

Medical Officer's Primary Review of Efficacy and Safety

Oncology Drugs Advisory Committee Meeting of December 18, 2002

NDA 20-498/s012

Applicant AstraZeneca Pharmaceuticals LP
PO Box 8355
Wilmington, DE 19803-8355

Submission Type Efficacy supplement

Drug

Established name Bicalutamide

Trade name Casodex®

Drug Class Nonsteroidal anti-androgen

Proposed Indication *Original Indication (Submitted 20 December 2001 with NDA)*
Immediate hormonal therapy or adjuvant therapy to treatment of curative intent in patients with non-metastatic prostate cancer

First Revision of Indication (Submitted 10 May 2002)
Part 1: Adjuvant therapy to radical prostatectomy and radiotherapy of curative intent in patients with locally advanced non-metastatic prostate cancer who have a high risk for disease recurrence or
Part 2: Immediate treatment of non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated

Second Revision of Indication (Submitted 22 October 2002)
Part 1: (Unchanged from 10 May 2002 submission)
Part 2: Immediate treatment of localized non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated

Dosing Regimen One 150 mg tablet daily

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Urologic Drug Products

November 19, 2002

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EXECUTIVE SUMMARY

1 BRIEF OVERVIEW OF CLINICAL PROGRAM

1.1 Drug

Casodex (bicalutamide) is a nonsteroidal anti-androgen with no other known endocrine activity. It competitively inhibits the action of androgens by binding to cytosol androgen receptors in the target tissue.

1.2 Design of the Clinical Program

The Sponsor submitted data from 3 placebo-controlled, randomized, double-blind, parallel-group clinical trials that enrolled men with local or locally advanced non-metastatic prostate cancer. The trials were conducted in (1) North America, predominantly the US [Trial 23], (2) Europe (other than Scandinavia), South Africa, Israel, Mexico, and Australia [Trial 24], and (3) Scandinavia [Trial 25]. Patients were randomized in a 1:1 ratio to treatment with either Casodex 150 mg per day or matching placebo. In all 3 trials, Casodex was investigated as adjuvant therapy in patients who had had previous therapy for their prostate cancer (i.e., radical prostatectomy or radiation therapy). In Trials 24 and 25 (but not Trial 23), Casodex also was investigated as monotherapy (i.e., in patients who had had no prior therapy and whose prostate cancer would otherwise be managed by watchful waiting or surveillance). In Trial 23, treatment was limited to a maximum of 2 years or until objective disease progression (whichever occurred first). In Trials 24 and 25, patients were to be treated for 5 years (adjuvant group in Trial 24) or indefinitely (all other groups) or until progression of disease (all patients).

2 EFFICACY

2.1 Proposed Label Claim

The Sponsor has proposed (revised indication of 10 May 2002) that Casodex 150 mg per day is indicated as (1) adjuvant therapy to radical prostatectomy and radiotherapy of curative intent in patients with locally advanced non-metastatic prostate cancer who have a high risk for disease recurrence and (2) immediate treatment of non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated.

2.2 Primary Efficacy Endpoints

The protocol-defined primary efficacy endpoints were (1) *objective disease progression* defined as local or distant progression of disease confirmed by bone scan, x-ray, CT scan, magnetic resonance imaging, ultrasonography, or biopsy and (2) *death* due to any cause in the absence of objectively confirmed progression. The protocol-defined primary efficacy analyses were *time to objective progression or death*. Because of the potential for assessment bias (the side effects of Casodex treatment were likely to unblind patient treatment assignments in many instances), the Division of Reproductive and Urologic Drug Products (DRUDP) requested that the primary efficacy endpoints be limited to (1) the events of (a) *bone scan documented disease progression* and (b) *death* due to any cause in the absence of bone scan confirmed progression and (2) events that occurred within 2 years of randomization.

2.3 Efficacy Population and Efficacy Results (Primary Endpoints and Analyses)

2.3.1 Demographics

A total of 8,113 patients were randomized to therapy (the intent-to-treat population) with 3292, 3603, and 1218 patients randomized to Trials 23, 24, and 25, respectively. Median patient-years of follow up for disease progression and survival (efficacy analyses) were 3.2 years (Trial 23), 2.6 years (Trial 24) and 3.0 years (Trial 25). Within each of the individual trials, baseline demographic and disease characteristics were well balanced across the Casodex and placebo treatment groups. In general, baseline patient characteristics across Trials 24 and 25 were similar but differed somewhat from those in Trial 23 in that patients in Trial 23 tended to be younger by several years, weighed slightly more, and had lower serum PSA values.

2.3.2 Sponsor's Preferred Endpoints and Analyses

The percentages of patients with disease progression or death in the absence of disease progression in each of the trials (based on the Sponsor's preferred protocol-defined endpoints) are summarized in Table A. The percentage of patients with disease progression in each of Trials 24 and 25 was numerically lower in the Casodex-treated patients. Based on this endpoint and a time to event analysis, there was a statistically significant reduction in the time to disease progression in Trial 24 (hazard ratio [HR] = 0.574, 95% confidence interval [CI]: 0.477 to 0.692) and Trial 25 (HR = 0.430, 95% CI: 0.336 to 0.552). There was no evidence of benefit from Casodex treatment in Trial 23 (the only trial conducted in the US).

Table A Disease Progression or Death (Based on Sponsor's Preferred Endpoints)

Event	Number (per cent) of patients with event					
	Study 23		Study 24		Study 25	
	Casodex (N = 1647)	Placebo (N = 1645)	Casodex (N = 1798)	Placebo (N = 1805)	Casodex (N = 607)	Placebo (N = 611)
Positive bone scan	21 (1.3)	15 (0.9)	60 (3.3)	116 (6.4)	32 (5.3)	95 (15.5)
Other objective events ¹	10 (0.6)	17 (1.0)	25 (1.4)	85 (4.7)	19 (3.1)	40 (6.5)
Death in absence of progression	52 (3.2)	55 (3.3)	96 (5.3)	92 (5.1)	48 (7.9)	44 (7.2)
Total (%) Patients	83 (5.0)	87 (5.3)	181 (10.1)	293 (16.2)	99 (16.3)	179 (29.3)

¹ Documented by magnetic resonance imaging, computerized tomography, sonography, or biopsy.

Exploratory subset analyses for Trial 24 (based on the sponsor's preferred endpoints) indicated a reduction in disease progression in the Casodex-treated patients in both the adjuvant therapy subgroups (patients treated by prior prostatectomy or radiotherapy) and the watchful waiting (immediate or monotherapy) subgroup. Results for the watchful waiting subgroup in Trial 25 (the only subgroup with more than 250 patients in this trial) also showed a numeric reduction in disease progression in Casodex-treated patients. The estimates of the hazard ratios and 95% CIs for the watchful waiting subgroups were 0.674 (Trial 24, 95% CI = 0.518 to 0.878) and 0.423 (Trial 25, 95% CI = 0.321 to 0.557).

2.3.3 FDA Requested Endpoints and Analyses

The percentages of patients with objective disease progression or death in the absence of objective progression within 2.5 years of randomization are presented in Table B. For Trials 24 and 25, the estimates of the odds ratios (OR) and 95% CIs were 0.645 (Trial 24, 95% CI = 0.500 to 0.832 and 0.515 (Trial 25, 95% CI = 0.365 to 0.729).

Table B Disease Progression or Death (Based on FDA Requested Endpoints)

Event	Number (per cent) of patients with event within 2.5 yr. of randomization					
	Study 23		Study 24		Study 25	
	Casodex (N = 1647)	Placebo (N = 1645)	Casodex (N = 1798)	Placebo (N = 1805)	Casodex (N = 607)	Placebo (N = 611)
Positive bone scan	14 (0.9)	11 (0.7)	42 (2.3)	98 (5.4)	22 (3.6)	72 (11.8)
Death in absence of progression	25 (1.5)	37 (2.2)	70 (3.9)	70 (3.9)	41 (6.8)	33 (5.4)
Total (%) of patients	39 (2.4)	48 (2.9)	112 (6.2)	168 (9.3)	63 (10.4)	105 (17.2)

Exploratory subset analyses for Trial 24 indicated that the proportions of Casodex-treated patients with disease progression were numerically lower in both the adjuvant therapy subgroups (patients treated by prior prostatectomy or radiotherapy) and the watchful waiting subgroup (Table C). The estimates of the odds ratios and 95% CIs for the subgroups were 0.616 (radical prostatectomy, 95% CI = 0.379 to 1.003), 0.625 (radiotherapy, 95% CI = 0.361 to 1.081), and 0.674 (watchful waiting, 95% CI = 0.471 to 0.964).

Table C Disease Progression or Death by Pre-randomization Treatment in Trial 24 (FDA Requested Endpoints)

Event	Number (per cent) of patients with event within 2.5 yr. of randomization					
	Radical Prostatectomy		Radiotherapy		Watchful Waiting	
	Casodex (N = 835)	Placebo (N = 813)	Casodex (N = 335)	Placebo (N = 325)	Casodex (N = 628)	Placebo (N = 666)
Positive bone scan	12 (1.4)	27 (3.3)	11 (3.3)	28 (8.6)	19 (3.0)	43 (6.5)
Death (any cause) in absence of progression	17 (2.0)	16 (2.0)	13 (3.9)	8 (2.5)	40 (6.4)	46 (6.9)
Total (%) Patients	29 (3.5)	43 (5.3)	24 (7.2)	36 (11.1)	59 (9.4)	89 (13.4)

Results for the watchful waiting subgroup in Trial 25 (the only subgroup with more than 250 patients in this trial) also showed a numeric reduction in disease progression in Casodex-treated patients. The estimate of the odds ratio and 95% CI for this subgroup was 0.498, 95% CI = 0.338 to 0.734.

2.3.4 Deaths

The total number and percentage of deaths due to prostate cancer or other causes in each of the trials at the data cutoff for the efficacy analyses (2 June 2000) and the data cutoff for the safety update (28 September 2001) are listed in Table D. There were no significant differences in the percentage of patients who died, either of prostate cancer or of other causes, in the Casodex and placebo groups within each of the trials. There were, however, differences across the trials.

Table D Total Number and (%) of Deaths due to Prostate Cancer or Other Causes

Cause of Death	Study 23		Study 24		Study 25	
	Casodex N= 1647	Placebo N=1645	Casodex N= 1798	Placebo N=1805	Casodex N= 607	Placebo N= 611
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Prostate cancer	8 (0.5)	3 (0.2)	26 (1.4)	38 (2.1)	24 (4.0)	28 (4.6)
Other	54 (3.3)	58 (3.5)	97 (5.4)	99 (5.5)	45 (7.4)	42 (6.9)
Total¹	62 (3.8)	61 (3.7)	123 (6.8)	137 (7.6)	69 (11.4)	70 (11.5)
Prostate cancer	14 (0.9)	6 (0.4)	56 (3.1)	66 (3.7)	49 (8.1)	56 (9.2)
Other	91 (5.6)	93 (5.7)	168 (9.4)	161 (9.0)	67 (11.1)	50 (8.2)
Total²	105 (6.5)	99 (6.1)	224 (12.5)	227 (12.7)	116 (19.2)	106 (17.4)

1. Data cutoff of 2 June 2000 (efficacy population). 2. Data cutoff of 28 September 2001 (safety population).

2.4 Unresolved Efficacy Issues

The relevance of the findings in Trials 24 and 25 to men with prostate cancer in the US who would be treated with Casodex (either adjuvant therapy or monotherapy) is unclear.

Adjuvant Therapy. Based on the data submitted by the Sponsor, patients similar to those enrolled in Trial 230 who are initially treated by radical prostatectomy or radiotherapy in the US would derive no benefit from Casodex adjuvant therapy. A supplemental analysis by the Sponsor, based on a subset of patients in Trial 23, also did not show convincing evidence of efficacy for Casodex adjuvant therapy. In addition, it was not possible (1) to adequately characterize the patients in Trials 24 and 25 because of lack of standardized Gleason scores and (2) to extrapolate the data from patients in Trials 24 and 25 to Trial 23 to identify US patients who might benefit from Casodex adjuvant therapy.

Immediate Treatment or Monotherapy. A watchful waiting subgroup was not included in Trial 23. The proposed indication does not adequately identify the population of prostate cancer patients in the US who might derive sufficient benefit from Casodex monotherapy to warrant the risks of treatment.

- **For local or early disease.** The Sponsor has not shown that patients presently managed by watchful waiting in the US would experience disease progression of sufficient magnitude to warrant treatment with Casodex and the side effects associated with such treatment.
- **For locally advanced disease.** Since the comparator in these trials was placebo and not active therapy (i.e., medical or surgical castration), it is not possible to adequately address the efficacy of Casodex monotherapy. This is a critical issue since survival may be shortened in patients treated with Casodex monotherapy instead of by medical or surgical castration (the present standard of care in the US for such patients).

3 SAFETY

3.1 Adequacy of Safety Testing

The database from Trials 23, 24, and 25 supporting the safety of Casodex 150 mg per day was large. It included 4,022 Casodex-treated patients, representing 9,387 patient-years of exposure. Patient exposure to Casodex in the controlled clinical trials was adequate to assess the likely safety profile of Casodex 150 mg per day in men with prostate cancer.

3.2 Overview of Safety Findings

Most patients in the controlled clinical trials (97.4% Casodex group, 88.2% placebo group) had at least 1 adverse event. The number of patients with at least 1 drug-related adverse event was approximately 3-fold higher in the Casodex group (90.5%) than the placebo group (31.4%). A

greater number of patients in the Casodex group also were withdrawn from treatment as a result of an adverse event (27.7% compared with 9.2% of placebo-treated patients). The number of patients who had at least 1 serious adverse event was similar across the treatment groups (33.6% Casodex group, 32.5% placebo group). Much of the difference between the Casodex and placebo treatment groups in each of the categories of (a) any adverse event, (b) drug-related adverse events, and (c) adverse events leading to withdrawal was due to the pharmacological (anti-androgenic and compensatory estrogenic) actions of Casodex.

Side effects associated with Casodex treatment can be classified for the most part into one of 2 categories: (1) those of a generally non-serious and non-life threatening nature that are due to the pharmacological actions of Casodex and which occur with a high incidence and (2) those that occur in a few percent of patients and which may be serious or life-threatening (primarily liver toxicity).

3.2.1 Common Adverse Events.

The most commonly reported adverse events that occurred more frequently in Casodex-treated patients and the percentage of Casodex-treated patients that experienced these adverse events were breast pain (73%), gynecomastia (67%), asthenia (11%), vasodilatation (9%), impotence (9%), alopecia (6%), and weight gain (6%). All of these adverse events (other than perhaps asthenia and weight gain) are likely to be due to the pharmacological actions of Casodex.

