue.

The sponsor was told (6/16/94) during a meeting that a "firm connection" had to be made between the to-be-marketed formulation (lyophilized microgranular pamoate salt) and the foreign studies that were performed with the alternative product (microspherical acetate salt). See the Biopharmaceutics review for further discussion of this issue.

On July 25,1996 a filing meeting was held and the division (DRUDP) found that that NDA 20-715 was acceptable for filing. On Jan. 17, 1997, the division asked for clarification regarding the administrative structure of the sponsor, which was detailed to the division in a letter on Jan.23,1997. A status meeting was held with Debio on Feb. 4, 1997 at which time a number of serious clinical and other concerns were expressed by the division. In a letter dated March 19,1997 the clinical concerns that were expressed at the meeting and in a letter by the division of Jan.29,1997 were addressed in detail by the sponsor. The sponsor's comments are discussed in section 8.0.

2.2 Clinical background and rationale for treatment of prostate cancer with Decapeptyl

Prostate cancer is the most common malignancy diagnosed in American men. It is the second leading cause of cancer deaths in this population resulting in approximately 35,000 deaths per year. Prostate cancer incidence rates have risen about 4% per year since the early 1980s because of an aging population and better detection methods. In autopsy studies of eighty year old men, the prevalence of histological prostate cancer is about 60% to 70%, however the prevalence of clinically significant prostate cancer is unknown.

Significant racial differences exist with this disease. There is a higher incidence and mortality among African-Americans compared to Caucasians. The incidence among Asians is less than Caucasians. Familial and dietary factors have also been found to be important. The two most significant factors are age and hormones. The incidence of prostate cancer increases with age. Eighty percent of all prostate cancer is diagnosed in men older than sixty-five years.

Endocrine factors contribute to normal growth of the prostate and to development of prostate cancer and benign prostatic hypertrophy. The low incidence of prostate cancer in eunuchs and patients with cirrhosis confirms this endocrine relationship. However, the exact interactions of androgens and other endocrine factors in the development of the disease are not fully understood. The pioneering work of Huggins (1941) demonstrated that surgical castration or estrogen therapy produced clinical remission in 80% of patients with advanced prostate cancer. This work has provided a rationale for the most effective treatment of prostate cancer. Androgen ablation causes apoptotic cell death of androgen-dependent cells. Unfortunately, initial response to androgen ablation is not maintained and metastatic disease eventually becomes androgen independent.

Since the early 40's, the "gold standard" for treatment of advanced prostate cancer has been bilateral orchiectomy. For many years, diethylstilbestrol (DES) was a medical alternative to orchiectomy. However while DES proved to be effective against prostate cancer, it was associated with a risk of adverse cardiovascular events. When considering various modalities for hormonal management, the clinician must be concerned with how the proposed option compares to orchiectomy or DES considering toxicity, cost, quality of life, and possible improvement of survival. In 1986, a trial was performed that compared 3mg. of DES with daily administration of the GnRH (gonadotropin releasing hormone) agonist, leuprolide, and demonstrated comparable survival rates.[1] Subsequently, another study compared bilateral orchiectomy with another GnRH agonist, goserelin, in patients with advanced prostate cancer. Survival was again comparable.[2] These clinical trials supported the concept that GnRH agonists produce response and survival rates similar to DES or bilateral orchiectomy. Another study generated the information that if patients were given the choice, they would choose a GnRH agonist over bilateral orchiectomy.[3] This study was one of the first to address quality of life issues that are becoming more important in the assessment of patients with metastatic disease.

Two GnRH agonists have been approved for the treatment of advanced prostate cancer. They are Zoladex (goserelin acetate) under NDA 20-578 and Lupron (leuprolide acetate) under NDA 20-708. When each of these drugs was initially submitted, efficacy was based on a comparison with surgical orchiectomy or DES. The primary endpoint was reduction of T levels. Clinical improvement parameters were secondary endpoints. New formulations of these drugs have been approved based on reduction of T as the primary endpoint.

Triptorelin pamoate (D-Trp^{6}-GnRH), the active peptide in Decapeptyl, is a synthetic decapeptide agonist analog of the naturally occurring gonadotropin releasing hormone (GnRH) also called luteinizing hormone releasing hormone (LHRH).

As shown in the amino acid sequence below, the major structural difference between Decapeptyl (triptorelin pamoate, lyophilized) and the other two GnRH agonists is the substitution of a different D-amino acid at position six, which is the link between the two bioactive portions of the peptide. All of the GnRH agonists retain those sequences of the GnRH decapeptide responsible for biological activity.

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[1] The Leuprolide Study Group: leuprolide versus diethylstilbestrol; for metastatic prostate cancer. N Engl. J Med. 1984;311:1281-86

[2] Peeling WB, Phase 3 studies to compare goserelin (Zoladex) with orchiectomy and with diethylstilbestrol in the treatment of prostatic carcinoma. Urology 1989; 33: 45-52.

[3] Cassileth BR, Soloway MS, Vogelzang NJ, et al. Patients choice of treatment in stage D prostate cancer. Urology 1989; 33:57-62.

Amino Acid Structures of GnRH and Three GnRH Agonists

	1	2	3	4	5	6	7	8	9	10
GnRH	(pyro) Glu-	His-	Trp-	Ser-	Tyr-	Gly-	Leu-	Arg-	Pro-	Gly-NH2
leuprolide	(pyro)Glu-	His-	Trp-	Ser-	Tyr,-	D-Leu-	Leu-	Arg-	Pro-	ethylamide
goserelin	(pyro) Glu-	His-	Trp-	Ser-	Tyr-	D-Ser(tBu)-	Leu-	Arg-	Pro-	Gly(Az)-NH2
triptorelin	(pyro) Glu-	His-	Trp-	Ser-	Tyr-	D-Trp-	Leu-	Arg-	Pro-	Gly-NH2

GnRH is synthesized in the cells of the hypothalamic neurons and secreted in a pulsatile fashion into the hypothalamic-hypophyseal portal circulation. GnRH stimulates the gonadotroph cells to synthesize and release the gonadotropins, luteinizing hormone(LH) and follicle stimulating hormone (FSH). LH and FSH bind to receptors in the ovary and testis and regulate gonadal function by promoting sex steroid production and gametogenesis. Hypothalamic release of GnRH and its action on the pituitary is controlled by bio-feedback mechanisms based on the amount of sex steroid in circulation. Secretion of LH and FSH are episodic with secretory bursts that occur each hour and are mediated by the episodic release of GnRH. The pulsatile nature of GnRH release is critical for sustaining gonadotropin secretion. A continuous administration of GnRH or GnRH agonist evokes an initial increase in LH and FSH followed by prolonged suppression of gonadotropin secretion. This phenomenon may be explained by down-regulation of GnRH receptors on the pituitary gonadotroph cells.

Therefore, in men, the chronic administration of a GnRH agonist will result in an initial stimulation of gonadotropins and thus testosterone for several weeks. This is followed by a significant, sustained and reversible decrease in testosterone levels usually to castrate levels. The sponsor believes that Decapeptyl produces a sustained hypotestosteronemia and therefore has an inhibitory effect on cancer of the prostate. The sponsor believes that in the submitted studies, Decapeptyl is equivalent to orchiectomy in reducing serum testosterone levels in men with cancer of the prostate.

Ideally, a drug used to suppress testosterone in patients with prostate cancer would suppress rapidly below castrate level and maintain that level while the drug is administered. The daily production of testosterone is 4 to 8 mg. per day. Ninety-five percent is produced in the Leydig cells of the testes with the remainder produced in the adrenal. Testosterone levels peak in the morning, decreasing during the day. The peak and nadir levels differ by approximately 30%. Castrate levels, measured in prostate cancer patients, post-orchiectomy, are considered to be less than 50ng./dL (or 1.73 nmol/L).

The chronic administration of GnRH agonists induces gonadal stimulation during the first week of so of therapy causing an elevation of testosterone to 140-170% of basal levels

(testosterone flare). By the end of the fourth week, testosterone levels should be below castrate levels. A small percentage of patients (5% or less) do not suppress to below castrate levels with approved drugs in this class.

There are two other forms of "failure" in this drug group. The first is "escape" of testosterone above castrate level after suppression has been achieved. The second is a stimulatory effect upon reinjection (acute on chronic effect or secondary flare) which results in an increase in testosterone level. All three forms of "failure" usually result in testosterone levels that are well below normal values and often only minimally above castrate range. The clinical significance of these phenomena is unclear and probably related to how much the testosterone exceeds castrate range in the individual patient. These phenomena occur in about 5% of the patients taking approved drugs in this class.

2.3 Clinical implications of preclinical studies

2.31 Chemistry, Manufacturing and Controls

Refer to Dr. Moo-Jong's review . As noted, the diluent and drug product powder have different expiration times, and the shortest is the diluent's, which is —. This is a problem because the diluent and the powder have to be mixed just before administration, which means the entire system would have a shelf-life of under —. The sponsor is aware of this problem and has not responded to this deficiency at the time of this review.

2.32 Microbiology

Refer to Dr. Uratani's review. After the microbiologist's initial review, an extensive list of deficiencies was conveyed to the sponsor. Their responses were reviewed and although some of the concerns were adequately addressed by the sponsor, the microbiologist concluded that "the submission does not contain sufficient information to assure the sterility and safety of the drug product. The NDA is, therefore, not recommended for approval as submitted."

2.33 Pharmacology/toxicology

Refer to Dr. Raheja's review. The preclinical pharmacology and toxicology data were found sufficient to support the NDA.

2.4 Clinical implications of human pharmacology studies

Refer to Dr. Barnett's review. Two major areas of deficiency were found by the clinical pharmacology reviewer. The first area relates to the lack of bioequivalence and pharmacodynamic equivalence between the formulation used in the pivotal trials as compared to the to-be-marketed formulation. The second is that the proposed dissolution method for quality control and release of drug product is not acceptable. An alternative dissolution method will be suggested to the sponsor.

Dr. Gary Barnett states in his review that "The proposed to-be-marketed formulation is not bioequivalent to the formulations used in the submitted pivotal clinical trials. The

sponsor maintains that the pharmacodynamic equivalence (maintenance and suppression of serum testosterone levels) exists. However, only single dose studies comparing the pharmacodynamics of the to-be-marketed formulation and that of the clinically tested formulations have been conducted. The difference in the triptorelin concentration versus time profiles of the relevant formulations may be clinically significant, due to spike levels of triptorelin that occur within 3 hours of dosing of the to-be marketed formulation that may be more readily induce a secondary flare (acute-on-chronic) of testosterone levels resulting in escapes from castrate levels than the clinically tested formulations which do not result in a spike level of triptorelin."

In the single multiple dose study (two administrations of one month depot) submitted, the effect of various doses of the clinically tested (acetate) formulation on serum testosterone is assessed in patients with advanced prostate cancer. Evaluation of the 3.75 mg dose revealed that 5 out of 5 patients escaped above castrate level (1.75 nmol/l) during the test period of 60 days.

Considering the above findings, the clinical pharmacology reviewer concluded that the sponsor has not provided sufficient evidence to warrant approval.

2.5 Statistical issues

See Dr. Taneja's review for further detail on the following issues. The sponsor submitted "pooled" data from the "pivotal" clinical trials and suggested that this data supported their contention that Decapeptyl is as safe and efficacious as orchiectomy in reducing testosterone to castrate levels and therefore palliating patients with advanced prostate cancer. The statistical reviewer states that the submitted studies cannot be pooled because of underlying differences between them. The studies were therefore analyzed separately.

The statistical reviewer also had specific comments regarding each of the three submitted studies. As for the Parmar study, there was no randomization and hence the study is not interpretable. Similarly, the Botto study was not randomized and statistical results cannot be interpreted. The De Sy study was poorly designed and conducted and there were large numbers of patient discontinuations. Therefore it is not feasible to do a meaningful statistical analysis hence this is a failed study.

2.6 International marketing experience

Decapeptyl Depot for IM administration every 28 days has been approved for the palliative treatment of advanced prostate cancer and other indications by the regulatory authorities in approximately sixty (60) countries. In these countries, Decapeptyl is marketed in a 3.75 mg dose in two acetate formulations. In addition, two pamoate formulations, one manufactured by Ipsen Biotech, the other by Debio R.P. have been recently registered in France and Brazil respectively. The latter formulation, lyophilized triptorelin pamoate microgranules 3.75 mg., is the NDA formulation intended for the U.S. market. Decapeptyl has not been withdrawn from marketing in any country for any reason. International postmarketing data is submitted as part of the NDA. Review of this

material reveals adverse events mostly consistent with the pharmacologic action of the drug. Much of the data is from spontaneous reporting.
Reviewer's comment: There are 34 reports of immunologic postmarketing adverse events possibly related to Decapeptyl collected over a period of 5 years during which [redacted] vials of Decapeptyl have been sold worldwide. These include 2 cases of angioedema and three of anaphylactic shock. There is insufficient information at this time to decide whether this risk is greater than with the approved drugs.

3. Summary of NDA clinical section
The clinical section of this application contains the study reports of the three "core" controlled clinical trials (Parmar-914CL14P, Botto-914CL17E and De Sy-914CL7P), a controlled trial (Kuhn-52014 ST 8040) comparing monthly Decapeptyl with monthly Entanone (leuprolide), eleven uncontrolled trials extracted from published foreign literature and a brief summary of studies conducted with Decapeptyl for indications other than prostate cancer.

3.1 Summary of submitted controlled trials of Decapeptyl
"Core studies"
Parmar-914CL14P
This was an open, randomized, parallel group, multicenter study comparing Decapeptyl Depot with orchiectomy in the palliative treatment of cancer of the prostate. One hundred and twenty-five patients with advanced prostate cancer (76 patients in the Decapeptyl group, 49 patients in the orchiectomy group) were enrolled in 6 centers in the UK. The study was initiated on Feb. 4, 1984 and completed on September 15, 1989. The patients were assessed monthly for three months and then every three months thereafter for 24 months. The primary efficacy variable was the ability of Decapeptyl to induce castrate levels of T at a comparable rate to surgical orchiectomy. The original protocol was designed with overall tumor response and survival as the primary efficacy variables but this was changed retrospectively at a pre-NDA meeting with the FDA on Jan18, 1995.

Botto-914CL17E
This was an open, randomized, parallel group, multicenter study comparing Decapeptyl Depot with orchiectomy in the palliative treatment of cancer of the prostate. There were 20 centers in this trial performed in France between 1983 and 1986. Eighty patients participated in the study (40 patients in the Decapeptyl group, 40 patients in the orchiectomy group). The patients were assessed monthly for three months and then every three months thereafter for 24 months. The primary efficacy variable was the ability of Decapeptyl to induce castrate levels of T at a comparable rate to surgical orchiectomy. The original protocol was designed with overall tumor response and survival as the primary efficacy variables but this was changed retrospectively at a pre-NDA meeting with the FDA on Jan18, 1995

De Sy -914CL7P

This was an open, randomized, parallel group, multicenter study comparing Decapeptyl Depot with orchiectomy in the palliative treatment of cancer of the prostate. Sixty patients participated in the study (44 patients in the Decapeptyl group, 16 patients in the orchiectomy group) at 5 study centers located in Belgium. The study began in March 1984 and was completed in December 1986. The patients were assessed monthly for three months and then every three months thereafter for 24 months. The primary efficacy variable was the ability of Decapeptyl to induce castrate levels of T at a comparable rate to surgical orchiectomy. The original protocol was designed with overall tumor response and survival as the primary efficacy variables but this was changed retrospectively at a pre-NDA meeting with the FDA on Jan18, 1995

Supportive study

Kuhn-5204 ST 8040

This was an open, randomized multicenter study comparing Decapeptyl (3.75 mg.) and Enantone (leuprolide) 3.75 mg. in patients with advanced prostate cancer. Sixty-seven patients participated in the study (33 patients in the Decapeptyl group, 34 patients in the Enantone group) at 9 centers in France between 1992 and 1995. Patients were given monthly injections of either of the two drugs for three months. The primary efficacy variable was the ability to induce castrate levels of T and maintain this level throughout therapy (defined as 0.5 ng./ml = 50 ng./dl). According to the protocol: "In order to prevent the effects of flare-up, flutamide was prescribed 1 week before and three weeks after the first injection at the dosage of 250 mg. tid; flutamide treatment could be prolonged at the discretion of the investigator. T levels fell below castrate levels in 88% to 100% of the patients during the study". The investigator concluded that the study demonstrated superior efficacy of Decapeptyl over Enantone.

Reviewer's comments:

1. **The investigator admits that the "superior performance of Decapeptyl may be as a result of the insufficient dose of Enantone." The dose of leuprolide used in this study is half the approved dose in the US. Therefore no conclusions about the efficacy of Decapeptyl, relative to leuprolide, can be drawn from this study.**

2. **The investigator comments that "In this study, the duration of anti-androgen treatment associated with GnRH analogue did not constitute a controlled factor. In fact, the decision to continue the anti-androgen treatment beyond the first month was left entirely to the investigator's discretion. Such a decision is unlikely to be amenable to any precise form of coding, and the analysis did not reveal any criteria to explain the continuation, or not, of treatment. The effect of the duration of anti-androgen treatment on plasma testosterone levels was investigated secondarily to the principal analysis since it has not been envisaged in the protocol. The observed results show a significant reduction in plasma testosterone levels in the group treated with three months with anti-androgen compared to the group treated for one month." Of the 33 patients that received Decapeptyl, 15 received antiandrogen for 1 month, 13 for 3 months and data is**

missing in 5. The analysis of the effect of Decapeptyl on suppression of testosterone levels is highly confounded by concomitant therapy with an antiandrogen, especially when given in an uncontrolled manner.

3.2 Summary of other clinical trials of Decapeptyl

Eleven studies were extracted from the literature. No CRF's were available on any of these studies. The results of these studies suggested that Decapeptyl induced castration in over 90% of the patients in the first month however dosing was variable. The claim was also made that tumor flare occurred in only 3 of the 11 trials.

Reviewer's comment: These trials are not available for critical review.

4.0 Clinical trial 914CL14P (Parmar study)

4.1 Design and conduct of trial: The sponsor stated that this was an open, comparative, parallel group, multicenter study. The objective was to evaluate the safety and efficacy of a sustained release formulation of Decapeptyl versus "orchiectomy" in patients with advanced prostate cancer. The principal investigator, Dr.Parmar, was responsible for the conduct of the study that was initiated on February 4,1984 and was completed on September 15,1989. Fifteen centers participated in the study; however, only 6 centers enrolled patients. Patients with advanced prostate cancer for which orchiectomy would be considered the best treatment were included in the study. These patients had stage D disease or stage C disease. The stage C patients were to have less than well-differentiated histology and or an increased prostatic acid phosphatase (PAP). The patients had been previously untreated systemically, with a performance status of more than three (World Health Organization), and had an expected survival of at least 90 days. Patients were excluded if they have had prior radical prostatectomy, severe liver, renal or cardiac impairment, brain metastasis or other cancers beside basal cell carcinoma.

At initial screening, a medical history was performed. A transabdominal ultrasound, bone scan, and x-rays of chest, spine and pelvis were accomplished. Laboratory studies included serum testosterone, prostatic acid phoshatase, hematology and chemistry. These were performed at day 0 or within 10 days of starting treatment. Patients were assessed for 24 months at monthly intervals for three months and thereafter at 3-month intervals for 21 months. After completion of the 2-year treatment period, all patients were followed to death.

According to the protocol, the patients were assigned either to receive Decapeptyl or to undergo orchiectomy by a balanced randomization list generated for each center. The randomization list was created in blocks of four to achieve an equivalent and balanced number of patients in each group. The balanced randomization lists were subsequently converted into envelopes numbered 1-20 and given to each center. The clinicians were asked to select the envelopes sequentially in numerical order for each new patient. Patients fulfilling the admission criteria were given a code number by rank of entry. The clinician then opened the envelope bearing the same number and found either "surgery" or "injections." If the treatment was "surgery," the patient had been randomly assigned to

undergo orchiectomy and this was proposed and explained to the patient. Patients who refused orchiectomy had the option of receiving estrogens or other treatment and were followed until death. These patients were included in the intent-to- treat group. If the treatment was "injections," the patient gave informed consent regarding participation in the study. Patients who refused to participate were followed until death so as to maintain the intention to treat principle even if they decided to undergo bilateral orchiectomy. In addition to the randomized patients, 6 patients received Decapeptyl on a "non-randomized" basis. These patients were included in the intent-to-treat but not the audited group.