Most Casodex-treated patients (86.2%) reported gynecomastia or breast pain. Of these patients, 16.1% withdrew from Casodex therapy because of these adverse events. Gynecomastia or breast pain was reported as severe in 8.6% of Casodex-treated patients. Breast pain was reversible in > 90% of patients after cessation of Casodex therapy. Gynecomastia, however, resolved in only 50% of patients after discontinuation of treatment. In the placebo-treated patients, only 12.4% patients reported gynecomastia or breast pain, and only 0.6% withdrew from treatment because of these adverse events.

3.2.2 Potentially Serious or Life-Threatening Adverse Events

Treatment with all nonsteroidal anti-androgens is associated with hepatotoxicity that can be serious and occasionally fatal. Hepatotoxicity appears to occur more frequently in patients being treated with flutamide than other nonsteroidal anti-androgens. In the combined findings from Trials 23, 24, and 25, patient withdrawals due to increased serum ALT and AST values or increased bilirubin values were higher in Casodex-treated patients (1.2% and 0.4%, respectively) than in placebo-treated patients (0.5% and 0.2%, respectively). Similarly, adverse events classified as serious due to increased serum ALT and AST values or increased bilirubin values were more frequent in Casodex-treated patients (0.3% and 0.2%, respectively) than in placebo-treated patients (0.0% and <0.1%, respectively). However, the number of patients reported to have died from hepatic failure or a primary hepatic neoplasm was similar in the 2 treatment groups (5 of 4,022 Casodex-treated patients and 5 or 6 of 4,031 placebo-treated patients).

Twelve (12) Casodex-treated patients and 5 placebo-treated patients developed myelodysplasia syndrome or leukemia (relative incidence Casodex/placebo = 2.4). Of these patients, 8 of the Casodex-treated patients and 4 of the placebo-treated patients have died as a direct or indirect result of their underlying hematologic disorder. The significance of this numeric imbalance and its possible relationship to treatment with Casodex are not known at this time.

3.2.3 Deaths

As of the data cutoff date for the Safety Update (28 September 2001), 445 of 4,022 patients (11.1%) who received Casodex and 432 of 4,031 patients (10.7%) who received placebo had died. Prostate cancer was the listed cause of death in 2.96% and 3.18% of patients in the Casodex- and placebo-treatment groups, respectively. Among non-prostate cancer causes of death, cardiovascular events

were the major cause of death with 77 cases reported in Casodex-treated patients and 66 cases reported in placebo-treated patients. Deaths that linked to the respiratory system were the second most frequent in both treatment groups, occurring in 29 Casodex-treated and 36 placebo-treated patients. Deaths that linked to the digestive system were the third most frequent, affecting 24 Casodex-treated patients and 17 placebo-treated patients. Among this group, gastrointestinal carcinoma was the most common single cause of death, affecting 18 Casodex-treated patients and 10 placebo-treated patients.

4 DOSING REGIMEN

The proposed dosing-regimen is Casodex 150 mg per day for at least 2 years or until disease progression. The proposed dose appears to be appropriate based on dose-ranging data concerning suppression of serum PSA values in men with prostate cancer that were provided in an earlier submission (NDA 20-498/s006). The basis for the recommendation that treatment should continue for at least 2 years is unclear since treatment in Trial 24 and Trial 25 was to be for at least 5 years or until disease progression.

CLINICAL REVIEW

1 INTRODUCTION AND BACKGROUND

1.1 General Information

- **NDA** 20-498/s012
- **Applicant** AstraZeneca Pharmaceuticals Lupron
PO Box 8355
Wilmington, DE 19803-8355
- **Submission Type** Efficacy supplement
- **Drug**
 - **Established name** Bicalutamide
 - **Trade name** Casodex®
 - **Drug Class** Nonsteroidal anti-androgen
 - **Proposed Indication** Original Indication
Immediate hormonal therapy or adjuvant therapy to treatment of curative intent in patients with non-metastatic prostate cancer

First Revision of Indication (Submitted 10 May 2002)
(1) Adjuvant therapy to radical prostatectomy and radiotherapy of curative intent in patients with locally advanced non-metastatic prostate cancer who have a high risk for disease recurrence or
(2) Immediate treatment of non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated

Second Revision of Indication (Submitted 22 October 2002)
(1) (Unchanged from 10 May 2002 submission).
(2) Immediate treatment of localized non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated
- **Dosing Regimen** One 150 mg tablet daily

1.2 Carcinoma of the Prostate

1.2.1 Epidemiology

Cancer of the prostate is the most frequent noncutaneous malignancy in men, and after lung cancer, the second most frequent cause of death from cancer in men over 50 years of age. It is estimated that approximately 200,000 new cases of prostate cancer were diagnosed and that 30,000 deaths occurred from the disease in the year 2001. Prostate cancer is a major social, economic, and health issue.

1.2.2 Treatment of Prostate Cancer

Treatment options for prostate cancer include radical prostatectomy, radiotherapy, androgen ablation or deprivation therapy (achieved by surgical castration, GnRH analogs, or nonsteroidal antiandrogens), and no active therapy (watchful waiting or surveillance). Selection of the most appropriate treatment depends on many factors that include the clinical stage of the tumor (localized to the prostate, local extension beyond the prostate, or distant or bony metastases), status of regional lymph nodes, degree of tumor differentiation (generally assessed as Gleason grade), serum prostate specific antigen (PSA) concentration, and the patient's likely life expectancy due to the presence of other co-morbid conditions.

Patients with tumors that are localized to the prostate gland may be cured of their disease by a radical prostatectomy or radiation therapy. Patients with local extension of their tumor beyond the prostate gland also may be candidates for a curative procedure (radical prostatectomy or radiotherapy) in some instances, particularly if the tumor is well- or moderately well-differentiated and is associated with a serum PSA of < 10 ng/mL at the time of diagnosis. Patients with extensive local disease generally are not candidates for a curative procedure, particularly if the tumor is poorly differentiated and the serum PSA is > 10 ng/mL. Such patients are often managed by androgen ablation therapy alone or androgen ablation therapy plus radiotherapy. Patients with bony metastases or non-local soft tissue metastases are generally treated with androgen ablation therapy alone.

A minority of patients in the US (perhaps 10% of newly diagnosed cases) are initially managed by watchful waiting or surveillance. In the US, men who initially receive no active therapy tend to be older (generally > 75 years of age at diagnosis), have low grade and localized tumors, have no symptoms from their prostate cancer, and often have a life expectancy of < 10 years. The rationale for management by watchful waiting or surveillance is the expectation that prostate cancer will remain asymptomatic in the majority of these men, and they will likely die from a disorder unrelated to prostate cancer.

1.2.3 Rationale for the Use of Androgen Ablation Therapy

Growth of prostate glandular tissue is regulated by a complex of growth factors of which androgens play a pivotal role. In most men, prostate cancer is at least partially an androgen-dependent tumor at the time of initial presentation. Prostate cancer also is partially androgen-dependent in most men at the time of initial progression (either local or metastatic) if the patient has not been treated previously with androgen ablation or deprivation therapy.

Because of the androgen-dependence of prostate cancer and the availability of GnRH analogs and nonsteroidal antiandrogens, androgen ablation therapy has been used as adjuvant therapy in conjunction with radical prostatectomy and radiation therapy. There are limited data on the benefits of androgen deprivation adjuvant therapy following radical prostatectomy, particularly in men with lymph node negative disease.¹ A report demonstrating the benefit of androgen deprivation adjuvant therapy in men with positive lymph nodes was that of Messing et al.² In this study, 98 men with positive lymph nodes at the time of radical prostatectomy were randomized to receive either immediate androgen deprivation therapy (with either a GnRH analog or surgical castration) or placebo therapy. After 7.1 median years of follow up, 7 of 47 men who received immediate androgen deprivation therapy had died as compared with 18 of 51 men in the placebo group ($p < 0.02$).

The potential benefit of androgen ablation therapy in conjunction with radiotherapy, generally for locally advanced or high-grade prostate carcinoma, has been investigated in several clinical trials. In one such trial (Bolla et al ³), 415 men with locally advanced prostate cancer were treated with external beam radiotherapy alone or radiotherapy plus a GnRH analog. At a median follow up of 45 months, estimates of overall survival at 5 years were 79% and 62% for patients treated with adjuvant GnRH analog compared to placebo ($p = 0.001$). Other studies in which men were treated with radiotherapy and adjuvant androgen ablation therapy have shown improvement in local control of disease or improved survival in subgroups (Hellerstedt BA and Pienta KJ ⁴).

Based in part on these findings in men with prostate cancer and the demonstrated benefits of adjuvant anti-estrogen therapy in women with carcinoma of the breast, AstraZeneca initiated 3 clinical trials (the pivotal trials in support this supplemental NDA) in men with non-metastatic prostate cancer. In each of the trials, the potential benefit of adjuvant therapy with Casodex immediately following either radical prostatectomy or radiotherapy was compared to placebo. In 2 of the trials, the potential benefit of Casodex monotherapy (compared to placebo) was investigated in men with non-metastatic prostate cancer who otherwise would be managed by watchful waiting or surveillance.

1.2.4 Pharmacology of Casodex and Other Nonsteroidal Anti-androgens

Nonsteroidal anti-androgens (NSAAs) currently available for clinical use in the US include flutamide (Eulexin), nilutamide (Nilandron), and bicalutamide (Casodex). All three are approved for use in the US in combined androgen blockade therapies: Casodex (50 mg per day) and flutamide in combination with a GnRH agonist and nilutamide in combination with surgical castration are approved for the treatment of advanced prostate cancer. No NSAA is presently licensed in the US as single agent monotherapy.

The mode of action of NSAAs such as Casodex differs from that of medical (i.e., GnRH-induced) or surgical castration. Whereas castration causes a reduction in circulating levels of androgens, Casodex is a competitive antagonist of testosterone and dihydrotestosterone action at the level of the intracellular androgen receptor. Casodex binds competitively and reversibly to the androgen receptor without activating gene expression, and thus inhibits the stimulatory effect of androgens. This action of Casodex and other NSAAs markedly reduces the effects of circulating androgens on prostate cancer cells.

1.3 Other Relevant Information

1.3.1 Earlier Submission (NDA 20-498/s006)

In February 2000, AstraZeneca submitted an efficacy supplement (NDA 20-498/s006) for the treatment of locally advanced, non-metastatic (Stages T3-T4, NX, M0) prostate cancer with Casodex monotherapy (150 mg/d). Two pivotal trials (Trials 0306 and 0307) were submitted in support of the application. The trials were similar in design but conducted in different geographic locales. Neither study was conducted in North America. Both were open-label, active comparator trials that compared Casodex monotherapy to medical or surgical castration. The studies originally included patients with metastatic disease (Stage M1) as well as non-metastatic (M0) disease. Based on an interim analysis of survival, the Data Safety Monitoring Board (DSMB) recommended that Casodex treatment be discontinued in M1 patients. The data at the time of their recommendation indicated that the risk of death

was 25% and 31% higher in the Casodex M1 groups compared to the castration M1 groups in Trails 0306 and 0307, respectively. The trials continued thereafter with only patients who had Stage M0 disease at the time of entry.

Survival in the Casodex-treated M0 patients, compared to that in the patients treated by castration, differed across Trials 0306 and 0307. In Trial 0306 (n = 140 M0 patients), the risk of death was calculated as 36% lower in the Casodex group while in Trial 0307 (n = 352 M0 patients), the risk of death was calculated as 25% higher in the Casodex group. Both the primary medical reviewer and statistical reviewer recommended that the application not be approved for several reasons that included (1) the conflicting trial results with the larger trial demonstrating a survival disadvantage in the Casodex treatment group for M0 patients, (2) a survival disadvantage for M1 patients treated with Casodex in both clinical trials, and (3) a combined statistical analysis that (a) did not fully meet the Sponsor's original definition of noninferiority and (b) was considered to be statistically inappropriate. Upon learning that the application would not be approved, AstraZeneca withdrew the supplemental NDA in December 2000.

1.3.2 Regulatory and Marketing Status

1.3.2.1 Casodex 50 mg Tablets

Casodex at a daily dose of 50 mg in combination with medical or surgical castration is registered world-wide for the treatment of advanced prostate cancer. In some markets, the mode of castration is limited to one or the other method. The product was approved in the US in 1995 for the treatment of metastatic prostate cancer (Stage D2) in combination with GnRH analog therapy.

1.3.2.2 Casodex 150 mg Monotherapy

Casodex and other NSAAs are not approved as monotherapy in the US.

Locally advanced prostate cancer. The applicant stated that "Product Licences have been granted for the use of Casodex 150 mg monotherapy in the treatment of locally advanced, non-metastatic prostate cancer in 35 countries. Applications are currently under review in a number of other countries." Representative approved labeling for Casodex 150 mg monotherapy for locally advanced non-metastatic prostate cancer is presented below:

Sweden: Casodex 150 mg per day monotherapy is indicated for the treatment of patients with locally advanced, non-metastatic prostate cancer, for whom hormonal treatment is indicated, but surgical or medical castration is considered inappropriate.

UK: Casodex 150 mg is also indicated for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical castration or other medical intervention is not appropriate or acceptable.

A supplemental NDA (20-498/s006) was submitted to the FDA in February 2000 seeking approval for Casodex monotherapy (150 mg per day) for the treatment of locally advanced non-metastatic prostate cancer. The application was withdrawn in December 2000 after the applicant learned that the sNDA would not be approved (see Section 1.3.1).

Localized or locally advanced prostate cancer. Following submission of additional data regarding the use of Casodex in men with early prostate cancer (Clinical Trials 7054IL/0023,

7054IL/0024, and 7054IL/0025 [the pivotal trials in sNDA 20-498/s012 as well]), the Product Licenses for Casodex monotherapy were broadened in several countries. As of 1 March 2002 according to the Sponsor, Casodex (150 mg per day) had been approved in 12 countries as therapy for men with localized or locally advanced prostate cancer, either alone as monotherapy or as adjuvant therapy to radical prostatectomy or radiation therapy of curative intent. These 12 countries are (in order of approval date) Slovakia, Italy, UK, Greece, Austria, Portugal, Belgium and Luxembourg, Czech Republic, Mexico, Norway, and Hungary.