The sponsor stated that due to the non-availability of the slow release formulation, 3 patients received a subcutaneous injection of Decapeptyl 100 micrograms daily for the first 21 days, followed by IM injection of the slow-release formulation every four weeks thereafter for up to 24 months. The sustained-release formulation of Decapeptyl was given on Days 1, 8, and 28 and every 4 weeks thereafter for up to 24 months. Each syringe contained 3.75 mg. of triptorelin in order to deliver a minimum dose of 3 mg. of triptorelin.

In the original protocol, the primary endpoints were the comparison of Decapeptyl with orchiectomy on the quality and duration of life of patients with advanced prostate cancer. The primary endpoints were retrospectively changed based on discussions at a pre-NDA meeting with FDA on Jan. 18, 1995. The primary endpoints were established as:

1. Reduction of T to castrate levels. This was to be established by showing that Decapeptyl and orchiectomy were similarly effective in reducing T to castrate level (at or below 1.735 nmol/L).

2. Relief of clinical symptoms such as bone pain and urinary symptoms.

Secondary endpoints were prostatic acid phosphatase (PAP) level and survival.

Reviewer's Comments:

1. **The patients were assessed monthly for three months and then every three months thereafter for 24 months. This is inadequate to evaluate two forms of failure seen in this drug class, "secondary flare" and "escapes." More frequent sampling of T levels would be necessary to establish that Decapeptyl consistently maintains T levels below castrate range.**

2. **There is no documentation regarding reliability of laboratory data. There is no indication of what laboratories were used and what the norms for the laboratory tests are. This is of particular concern for T determinations as there can be significant variation between and within laboratories.**

3. **Randomization was incorrectly performed. Patents were told about which arm of the trial they were in after they were selected to the arm. At that point, they were given a choice to be included or not. All patients should have been totally**

informed before randomization. The randomization list was created in blocks of four and then the lists were converted into envelopes numbered 1 to 20 and given to each center. The clinicians were asked to select the envelopes sequentially. With block assignment, it is possible for the clinician to "deduce" many of the assignments. The assignments should have been made centrally by someone with no clinical knowledge of the patient. The clinicians should not be allowed "to select the envelopes sequentially." No randomization codes could be found for any of the centers. This calls into question whether randomization occurred at all.

4. **Because of the manner in which randomization was handled as described above, patients were not properly informed as to the full scope of the study.**

5. **The dose and administration of Decapeptyl in the first month were different in this trial than in the proposed label. It is impossible to decide how well the proposed drug will initially suppress T, from this clinical trial. Ability to suppress T by 30 days is an important parameter for this class of drug. This information cannot be ascertained form this trial. In addition the formulation used in this study is different from the one being marketed. This issue will be discussed further under bioequivalance review.**

6. **The sponsor's secondary analysis of the data with 3.47 nmol/l as the castrate level is not standard and cannot be accepted as valid.**

4.2 Study Population

A total of 125 patients were included in the intent-to treat analysis (ITT). There were 76 patients in the Decapeptyl group and 49 in the orchiectomy group. The audited patient analysis included all patients who had retrievable source documentation and no major protocol violations. This was a total of 88 (70% of ITT) patients (fifty-one in the Decapeptyl group and 37 in the orchiectomy group). In the ITT group, the mean ages were 73.5years and 73.3 years while the mean weights were 71.8 kg and 70.3kg in the Decapeptyl and orchiectomy groups respectively. These parameters were similar in the audited groups. There were no statistical differences between weight and age at baseline for the ITT and audited groups.

Other baseline variables had statistically different values between the Decapeptyl and orchiectomy groups at baseline in the ITT population. A statistically significant higher percentage of patients in the orchiectomy group reported a prior prostate biopsy as 'yes' for metastasis compared to the Decapeptyl group. Details on how metastases were evaluated are not available. The comparison of bone pain revealed a statistically higher incidence in the Decapeptyl group. A statistically higher percentage of patients in the orchiectomy group reported urinary obstruction compared to the Decapeptyl group. A statistically higher percentage of patients in the Decapeptyl group compared to the orchiectomy group had abnormal PAP levels (see table 11 page 055 vol.66).

Reviewer's Comment: Since there were significant differences at baseline between the two treatment groups, and because the randomization procedure was flawed, the possibility of bias must be entertained. In a meeting at FDA on Feb.7, 1997, the sponsor maintained that the bias was in favor of the more severely effected patients being in the Decapeptyl group. The sponsor stated that "Dr. Parmar subsequently informed Debio that randomization schedules were not strictly followed so that patients with poorer prognoses, who were less likely to tolerate surgical complications, were assigned to the Decapeptyl group." It is not at all clear that the more severely affected patients were in the Decapeptyl group because the orchiectomy group was worse by the parameters of metastasis and urinary obstruction. What is evident is that the Decapeptyl and orchiectomy groups were not comparable at baseline.

4.3 Withdrawals and compliance

In either group, if the physician felt that the treatment was ineffective, he was to rate the patient as a "treatment failure" on that date and continue to follow the patient until death, regardless of subsequent treatment. In the Decapeptyl group, the treatment with Decapeptyl could be stopped and replaced by another type of treatment or maintained with other treatments added. The clinician made the decision and in either case the patient was classified as a "treatment failure." Intent-to treat patients were defined as all patients who had the following information recorded on the "Patient Identification" section of the Case Report Form at Visit 0: Randomization (yes or no)-Orchiectomy or Decapeptyl. Audited Patients were defined as all patients who were enrolled in the audited center, were treated with Decapeptyl or orchiectomy, had hospital records that were retrieved, and no major protocol violations. Major protocol violations included patients that did not fulfill the inclusion/exclusion criteria, were not randomized, had no pretreatment assessment or had incorrect dosage regimen.

At month 24, 47% (36 of 76) of patients treated with Decapeptyl and 57% (28 0f 49) of patients who underwent orchiectomy remained in the study (see table 1). The difference between treatment groups with respect to dropouts was not significant for any treatment period. The major reason for discontinuation from the ITT was death. Eighty-eight patients were included in the audited analysis. At month 24, 59% (30 of 51) of patients in the Decapeptyl group and 65% (24 of 37) of patients who underwent orchiectomy remained in the study. The difference between treatment groups was not significant. A listing of patients who discontinued the study in the ITT group can be found on page 046 vol. 66 (table 5) and page 049 vol. 66 (table 6) of the submission.

According to the sponsor as reported in the submission, no steps were taken in the collection of retrospective dosing data between visits. Therefore, there is no record of patient compliance with the dosing regimen for Day 8 or for administration of the 4-week dosage of Decapeptyl that fell between the scheduled visits.

TABLE 1
PATIENTS AVAILABLE FOR ANALYSIS OVER THE COURSE OF THE STUDY
PARMAR

TIME	0 months	3 months	6 months	12 months	24 months
Decapeptyl-total	76	70	68(89%)	60(79%)	36(47%)
died	0	6	7(9%)	15(20%)	37(49%)
lost to f/u	0	0	1(1%)	1(1%)	3(4%)
Orchiectomy-total	49	44	42(86%)	38(78%)	28(57%)
died	0	5	9(18%)	11(22%)	19(39%)
lost to f/u	0	0	0(0%)	0(0%)	2(4%)

Reviewer's comment:

1. **Because compliance is suspect for monthly dosing between visits, one cannot be sure how much time elapsed since previous administrations of Decapeptyl after the first three months. This makes the meaning of T levels obtained after three months unclear. Variation in the dosing schedule of Decapeptyl before T level is obtained would effect the ability to determine whether Decapeptyl produces an effect that lasts a month. It also brings into question the validity of the entire dosing schedule during the period.**

4.4 Efficacy analysis

The first primary endpoint was reduction of testosterone to castrate levels. This was done in comparison to orchiectomy, the "gold standard" for this purpose (see table 2). The accepted T level for achieving castration is 1.735 nmol/L and below. Testosterone levels at each measured point were compared between Decapeptyl and orchiectomy groups. Significance was assessed by the Pearson chi-square test or Fisher's exact test. The odds ratio and the 95% confidence interval were computed. The sponsor concluded that Decapeptyl treatment and orchiectomy were similarly effective in reducing testosterone to castration levels (see vol.66, pg.072). For all time points, the percentage of patients at or under the castration level was higher in the Decapeptyl group than in the orchiectomy group in the intent-to-treat population. The chi-square test comparing the two treatment groups showed a difference at month 9 only; 74.1% in the Decapeptyl group reach castrate level vs. 45% in the orchiectomy group. The audited group had similar results.

Table 2
The number and percentage of patents achieving castrate level at selected time periods in the ITT population (Parmer study)

Treatment	Decapeptyl n/N*, (%)	orchiectomy n/N*, (%)	p value
month 1	26/47, (55)	13/30, (43)	0.3
month 3	30/40, (75)	16/29, (55)	0.09
month 6	23/38, (60)	14/22, (64)	0.8
month 12	17/22, (77)	12/20, (60)	0.23
month 24	14/16, (88)	6/9, (67)	0.3

*n is the number of patients below or equal to castrate level (1.735 nmol/L)
N is the total number of patients remaining in the study

Reviewer's comments:

1. **There were major deficiencies in the efficacy analysis of the primary variable. The first problem was that a large percentage of the surgically castrated patients does not achieve castrate level. There was wide variation in this parameter. Forty-three percent achieved castration at month one (the lowest percentage to achieve castration), 64% at month 6 and 72% at month 21 (the highest percentage to achieve castrate level). In a meeting with the Division on Feb.4,1997, Debio postulated that this problem could best be explained by assuming that the clinical laboratories had not calibrated their assays for evaluation of castrated males. Debio proposed to reanalyze the testosterone data for each study using a cut-off value based on the mean + or - 2SD for all values obtained for the surgically castrated patients, this would result in a 'castrate level' of 3.09 nmol/L. Division believes that this analysis is flawed because there was no central laboratory and thus no standardization of laboratory norms. In addition, the castrations may have been surgically inadequate. An operation called subcapsular orchiectomy was popular at the time of the studies in which the Tunica Albuginia was incised and the testicular substance was cored out leaving the patient with testicular like bodies in the scrotum. This procedure can result in inadequate castration. Therefore Decapeptyl might have been compared to a flawed 'gold standard.' Demonstrating equivalence in this situation does not prove efficacy. The sponsor suggested that the T values be recalculated for the orchiectomy group by eliminating those patients that had elevated T levels throughout. This type of retrospective alteration of data is notacceptable.**

2. **The sponsor presented a cross-sectional analysis of the data comparing Decapeptyl with orchiectomy at each time point. This analysis is not sufficient because the ideal for a drug in this class is to induce T levels to below castrate by one month and maintain these levels while the drug is being administered. Other drugs in the class succeeded in doing this in 90 % of the patients treated. The Division determined the success rate of Decapeptyl by calculating the percentage of patients in which the T level fell below castrate level by 30 days and maintained a level below castrate throughout the period of administration of the drug. As is illustrated in the chart below, Decapeptyl succeeded in only 28% of the cases (table 3).**

3. **Another problem is that only 55% of Decapeptyl patients achieved castration levels at one month. Other similar drugs achieved a suppression rate at 30 days of approximately 95%. The percentage of patients that achieved castration levels with Decapeptyl varied from 65% to 75% in months 2 to 21. At month 24, 88% achieved castration levels, but at this point there are only 16 of the original patients in the Decapeptyl arm. This compares poorly to other drugs in this class.**

Table 3
Success/Failure analysis of Decapeptyl and orchiectomy in the Parmar study
by number of patients and percentage of ITT population

Parmar
Study

Treatment	Success	Failure of 1st Kind	Failure of 2nd Kind	Total
Decapeptyl	20 (27.8%)	34 (47.2%)	18 (25.0%)	72 (100%)
Orchiectomy	8 (18.2%)	26 (59.1%)	10 (22.7%)	44 (100%)
Total	28	60	28	116

Failure of the 1st kind is defined as failure to fall below castrate level (1.735 nmol/L) at one month.

Failure of 2nd kind is defined as having a T level below castrate at one month but then exceeding castrate at least one other time during the study.

A patient was a success if he was not a failure

Secondary endpoints: Improvement of urinary symptoms and bone pain were secondary endpoints. The percentage of ITT patients who experienced a decrease in bone pain was higher (statistically significant) at months 2, 6, and 24 in the Decapeptyl group compared to the orchiectomy group.

Reviewer's comment: This finding makes no physiologic sense and is probably due to baseline variation between the two groups.

There was no difference between groups in the other secondary endpoint analyses for urinary symptoms and normalization of prostatic acid phosphatase. In the ITT analysis there was no difference in survival, however in the audited analysis, survival was statistically superior in the orchiectomy group.

Reviewer's comment: Because of the questionable nature of the orchiectomy group, achieving equivalence with the orchiectomy group cannot prove efficacy for Decapeptyl.

4.5 Safety analysis

Deaths

Of the 125 patients considered in the survival analysis during the study period for the ITT population (76 patients in the Decapeptyl group and 49 patients in the orchiectomy group), a total of 60 died. Of these 41 out of 76 (53.9%) died in the Decapeptyl group and 19 out of 49 (38.8%) died in the orchiectomy group. The difference between the two rates was not significant. The Division's calculation of cause of death reveals that in the Decapeptyl group death rates were as follows: 70% -cancer, 15% -other (usually diseases consistent with patient's age) and 15% unknown. In the orchiectomy group the rates were 53%- cancer, 12%-other (CVAx2) and 35% unknown. Analysis of the noncancer related deaths in the Decapeptyl group, does not indicate that the deaths were related to the drug. However, in 15% of these patients the cause of death could not be documented and therefore there is inadequate data to say conclusively that the drug was not a causative factor.

Serious or severe adverse events

Two patients (2.8%) in the Decapeptyl group and 5 patients (12.2%) of the orchiectomy group reported at least one severe event. No patient in either treatment group had an adverse event that contributed to discontinuation of the study.

Reviewer's comments:

1. **The coding of the severity of adverse events appeared to be highly subjective. One of the Decapeptyl and all five of the orchiectomy adverse events reported above were impotence. An episode of angina in the orchiectomy group was reported as a mild event. In the Decapeptyl group, impotence/decreased libido was reported as a mild event in 25 patients, moderate in 45 and severe in one.**

Review of the actual reported adverse events does not appear to reveal any difference between the two groups.

2. **Dr. Raheja noted in the Pharmacology/toxicology review that in the label for the approved GnRH agonists, under Contraindications, it is stated that these analogs are not to be used in patients that have a known hypersensitivity to GnRH, GnRH agonist analogs or any other component of the product. In the proposed label for Decapeptyl, it is stated that three cases of anaphylactic shock and two cases of angioedema have been reported and were related to triptorelin. It is unclear whether this indicates a real increased incidence in significant allergic reactions with triptorelin over the approved drugs. Because of inadequate data one cannot determine whether some of the deaths in this study were secondary to anaphylaxis.**

All adverse events
At lease one adverse event was reported by 100% of the Decapeptyl group and 95% of the orchiectomy group. The vast majority of these events in both groups were related to hypogonadism, i.e., impotence, decrease libido and hot flushes. One patient in the Decapeptyl group had a local reaction to the injection at month three and six of the orchiectomy patients had local surgical reaction. The adverse events are comparable between the two groups and mostly related to the pharmacologic action of the drug.

Laboratory abnormalities
There were several significant differences in laboratory values between the two groups. The BUN was approximately 20 mg/dl higher in the Decapeptyl group compared to the orchiectomy group ($p < .03$). FSH decreased in the Decapeptyl group and increased in the orchiectomy group in a statistically significant fashion. LH decreased in the Decapeptyl group and increased in the orchiectomy group in a statistically significant fashion.
Reviewer's comments: The increase in BUN in the Decapeptyl group may have been an indication that the drug was less able to control local tumor growth and thus ureteral obstruction compared to orchiectomy. The changes in gonadotropin levels are consistent with the physiologic effects of the interventions.

4.6 Reviewers assessment of safety and efficacy
The sponsor concludes that monthly IM injection of the slow release preparation of Decapeptyl 3.75 mg. suppressed T to an extent similar to surgical orchiectomy and that the effectiveness of this suppression in treating advanced prostate cancer was confirmed by a reduction in the clinical symptoms for bone pain and urinary symptoms that were comparable between the two groups. In terms of adverse events both therapeutic modalities were comparable. Therefore, the sponsor concludes that IM Decapeptyl is an effective and safe treatment for advanced prostate cancer.

The claim that Decapeptyl is an effective treatment for advanced prostate cancer is not proven by this study. The study did not prove that Decapeptyl reduced T to castrate

levels and maintained it there (the primary endpoint). Because of design flaws the sponsor did not prove that clinical improvement was equivalent between Decapeptyl and orchiectomy. In addition, safety is not assured since there are a number of deaths of unknown cause. Detailed analysis is given in the reviewer's comments but the major deficiencies were as follows:

1. No documentation regarding laboratories, laboratory data, randomization or dosing schedule.
2. Surgical orchiectomy group is suspect regarding the success of some of the procedures.
3. Even if one accepts the data, Decapeptyl suppressed T much less effectively than other approved drugs in this class.
4. Since there was no documented randomization and since baseline variables were different between the Decapeptyl and the orchiectomy group and further since the surgical orchiectomies were of questionable success, a claim of equivalent improvement in clinical parameters between the two groups does not prove the efficacy of Decapeptyl.
5. Testosterone escapes and secondary flares, a problem in other drugs in this category, were not evaluated in this trial because of incomplete T monitoring.
6. There were deaths in the study of unknown cause. Since Decapeptyl is known to cause anaphylactic reactions "unknown" deaths are a disturbing problem.

5.0 Clinical trial 914CL17E (Botto Study)

5.1 Design and conduct of the trial

This is a multicenter open-label, parallel-group study sponsored by the Laboratoires BEAUFOUR, Paris comparing Decapeptyl and orchiectomy conducted between 1983 and 1986. There were 20 centers in this trial performed in France. Eighty patients were enrolled, forty in the Decapeptyl group and forty in the orchiectomy group. The objective was to evaluate the safety and efficacy of Decapeptyl versus orchiectomy for advanced prostate cancer. The study included patients with stage C or D prostate cancer, who had a performance status of 3 (WHO) or better and a life expectancy of at least 90 days. Patients were excluded if they had previously been treated with hormonal therapy or radiotherapy.

An initial screening was performed at Day 0 or within 10 days preceding the start of treatment. It consisted of a complete physical exam, medical history and laboratory and imaging assessment (see figure 1 pg.036 vol.71).

The sponsor stated that during the first 6 months of the trial, blood was drawn immediately before injection of the sustained release formulation, in order to measure T level. Thus the investigator regulated the level of the T, and if necessary, shortened the time period between injections. During the 24 months of the study period, patients were assessed at monthly intervals for 3 months and at 3-month intervals thereafter for 21 months. After the completion of the 24 month period, patients were followed to death.

Eligible patients were assigned according to his entry into the study. Patients were "randomized" to either Decapeptyl or orchiectomy. However, no randomization scheme

or codes were available. If the patient was in the Decapeptyl group, for the first seven days an ampoule of standard formulation (100 micro grams of drug) was administered sc. daily. From day 8 onwards: administration of 3mg.of sustained release formulation was given IM at day 8,and day 28. Thereafter injections of Decapeptyl were to be given every 4 weeks. Patients assigned to surgery had bilateral orchiectomy. It is noteworthy that in information included regarding consent in this submission, the operation was described as bilateral pulpectomy. This same description is used by Dr. Botto in a paper he published in 1989 on this study.

The first primary efficacy variable was reduction of T to castration levels and maintenance at that level. The second primary efficacy variable was relief of clinical symptoms of bone pain and urinary dysfunction. Secondary efficacy variables were Prostatic Acid Phosphatase (PAP) level, survival time, analgesic use, performance status and Overall Response. No central laboratory was used for measurements for either T or PAP. No monitoring of investigators or investigative sites by sponsor personnel was carried out.