Medical Officer's Comments

- *All of the 12 countries listed above in which Casodex monotherapy has been approved for localized prostate cancer had previously approved Casodex monotherapy for locally advanced prostate cancer based on the results of clinical trials 0306 and 0307. These were the pivotal clinical trials in NDA 20-498/s006 that was withdrawn by the Sponsor in December 2000.*
- *The approved indication of treatment of men with Casodex for localized or locally advanced prostate cancer differs slightly across the 12 countries. The most significant difference appears to be in the approved indications for patients the United Kingdom, Greece, Austria, and Portugal. In these latter countries, Casodex 150 mg per is approved as immediate therapy for patients with localized prostate cancer only if they are not being treated by radical prostatectomy or radiation therapy (i.e., patients being managed by watchful waiting). In these markets, it has not been approved as adjuvant therapy for patients with local disease if they have previously received therapy of curative intent.*
- *In response to a request for additional information regarding the approval of Casodex monotherapy in markets outside of the US, the Sponsor informed DRUDP in their submission of 22 May 2002 that Casodex monotherapy had been recommended for approval by the Australian Drug Evaluation Committee (ADEC) for the treatment of local and locally advanced prostate cancer. This Committee had previously rejected the Sponsor's application for treatment with Casodex monotherapy for locally advanced non-metastatic prostate cancer based solely on the results of Trials 0306 and 0307.*

1.3.2.3 Postmarketing Experience

According to the Sponsor, the estimated postmarketing worldwide exposure to Casodex (50 mg or 150 mg) from 1995 until 28 September 2001 was approximately 687,000 patient years. Approximately 9,800 patient-years of the total exposure was to Casodex 150 mg.

1.4 Important Issues with Pharmacologically Related Agents

Two other nonsteroidal anti-androgens, flutamide and nilutamide, are approved for use in men with prostate cancer. All of the nonsteroidal anti-androgens have similar pharmacologically-related side effects. Pharmacologically-related adverse events are secondary to either the direct anti-androgenic actions of the drugs (e, g, increased incidence of erectile dysfunction, decreased libido, and anemia) or indirect compensatory estrogenic effects of the drugs (increased incidence of breast pain and gynecomastia).

All nonsteroidal anti-androgens are hepatotoxic to varying degrees. Treatment with nilutamide (but not flutamide or Casodex) also has been reported to be associated with an increased incidence of interstitial pneumonia.

Medical Officer's Comment

- *Hepatotoxicity is a common adverse event associated with the use of flutamide. It can be serious and even fatal in patients being treated with flutamide. The incidence of significant flutamide-related hepatotoxicity has been estimated to be 2.5 per 100000 prescriptions in the US (Wysowski 1996⁵) against a background incidence in a similar US population of 0.2 per 100000 prescriptions in patients not exposed to drugs. Serious adverse events related to hepatic toxicity (primarily increased serum transaminase levels) and withdrawals due to hepatic toxicity were 2-3 fold greater in Casodex-treated patients compared to placebo-treated patients in the controlled trials in NDA 20-498/s012. However, fatal events related to hepatotoxicity appear to be rare in Casodex-treated patients (Section 5.8.3 and Section 5.9.3).*

2 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

2.1 Pharmacokinetics

2.1.1 Pharmacokinetics

Casodex is a racemate with the anti-androgenic activity almost exclusively in the (R)-enantiomer; the (S)-enantiomer is essentially inactive. Casodex is well absorbed following oral administration, although the absolute bioavailability is unknown. The pharmacokinetics of Casodex were dose proportional over the range of 10 mg to 150 mg doses. Co-administration of Casodex with food had no clinically significant effect on rate or extent of absorption. Casodex is highly protein-bound (>90%) and may displace other highly protein bound drug substances, thus increasing their free plasma concentrations.

2.1.2 Potential for Interactions as Substrate, Inhibitor, or Inducer

R-Casodex significantly inhibited CYP 3A4, 2C9, 2C19, 2D6, and 1A2, in vitro, while no significant inhibition was noted with S-Casodex.

2.1.3 Effects of Renal or Hepatic Insufficiency and Age

Renal impairment (as measured by creatinine clearance) had no significant effect on the elimination of total bicalutamide or the active R-enantiomer in doses up to 450 mg. No clinically significant difference in the pharmacokinetics of either enantiomer of bicalutamide was noted in patients with mild-to-moderate hepatic disease as compared to healthy controls. However, the half-life of the R-enantiomer was increased approximately 76% (5.9 and 10.4 days for normal and impaired patients, respectively) in patients with severe liver disease (n=4). In studies in patients given up to 450 mg daily, no significant relationship between age and steady-state levels of total bicalutamide, or the active R-enantiomer has been shown.

2.2 Pharmacodynamics

Casodex is a nonsteroidal anti-androgen with no other known endocrine activity. It competitively inhibits the action of androgens by binding to androgen receptors in the target tissue. No pharmacodynamic data were submitted with the present efficacy supplement. At

the request of the medical reviewer, the Sponsor submitted information on the effects of treatment with Casodex on serum concentrations of testosterone, dihydrotestosterone (DHT), and estradiol obtained from a clinical study that was not included in the present application.

In this study, mean serum concentrations of testosterone during treatment with 150 mg Casodex increased from 3.15 nmol/L at baseline (n=23) to a maximum of 6.00 nmol/L at Month 2 (n=21). At Month 6 of treatment, mean serum concentrations of testosterone were 5.22 nmol/L (n=21). Mean serum concentrations of DHT in these patients were 0.29 ng/mL (baseline), 0.35 ng/mL (Month 2) and 0.34 ng/mL (Month 6). Mean serum concentrations of free testosterone in these patients were 8.77 [no units provided] at baseline, 13.47 at Month 2, and 13.55 at Month 6. Mean serum concentration of estradiol in these patients increased from 34.4 pmol/L at baseline to 55.8 pmol/L at Month 6.

Medical Officer's Comments

- *Based on the numeric values for serum concentrations of testosterone and the values and units for DHT (ng/mL), the correct units for serum testosterone concentrations are probably also ng/mL and not nmol/L as reported by the Sponsor.*
- *During treatment with Casodex and other NSAAs, there is an increase in serum concentrations of testicular androgens and estradiol because of partial inhibition of gonadal steroid negative feedback at the level of the hypothalamus and/or pituitary gland and a compensatory increase in the secretion of pituitary gonadotropins. It is likely that the reduction in effective androgen levels at the level of the prostate cancer cells (i.e., reduction in stimulation of androgen receptors in prostate cancer cells) is less than that which follows treatment with a GnRH analog or surgical castration. This is supported by the previously described observations from Clinical Trials 0306 and 0307 in which median survival in men with metastatic prostate cancer (Stage M1 disease) treated with Casodex was less than that in men treated with a GnRH analog or surgical castration.*
- *The increase in serum estradiol, perhaps further compounded by the reduction in effective androgen levels, is responsible for the most common side effects associated with Casodex treatment in men, namely, gynecomastia and breast pain.*

3 DESCRIPTION OF CLINICAL DATA AND SOURCES

3.1 Sources of Clinical Data

3.1.1 Clinical Trials

The sponsor submitted efficacy and safety data from 3 Phase III clinical trials (Trials 7054IL/0023, 7054IL/0024, and 7054IL/0025, hereafter referred to as Trials 23, 24, and 25, respectively) on 20 December 2001. The trials were conducted in (1) North America, predominantly the US [Trial 23], (2) Europe (other than Scandinavia), South Africa, Israel, Mexico, and Australia [Trial 24], and (3) Scandinavia [Trial 25]. On 18 April 2002, the sponsor provided an integrated, comprehensive 4-month Safety Update for Trials 23, 24, and 25. Throughout the review process, the sponsor submitted additional data and analyses in response to requests from DRUDP.

3.2 Overview of Clinical Trials

Complete Final Study Reports for 3 Phase III clinical trials were submitted with NDA 20-498/s012 to support the safety and efficacy of Casodex 150 mg tablets for the treatment of men with localized and locally advanced prostate cancer. Enrollment in the 3 clinical trials was initiated in August 1995 (Trial 23), September 1995 (Trial 24), and October 1995 (Trial 25). The last patients were enrollment in August 1997 (Trial 23) and July 1998 (Trials 24 and 25). The data cutoff date for each of the Final Study Reports was 2 June 2000. The applicant also submitted a separate safety addendum for each of the clinical trials (data cut-off date of 23 February 2001 for each addendum). The study number and title of each of the trials are listed below.

1. Trial Number 7054IL/0023. “A Randomized Double-Blind Comparative Trial of Bicalutamide (CASODEX™) Versus Placebo in Patients with Early Prostate Cancer.” (First patient recruited: 01 August 1995; last patient recruited: 29 August 1997).
2. Trial Number 7054IL/0024. “A Randomised, Double-Blind, Parallel-Group Trial Comparing CASODEX™ 150 mg Once Daily with Placebo in Patients with Non-metastatic Prostate Cancer.” (First patient recruited: 21 September 1995; last patient recruited: 27 July 1998).
3. Trial Number 7054IL/0025. “A Randomised, Double-Blind, Parallel-Group Trial Comparing CASODEX™ 150 mg Once Daily with Placebo in Patients with Non-metastatic Prostate Cancer (SPCG-6).” (First patient recruited: 4 October 1995; last patient recruited: 30 July 1998).

Each of the clinical trials was a comparative, randomized, double blind, parallel-group, multicenter trial. In each trial, the efficacy and safety of Casodex (150 mg per day) was compared to that of placebo. Additional information concerning each of the clinical trials is provided in Table 1.

Table 1. Studies Supporting Safety and Efficacy of Casodex for Localized or Locally Advanced Prostate Cancer.

Study No. Study Title	Study Design Study Status	No. of Patients ¹ Age of Pt. Mean (range) Racial Distribution	Total No. of Sites Country and (No. Pt. per country)	Treatment Study Drug: number patients ¹ Duration of Treatment
7054IL/0023 “A Randomized Double-Blind Comparative Trial of Bicalutamide (CASODEX™) Versus Placebo in Patients with Early Prostate Cancer	Phase 3, randomized, blinded, placebo controlled, and multicenter. Treatment completed; follow up for survival ongoing.	3292 men 64.5 years (38-85 years) White 2760 Black 379 Hispanic 106 Other 47	96 Sites United States (n=2974), Canada (n=318).	Treatment Casodex: 1647 patients Placebo: 1645 patients Duration All patients 2 years or until objective progression
7054IL/0024 “A Randomized, Double-Blind, Parallel-Group Trial Comparing CASODEX™ 150 mg Once Daily with Placebo in Patients with Non-metastatic Prostate Cancer.”	Phase 3, randomized, blinded, placebo controlled, and multicenter. Treatment ongoing.	3603 men 68.7 years (42-93 years) White 3423 Hispanic 62 Mixed 61 Afro-Caribbean 30 Other 27	191 Sites Australia (n=14), Austria (n=62), Belgium (n=236), Czech Rep (n=184), France (n=348), Germany (n=107), Holland (n=220), Hungary (n=70), Ireland (n=23), Israel (n=193), Italy (n=94), Mexico (n=77), Poland (n=7), Portugal (n=170), South Africa (n=394), Spain (n=506), and UK (n=898).	Treatment Casodex: 1798 patients Placebo: 1805 patients Duration Adjuvant patients 5 years or until progression Non-adjuvant patients Until progression
7054IL/0025 “A Randomized, Double-Blind, Parallel-Group Trial Comparing CASODEX™ 150 mg Once Daily with Placebo in Patients with Non-metastatic Prostate Cancer (SPCG-6).”	Phase 3, randomized, blinded, placebo controlled, and multicenter. Treatment ongoing.	1218 men 68.5 years (46-87 years) White 1213 Hispanic 3 Other 2	62 Sites Denmark (n=173), Finland (n=277), Norway (n=509), and Sweden (n=259).	Treatment Casodex: 607 patients Placebo: 611 patients Duration All patients Until progression

1. Number of patients randomized (i.e., the efficacy population). Not all patients received study drug.
 Source: Prepared by Medical Officer from various sources.

4 INTEGRATED REVIEW OF EFFICACY

4.1 Brief Statement about Efficacy

The Sponsor has provided statistically significant evidence in two non-US clinical trials (Trials 24 and 25) that treatment with Casodex 150 mg per day, compared to treatment with placebo, in men with non-metastatic prostate cancer at entry delayed progression of disease as assessed by (1) bone scan confirmed metastases or (2) death from any cause in the absence of disease progression. In these trials, Casodex was studied as (1) adjuvant therapy in men previously treated by radical prostatectomy or radiotherapy or (2) monotherapy in men who would otherwise be managed by watchful waiting. In Trial 23 (the only trial conducted in the US and the trial most relevant to patients in the US), there was no evidence that treatment with Casodex delayed disease progression. The relevance of benefit from treatment with Casodex in the 2 non-US trials for men with prostate cancer in the US who might be treated with Casodex adjuvant therapy or Casodex monotherapy is unknown.

There was no evidence that treatment with Casodex improved survival in any of the trials or in the combined analysis. Evidence of improved survival, however, was not anticipated by the cut-off date for efficacy data (2 June 2000) or the cut-off for the Safety Update (28 September 2001) as the survival data were expected to be immature.

4.2 General Approach to the Review of the Efficacy of the Drug

The clinical component of NDA 20-498/s012 consisted of 3 pivotal Phase III clinical trials (Trials 23, 24, and 25). Efficacy data from each of the Phase III clinical trials were reviewed separately and collectively. The 3 clinical trials were very similar in design. Efficacy assessments were identical across studies, and each trial had nearly identical primary and secondary efficacy endpoints; consequently, the 3 pivotal efficacy trials are presented, for the most part, in an integrated manner in the review that follows.

4.3 Clinical Trials to Support Sponsor's Efficacy Claim

4.3.1 Overall Study Design

The 3 Phase III clinical trials were comparative, multicenter, randomized, double-blind, parallel-group trials. Table 1 provides an overview of these trials. The trials were conducted in (1) North America (Trial 23), (2) Europe (other than Scandinavia), South Africa, Israel, Mexico, and Australia (Trial 24), and (3) Scandinavia (Trial 25). All patients who qualified for enrollment were randomized in a 1:1 ratio to treatment with either Casodex 150 mg per day or matching placebo. Table 2 provides a comparison of the similarities and differences across the 3 trials. All trials excluded the enrollment of patients with metastatic disease beyond that of positive regional lymph nodes; however, in Trial 23, patients with positive regional lymph nodes also were not eligible. All 3 trials investigated Casodex as adjuvant therapy in patients who had had previous therapy for their prostate cancer (i.e., radical prostatectomy or radiation therapy). Trials 24 and 25 (but not Trial 23) also investigated Casodex monotherapy (patients who had had no prior therapy and whose prostate cancer would otherwise be managed by watchful waiting or surveillance). The maximal period of treatment with study drug varied in each of the studies. In Trial 23, treatment was limited to a maximum of 2 years or until objective disease progression (whichever occurred first). In

Trial 25, patients were to be treated indefinitely or until progression of disease. In Study 24, patients with prior therapy (adjuvant patients) were to be treated for a maximum of 5 years. Patients in each of the clinical trials were to have a bone scan at 2 years after enrollment unless objective progression of their disease had been confirmed prior to this time.