Reviewer's Comments:

1. **The patients were assessed monthly for three months and then every three months thereafter for 24 months. This was inadequate to evaluate two forms of failure seen in this drug class, "secondary flare" and "escapes." More frequent sampling of T levels would be necessary to establish that Decapeptyl consistently maintains T levels below the castrate range. It is stated in this study that T levels were drawn before each injection during the first six months but the data submitted do not reflect this. Because the protocol allowed "shortening the time period between injections" in the first six months, the T data during this time period cannot be interpreted and compared to other drugs in this category.**

2. **There was no documentation regarding reliability of laboratory data. There is no indication of what laboratories were used and what the norms for the laboratory tests are. This is of particular concern for T determinations as there can be significant variation between and within laboratories.**

3. **No randomization codes were found for any of the centers. This brings into question whether randomization occurred at all.**

4. **The dose and administration of Decapeptyl in the first month were different in this trial than in the proposed label. It is impossible to decide how well the proposed drug will initially suppress T, from this clinical trial. Ability to suppress T by 30 days is an important parameter for this class of drug. This information cannot be ascertained from this trial. In addition the formulation used in this study was different from the one being marketed. This issue is discussed further under bioequivalance review.**

5. **Decapeptyl was compared to bilateral orchiectomy which is the 'gold standard' for producing castration levels of T. However Dr. Botto, himself describes the operation as a bilateral testicular pulpectomy. This may be the same as a subcapsular orchiectomy which is an operation in which the tunica albuginea is opened and the testicular "pulp" is removed. In Urologic Surgery edited by Dr. James Glenn published in 1991 it states on page 900 that "Subcapsular orchiectomy removes only the contents of the tunica albuginea but is generally considered less desirable for androgen ablation."**

5.2 Study population

Male patients with histologically proven carcinoma of the prostate at stages C and D for whom orchiectomy was considered the best available treatment were included in the study. The Intent-to-Treat (ITT) population consisted of 80 men, 40 in the Decapeptyl group and 40 in the orchiectomy group. The audited analysis was performed on 19 patients in the Decapeptyl group and 30 in the orchiectomy group. The ITT patient population consisted of men with a mean age of 70.5 years in the Decapeptyl group and 72.5 in the orchiectomy group. Mean weight was 68.8 kg in the Decapeptyl group and 69.5kg. in the orchiectomy group. There was no statistically significant difference between the two treatment groups with respect to age or weight. Audited results were similar.

The proportion of patients with disease stages C and D was similar between Decapeptyl and orchiectomy groups in both ITT and audited populations. In the ITT population 22.5 % of the Decapeptyl group and 42.5% of the Orchiectomy group had previous treatment including prostatectomy. The incidence of abnormal EKG's was significantly lower in the Decapeptyl group than the orchiectomy group in the ITT analysis(5.1% vs. 22.5%). There were similar results in the audited group.

There were no statistical differences in bone pain, urinary symptoms, performance or analgesic consumption between the two groups. Of the ITT patients 81% of the Decapeptyl group and 52% of the orchiectomy group had abnormal PAP (p=.01) There were similar results in the audited population.

Reviewer's comments:

1. **There was strong evidence that the Decapeptyl and orchiectomy groups were not equivalent at baseline.**

2. **There was no detailed description of how randomization was performed either in the original protocol of the Integrated Summary. Beyond this, there were no randomization codes available and no justification for sample size was made.**

3. **EKG abnormalities and abnormal PAP levels were higher in the Decapeptyl group indicating that selection for groups was indeed not random. One could infer that clinicians chose patients who were felt not to be candidates for surgery**

to be placed in the Decapeptyl group. Thus comparisons between the Decapeptyl and orchiectomy groups were not valid.

5.3 Withdrawals and compliance

Treatment was suspended as a consequence of: 1. Persistence of severe pain after 30 days, not controlled by analgesics, 2. Continuing increase in PAP levels during the first three months, 3. Appearance of new metastases or size increase of preexisting lesion, and 4. Development of hypercalcemia. In the Decapeptyl group, the treatment with Decapeptyl could be stopped and replaced by another type of treatment, or maintained and other treatments added. In either case the patient was classified as a treatment failure.

The sponsor states that the ITT patients were randomized to treatment (Decapeptyl or orchiectomy), according to treatment actually received. Audited patients were those that had hospital records, who had no major protocol violations and no other life threatening disease. At the beginning of the study there were 80 patients in the ITT population (40 Decapeptyl and 40 orchiectomy) and 49 patients in the audited group. Because of discontinuations (lost to follow-up, treatment failures and deaths) and No Longer Followed patients (patients who after a particular visit no longer contributed any safety data. The discontinuation status was not known). There were no patients left in the study at 24 months. There were no patients left in the study at 18 months and only 25 after 12 months (see table 4). The reasons patients were excluded from the audited group included protocol violations and lack of documentation.

In the ITT population, 27.5% died in the Decapeptyl group and 35% in Orchiectomy group. In the audited patient analysis 58% of the Decapeptyl group and 33.3% of the orchiectomy group died.

According to the sponsor, visits were identified in the Case Report Forms according to the month (month 1 for example) and not with an explicit date. Accordingly, the visit schedule could not be verified. Moreover, dosing information was largely missing in the hospital source files. There was no record of patient compliance with the dosing regimen for scheduled visits for those who fell between visits.

TABLE 4
PATIENTS AVAILABLE FOR ANALYSIS OVER THE COURSE OF THE STUDY
BOTTO

TIME	O months	3 months	6 months	12 months	24 months
Decapeptyl-total	40	40	37(93%)	13(33%)	0(0%)
died	0	0	2(5%)	4(10%)	5(13%)
lost to f/u	0	0	1(3%)	23(58%)	35(88%)
Orchiectomy-total	40	37	37(93%)	12(30%)	0(0%)
died	0	1	1(3%)	4(10%)	5(13%)
lost to f/u	0	2	2(5%)	24(60%)	35(88%)

Reviewer's comments:

1. **A very large proportion of patients dropped out or were lost to follow-up. This makes comparative analysis at many of the monthly points invalid or misleading. It is difficult to understand the basis for the survival analysis especially in light of the large drop-out rate.**

2. **Compliance records were so poor, it is difficult to conclude anything about monthly parameters since dosing intervals may not have been standard.**

5.4 Efficacy analysis

The first primary efficacy variable was percentage of patients below castrate level in the Decapeptyl group compared to the orchiectomy group. At day 15, 13% of the Decapeptyl compared to 69% of the orchiectomy patients achieved castration. For all other time-points, the were no differences between the Decapeptyl and orchiectomy groups using a chi-square test (vol.71 pg. 073) Similar results were observed in the audited population.

At month 1, 85% of the Decapeptyl group and 92% of the orchiectomy group achieved castration (less than or = 1.735 nmol/L). Percentages of patients below castrate level remained above 90% until month 15 when the percentages fell (see table 5).

Table 5
The number and percentage of patients achieving castrate level at selected time periods in the ITT population (Botto study)

Treatment	Decapeptyl n/N*, (%)	orchiectomy n/N*, (%)	p value
month 1	34/40, (85)	33/36, (92)	0.45
month 3	37/39, (95)	33/35, (95)	1.0
month 6	36/37, (97)	34/35, (98)	1.0
month 12	25/27, (93)	19/20, (95)	1.0
month 24	5/9, (56)	3/3, (100)	0.49

*n is the number of patients below or equal to castrate level (1.735 nmol/L)

N is the total number of patients remaining in the study

Reviewer's comments:

1. **Although the data could suggest that Decapeptyl had a similar ability to reduce T to castrate levels as orchiectomy, dosing intervals are unclear in this study and therefore it is difficult to make conclusions regarding this "one month" preparation. In addition, information about "escapes" and "secondary flares" cannot be made in this study because of inadequate T sampling.**

2. **The sponsors presented a cross-sectional analysis of their data comparing Decapeptyl with orchiectomy at each time point. This analysis is not sufficient because the ideal for a drug in this class is to induce T level to below castrate by one month and maintain these levels while the drug is being administered. Other drugs in the class succeed in doing this in 90 % of the patients treated. The Division determined the success rate of Decapeptyl by calculating the percentage of patients in which the T level fell below castrate level by 30 days and maintained a level below castrate throughout the period of administration of the drug. As is illustrated in the chart below (table 6), Decapeptyl succeeded in only 48% of the cases.**

Table 6
Success/Failure analysis of Decapeptyl and orchiectomy in the Botto study
by number of patients and percentage of ITT population

Botto Study

Treatment	Success	Failure of 1st Kind	Failure of 2nd Kind	Total
Decapeptyl	19 (47.5%)	13 (32.5%)	8 (20.0%)	40 (100%)
Orchiectomy	29 (74.4%)	4 (10.3%)	6 (15.3%)	39 (100%)
Total	48	17	14	79

Failure of the 1st kind is defined as failure to fall below castrate level (1.735 nmol/L) at one month.

Failure of 2nd kind is defined as having a T level below castrate at one month but then exceeding castrate at least one other time during the study.

A patient was a success if he was not a failure

Secondary endpoints: These were improvement in bone pain and urinary symptoms. There were no differences between the two groups except at month 21(ITT) when the Decapeptyl group had a significantly lower urinary symptom rate.
Reviewer's comment: At month 21 there are only 9 Decapeptyl and 4 orchiectomy patients left.

Analyses of the secondary efficacy variables showed similarity between the groups and in some cases increased improvement in the Decapeptyl group for both the ITT and audited populations. The average percentage reduction of PAP from baseline at monthly intervals was not significantly different. A higher percentage of patients in the Decapeptyl group showed a decrease in the use of analgesics at all visits. The difference was significant at month 15 and 21. The sponsor believes that descriptive data for prostate ultrasound and rectal exams showed a higher percentage improvement in the Decapeptyl group.

Table 34 pg.90 vol. 71 illustrated the evaluation of physical activity status at the end of treatment (ITT). However, it had the same numbers as table 21, (pg.70 vol.71) which are

the baseline numbers. In the ITT analysis the "overall response" (improved, stabilized, worsened) was better in the Decapeptyl group but not statistically significant. In the audited population the differences were statistically significant.

Reviewer's comments:

1. **A claim for equivalence for Decapeptyl cannot be made based on these data because randomization is suspect and baseline variables are not equivalent. The descriptive data of prostate ultrasound and rectal exams are subjective and the investigators may have been biased. Even a claim for equivalence may not be statistically sound.**

2. **It is not clear information on how the "overall response" was assessed. It may be highly subject to bias.**

5.5 Safety analysis

Deaths

The sponsor stated that for the 80 (40 patients in the Decapeptyl group, 40 patients in the orchiectomy group) patients in the ITT analysis, during the 24 month study period, 6 Decapeptyl(15%) and 10 orchiectomy (25%) died. The KM estimate of survival (alive at 24 months) was 69.6% for Decapeptyl group and 69.6% for orchiectomy group.

Reviewer's comment: This analysis is not informative because the cause of death is not known for any of these cases in either the Decapeptyl or orchiectomy group. In addition, 68% of the Decapeptyl and 53% of the orchiectomy group were in the "No Longer Followed" category within the study period. This means their status (deaths, adverse events, etc.) is unknown. Survival analysis is not valid in this context.

Serious adverse events

The sponsor stated that 24 (60%) patients in the Decapeptyl group and 15 (38%) of the patients in the orchiectomy group reported at least one adverse event. The events were not listed by severity. Several episodes of hypertension in each group and an episode of asthma in the Decapeptyl group were reported. One could consider these "serious" events.

Reviewer's comments:

1. **Meaningful analysis of the serious adverse event rate was impossible because of the very high lost-to-follow-up rate.**

Dr. Raheja noted in the Pharmacology/toxicology review that in the label for the approved GnRH agonists, under Contraindications, it is stated that these analogs are not to be used in patients that have a known hypersensitivity to GnRH, GnRH agonist analogs or any other component of the product. In the proposed label for Decapeptyl, it is stated that three cases of anaphylactic shock and two cases of angioedema have been reported and were related to triptorelin. It is unclear whether this indicates a real increased incidence in significant allergic reactions with triptorelin over the approved drugs. Because of inadequate data one cannot determine whether some of the deaths in this study were secondary to anaphylaxis.

All adverse events

The percentage of patients that report at least one adverse event was reported above. Most of these events are related to the induction of hypogonadism in the patients. The sponsor reports that the incidence of these events was statistically higher in the Decapeptyl group. **Reviewer's comment: Meaningful analysis of all adverse events was impossible because of very high lost-to-follow-up rate.**

Laboratory abnormalities

There was no clinical or statistical difference in laboratory data between the two groups. **Reviewer's comment: A clinically or statistically meaningful comparison between the two groups for these parameters was impossible because of the high lost-to-follow-up rate in this study.**

5.6 Reviewer's assessment of safety and efficacy

The sponsor concluded that monthly administration of the sustained release formulation of Decapeptyl suppressed T to castrate levels to an extent similar to surgical orchiectomy. Concomitantly, there was relief of the clinical symptoms of advanced prostate cancer in both treatment groups. The difference observed between treatment groups in terms of adverse events is essentially due to the greater incidence of hot flashes and impotence reported in the Decapeptyl group, which is related to the main action of the drug. The sponsor believed the results of this study indicate that Decapeptyl is safe and effective in treating patients with advanced prostate cancer.

This study had major deficiencies. Because of these deficiencies, this study failed to support the sponsor's belief that the submitted drug is safe and efficacious. The deficiencies are listed here but explained in more detail in the Reviewer's comments:

1. No documentation regarding laboratories, laboratory data, randomization or dosing schedule (compliance records are particularly poor in this study).
2. Surgical orchiectomy group was suspect regarding the success of some of the procedures (testicular pulpectomy was performed), it cannot be a "gold standard" for comparison.

3. Testosterone escapes and secondary flares, a problem in other drugs in this category, cannot be completely evaluated in this trial because of incomplete T monitoring.
4. Dosing was inconsistent the first month, so a comparison to other drugs in this field as far as reducing T to castrate levels at 30 days cannot be performed.
5. There was an exceedingly large dropout rate and poor follow-up in this study.
6. There was clear bias in selection of patients between the Decapeptyl and orchiectomy groups, as patients who were not candidates for surgery were placed in the Decapeptyl group.
7. Because of incomplete date, no meaningful conclusion can be made regarding deaths, adverse events or laboratory parameters. Since Decapeptyl is known to cause anaphylactic reactions "unknown" deaths are a disturbing problem.

6.0 Clinical trial 914CL7P (De Sy study)

6.1 Design and conduct of the trial

The sponsor stated that the clinical trial was an open, randomized, comparative, parallel group, multicenter study. Five study centers participated and each of these sites enrolled a minimum of 4 and a maximum of 16 patients during the first six months of the trial. Afterwards, no more patients were admitted to the study. The study was initiated in March,1984 and was completed December,1986 in Belgium. Male patients with histologically proven prostate cancer of any stage for whom orchiectomy was considered to be the most adequate treatment in the absence of GnRH analogue therapy. Patients were included if they had stage C or D prostate cancer that had not been previously treated. A performance status of more than 3 (WHO) and an expected survival of at least 90 days was required. Brain metastases or current treatment with any hormonal or cytotoxic agents would exclude the patients.

At the initial screening visit, a complete physical exam, history, and laboratory studies were accomplished. Some of these were then done periodically thereafter (see study flow chart pg.012 vol.73).

Assessments were made monthly the first three months and then every three months thereafter for 24 months. During the first month, T measurements were made also on day 7, 14 and 21 after treatment.

The sponsor stated that the randomization codes were included in the submission. The randomization scheme was unbalanced in the ratio of 2:1 for Decapeptyl: orchiectomy. If the treatment was "operation," the patient had been randomized to orchiectomy and this was proposed and explained to the patient without mentioning the existence of a GnRH analogue. Patients who refused orchiectomy were given the option of receiving estrogens or any other treatment. They were followed until death, but were not included in the study. If the treatment was "injection," informed consent of the patient was obtained for participation in the long term study. Patients who, after being informed, refused to sign the consent form were followed until death but not included in the study.

Patients were administered Decapeptyl (sustained- release preparation) 3mg IM on days 1, 28 and once each month for up to 28 months. Patients who accepted surgery had bilateral orchiectomy. Synthetic implants were inserted in some patients at the time of surgery.

The first primary efficacy variable was achievement of castration level. Achievement of a castration level was defined as less than or = to 1.735 nmol/L or less than or = to 3.47 nmol/L for those patients with pre-treatment levels that were above castration levels. The second primary efficacy variable was clinical improvement as measured by urinary symptoms and bone pain. The secondary efficacy variables were decrease of PAP level toward normal (according to the normal value of the laboratory where PAP was assessed), and survival time. Other parameters monitored were analgesic use, change in clinical status, change in tumor volume and change in bone metastases from the baseline.

Reviewer's Comments:

1. **The patients were assessed monthly for three months and then every three months thereafter for 24 months. This was inadequate to evaluate two forms of failure seen in this drug class, "secondary flare" and "escapes." More frequent sampling of T levels would be necessary to establish that Decapeptyl consistently maintains T levels below castrate range.**

2. **There was no documentation regarding reliability of laboratory data. There is no indication of what laboratories were used and what the norms for the laboratory tests are. This is of particular concern for T determinations as there can be significant variation between and within laboratories.**

3. **Randomization was incorrectly performed. Patents were told about which arm of the trial they were in after they were selected to the arm. At that point, they were given a choice to be included or not. There was probably bias toward selection to Decapeptyl arm because more patients will refuse orchiectomy than injections.**

4. **The patients in the surgery arm were not given proper informed consent.**

5. **Dr. De Sy's analysis of the data with 3.47 nmol/L as castrate level is not standard and cannot be accepted as valid.**

6.2 Study population

The ITT population included all patients randomized to treatment, according to treatment received (44 patients in the Decapeptyl group and 16 patients in the orchiectomy group). The audited analysis included all patients who had retrievable source documentation (33 patients in the Decapeptyl group and 13 patients in the orchiectomy group). In the ITT population, at baseline, the Decapeptyl group had a mean age of 74.7 years, weight 71.8 Kg. and height 171 cm.. the orchiectomy group had a mean age of 75.3, weight 67.2 and

height 167 cm. Comparison of the two groups showed a statistically significant difference in height only. Audited analysis was similar expect for difference in height.

The was no statistically significant difference at baseline between Decapeptyl and orchiectomy group in the ITT or audited population for the following parameters: Disease stage, bone pain, urinary problems, disease stage, performance status, prostate size (by ultrasound) or analgesic use.

The overall comparison revealed a significant difference in the ITT population in percentage with normal PAP levels. Decapeptyl (69.7%) compared to Orchiectomy (38.5%) at the p=.05 level. The audited population was similar in that more Decapeptyl patients (69.7%) compared to orchiectomy patients (38.5%) had normal PAP levels. There was no statistically significant difference between the proportion of patients above castrate level between Decapeptyl and orchiectomy group. This was true for ITT and audited populations.
Reviewer's comments: The Decapeptyl group had a larger proportion of patients with normal PAP. This would indicate some bias toward the Decapeptyl arm for patients with less extensive disease. Although not indicated in the protocol perhaps some clinicians chose to have their patients with more extensive disease undergo the proven therapy (orchiectomy). The Decapeptyl group were taller raising the question of less bone disease.

6.3 Withdrawals and compliance
Sixty patients were enrolled in the study. Sixty-seven patients were initially described, CRF's for only 60 patients could be recovered. These made up the ITT population (44-Decapeptyl, 16 orchiectomy). Only 13.3% finished the study, 7 Decapeptyl and 1(one) orchiectomy see (table7). The audited population included all patients for whom source documents could be found. This left 11 in the Decapeptyl and 3 in the orchiectomy group in the study for the audited population (see table 7 vol. 73 pg.24).

Sixty patients were initially included in the ITT analysis, however many patients were lost to the study. By 12 months, only 26 Decapeptyl and 8 orchiectomy patients were in the study. (Table 1 vol.73 pg.15.)

The most common reason by far for dropouts from the study was "no longer followed" (56.3%). These were patients who after a particular visit no longer contributed any safety data. The discontinuation status is unknown. Known deaths only accounted for 12.5% of the dropouts. Four patients in the Decapeptyl group underwent orchiectomy and were counted as treatment failures (see table 5 vol.73 pg. 17).