Table 2 Overview of Phase III Clinical Trials (Similarities and Differences)

Design Element	Trial 23 North America	Trial 24 Europe, South Africa, Israel, Mexico, Australia	Trial 25 Scandinavia
Double-blind, placebo controlled	Yes	Yes	Yes
Number of patients randomized	3292	3603	1218
Tumor staging criteria	T1b-T4, N0 or NX (N+ excluded), M0	T1b-T4, any N, M0	Same as 0024
Permitted standard care			
Radical prostatectomy or radiotherapy	Yes	Yes	Yes
Watchful waiting	No	Yes	Yes
Intended period of randomized treatment	2 yr.	5 yr. for adjuvant patients Until progression in non adjuvant patients	Until progression for all patients
2-yr. bone scan to determine progression	Yes	Yes	Yes
Follow-up for progression and survival	Yes ¹	Yes	Yes

¹ Monitored only for survival and serum PSA. Bone scans to be obtained at discretion of Investigator.

4.3.2 Study Objectives

The primary and secondary objectives of the 3 clinical trials are listed in Table 3. They were very similar across the 3 trials with some exceptions. Survival was a secondary objective in Trial 24 instead of a primary objective as in Trials 23 and 25. Sexual satisfaction was assessed only in Study 25.

Table 3 Primary and Secondary Objectives of the Clinical Trials**Primary Objectives:**

- To compare Casodex 150 mg once daily with placebo in terms of time to objective progression
- To compare Casodex 150 mg once daily with placebo in terms of overall survival ¹
- To evaluate the tolerability of Casodex 150 mg compared with placebo ²

Secondary objectives:

- To compare Casodex 150 mg once daily with placebo in terms of time to treatment failure
- To compare Casodex 150 mg once daily with placebo in terms of the time for prostate specific antigen (PSA) to double
- To assess sexual function using the Golombok Rust Inventory ³

¹ Secondary objective in Study 24.² Secondary objective in Study 23.³ Included only in Study 25.**4.3.3 Study Patients and Enrollment Criteria**

Only patients with non-metastatic prostate cancer (Stage M0) were potentially eligible for enrollment in the clinical trials. Entry criteria were generally similar across the 3 clinical trials although there were some significant differences, particularly in the entry criteria for Trial 23 compared to those for Trials 24 and 25. These differences included exclusion of patients from Trial 23 who (1) had positive local or regional lymph nodes and (2) had not undergone either a radical prostatectomy or radiation therapy with the expectation that the procedure would be curative. Thus patients who had not received active therapy for their prostate cancer (patients initially managed by watchful waiting) were excluded from Trial 23.

Inclusion Criteria Included

- Histologically or cytologically confirmed adenocarcinoma of the prostate gland
- Clinical or pathological stage T1b, T1c, T2, T3, or T4 disease
- No distant metastases (Stage M0) as confirmed by a negative bone scan
- Any N (local nodal status) for Studies 24 and 25; only N0 for Study 23
- For Study 23 only, patient must have received one of the following:
 - a radical prostatectomy (nerve or non-nerve sparing) defined as the total extirpation of the prostate including the seminal vesicles performed within 16 weeks before randomization
 - radiation to the prostate initiated within 16 weeks before randomization
- At least 18 years of age
- Informed consent to participate in the trial

Exclusion Criteria Included

- Previous systemic therapy for prostate cancer other than neoadjuvant therapy prior to primary therapy of curative intent or therapy with 5-alpha-reductase inhibitors
- History or presence of another malignancy within the last 5 years, other than prostate cancer or treated squamous/basal cell carcinoma of the skin

- A serum bilirubin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) concentration >2.5x the upper limit of normal (World Health Organization grade 2 toxicity)
- Any physical or mental condition which, in the opinion of the investigator, might interfere with the patient's ability to comply with scheduled visits and assessments
- For Study 23 only:
 - A patient whose prostate cancer was not confined to the surgical specimen
- For Study 25 only:
 - Patients for whom long-term therapy was considered inappropriate because of their expected survival times (i.e., patients with undetectable PSA levels and negative margins following radical prostatectomy or radiotherapy to the prostate bed)

Medical Officer's Comments

- *Although the inclusion and exclusion criteria were identical for the most part, the few differences across studies had the potential to have a significant effect on the outcomes of the respective studies.*
- *In Trial 25, exclusion of patients with negative PSA values or negative tissue specimen margins after prostatectomy would likely have excluded virtually all surgically treated patients with early or localized prostate cancer. In contrast, patients with early or localized disease comprised the majority of patients enrolled into Trial 23.*

4.3.4 Study Drugs

4.3.4.1 Rationale for Choice of Comparator

According to the Sponsor, it was not common clinical practice or established policy at the time that these trials were initiated, to use immediate rather than deferred therapy in patients with localized disease. There also was not a consensus of opinion on the use of hormonal therapy as adjuvant therapy following radical prostatectomy or radiation treatment for localized disease. The Sponsor therefore chose to compare the effects of treatment with Casodex to those of treatment with placebo.

Medical Officer's Comments

- *Use of placebo therapy as the comparator for patients with localized disease, treated by either prostatectomy or radiation therapy, was a reasonable decision as no therapy has been shown to be of benefit in this population.*
- *The use of placebo for locally advanced disease in patients who were to receive no active therapy is more controversial as such patients are not generally managed by watchful waiting in the US. However, watchful waiting as initial management for such patients outside of the US, particularly in Scandinavia, is not uncommon.*

4.3.4.2 Rationale for Dose Selection of Casodex

The applicant had previously conducted a series of dose-ranging trials with Casodex (Trials 0002, 0003, and 0005) to identify the lowest dose of Casodex that appeared to exert maximal anti-androgenic effects. In these studies, the percentage inhibition of PSA was used

as a measure of the anti-androgenic effect of Casodex. Following 3 months of administration, Casodex doses of 100 to 200 mg produced the maximal suppression of serum PSA. Doses of 100 mg and 150 mg were subsequently selected for comparison with castration in a Phase III clinical program (Trials 0306 and 0307) that were conducted in support of an earlier application (NDA 20-498/s006). Based on a planned, early evaluation of these 2 doses, Casodex 150 mg per day was selected for (1) continued evaluation in these latter 2 trials and (2) the early prostate cancer program (Trials 23, 24, and 25 in the present application).

Medical Officer's Comments

- *Based on the results of these earlier trials, the use of Casodex 150 mg per day is a reasonable dose for Clinical Trials 23, 24, and 25.*

4.3.4.3 Assignment to Study Drug and Treatment Schedules

Randomized study drugs were administered in tablet form as a once daily oral dose and were supplied as white tablets containing either 150 mg of Casodex or placebo. Patients were randomly assigned in a 1:1 ratio to treatment with either Casodex or placebo. Treatment was to be initiated as soon as possible after randomization, but in no case was this period to exceed 2 weeks. Treatment with study drug initially was to be for 2 years in all 3 of the clinical trials. Prior to the first patient completing 2 years of treatment, the Data and Safety Monitoring Committee (DSMC) reviewed the blinded patient safety data across the whole program. The DSMC concluded that both treatments (Casodex and placebo) were well tolerated and that there were no safety concerns to prevent treatment of patients beyond 2 years (96 weeks) in any of the trials. However, the final decisions regarding extending treatment beyond 2 years differed for each of the 3 trials. These differences were based, according to the Sponsor, upon investigator preferences.

Trial 23. It was decided that treatment would not extend beyond 2 years as the investigators thought this treatment period was sufficient for the study population.

Trial 24. It was decided that adjuvant patients (patients who had initially received primary treatment by either radical prostatectomy or radiation therapy) would continue to receive blinded treatment for a total of 5 years. However, therapy in these patients could continue treatment beyond 5 years based at the individual investigator's discretion. For other patients (i.e., those initially managed by watchful waiting), there would be no limit on the duration of treatment. For both groups of patients, it also was recommended that treatment with study drug be discontinued if objective disease progression was documented or if a patient reached any treatment failure endpoint as defined in Section 4.5.2.

Study 25. It was decided that all patients would continue to receive randomized treatment until they had reached a treatment failure endpoint.

Until such time as objective disease progression had been documented, patients were not to receive any systemic treatment other than randomized study therapy. If the investigator considered that it was in the patient's best interest to initiate alternative systemic therapy for prostate cancer before progression had been documented, this was considered a treatment failure, and the patient's randomized therapy was to be discontinued.

Medical Officer's Comment

- *Although assignment to treatment was randomized and blinded, it was unlikely that treatment assignments were actually blinded because of the pharmacological actions of Casodex. Patients receiving Casodex were much more likely to develop gynecomastia and/or breast pain in contrast to placebo-treated patients. In addition, Casodex-treated patients (but not placebo-treated patients) who had detectable PSA values at randomization were likely to show a decrease in PSA values.*

4.4 Study Procedures and Study Conduct

4.4.1 Schedule of Study Assessments and Procedures

The schedule for study assessments and procedures is summarized in Table 4. During the baseline or screening period, a potential patient's eligibility for participation was determined according to the inclusion and exclusion criteria described in Section 4.3.3). Baseline assessments included a physical examination and medical history, a bone scan if not previously performed within the prior 24 weeks (later amended to 30 weeks), measurements of serum PSA and liver transaminases, and completion of the Golombok Rust Inventory of Sexual Satisfaction (GRISS) questionnaire (Trial 25 only).

Study Weeks 1-96

During the first 96 weeks of each clinical trial, patients were to be assessed every 12 weeks for clinical evidence of disease progression and monitoring of liver function and adverse events. A bone scan to detect distant metastases of prostate cancer was to be performed at Week 96 in all patients (regardless of treatment status) unless the patient previously had had a positive on-treatment bone scan. Patients in Trial 25 also completed the GRISS questionnaire at Weeks 12, 24, 36, and 48. Patients who terminated treatment prior to Week 96 for a reason other than objective disease progression were to continue with clinical visits every 12 weeks for monitoring for clinical disease progression and measurement of serum PSA. Following documentation of objective disease progression, patients were to be assessed every 24 weeks for survival.

Table 4 Schedule of Study Assessments and Procedures

Procedure	Weeks after randomization											
	Baseline	Wk 12	Wk 24	Wk 36	Wk 48	Wk 60	Wk 72	Wk 84	Wk 96	After Early Termination ¹	Post Wk 96 ^{1a}	
Physical examination	X ²	X	X	X	X	X	X	X	X	X	X	
Bone scan	X ³								X ^{3a}			X ⁴
PSA ⁵	X	X	X	X	X	X	X	X	X	X	X	X ⁵
ALT, AST, bilirubin	X	X	X	X	X	X	X	X	X			
Assess for clinical progression ⁶		X	X	X	X	X	X	X	X	X	X	X
GRISS questionnaire ⁷	X	X	X	X	X							
Adverse events		X	X	X	X	X	X	X	X	X	X	
Concomitant therapy	X	X	X	X	X	X	X	X	X			
Daily dosing with Study Drug ⁸		X	X	X	X	X	X	X	X			X

1. Patients were to be assessed every 12 weeks until progression irrespective of whether they had stopped randomized treatment; following progression, patients were to be assessed every 24 weeks.
- 1a In Trial 23, patients were to have clinical visits every 6 months through 4 years post randomization and annually thereafter until death. In Trials 24 and 25, patients were to continue to have a clinic visit every 12 weeks while continuing to receive randomized treatment. Following discontinuation of randomized treatment or documentation of disease progression, patients were to have a clinic visit every 6 months until death.
2. Included demographic and medical history at baseline visit.
3. To be performed within 24 weeks (Trials 24 and 25) or 30 weeks (Trial 23) before randomization.
- 3a. All patients were to have a bone scan at Week 96 unless they previously had had an on-treatment positive bone scan documenting progression of disease.
4. Additional assessments performed every 96 weeks thereafter for Trials 24 and 25 only.
5. PSA measurements were to be obtained (1) at each 12-week clinical visit until disease progression in Trials 24 and 25 or (2) at each 6-month or annual clinical visit until disease progression in Trial 23.
6. Patients were assessed, as warranted by clinical symptoms and findings, for local and regional disease and distant metastases at each clinical visit until objective progression was documented.
7. Golombok Rust Inventory of Sexual Satisfaction (GRISS). Performed only in Trial 25.
8. In all trials, dosing with blinded study drug was to continue through Week 96 or until objective progression of disease. Dosing in Trial 23 was limited to a maximum of 2 years. In Trials 24 and 25, dosing was to continue through 5 years (adjuvant group in Trial 24) or indefinitely (all other groups) or until objective disease progression.

After Study Week 96

Trial 23. Treatment with study drug was limited to 96 weeks in Trial 23. Subjects who completed 96 weeks of treatment without documented evidence of clinical progression were to be contacted every 3 months thereafter. In addition, they were to have a clinical visit every 6 months for a physical examination and PSA assessment, up to and including Month 48 and annually thereafter. A bone scan also was to be performed at the discretion of the investigator if progression was suspected. Subjects who had documented evidence of clinical progression were to be contacted every 3 months to determine their survival status.

Trials 24 and 25. Treatment with study drug was to continue for at least 5 years or until disease progression in Trials 24 and 25 (See Section 4.3.4.3 for further details). During treatment with randomized therapy, patients were to continue to have clinical visits every 12 weeks. At each visit, they were to be assessed for clinical progression of disease and adverse events. A blood specimen for the measurement of PSA, ALT, AST, and bilirubin concentrations was to be collected. In addition to the assessments performed every 12 weeks, a repeat bone scan was to be performed every 96 weeks, or earlier, if warranted by clinical findings until objective progression of disease was documented.

Following discontinuation of treatment with study drug, patients were to be seen in the clinic every 24 weeks until objective disease progression and/or death. Patients who had gynecomastia or breast pain at termination of treatment with study drug, were to be assessed for improvement or resolution of these signs or symptoms at each post treatment visit.

Medical Officer's Comment

- *Not requiring bone scans at 2 year intervals after Week 96 in Trial 23, is a significant problem in the design of this Trial. Since these patients had minimal disease at entry and have shown a very low rate of disease progression (see Section 4.6.3.1), failure to require bone scans at 2-year intervals as in Trials 24 and 25 markedly limits the likelihood that a benefit for treatment with Casodex will be demonstrated.*

4.4.2 Efficacy Assessments

At each clinical visit, patients were assessed for signs of disease progression. These assessments included a physical examination and measurement of serum PSA concentration. These assessments were performed every 12 to 24 weeks in accordance with the schedule of assessments listed in Table 4. In addition, bone scans were to be performed at Study Week 96 if objective disease progression (as defined below) had not been documented previously. Evidence of disease progression (either local or distant progression) was classified by the Sponsor as either objective or non-objective depending upon the clinical or laboratory method of documentation.

4.4.2.1 Objective Progression

Imaging procedures or biopsy. Objective progression required confirmation of disease progression by either an imaging procedure (e.g., bone scan, x-ray, magnetic resonance imaging, computerized tomography, or ultrasonography) or biopsy.