The overall survival (in weeks) was analyzed by the log-rank method and Kaplan-Meier estimates. K-M estimates and log-rank estimates were also computed for the 24-month period. For the ITT population the K-M estimate of survival (alive after 2.5years) was 81.5% in the Decapeptyl group and 38.5% in the orchiectomy group. No statistical

difference was found in the log-rank test. Similar results were found in the Audited population. For survival during the 24-month period for the ITT population the K-M estimate was 81.5% in the Decapeptyl group 76.9 % in the orchiectomy group. No statistical difference between the groups was found. The audited population had similar results.

It was stated in the submission that no monitoring of investigators or investigation sites by sponsor personnel was carried out. In additions nothing is stated in the submission regarding compliance. Therefore compliance cannot be assured.

TABLE 7
PATIENTS AVAILABLE FOR ANALYSIS OVER THE COURSE OF THE STUDY
De Sy

TIME	0 months	3 months	6 months	12 months	24 months
Decapeptyl-total	44	41	35(80%)	27(61%)	7(16%)
died	0	0	3(7%)	4(9%)	5(11%)
lost to f/u	0	3	10(23%)	13(30%)	32(73%)
Orchiectomy-total	16	13	10(63%)	9(56%)	1(6%)
died	0	0	1(6%)	1(6%)	2(13%)
lost to f/u	0	3	5(31%)	6(38%)	13(81%)

Reviewer's comments:

1. **A very large proportion of patients dropped out or was lost to follow-up. This makes comparative analysis at many of the monthly points invalid or misleading. It is difficult to interpret the survival analysis especially in light of the large drop-out rate.**

2. **It is difficult to have confidence in compliance, or any data resulting from this study because of poor monitoring.**

3. **Seven CRF's were missing at the start of the study. This causes concern regarding record keeping in this study.**

6.4 Efficacy analysis

The first primary efficacy variable was reduction of T to castrate levels comparing the Decapeptyl group with the orchiectomy group. By day 30, 88% of the Decapeptyl and

82% of the orchiectomy group achieved castrate level with no significant difference between the groups in the ITT population using a chi-square test (see table 8). There was no difference between the groups for all time periods measured. For all time periods the percentage achieving castration was as low as 50% in the Decapeptyl group (month 24) and 72 % in the orchiectomy group (month 3). See table 18 vol.73 pg.36. There were similar results in the audited group.

Table 8
The number and percentage of patients achieving castrate level at selected time periods in the ITT population (De Sy study)

Treatment	Decapeptyl n/N*, (%)	orchiectomy n/N*, (%)	p value
month 1	28/32, (88)	9/11, (82)	0.64
month 3	29/31, (94)	5/7, (71)	0.12
month 6	19/21, (91)	6/6, (100)	1.0
month 12	17/21, (81)	6/6, (100)	1.0
month 24	2/4, (50)	1/1, (100)	1.0

*n is the number of patients below or equal to castrate level (1.735 nmol/L)

N is the total number of patients remaining in the study

Reviewer's comments:

1. **The sponsors present a cross-sectional analysis of their data comparing Decapeptyl with orchiectomy at each time point. This analysis is not sufficient because the ideal for a drug in this class is to induce T levels below castrate by one month and maintain these levels while the drug is being administered. Other drugs in the class succeed in doing this in 90 % of the patients treated. The Division determined the success rate of Decapeptyl by calculating the percentage of patients in which the T level fell below castrate level by 30 days and maintained a level below castrate throughout the period of administration of the drug. As is illustrated in the chart below, Decapeptyl succeeded in only 52% of the cases (see table 9).**

2. **A large proportion of the orchiectomized patients were not below castrate level at many time periods, perhaps due to inadequate orchiectomy. Therefore comparing the Decapeptyl patients to this orchiectomized group does not prove efficacy (table9).**

Table 9
Success/Failure analysis of Decapeptyl and orchiectomy in the De Sy study
by number of patients and percent of ITT population

De Sy Study

Treatment	Success	Failure of 1st Kind	Failure of 2nd Kind	Total
Decapeptyl	22 (52.4%)	9 (21.4%)	11 (26.2%)	42 (100%)
Orchiectomy	10 (66.7%)	2 (13.3%)	3 (20.0%)	15 (100%)
Total	32	11	14	57

Failure of the 1st kind is defined as failure to fall below castrate level (1.735 nmol/L) at one month.

Failure of 2nd kind is defined as having a T level below castrate at one month but then exceeding castrate at least one other time during the study.

A patient was a success if he was not a failure

Secondary endpoints: For both the ITT and audited group, there was no significant difference between Decapeptyl and orchiectomy patients with respect to change in pain from baseline after any treatment period. Analgesic use was not different between the two groups. There was essentially no difference between urinary symptoms when comparing the two groups.

The sponsor stated that none of the between-treatment differences for the reversion to normal levels of PAP were statistically significant for either ITT or audited population. The PAP could only be reported in terms of percentage achieving normal values because of differences of laboratories and units.

1. **At many of the time points there are very few patients. Therefore, no meaningful conclusions can be drawn.**

2. **The sponsor states that "There were neither pages in the CRF that reported concomitant therapy data nor reference in the protocol on the issue of**

concomitant therapy." This would make analysis of many of the clinical and possibly laboratory parameters suspect.

6.5 Safety analysis

Deaths

Of the 60 patients in the ITT population (44 patients in the Decapeptyl group and 16 patients in the orchiectomy group) during the study period, 6 (14%) died in the Decapeptyl and 2 (12.5%) died in the orchiectomy group. A KM estimate was made and no statistically significant difference between the groups was found.

Reviewers comment:

1. **The cause of death is either unclear or unknown with all these deaths even after reviewing the narrative summaries.**

2. **Fifty-three percent of the Decapeptyl and 57% of the orchiectomy patients are in the "No Longer Followed" category which means their clinical status is unknown. Therefore death rates and cause of death within and between the study groups can not be assessed.**

Serious or severe adverse events

According to the sponsor, sixty-four percent (28) of patients in the Decapeptyl group and 56% (9) of patients in the orchiectomy group experienced an adverse event. No information was available on the severity of the events or their relationship to treatment. However, none of the adverse events resulted in discontinuation of treatment.

Reviewer's comment:

1. **Meaningful analysis of the serious adverse event rate is impossible because of the very high lost-to-follow-up rate.**

2. **Dr. Raheja notes in the Pharmacology/toxicology review that in the label for the approved GnRH agonists, under Contraindications, it is stated that these analogs are not to be used in patients that have a known hypersensitivity to GnRH, GnRH agonist analogs or any other component of the product. In the proposed label for Decapeptyl, it is stated that three cases of anaphylactic shock and two cases of angioedema have been reported and were related to triptorelin. It is unclear whether this indicates a real increased incidence in significant allergic reactions with triptorelin over the approved drugs. Because of inadequate data one cannot determine whether some of the deaths in this study were secondary to anaphylaxis.**

All adverse events

The percentage of patients that reported at least one adverse event was reported above. In this study the most common events in both groups were: injection site pain (surgical site pain), heart disorder, impotence, and "nervousness." According to the sponsor, incidence was not different between the groups.

Reviewer's comment: Meaningful analysis of all adverse events is impossible because of a very high lost-to-follow-up rate.

Laboratory abnormalities
The laboratory parameters did not reveal any clinically important variations except for one. Thirty-three percent of the Decapeptyl group compared to 6.3% of the orchiectomy group had abnormal shifts in the alkaline phosphatase during treatment ($p<.04$). This might indicate decreased ability of Decapeptyl to prevent bony metastases.
Reviewer's comment: It is inappropriate to make clinical or statistical conclusions from the laboratory data because of the high lost-to-follow-up rate.

6.6 Reviewer's assessment of safety and efficacy
The sponsor concluded that monthly injection of the sustained release formulation of Decapeptyl suppressed T to castration level to an extent similar to surgical orchiectomy after 21 days of treatment and onwards and that this suppression was accompanied by improvement of the clinical symptoms of advanced prostate cancer, namely bone pain and urinary symptoms which was comparable in the two treatment groups. There were no significant differences in adverse event profile between the two treatment groups. Therefore, the sponsor concludes that Decapeptyl was as safe and effective as orchiectomy in treating patients with advanced prostate cancer.

The study has major deficiencies. Because of these deficiencies, this study failed to support the sponsor's belief that the submitted drug is safe and effective. The deficiencies are listed here but explained in more detail in the Reviewer's comments.

1. No documentation regarding laboratories or laboratory data. Compliance is suspect because of poor monitoring.
2. Randomization was incorrectly performed. There appeared to be a biased assignment of treatment which would favor the Decapeptyl group.
3. The patients in the surgery arm were not given proper informed consent.
4. Surgical orchiectomy group is suspect regarding the success of some of the procedures; it cannot be a "gold standard" for comparison.
5. Testosterone escapes and secondary flares, a problem in other drugs in this category, cannot be completely evaluated in this trial because of incomplete T monitoring.
6. Proportions of patients reaching castrate level by 30 days were less than other drugs in this class.
7. There was an excessively large dropout rate and poor follow-up in this study.
8. Seven CRF's were missing at the start of this study, causing concern regarding record keeping.
9. There was no documentation of concomitant therapy that could affect efficacy parameters. Therefore comparison between the two groups is suspect.
10. Because of incomplete data, no meaningful conclusion can be made regarding deaths, adverse events or laboratory parameters. Since Decapeptyl is known to cause anaphylactic reactions "unknown" deaths are a disturbing problem.

7.0 Safety Update Report

Debio reported on the safety data from Jan. 7, 1995 to Dec. 12, 1996. The reports were generated from a population that received approximately [redacted] doses of Decapeptyl one month and three month Depot. This information was mainly supplied by Ipsen Biotech group, a licensee of Debio. In addition, safety reports from approximately 2000 patients currently in clinical trials under the direction of Debio and Ipsen Biotech were included. The data comes from patients using Decapeptyl for all indications such as endometriosis, precocious puberty and advanced prostate cancer. In addition, the literature was searched for reports during the covered period.

Deaths: There were ten deaths included in the report. All were men with advanced prostate cancer or cause was not documented. The deaths all were related to the patient's disease except two. In these cases, the patients were described as dying from "asthma" not related to the medication. Detailed reports were not submitted on these patients but they could represent hypersensitivity reactions.