Medical Officer's Comment

- *With the exception of death due to prostate cancer, disease progression documented by bone scan was considered by this reviewer and other Medical Officers both within*

DRUDP and the Division of Oncology Drug Products to be the most clinically significant evidence of disease progression.

4.4.2.2 Non-objective Progression

Signs and Symptoms. Non-objective progression included signs or symptoms that were compatible with disease progression (e.g., ureteral obstruction, lymphedema of the lower extremities, vesical obstruction) but which were not confirmed by an imaging procedure or biopsy. Investigators were instructed to confirm non-objective progressive events by an objective procedure whenever possible.

Serum PSA. Increases in serum PSA values by themselves were not considered to be objective evidence of disease progression. PSA samples obtained at baseline (immediately prior to randomization) and following randomization were, for the most part, measured at one of two central laboratories using the Hybritech™ Assay. For Trial 23, PSA assays were performed at Quest Diagnostics (formerly SmithKline Beecham Laboratories), Clinical Trials Center, Van Nuys, CA. For Trials 24 and 25, PSA assays were performed at AstraZeneca's Central Laboratory, Mereside, Alderley Park, Cheshire, UK. PSA samples obtained prior to radical prostatectomy or radiation therapy (i. e., prior to screening for enrollment into the clinical trials) may have been analyzed by other assay procedures at the respective study site.

4.4.2.3 Bone Scans

In each of the clinical trials, a bone scan was to be obtained at Study Week 96 or sooner if warranted by the patient's symptoms or clinical findings. If a bone scan was obtained prior to Week 96 for clinical reasons and was found to be negative, the bone scan was to be repeated at Study Week 96. All bone scans were performed at the study sites and read locally.

Medical Officer's Comments

- *It was likely that blinding of treatment assignment would not be maintained for many patients because of the high incidence of gynecomastia and breast pain and decrease in serum PSA concentrations in Casodex-treated patients; consequently, there was concern that local readings of bone scans could be biased. The Division requested that the bone scans be reread by a group of blinded reviewers at a central facility.*
- *Based on this request, the sponsor proposed that all positive scans and a representative subset of negative scans would each be reread by at least 2 blinded reviewers at a central facility (Columbia Presbyterian Medical Center, New York). The objective of the blinded, central reread would be to assess the potential for bias in the Sponsor's primary analysis of time to objective disease progression. The procedures employed and the outcome of the central reread are described in Section 4.6.3.8.*
- *Details of the conduct of the central reread are provided in the separate review of Robert Yaes MD, Medical Officer, Division of Medical Imaging and Radiological Drug Products (HFD 160).*

4.5 Efficacy Endpoints and Analyses

The primary and secondary efficacy endpoints in each of the 3 clinical trials and in the sponsor's combined analysis are listed in Table 5. They were identical in each of the trials with one exception, time to death was a secondary endpoint in Trial 24 but a primary endpoint in Trials 23 and 25 as well as in the combined analysis. Each of these endpoints is described further in Sections 4.5.1 and 4.5.2. The Sponsor chose a data cutoff date of 2 June 2000 for efficacy data, which allowed (according to the Sponsor) for at least 2 years of follow up after randomization for each patient in each clinical trial.

Table 5 Summary of Primary and Secondary Endpoints and Analyses

Endpoint	Definition	Trial			Com- bined ¹
		23	24	25	
		Primary or Secondary ²			
Time to objective progression³	Time from randomization to: 1. Objectively confirmed progression 2. Death in the absence of objectively confirmed progression	1°	1°	1°	1°
Time to death (overall survival)	Time from randomization to death from any cause	1°	2°	1°	1°
Time to treatment failure	Time from randomization to the first of: 1. Additional systemic therapy or radiotherapy 2. Withdrawal of trial therapy 3. Objective progression 4. Death from any cause	2°	2°	2°	2°
Time to PSA doubling	Time from randomization to the first of: 1. An increase of serum PSA to twice that at randomization 2. Objectively confirmed progression 3. Death from any cause	2°	2°	2°	2°

¹ Sponsor's combined analysis for Trials 23 + 24 + 25.

² 1° = primary endpoint; 2° = secondary endpoint.

³ Objectively confirmed progression = local or distant progression of disease confirmed by bone scan, x-ray, CT scan, magnetic resonance imaging, ultrasonography, or biopsy.

4.5.1 Primary Efficacy Endpoints and Analyses

Objective progression. Objective progression, as defined previously in Section 4.4.2.1, was examined in each of the clinical trials and in the combined analyses. Time to objective progression (TTP) was defined as the number of days between randomization and the documented date of objective progression or death (by any cause in the absence of objective disease progression).

Overall survival (time to death). Time to death (TTD) was a primary efficacy endpoint in 2 of the 3 clinical trials (Trials 23 and 25) and in the Sponsor's combined analysis. Time to death was defined as the number of days between randomization and the documented date of the patient's death from *any cause*.

Medical Officer's Comments

- *Although treatment assignment was to be blinded, it was recognized by both the Sponsor and the Division that there could be assessment bias in a time-to-event analysis. The basis for this potential bias was related to the high incidence of gynecomastia and breast pain and lower serum PSA values in Casodex-treated patients. Because of this concern, the Division requested, and the Sponsor provided, additional binary analyses for objective progression based on the incidence of bone scan confirmed progression or death in the absence of progression within 2 years of randomization. The 2-year time point was selected because all patients were to have a bone scan at 2 years per protocol unless objective progression had previously been documented.*
- *The Study Protocols did not provide specific criteria by which to judge whether local progression had occurred. No instances of progression, with the exception of selected bone scans that were reviewed centrally, were reviewed by a central, blinded panel. The possibility of local bias in these other assessments of disease progression cannot be excluded.*

4.5.2 Secondary Efficacy Endpoints and Analyses

Secondary efficacy endpoints were time to treatment failure and time to a PSA doubling event.

Time to treatment failure (TTF). Time to treatment failure was defined as the number of days from the date of randomization until the earliest of the following events:

- death from any cause
- objective progression of disease
- withdrawal of trial therapy
- administration of an additional systemic therapy or radiotherapy for prostate cancer

The reason for treatment failure was defined as the first of these events to occur.

Time to a PSA doubling event (TTPSAd). Time to a PSA doubling event was defined as the number of days from the date of randomization until the earliest of the following events:

- PSA sample time at which PSA had doubled compared with the value recorded immediately prior to randomization
- time of objective disease progression
- time of death.

4.5.3 Overview of Statistical Analyses

4.5.3.1 Efficacy Population

Efficacy data were analyzed on an intent-to-treat (ITT) basis (analyzed as randomized). Therefore, all randomized patients with data were included in the efficacy analyses

regardless of whether the patient had met all the entry criteria (protocol violations), had departed from the protocol design or procedures after entry into the trial (protocol deviations), had not received randomized therapy, or had received subsequent non-randomized prostate cancer therapy.

4.5.3.2 Sponsor's Analyses of Primary Efficacy Endpoints

Time to objective progression was analyzed for each individual trial and for pooled data from all 3 contributing trials. The analyses were achieved by fitting a Cox proportional hazards regression model to the data. Terms were fitted allowing for the effects of randomized treatment and the following covariates:

- Trial
- PSA concentrations
- Stage of prostate cancer
- Previous therapy of curative intent
- Gleason category

From the model including these main effects, the hazard ratio (Casodex/placebo) was estimated together with its associated 95% confidence interval and p-value. Data also were displayed graphically using Kaplan-Meier plots. For the purpose of the analyses, only patients with objectively confirmed disease progression (positive bone scan or other objective event) or who had died (from any cause) in the absence of objective progression were considered to have had disease progression.

Medical Officer's Comments

- *The Sponsor claimed that a combined analysis of all 3 contributing trials was justified for the following reasons: (1) the trials were of similar statistical design; (2) they recruited patients with overlapping demographic characteristics via similar inclusion/exclusion criteria, and (3) they assessed identically-defined efficacy endpoints of time to objective progression, survival, and time to treatment failure.*
- *Although the inclusion/exclusion criteria were similar across the 3 clinical trials, review of the demographic and baseline disease characteristics disclosed significant differences between Trial 23 (North American Trial) and Trials 24 and 25; consequently, both the medical and statistical reviewers do not believe that a combined efficacy analysis that includes Trials 23, 24, and 25 is appropriate. Specific differences among the study populations are described in Section 4.6.2.*

4.5.3.3 FDA Requested Analyses

The FDA requested that the primary analyses for disease progression utilize only the results of (1) bone scans obtained at the protocol-mandated 2-year time point and (2) death in the absence of progression within 2 years of randomization as these endpoints were least likely to be influenced by potential bias. The results the FDA-requested analyses (i.e., the proportion of patients with disease progression or death **at 2 years after randomization**) as well as analyses based on bone scan documented progression or death in the absence of objective progression **within 2 years of randomization** were provided. The Sponsor stated in the Application that the within 2 years of randomization was the more appropriate analysis. The rationale for the Sponsor's position was that in accordance with the protocol, bone-scans

could be taken at times prior to the 2-year time point if clinically indicated. If the bone scan was positive, these patients were not required to have another bone scan at the 2-year time point. Such patients would therefore be incorrectly classified in the analyses as not having had objective progression of disease if a strict definition of “at 2 years after randomization” was employed.

The results of these analyses were expressed in terms of an odds ratio of Casodex relative to placebo, together with the associated 95% confidence limits and p-value. Results also were expressed in terms of relative risk and simple incidence rates. Confidence intervals for relative risks also were calculated.

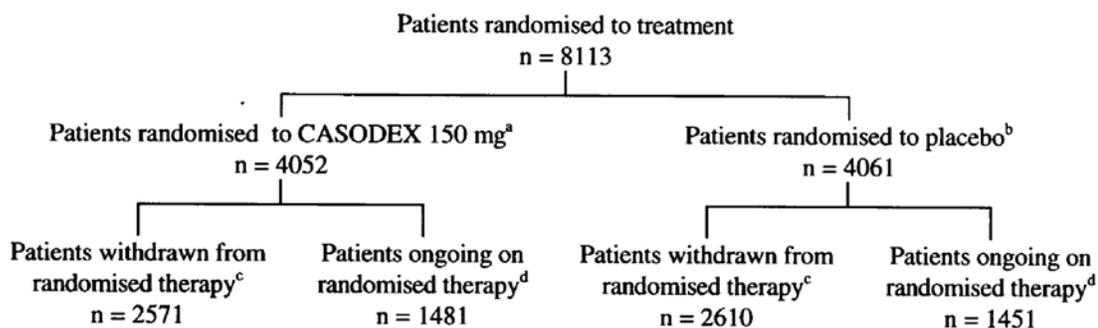
Medical Officer’s Comments

- *This Medical Officer concurs with the Sponsor that the more appropriate analysis is that which included events that occurred **within 2 years of randomization** and not only those events that were based on the protocol mandated bone scan at 2 years post randomization.*
- *The actual statistical analyses employed by the Sponsor used a window of 2 years plus 6 months both for bone scan documented progression and death. The rationale for this window was that some protocol mandated 2-year bone-scans were actually obtained a short time after 2 years from randomization. For consistency, deaths in the absence of bone-scan progression occurring within 2 years plus 6 months of randomization also were included in the analyses. This reviewer believes that the Sponsor’s rationale for extending the period of assessment from 2 years to 2 years plus 6 months is acceptable.*

4.6 Results

4.6.1 Enrollment and Patient Disposition

A total of 8113 patients were randomized to treatment in the 3 clinical trials that were submitted in support of this Application. Of these, 4052 patients were randomized to receive Casodex 150 mg per day and 4061 patients were randomized to receive placebo. The disposition of the patients at the time of the efficacy data cutoff (2 June 2000) is shown in Figure 1.

Figure 1 Efficacy Analysis Population and Treatment Status at Time of Data Cutoff

^aThirty patients randomised to CASODEX received no trial therapy.

^bThirty patients randomised to placebo received no trial therapy.

^cIncludes patients who did not receive trial therapy and patients who completed the scheduled 2-year dosing period in Trial IL0023.

^dAt the data cut-off date of 2 June 2000.

A total of 3292, 3603, and 1218 patients were randomized to treatment in Trial 23, Trial 24, and Trial 25, respectively. The first patients were enrolled in August 1995 (Trial 23), September 1995 (Trial 24), and October 1995 (Trial 25). The last patients were enrolled in August 1997 (Trial 23) and July 1998 (Trials 24 and 25). The clinical trials included a total of 349 investigative sites (Trial 23: 96 sites; Trial 24: 191 sites; and Trial 25: 62 sites). Each of the trials was conducted in a different geographic area. Trial 23 was conducted in North America, with approximately 90% of patients from the United States and the remainder from Canada. Trial 24 was conducted in Europe (other than Scandinavia), South Africa, Israel, Mexico, and Australia. Trial 25 was conducted in Scandinavia (Denmark, Finland, Norway, and Sweden). Table 1 lists the number of patients enrolled in each country in each of the clinical trials.

Patient enrollment and patient status (i.e., terminated treatment prematurely, completed treatment, or continuing treatment) in each of the 3 trials as of 2 June 2000 (efficacy data cutoff date) is summarized in Table 6. In Trial 23, treatment was limited to a maximum of 2 years and the maximum treatment period for all patients had been reached by 2 June 2000. Thirty eight percent (38%) of patients in the Casodex group and 20.2% of patients in the placebo group terminated treatment before completing 2 years. In Trials 24 and 25, treatment was on going at the time of data cutoff. In Trial 24, 40.3% and 37.2% of the patients in the Casodex and placebo treatment groups had terminated treatment as of 2 June 2000. In Trial 25, 31.9% and 47.0% of the patients in the Casodex and placebo treatment groups had terminated treatment as of 2 June 2000.

Table 6 Patient Enrollment and Treatment Status as of June 2, 2000¹

	Trial 23		Trial 24		Trial 25	
	Casodex	Placebo	Casodex	Placebo	Casodex	Placebo
Number of patients randomized	1647	1645	1798	1805	605	611
Number of patients treated	1627	1627	1790	1795	605	609
Patient disposition						
Terminated prematurely (% of pt.) ^{2, 4}	38.0%	20.2%	40.3%	37.2%	31.9%	47.0%
Completed treatment (Trial 23 only) or treatment ongoing (% of pt.) ^{3, 4}	62.0%	79.8%	59.7%	62.8%	68.1%	53.0%

1. June 2, 2000 was the efficacy data cutoff date.

2. Includes patients withdrawn from treatment because of disease progression, adverse events, need for prohibited therapy and other reasons.

3. Treatment period in Study 23 was up to a maximum of 2 years; treatment period in Trial 23 completed prior to June 2, 2000.

4. Percentages based on number of patients treated (i.e., those who received study drug).

Source: Text Table T3.8 (Final Study Reports for Trials 23, 24, and 25).

Patient exposure to randomized study drugs and follow up times for disease progression in each of the clinical trials is summarized in Table 7. Median patient exposure to study drug ranged from 1.8 years in Trial 23 (Casodex and placebo treatment groups) to 2.5 years in Trial 25 (Casodex treatment group). Median patient years of follow up for disease progression and survival (efficacy analyses) were 3.2 years (Trial 23), 2.6 years (Trial 24) and 3.0 years (Trial 25).

Table 7 Patient Years of Exposure to Study Drug and Follow-up¹

	Trial 23		Trial 24		Trial 25	
	Casodex	Placebo	Casodex	Placebo	Casodex	Placebo
Patient exposure to study drug						
Total pt yr.	2276	2660	3820	4024	1531	1419
Median pt yr.	1.8	1.8	2.2	2.3	2.5	2.3
Follow up for progression and survival						
Total pt yr.	5430	5428	4817	4811	1807	1794
Median pt yr.	3.2	3.2	2.6	2.6	3.0	3.0

1. As of efficacy data cutoff date of June 2, 2000.

Source: Tables T5.1.1 and T5.2.1 from Final Study Reports for Trials 23, 24, and 25.

4.6.2 Demographics and Baseline Disease Characteristics

4.6.2.1 Baseline Demographics

Baseline demographic characteristics for each of the 3 trials are summarized in Table 8. Mean treatment group ages at enrollment ranged from 64.4 and 64.5 years (Trial 23) to 68.6 and 68.7 years (Trial 24). Individual patient ages ranged from 38 years to 93 years. Mean treatment group weights ranged from 77.3 and 78.1 kg in Trial 24 to 85.4 and 84.6 kg in Trial 23.

Medical Officer's Comments

- *Within each trial, demographic characteristics in the Casodex and placebo treatment groups were well balanced. In general, demographic characteristics across Trials 24 and 25 were very similar but differed somewhat from those in Trial 23.*
- *Patients in Trial 23 tended to be younger (mean difference about 4 years) than those in Trials 24 and 25. Approximately 45% of patients in Trial 23 were less than 65 years old compared to approximately 25% of patients (Trial 24) or <20% of patients (Trial 25).*
- *The mean weights of patients in Trial 23 were approximately 4-6 kg greater than those of patients in Trials 24 and 25.*
- *Approximately 11.5% of patients in Trial 23 were black in contrast to < 1% and 0% in Trials 24 and 25, respectively.*

Table 8 Baseline Demographic Characteristics (Trials 23, 24, and 25)

Demographic Characteristic	Trial 23		Trial 24		Trial 25	
	Casodex (N=1647)	Placebo (N=1645)	Casodex (N=1798)	Placebo (N=1805)	Casodex (N=607)	Placebo (N=611)
Age (yr.)						
Mean	64.5	64.4	68.6	68.7	68.5	68.5
Range	42 to 85	38 to 83	42 to 93	46 to 93	46 to 87	52 to 77
Age Distribution (n,%)						
<55 yr.	151 (9.2)	155 (9.4)	62 (3.4)	51 (2.8)	10 (1.6)	4 (0.7)
55 to < 65 yr.	614 (37.3)	607 (36.9)	422 (23.5)	432 (23.9)	99 (16.3)	113 (18.5)
65 to <75 yr.	780 (47.4)	785 (47.7)	936 (52.1)	934 (51.7)	475 (78.3)	468 (76.6)
≥75 yr.	102 (6.2)	98 (6.0)	378 (21.0)	388 (21.5)	23 (3.8)	26 (4.3)
Weight (kg)						
Mean	85.38	84.60	77.28	78.08	79.31	80.61
Range	49 to 166	46 to 160	45 to 132	40 to 135	46 to 143	48 to 125
Race (n, %)						
White	1369 (83.1)	1391 (84.6)	1714 (95.3)	1709 (94.7)	606 (99.8)	607 (99.3)
Black	191 (11.6)	188 (11.4)	17 (0.9)	13 (0.7)	0	0
Other	87 (5.3)	66 (4.0)	67 (3.7)	83 (4.6)	1 (0.2)	4 (0.7)

Source: Text table 4, pg. 29, ISE.

4.6.2.2 Baseline Disease Characteristics

Baseline disease characteristics (other than serum PSA values) in each of the 3 trials are summarized in Table 9. The distribution of disease characteristics is expressed in terms of percentage of patients with the specific characteristic in each category. Within each of the individual trials, baseline disease characteristics were well balanced across the Casodex and placebo treatment groups. In each of the trials, more than 50% of patients had Stage T1/T2 disease (early or localized disease). A slightly greater percentage of patients in Trial 24 (approximately 35%) and Trial 25 (approximately 40%) had Stage T3/T4 disease (locally advanced disease) than in Trial 23 (less than 30%). Based on reported Gleason scores, a greater percentage of patients in Trial 23 (47-48%) had poorly differentiated tumors (Gleason

scores of 7-10) than in either Trial 24 (26-27%) or Trial 25 (11-12%). In accordance with the inclusion criteria for Trial 23, all patients had received prior therapy of curative intent with approximately 80% of patients having had a radical prostatectomy. In contrast, 35-37% of patients in Trial 24 and 80-83% of patients in Trial 25 were being managed by watchful waiting (i.e., had not had therapy) prior to randomization.

Table 9 Disease Characteristics at Baseline

Characteristic	Percentage of patients within each category					
	Study 23		Study 24		Study 25	
	Casodex (N=1647)	Placebo (N=1645)	Casodex (N=1798)	Placebo (N=1805)	Casodex (N=607)	Placebo (N=611)
Tumor stage: T category						
T1	9.6	9.7	25.5	25.2	19.8	22.4
T2	62.7	63.2	38.8	41.1	39.7	38.1
T3	27.4	26.9	33.2	31.2	38.9	37.0
T4	0.2	0.2	2.6	2.5	1.5	2.3
Gleason score						
Well differentiated (2,3,4)	4.2	4.8	31.0	31.2	42.7	43.2
Moderately differentiated (5,6)	47.9	48.5	40.5	41.1	43.7	45.2
Poorly differentiated (7,8,9,10)	47.9	46.7	26.7	26.1	11.9	11.1
Lymph node category						
N-	72.0	71.2	61.3	60.4	21.7	20.0
N+	0.1	0.0	2.6	2.7	4.6	4.3
NX	27.9	28.8	36.0	36.9	73.6	75.8
Previous therapy						
Radical prostatectomy	80.3	80.5	46.4	45.0	13.0	13.1
Radiotherapy only	19.7	19.5	18.6	18.0	6.4	4.3
Watchful waiting	0.0	0.0	34.9	36.9	80.1	82.7

Source: Text table 5, pg. 30, ISE

Median serum PSA concentrations, both prior to prostatectomy or radiation therapy in patients who had had prior active therapy and at the time of randomization in all patients, are listed in Table 10 for each of the trials. Median serum PSA values prior to prostatectomy or radiation ranged from 7.1 µg/L in Trial 23 to 17.0 µg/L in Trial 25. Median pre-randomization serum PSA values were lowest in patients who had been treated by radical prostatectomy (median range: below the limit of detection [NQ, Trials 23 and 24] to 1.2 µg/L [Trial 25]) and highest in patients managed by watchful waiting (median range: 11.0 µg/L [Trial 24] to 17.8 µg/L [Trial 25]). Within each initial treatment group, median serum PSA concentrations at randomization tended to be lowest in Trial 23 (or Trial 24 for watchful waiting patients) and highest in Trial 25.

Table 10 Serum PSA (Prior to Prostatectomy or Radiotherapy and/or at Randomization)

Time of Measurement or Pre-randomization Group	Trial 23		Trial 24		Trial 25	
	Casodex	Placebo	Casodex	Placebo	Casodex	Placebo
PSA ($\mu\text{g/L}$) prior to prostatectomy or radiation therapy						
Number patients ¹	1578	1581	1152	1122	109	99
Median PSA	7.1	7.1	12.0	11.5	17.0	16.0
PSA ($\mu\text{g/L}$) at time of randomization						
Prostatectomy patients						
Number patients	1312	1316	800	795	78	78
Median PSA	NQ ²	NQ	NQ	NQ	1.2	1.1
Radiotherapy patients						
Number patients	323	317	330	310	39	25
Median PSA	2.9	3.0	3.5	3.4	8.2	8.0
Watchful waiting patients						
Number patients	0	0	604	642	483	497
Median PSA	--	--	11.0	11.6	16.6	17.8
All treatments (all patients)						
Number patients	1635	1633	1734	1748	603	600
Median PSA	NQ	NQ	1.3	1.3	12.6	13.8

1. Number of patients for whom PSA values were available.

2. NQ = non quantifiable (i.e., below the minimal detectable value).

Source: Text table 7, pg. 32, ISE.

Medical Officer's Comments

- *Within each of the individual trials, baseline disease characteristics were well balanced across the Casodex and placebo treatment groups although there were significant differences across the 3 trials, particularly between Trial 23 and Trials 24 and 25.*
- *The most surprising difference between Trial 23 and Trials 24 and 25 was the low percentage of patients in Trials 24 and 25 with poorly differentiated tumors (Gleason grades of 7-10). Based on the observed incidence of positive bone scans at Study Year 2 (higher in Trials 24 and 25 than in Trial 23), one would have anticipated a higher percentage of poorly differentiated tumors in Trials 24 and 25 than in Trials 23.*
- *Trials 24 and 25, but not Trial 23, allowed the enrollment of patients who were being managed by watchful waiting. Although it is estimated that 10% or less of men with prostate cancer in the United States are managed by watchful waiting, this is a more frequently employed therapeutic option in other countries. In Trials 24 and 25, approximately 35% and 80% of patients, respectively, were initially managed by watchful waiting and received only Casodex monotherapy for treatment of their prostate cancer.*

4.6.3 Primary Efficacy Outcomes

In the following Section on primary efficacy outcomes, the Sponsor's preferred endpoints and the outcomes related to these endpoints are first presented and reviewed. This is

followed by presentation and review of the efficacy outcomes based on the FDA-requested endpoints and analyses. The FDA-requested analyses were performed, for the most part, by the Sponsor.

4.6.3.1 Objective Disease Progression or Death in Absence of Progression (Sponsor's Preferred Endpoints and Analyses)

Objective disease progression or death in the absence of objective progression in each of the clinical trials is summarized in Table 11. This Table lists by trial and treatment group the total number (%) of patients with (1) a positive bone, (2) other objective events classified as disease progression by the Sponsor, and (3) death in the absence of objective progression. The percentage of patients with bone scan confirmed objective evidence of disease progression was lowest in Trial 23, intermediate in Trial 24, and highest in Trial 25. In each of Trials 24 and 25, the percentage of patients with either (1) a positive bone scan or (2) other objective events of disease progression was numerically lower in the Casodex treatment group compared to the placebo group. In Trial 23, there were no differences between the Casodex and placebo treatment groups in the proportions of patients with disease progression.

Table 11 Objective Disease Progression or Death in Trials 23, 24, and 25

Event	Number (per cent) of patients with event ¹					
	Study 23		Study 24		Study 25	
	Casodex (N = 1647)	Placebo (N = 1645)	Casodex (N = 1798)	Placebo (N = 1805)	Casodex (N = 607)	Placebo (N = 611)
Positive bone scan	21 (1.3)	15 (0.9)	60 (3.3)	116 (6.4)	32 (5.3)	95 (15.5)
Other objective events ²	10 (0.6)	17 (1.0)	25 (1.4)	85 (4.7)	19 (3.1)	40 (6.5)
Death in absence of progression	52 (3.2)	55 (3.3)	96 (5.3)	92 (5.1)	48 (7.9)	44 (7.2)
Total (%) Patients	83 (5.0)	87 (5.3)	181 (10.1)	293 (16.2)	99 (16.3)	179 (29.3)

1. Based on Sponsor's preferred endpoints.

2. Other objectively confirmed progression (documented by magnetic resonance imaging, computerized tomography, sonography, or biopsy).

Source: Table T4.1, ISE.

Medical Officer's Comments

- *Disease progression documented by a positive bone scan in a patient with a bone scan that was previously negative is a more reliable indicator of clinically significant disease progression than the category of "other objective events." This latter category includes objectively confirmed local events that may have less significance as a prognostic sign than the appearance of new bone metastases.*
- *In Trial 23, the proportion of patients with events considered to reflect progression of disease or death in the absence of progression was very low in both the Casodex and placebo treatment groups. There was no evidence that treatment with Casodex offered any clinical benefit in this Trial.*
- *The Sponsor stated that the low incidence of progressive disease events in Trial 23 was not surprising based on the baseline disease characteristics of the patients. The Sponsor noted that patients in Trial 23, compared to those in Trials 24 and 25, were younger by*

about 4 years, weighed more (5-7 kg), had lower preprocedure serum PSA values, and all had had prior therapy of curative intent. However, a higher proportion of patients in Trials 24 and 25 had Stage T1 disease and well differentiated tumors (based on Gleason scores) than patients in Trial 23.

- *Although Casodex treatment reduced the proportion of patients with positive bone scans and other objective events of progression in Trials 24 and 25, it did not reduce the proportion of patients who died of any cause in the absence of progression. Overall survival and death specifically due to prostate cancer in each of the trials is discussed in Section 4.6.3.9 .*

The Sponsor's primary analyses of time to disease progression (TTP) for each of the individual trials and the trials combined are presented in Table 12. Hazard ratios were 0.933 (Trial 23), 0.477 (Trial 24), 0.430 (Trial 25), and 0.509 (combined analysis). All hazard ratios, other than that for Trial 23 were highly statistically significant ($p < 0.0001$).

Table 12 Time to Objective Progression or Death in Absence of Progression

Study	Number (%) of patients with event (objective progression or death)				Hazard ratio ¹	95% confidence interval	P value
	Casodex		Placebo				
	Number	(%)	Number	(%)			
23	83/1647	(5.0)	87/1645	(5.3)	0.933	0.691 to 1.261	0.653
24	181/1798	(10.1)	293/1805	(16.2)	0.574	0.477 to 0.692	<0.0001
25	99/607	(16.3)	179/611	(29.3)	0.430	0.336 to 0.552	<0.0001
Combined Data (Trials 23+24+25)	363/4052	(9.0)	559/4061	(13.8)	0.581	0.509 to 0.663	<0.0001

1. Based on Sponsor's preferred endpoints and analyses.

Source: Table T4.2, ISE.