Serious Adverse reactions: The reactions reviewed generally were either unrelated to the drug, known adverse events related to the drug or insufficiently documented making etiology of the reaction indeterminable. There was one report of an ischemic cerebrovascular accident in a woman with fibroids that may have been related to the "estrogen flare" causing a thrombogenic event. This is a new report of an adverse event probably related to the drug.

All adverse events: Review of all events revealed that they are either not related to the drug or known adverse events related to the drugs pharmacologic action. There were three reports of non fatal allergic reactions. There is insufficient evidence at this point to determine whether allergic reactions are more common with this drug than other GnRH agonists.

It appears that the safety profile of Decapeptyl is similar to the other GnRH agonists with the possible exception of hypersensitivity reactions.

8.0 Reviewer's assessment of safety and efficacy of Decapeptyl

This application is not approvable because the data provided do not establish that Decapeptyl is a safe and effective drug for the treatment of advanced prostate cancer. The specific deficiencies that support this conclusion may be summarized as follows:

Clinical

1. The principal data submitted in support of the safety and efficacy of Decapeptyl as a treatment for advanced prostate cancer consisted of three clinical trials that compared Decapeptyl with orchiectomy [protocol numbers 914CL14 (Parmar), 914CL17E (Botto),

and 914CL7P (De Sy) respectively] in a total of 265 men with advanced prostate cancer. As discussed in the pre-NDA meeting on January 28, 1995, the primary evidence of efficacy was to be based on the demonstration that Decapeptyl and orchiectomy produced comparable levels of testosterone suppression. However, the data in the three clinical trials is insufficient to conclude that Decapeptyl is comparable in efficacy to surgical castration.

In this application, cross sectional analyses are provided comparing the percentages of patients who achieved castrate testosterone levels in the Decapeptyl and orchiectomy treatment groups at each time point. When the data is analyzed in this manner, it appears that 3 - 45% of patients in the Decapeptyl treatment group fail to achieve castrate levels at any given time point. Although the percentages of failures appear similar between treatment groups, the overall high percentage of patients who fail to achieve castration levels at any given time point is unacceptable.

Further, a more clinically meaningful analysis is demonstration of the reduction in castrate levels of testosterone within one month and maintenance of castrate levels throughout the course of therapy (this clinically defines a "successful" response to treatment). When such a responder analysis is performed, the following results are found (Table 10).

Table 10. FDA responder analyses of the percentages of patients who achieved castrate testosterone levels at one month and at each time point thereafter, by treatment group and clinical study.

	Response Rate (% success)	
Study	**Decapeptyl**	**Orchiectomy**
Parmar - 914CL14P	20/72 (27.8%)	8/44 (18.2%)
Botto - 914CL17E	19/40 (47.5%)	29/39 (74.4%)
De Sy - 914CL7P	22/42 (52.4%)	10/15 (66.7%)

Therefore, the results of neither the submitted cross-sectional analyses nor the FDA responder analyses support the efficacy of Decapeptyl given that currently approved drugs in this class achieve and maintain castrate levels of testosterone in excess of 90-95% of the time.

Additionally, because numerous deficiencies in the designs and conduct of these trials were identified, these studies can not be considered to be adequate and well-controlled investigations. These deficiencies may be summarized as follows:

2. Study design deficiencies

a. Absence of a central laboratory in each of the submitted studies

As stated in the correspondence dated March 14, 1997, none of the three studies utilized a central laboratory for the testosterone assays. The existence of a central laboratory in studies where the primary efficacy endpoint is laboratory-based is essential because of the known considerable variation between and within laboratories.

In the previously referenced correspondence, the information that was provided on the actual laboratories used in the studies highlights the problem of variability. In the 15/34 (44%) sites where the laboratory performing the testosterone levels was known, there is considerable variation in testosterone levels of normal men and special populations (pre-pubertal men, castrated men and women).

Due to the known high degree and laboratory variability, comparisons between treatment groups may not be valid. Further, uncertainties about the quality of the laboratory data may in part account for the unexpected observation that many "orchiectomized" patients did not have castrate levels of testosterone (see 3c, below).

b. Inadequate assessment frequency of testosterone levels.

In each of the three studies, testosterone was measured monthly for the first three months and then every three months thereafter. This schedule of testosterone measurement is insufficient. Testosterone levels must be monitored frequently during the first month (to

detect the primary flare of testosterone), and then before and after each monthly readministration (to detect the occurrence of secondary flares of testosterone due to readministration and escapes from therapy due to therapeutic failure).

c. Dosing schedule inconsistent with the proposed regimen.
The study reports note that Decapeptyl was administered according to different schedules during the first study month to some or to all patients. In the Parmar study (914CL14P), sustained release Decapeptyl was administered on study days 1, 8 and 28. However, some patients in this study appeared to have received the short acting formulation daily for the first 21 days. In the Botto study (914CL17E), a short acting formulation of Decapeptyl was administered for the first seven days.

The ability of an agent in this class to induce castrate level of testosterone at one month is an essential parameter in establishing its efficacy. Because the monthly depot was not consistently used in these studies, conclusions regarding the efficacy of the Decapeptyl depot cannot be inferred.

In the correspondence dated March 14, 1997, it is suggested that the results of protocol 52014ST8040 (Kuhn study) and clinical pharmacology studies demonstrate that castrate levels are achieved within one month with the depot formulation. However, the Kuhn study used an unapproved dose of leuprolide acetate as an active control and the results are confounded by the concomitant use of antiandrogens. The clinical pharmacology studies that were referenced, lacked an active control group and had small sample sizes. and enrolled, with few exceptions, healthy men. Therefore, there is no evidence from adequate and well-controlled studies that Decapeptyl consistently reduces testosterone levels to castrate ranges within one month and with a success rate comparable to surgery.

3. Study conduct deficiencies
a. Lack of randomization to treatment groups
Two of the study reports [protocols 914CL14P (Parmar) and 914CL17E (Botto)] state that randomization codes were unavailable and that the studies "cannot strictly speaking be called 'randomized.'" Further, although not so stated in the study report, FDA inspection of the third study [protocol 914CL7P (De Sy)] found that the randomization was presumed inadequate because of inadequate documentation. Lack of randomization makes statistical inference invalid.

b. Excessive loss to follow-up
Loss-to-follow-up (for reasons other than death) was unacceptably high. The highest rates of loss-to-follow-up occurred in the Botto - 914CL17E (58% by 12 months, 88% by 24 months) and De Sy - 914CL7P (30% by month 12, 73% by month 24). These high rates raise further questions regarding the legitimacy of any claims of safety and efficacy, even though loss-to-follow-up rates were comparable between treatment groups.

c. Failure to achieve castrate testosterone levels in active control (orchiectomy) group

Overall in the three studies combined, approximately 25% of the "orchiectomized" patients did not achieve castrate testosterone levels. This unexpected finding may be explained by two clinical design problems. First, because of the lack of a central laboratory and assay standardization, the "castrate" cutoff values used in the submitted analyses or proposed in the correspondence, dated March 14, 1997, may not be applicable to the actual laboratory assays utilized.

Second, it is possible, that in some instances, patients did not have a complete surgical removal of the testes (which is the orchiectomy procedure performed in the U.S.) but had a "testicular pulpectomy," an operation in which the tunica of the testicle is opened and the contents shelled out. In this procedure, there is a potential for leaving residual testes tissue. A literature report of the Protocol 914CL17E (Botto) describes that this operation was performed in his patients. Operative reports to confirm or refute this concern have not been submitted.

Therefore, because the completeness of the surgical castration can not be confirmed, any comparisons between drug and surgical treatment are uninterpretable.

d. Division of Scientific Investigations (DSI) violations

The investigator from DSI visited several sites in each of the Parmar (914CL14P) and De Sy (914CL7P) studies and found significant deficiencies at these sites (see form FDA-483). The deficiencies include the following: Lack of randomization (including the De Sy study), protocol violations, inclusion of patients without metastatic disease, record keeping "discrepancies" for clinical laboratory data, consent form violations (Parmar), and failure to report concomitant therapy. The report is not an exhaustive list of objectionable conditions.

9.0 Recommendation of regulatory action

This application is not approvable because the three "core" trials submitted in the application cannot support the safety and efficacy of Decapeptyl for the palliative treatment of patients with advanced prostate cancer.

The Division should issue a detailed not approvable letter that delineates the deficiencies outlined above (8.0).

10.0 Recommendation for future trials to gain approval for Decapeptyl

Approval of Decapeptyl would depend on the demonstration of safety and efficacy in adequate and well-controlled clinical trials. The sponsor could consider expanding study DEB-96- TYI-01 that is designed to demonstrate the pharmacodynamic equivalence of one month and three month Depot preparations of Decapeptyl. An active controlled arm with an approved GnRH agonist could satisfy the requirements for approval. The size of the study and other details should be discussed with the Division.

Daniel A. Shames MD
Medical Officer, DRUDP

Concur: - 6/27/97

CC/
James Bilstad MD
Lisa Rarick MD
Heidi Jolson MD
Jean Fourcroy MD
Alvis Dunson
Division File HFD 580

NDA 20 715 Amendment
May 15, 2000

MAY 18 2000

MEMO
Six Month Safety Update for
Complete Response to Non-Approval Letter
Of June 26, 1997

Drug product – triptorelin pamoate for injectable suspension
Drug name – TRELSTAR® Depot 3.75 mg
Drug class – synthetic GnRH competitive agonist
Dose and route – 3.75 mg depot dose intramuscular q 28 days
Indication – palliative treatment of advanced prostate cancer
Sponsor – Debio Recherche Pharmaceutique S.A.
Martigny, Switzerland
U.S. Representative – Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs
Target Research Associates
554 Central Avenue
New Providence, NJ 07974

All safety information necessary for review of this submission was included in the Complete Response to Non-Approval, received December 16, 1999. No further safety data was requested or required of the sponsor.

NMS 5/18/2000

Norman S. Marks, M.D., Medical Officer
HFD-580, Division of Reproductive and Urological Drug Products

NDA 20715
Decapeptyl™ (triptorelin pamoate)

Safety Update Review

Included in Medical Officer review dated 6/27/97