Medical Officer's Comments

- *Combining data from Trial 23 with that from Trials 24 and 25 is not appropriate. Based on the baseline disease characteristics for the patients in each of the 3 trials, the study population in Trial 23 was clearly different from those in Trials 24 and 25.*
- *The Sponsor attributes the apparent absence of a beneficial effect of treatment with Casodex in Trial 23 to (1) the immaturity of the data for this trial and (2) the relatively better prognostic factors for these patients at the time of randomization into the Trial.*

Objective disease progression or death in the absence of progression based on pre-randomization treatment (radical prostatectomy, radiation therapy, or watchful waiting) is summarized in Table 13. Data have been combined across the 3 clinical trials in the sponsor's analysis that is presented in the Table. Based on this combined analysis, the proportions of patients exhibiting progression based on either a positive bone scan or other objective events were numerically lower both in patients who had had prior therapy and in those who had not had prior therapy (watchful waiting treatment group). There was no effect

of treatment on the proportion of patients who experienced death in the absence of disease progression.

Table 13 Objective Disease Progression or Death in Absence of Progression Based on Pre-randomization Treatment (Data for Trials 23, 24, and 25 Combined)

Event	Number (per cent) of patients with event ¹					
	Radical Prostatectomy		Radiotherapy		Watchful Waiting	
	Casodex (N = 2236)	Placebo (N = 2218)	Casodex (N = 699)	Placebo (N = 671)	Casodex (N = 1114)	Placebo (N = 1171)
Positive bone scan	33 (1.5)	58 (2.6)	28 (4.0)	45 (6.7)	51 (4.6)	123 (10.5)
Other objective events ²	22 (1.0)	58 (2.6)	11 (1.6)	20 (3.0)	21 (1.9)	64 (5.5)
Death in absence of progression	60 (2.7)	54 (2.4)	36 (5.2)	38 (5.7)	100 (9.0)	99 (8.5)
Total (%) Patients	115 (5.1)	170 (7.7)	75 (10.7)	103 (15.4)	172 (15.4)	286 (24.4)

1. Based on Sponsor's preferred endpoints.

2. Other objectively confirmed progression (documented by magnetic resonance imaging, computerized tomography, sonography, or biopsy).

Source: Table T4.4, ISE.

The Sponsor's analyses of time to progression in the radical prostatectomy, radiation therapy, and watchful waiting treatment groups (data combined across the 3 trials) are summarized in Table 14. Hazard ratios ranged from 0.53 (watchful waiting group) to 0.63 (adjuvant treatment groups).

Table 14 Time to Objective Progression or Death (Trials 23, 24, and 25 Combined)

Patient Subgroup	Number (%) of patients with event (objective progression or death)				Hazard ratio ¹	95% confidence interval
	Casodex		Placebo			
	Number	(%)	Number	(%)		
All adjuvant patients	190/2935	(6.5)	273/2889	(9.4)	0.63	0.52 to 0.76
Radical prostatectomy patients	115/2236	(5.1)	170/2218	(7.7)	0.63	0.50 to 0.80
Radiotherapy patients	75/699	(10.7)	103/671	(15.4)	0.63	0.46 to 0.85
All watchful waiting patients ²	172/1114	(15.4)	286/1171	(24.4)	0.53	0.44 to 0.64

1. Based on Sponsor's preferred endpoints and analyses.

2. Includes only patients from Trials 24 and 25.

Source: Table T4.13, ISE.

Medical Officer's Comments

- *Combined analyses that merge data from Trial 23 with that from Trials 24 and 25 are not appropriate because of clinically significant differences in baseline disease characteristics. However, certain conclusions can still be made from these analyses.*
- *Based on all objective events of disease progression (as defined by the Sponsor's protocol), treatment with Casodex appears to have statistically reduced the proportion of*

patients who had disease progression in both the adjuvant and watchful waiting treatment groups in Trials 24 and 25. This observation, however, cannot be extrapolated to patients in Trial 23. In Trial 23, there was no evidence that treatment with Casodex offered any clinical benefit.

At the request of the Medical Reviewer, the Sponsor provided additional subset analyses for Trial 24 (Table 15) and Trial 25 (Table 16). In each of the subgroups (radical prostatectomy, radiotherapy, and watchful waiting) in Trial 24 and Trial 25, the proportion of patients with disease progression was numerically lower in the Casodex-treated patients.

Table 15 Objective Disease Progression or Death in Absence of Progression in Subgroups Based on Pre-randomization Treatment (Trial 24)

Event	Number (per cent) of patients with event ¹					
	Radical Prostatectomy		Radiotherapy		Watchful Waiting	
	Casodex (N = 835)	Placebo (N = 813)	Casodex (N = 335)	Placebo (N = 325)	Casodex (N = 628)	Placebo (N = 666)
Positive bone scan	17 (2.0)	36 (4.4)	17 (5.1)	32 (9.8)	26 (4.1)	48 (7.2)
Other objective events ²	14 (1.7)	42 (5.2)	4 (1.2)	15 (4.6)	7 (1.1)	28 (4.2)
Death in absence of progression	21 (2.5)	21 (2.6)	14 (4.2)	12 (3.7)	61 (9.7)	59 (8.9)
Total (%) Patients	52 (6.2)	99 (12.2)	35 (10.4)	59 (18.2)	94 (15.0)	135 (20.3)

1. Based on Sponsor's preferred endpoints

2. Other objectively confirmed progression (documented by magnetic resonance imaging, computerized tomography, sonography, or biopsy).

Source: Submission of April 3, 2002, Appendix 1.

Table 16 Objective Disease Progression or Death in Absence of Progression in Subgroups Based on Pre-randomization Treatment (Trial 25)

Event	Number (per cent) of patients with event ¹					
	Radical Prostatectomy		Radiotherapy		Watchful Waiting	
	Casodex (N = 79)	Placebo (N = 80)	Casodex (N = 39)	Placebo (N = 26)	Casodex (N = 486)	Placebo (N = 505)
Positive bone scan	2 (2.5)	11 (13.8)	4 (10.3)	9 (34.6)	25 (5.1)	75 (14.9)
Other objective events ²	1 (1.3)	3 (3.8)	4 (10.3)	1 (3.8)	14 (2.9)	36 (7.1)
Death in absence of progression	5 (6.3)	1 (1.3)	4 (10.3)	3 (11.5)	39 (8.0)	40 (7.9)
Total (%) Patients	8 (10.1)	15 (18.8)	12 (30.8)	13 (50.0)	78 (16.0)	151 (29.9)

1. Based on Sponsor's preferred endpoints.

2. Other objectively confirmed progression (documented by magnetic resonance imaging, computerized tomography, sonography, or biopsy).

Source: Submission of April 3, 2002, Appendix 1.

Estimates of the hazard ratios (and 95% confidence limits) for the differences between the time to disease progression in the Casodex-treated and placebo-treated patients are provided in Table 17. Hazard ratios ranged from 0.423 (watchful waiting patients in Trial 25) to 0.674 (watchful waiting patients in Trial 24).

Table 17 Hazard Ratios for Objective Disease Progression or Death (Any Cause) in Subgroups based on Pre-randomization Treatment (Trials 24 and 25)

Trial Number	Previous Treatment	Randomized Treatment	Number of events	Number of patients	% patients with event	Estimate of hazard ratio ¹	95% confidence limits
24	Radical prostatectomy	Casodex	52	835	6.2%	0.463	0.331 to 0.649
		Placebo	99	814	12.2%		
	Radiotherapy	Casodex	35	335	10.4%	0.564	0.370 to 0.860
		Placebo	59	325	18.2%		
	Watchful waiting	Casodex	94	628	15.0%	0.674	0.518 to 0.878
		Placebo	135	666	20.3%		
25	Radical prostatectomy	Casodex	9	82	11.0%	0.530	0.230 to 1.220
		Placebo	15	80	18.8%		
	Radiotherapy	Casodex	12	39	30.8%	0.436	0.194 to 0.979
		Placebo	13	26	50.0%		
	Watchful waiting	Casodex	78	486	16.0%	0.423	0.321 to 0.557
		Placebo	151	505	29.9%		

1. Based on Sponsor's preferred endpoints and analyses.

Source: Submission of 3 April 2002 Appendix 2.

Medical Officer's Comments

- *Although these were exploratory subgroup analyses, the outcomes were consistent in that all of them suggested that treatment with Casodex reduced the proportion of patients with disease progression (as defined by the Sponsor) and delayed disease progression. However, there was no suggestion that treatment with Casodex improved disease-specific survival or overall survival (see Section 4.6.3.9).*
- *These subgroup analyses support the sponsor's contention that the overall positive treatment effect of Casodex in Trial 24 and Trial 25 was not entirely dependent on the findings in the watchful waiting patients.*
- *These positive finding, however, do not address the questions of (1) relevance of these findings to US patients, (2) the clinical significance of "objective progression" that was not documented by a positive bone scan, and (3) potential assessment bias due to the likely unblinding of treatment assignment in many patients.*

4.6.3.2 Efficacy Outcomes (FDA-Requested Endpoints and Analyses)

As discussed earlier in Section 4.5.3.3, the Division of Reproductive and Urologic Drug Products (DRUDP) was concerned about the possibility of assessment bias in a time-to-event analysis because treatment blinding could not assured; consequently, DRUDP requested that the efficacy outcomes be evaluated by means of a binary analysis based on the proportion of patients with bone scan confirmed progression **at 2 years** or death in the absence of disease progression. The Sponsor provided the requested analyses as well as a slightly modified analysis – bone scan confirmed progression or death in the absence of progression **within 2.5 years of randomization**. Findings based on this latter analysis are presented in the remainder of this section.

Table 18 lists the number and percentage of patients with bone scan confirmed progression or death in the absence of progression within 2.5 years of randomization in each of the trials. In Trial 23, there was no evidence of a significant reduction in the proportion of patients with disease progression or death in the Casodex group (2.4%) compared to the placebo group (2.9%). In each of Trials 24 and 25, the proportion of patients with disease progression or death was lower in the Casodex group compared to the placebo group (Trial 24: 6.2% vs. 9.3%; Trial 25: 10.4% vs. 17.2%).

Table 18 Bone Scan Confirmed Disease Progression or Death in the Absence of Progression within 2.5 Years after Randomization

Event	Number (per cent) of patients with event ¹					
	Study 23		Study 24		Study 25	
	Casodex (N = 1647)	Placebo (N = 1645)	Casodex (N = 1798)	Placebo (N = 1805)	Casodex (N = 607)	Placebo (N = 611)
Positive bone scan	14 (0.9)	11 (0.7)	42 (2.3)	98 (5.4)	22 (3.6)	72 (11.8)
Death in absence of progression	25 (1.5)	37 (2.2)	70 (3.9)	70 (3.9)	41 (6.8)	33 (5.4)
Total (%) of patients	39 (2.4)	48 (2.9)	112 (6.2)	168 (9.3)	63 (10.4)	105 (17.2)

1. Based on FDA-requested endpoints.

Source: Table A4, pg. A56-A58, ISE.

Medical Officer's Comments

- *This medical reviewer concurs with the Sponsor's rationale for recommending the use of the analysis based on events that occurred within 2.5 years of randomization and not just those that occurred at 2 years. (See Section 4.5.3.3 for the basis for this opinion).*
- *The findings summarized in Table 18 are based on the FDA-requested endpoints and binary analysis and are less likely to be affected by assessment bias than a time-to-event analysis. The events listed in the Table also do not include disease progression based on local changes or non-osseous findings that may be of limited clinical significance.*

The estimates of the odds ratio (and 95% confidence limit) for disease progression in Casodex-treated patients compared to placebo-treated patients for each of Trials 23, 24, and 25, based on the requested FDA analysis, are listed in Table 19.

Table 19 Odds Ratios for Bone Scan Confirmed Progression or Death in Absence of Progression within 2.5 Years after Randomization

Trial	Treatment	No. of events	No. of patients	% patients with event	Estimate of Odds Ratio ¹	95% confidence limit
23	Casodex	39	1647	2.4%		
	Placebo	48	1645	2.9%	0.81 ²	0.52 to 1.24 ¹
24	Casodex	112	1798	6.2%		
	Placebo	168	1803	9.3%	0.645	0.500 to 0.832
25	Casodex	63	607	10.4%		
	Placebo	105	611	17.2%	0.515	0.365 to 0.729

1 Based in FDA-requested endpoints and analyses.

2 Values for Trial 23 calculated by FDA statistician. Values for Trials 24 and 25 calculated by Sponsor.

Source: Submission of 17 May 2002, Appendix 2.

Medical Officer's Comments

- *Based on these analyses, it appears that the reductions in the proportion of patients with bone scan confirmed disease progression or death in the Casodex treatment groups in Trials 24 and 25 were statistically significant.*
- *The actual reductions in the proportion of patients with disease progression or death, however, were relatively small and were 3.1% (Trial 24) and 6.8% (Trial 25).*
- *The differences between the treatment groups are a result of a reduction in bone scan confirmed disease progression and not improved survival as shown by the data in Table 18 and Table 30 as discussed later in this review.*
- *Because the studies are immature relative to anticipated survival with a median follow up of approximately 3 years, the long-term clinical significance of these modest reductions in bone scan confirmed disease progression is unknown at this time.*

To obtain a more complete picture of which treatment subgroup(s) may have derived benefit from treatment with Casodex, the Sponsor was asked to provide additional subgroup analyses based on the patient's treatment prior to randomization (i.e., radical prostatectomy, radiotherapy, or management by watchful waiting). The descriptive analyses for each of the trials are summarized in Table 20, Table 21, and Table 22. For each of the trials, the proportion of patients with bone scan confirmed disease progression or death from any cause in the absence of disease progression was numerically lower in Casodex-treated patients in each of the subgroups. For Trial 23, the reductions in total events in Casodex-treated patients compared to placebo-treated patients were (1) very small (0.3% in the prostatectomy subgroup; 1.6% in the radiotherapy subgroup group), (2) based on a very small number of events, and (3) were not related to a reduction in the proportion of patients with positive bone scans.

Table 20 Bone Scan Confirmed Disease Progression or Death within 2.5 Years after Randomization (Trial 23: Prior Treatment Subgroups)

Event	Number (per cent) of patients with event ^{1,2}			
	Radical Prostatectomy		Radiotherapy	
	Casodex (N = 1322)	Placebo (N = 1325)	Casodex (N = 325)	Placebo (N = 320)
Positive bone scan	10 (0.8)	8 (0.6)	4 (1.2)	3 (0.9)
Death (any cause) in absence of progression	16 (1.2)	22 (1.7)	9 (2.8)	15 (4.7)
Total (%) Patients	26 (2.0)	30 (2.3)	13 (4.0)	18 (5.6)

1. Based on FDA-requested endpoints.

2. Patients previously managed by watchful waiting were not eligible for this Trial.

Source: Submission of 3 April 2002, Appendix 3.

Table 21 Bone Scan Confirmed Disease Progression or Death within 2.5 Years after Randomization (Trial 24: Prior Treatment Subgroups)

Event	Number (per cent) of patients with event ¹					
	Radical Prostatectomy		Radiotherapy		Watchful Waiting	
	Casodex (N = 835)	Placebo (N = 813)	Casodex (N = 335)	Placebo (N = 325)	Casodex (N = 628)	Placebo (N = 666)
Positive bone scan	12 (1.4)	27 (3.3)	11 (3.3)	28 (8.6)	19 (3.0)	43 (6.5)
Death (any cause) in absence of progression	17 (2.0)	16 (2.0)	13 (3.9)	8 (2.5)	40 (6.4)	46 (6.9)
Total (%) Patients	29 (3.5)	43 (5.3)	24 (7.2)	36 (11.1)	59 (9.4)	89 (13.4)

1. Based on FDA-requested endpoints.

Source: Submission of 3 April 2002, Appendix 3.

Table 22 Bone Scan Confirmed Disease Progression or Death within 2.5 Years after Randomization (Trial 25: Prior Treatment Subgroups)

Event	Number (per cent) of patients with event ¹					
	Radical Prostatectomy		Radiotherapy		Watchful Waiting	
	Casodex (N = 79) ²	Placebo (N = 80)	Casodex (N = 39)	Placebo (N = 26)	Casodex (N = 486)	Placebo (N = 505)
Positive bone scan	1 (1.3) ³	7 (8.8)	3 (7.7)	6 (23.1)	17 (3.5)	59 (11.7)
Death (any cause) in absence of progression	5 (6.3)	1 (1.3)	4 (10.3)	3 (11.5)	32 (6.6)	29 (5.7)
Total (%) Patients	6 (7.6)	8 (10.0)	7 (17.9)	9 (34.6)	49 (10.1)	88 (17.4)

1. Based on FDA-requested endpoints.

2. Does not include 3 patients who were initially treated by radical prostatectomy followed by local radiotherapy.

3. Does not include 1 patient who was initially treated by radical prostatectomy followed by local radiotherapy.

Source: Submission of 3 April 2002, Appendix 3.

Medical Officer's Comments

- *The proportions of patients with bone scan confirmed disease progression in the placebo treatment groups in Trial 23 were < 1%; consequently, there was no opportunity for Casodex to be of benefit as these patients, at the time of data cutoff, were essentially free of metastatic disease.*
- *Based on the findings in Trial 23, there are no data that suggest that patients with early or localized prostate cancer who are treated by either radical prostatectomy or radiation therapy would derive any benefit from adjuvant treatment with Casodex.*
- *Each of the subgroups in Trial 24 had a sizable number of patients. In this Trial, the effect of treatment with Casodex was similar in each subgroup in that the proportion of patients with bone scan documented disease progression (excluding death in the absence of progression) was reduced by slightly more than 50%. The actual percent reductions in each subgroup, however, were relatively small and were 1.9% (radical prostatectomy), 3.5% (watchful waiting), and 5.3% (radiotherapy).*
- *The radical prostatectomy and radiotherapy subgroups in Trial 25 contained only small numbers of patients and very few events. The subgroup of watchful waiting included almost 1000 patients. The proportion of patients with positive bone scans was reduced from 59 of 505 patients (11.7%) in the placebo group to 17 of 486 patients (3.5%) in the Casodex group, a reduction of 8.2%.*

The estimate of the odds ratio (and 95% confidence interval) for the proportion of patients with bone scan confirmed disease progression or death in each of the subgroups is listed in Table 23. In all instances other than the subgroup of watchful waiting, the upper bound of the 95% confidence limit exceeded 1.000. In Trial 24, however, the upper bound of the 95% confidence limit for the radical prostatectomy and radiotherapy subgroups barely crossed 1.000 and was 1.003 and 1.081, respectively.

Table 23 Odds Ratios for Bone Scan Confirmed Progression or Death from Any Cause within 2.5 Years after Randomization in Treatment Subgroups

Trial Number	Previous Treatment	Randomized Treatment	Number of events	Number of patients	% patients with event	Estimate of Odds Ratio ¹	95% confidence limits	
23	All treatments	Casodex	39	1647	2.4%	0.81 ²	0.52 to 1.24 ²	
		Placebo	48	1645	2.9%			
	Radical prostatectomy	Casodex	26	1322	2.0%	0.862	0.506 to 1.467	
		Placebo	30	1325	2.3%			
	Radiotherapy	Casodex	13	325	4.0%	0.672	0.321 to 1.408	
		Placebo	18	320	5.6%			
24	All treatments	Casodex	112	1798	6.2%	0.645	0.500 to 0.832	
		Placebo	168	1805	9.3%			
	Radical prostatectomy	Casodex	29	835	3.5%	0.616	0.379 to 1.003	
		Placebo	43	814	5.3%			
	Radiotherapy	Casodex	24	335	7.2%	0.625	0.361 to 1.081	
		Placebo	36	325	11.1%			
	Prostatectomy or Radiotherapy	Casodex	53	1170	4.5%	0.619	0.430 to 0.890	
		Placebo	79	1139	6.9%			
	Watchful waiting	Casodex	59	628	9.4%	0.674	0.471 to 0.964	
		Placebo	89	666	13.4%			
	25	All treatments	Casodex	63	607	10.4%	0.515	0.365 to 0.729
			Placebo	105	611	17.2%		
Radical prostatectomy		Casodex	7	82	8.5%	0.836	0.282 to 2.480	
		Placebo	8	80	10.0%			
Radiotherapy		Casodex	7	39	17.9%	0.397	0.123 to 1.285	
		Placebo	9	26	34.6%			
Prostatectomy or Radiotherapy		Casodex	14	121	11.6%	0.584	0.264 to 1.292	
		Placebo	17	106	16.0%			
Watchful waiting		Casodex	49	486	10.1%	0.498	0.338 to 0.734	
		Placebo	88	505	17.4%			

1. Based on FDA-requested endpoints and analyses.

2. Values calculated by FDA statistician. Other values calculated by Sponsor.

Source: Submission of 3 April 2002, Appendix 4 and Submission of 17 May 2002, Appendix 2.

Medical Officer's Comments

- Although these were exploratory analyses, they support the Sponsor's claim that treatment with Casodex is of benefit to patients who would otherwise have their prostate cancer managed entirely by watchful waiting. However, it is not known at this time if this benefit (1) extends to patients in the US and (2) extends beyond that of delaying the development of osseous metastases. It also is not known if the benefit of treatment with Casodex in this population would be comparable to that of treatment with a GnRH agonist. GnRH therapy is often used in the US for patients who are not candidates for radical prostatectomy or who decline to have a radical prostatectomy or radiotherapy.*

Data from Clinical Trials 0306 and 0307 previously submitted by the Sponsor in NDA 20-498/s006 suggested that Casodex treatment for locally advanced non-metastatic prostate cancer may have been less effective than medical or surgical castration.

- *The exploratory subset analyses presented in Table 23 also suggest that in Trial 24 adjuvant treatment with Casodex reduced bone scan confirmed disease progression or death in the absence of progression in patients previously treated by radical prostatectomy. However, in Trial 23 (the North American trial and the trial of most relevance to men with prostate cancer in the United States) there was no apparent benefit of Casodex adjuvant therapy.*
- *The proportion of placebo-treated patients with bone scan documented disease progression in the subgroups of radical prostatectomy and radiotherapy were several fold higher in Trial 24 compared to that in Trial 23. It thus appears that patients enrolled into Trial 24 for adjuvant therapy either had less favorable baseline disease characteristics or underwent less effective primary therapies, or both.*
- *A meaningful comparison of baseline disease characteristics in Trial 23 to those in the non-North American trials (Trials 24 and 25) has not been possible, in part, because of failure by the Sponsor to require standardized criteria for assigning Gleason scores to tumor tissues. It is recommended that the Sponsor attempt to have the tumor specimens from the 3 clinical trials reread either centrally or by common criteria to facilitate meaningful cross study comparisons of the degree of tumor differentiation. Obtaining such information might help the Sponsor to identify the group of patients in the US who might benefit from adjuvant therapy with Casodex.*
- *Based on the information in the present application, one can only identify those patients in the US who would not likely derive benefit from Casodex adjuvant therapy (i.e., those types of patients enrolled into Trial 23). The information in the present application does not identify patients with local or locally advanced prostate cancer in the US for whom adjuvant therapy might be of benefit. (See Section 4.6.3.3 for additional discussion).*

4.6.3.3 Additional Subset Analyses to Support Adjuvant Use of Casodex

On 25 April 2002, a teleconference between the Sponsor and DRUDP was held. The purpose of the teleconference was to provide the Sponsor with an update as to the status of the review and to inform the Sponsor that there were several unresolved review issues. Prior to the teleconference, the Sponsor was provided with a list of questions that included the following:

1. How do you explain the disparity between the efficacy findings of Trial 23 (North American study) and those of Trials 24 and 25?
2. Based on the findings in Trial 23 as of 2 June 2000 (data cutoff date), it appears that Casodex does not offer a significant benefit for men with early prostate cancer who initially are treated by radical prostatectomy or radiation therapy with a curative intent. In light of this observation, what population of patients with prostate cancer in the US, who are initially treated with radical prostatectomy or radiation therapy of curative intent, would benefit from adjuvant treatment with Casodex?
3. Since there was not a watchful waiting group in Trial 23, can you tell us how men treated by watchful waiting in Trials 24 and 25 compare to those that are likely to be treated by

watchful waiting in the US. In particular, how do we know that such patients in the US would respond in a similar fashion as patients in Trials 24 and 25?

4. Please explain the criteria that were used to obtain Gleason scores for the tumors in each of the clinical trials. Did all pathologists use the same criteria?
5. There appears to be a lack of correlation between Gleason scores and preprocedure PSA values. Patients in Trial 23 had higher Gleason scores (more severe disease) but lower PSA values. How do you explain this?

These questions initially were addressed by the Sponsor during the teleconference and subsequently more completely in a written response of 10 May 2002. The Sponsor's written response included the following information and explanations regarding the 5 questions listed above.

1. "The disparity in efficacy findings between Trial 23 and Trials 24 and 25 is related to the immaturity of Trial 23. At data cutoff, only 5.2% of patients had objective progression, with the majority of progression events being non-prostate cancer related deaths."
2. "... on closer examination of the data, by means of the multivariate analysis, several groups of patients were identified in which a clear and consistent benefit for Casodex was found. These patients were as follows:
 - patients who underwent prostatectomy with locally advanced disease and detectable postsurgical PSA levels and
 - patients who underwent radiotherapy with locally advanced disease and elevated preradiation PSA levels"

"AstraZeneca believes that patients with locally advanced non-metastatic prostate cancer who undergo radical prostatectomy but are at high risk for disease recurrence (e.g., patients with detectable postsurgical PSA levels) would benefit from adjuvant treatment with Casodex."

3. "These data and guidelines [e.g., the American Urologic Association's Prostate Cancer Clinical Guidelines Panel Report] clearly show that watchful waiting is a well-recognized and practiced treatment option in the US, with the guidelines also recognizing this treatment for the types of patients represented in the watchful waiting cohorts in Trials 24 and 25."
4. "In the Casodex EPC program, the local pathologist assessed Gleason grade. In Trial 23, the actual numerical score was captured, but in Trials 24 and 25, the grade was captured only in terms of well, moderately, or poorly differentiated with guidance that 'well' represented a Gleason score of 2 to 4; moderate, a score of 5 or 6; and poorly, a grade of ≥ 7 ."
5. "The reason for the lack of correlation between Gleason grade and PSA is unclear, but may relate to the fact that they measure different aspects of the tumor. Therefore, as noted in Question 2, AZ does not believe that conclusions can be drawn in this program on the basis of Gleason grade."

Medical Officer's Comment

- *The Sponsor's responses to questions 1, 4, and 5 did not provide new information but rather confirmed this reviewer's initial interpretation of previously submitted information. The Sponsor's confirmation that Gleason grades or scores were not assigned in accordance with specific guidelines is problematic. Most US physicians consider the Gleason grade of the tumor an important prognostic indicator. The lack of concordance between the US and non-US Gleason grades further limits one's ability to make comparisons between Trial 23 (the sole US study) and the 2 non-US trials.*

With the written response of 10 May 2002, the Sponsor provided additional information in support of their contention that patients who would benefit from adjuvant Casodex therapy included those with locally advanced disease (Stage T3/T4) prior to initial therapy and either (1) a serum PSA concentration > 0.2 ng/mL following radical prostatectomy or (2) a serum PSA concentration > 10 ng/mL prior to radiotherapy. Table 24 summarizes objective disease progression or death in the absence of progression for the subset of patients with Stage T3/T4 tumors and post prostatectomy PSA values > 0.2 ng/mL. Events represented in Table 24 are based on the Sponsor's preferred endpoints.

Table 24 Disease Progression in Patients with Locally Advanced (Stage T₃/T₄), M₀ Prostate Cancer and Post Prostatectomy PSA Values > 0.2 ng/mL

Event	Number (%) of patients with event ^{1,2}		Hazard Ratio (95% CL)
	Casodex Number (%)	Placebo Number (%)	
Trial 23			
Total Pts Enrolled (158/2647 [6.0%]) ³	83⁴	75⁴	
Number of Pts with Event	8 (9.6%)	12 (16.0%)	0.53 (0.21, 1.37)
Bone Scan Positive	5	4	
Other Objective Events	2	4	
Deaths ^{5,6}	1	4	
Trial 24			
Total Pts Enrolled (277/1648 [16.8%]) ³	133⁴	144⁴	
Total Events	20 (15.0%)	35 (24.3%)	0.55 (0.32, 0.96)
Bone Scan Positive	11	15	
Other Objective Events	4	16	
Deaths ⁵	5	4	
Trial 25			
Total Pts Enrolled (74/159 [46.5%]) ³	33⁴	41⁴	
Total Events	4 (12.1%)	11 (26.8%)	0.49 (0.15, 1.58)
Bone Scan Positive	2	8	
Other Objective Events	1	2	
Deaths ⁵	1	1	

1. Based on Sponsor's preferred endpoints of positive bone, other objective events, or death from any cause at any time post-randomization.
 2. Values (other than for category of "Total Events") compiled by medical reviewer from Submission of 22 May 2002.
 3. The value expressed as [%] represents the percentage of patients in the Trial previously treated by radical prostatectomy who were clinical stage T₃ or T₄ and had a postsurgical PSA value > 0.2 ng/mL relative to all patients previously treated by prostatectomy.
 4. Total number of patients enrolled in the Casodex or placebo treatment group previously treated by radical prostatectomy who were clinical stage T₃ or T₄ and had a postsurgical PSA value > 0.2 ng/mL.
 5. Death from any cause.
 6. All deaths in Trial 23 (other than 1 case in the placebo group) were due to causes other than prostate cancer.
- Source: Submission of 10 May 2002, Table 2; Submission of 22 May 2002, Appendix 3.

Medical Officer's Comments

- *The sponsor initially provided data only for "total events" expressed as percentages in each of the 3 trials. These data showed a numeric advantage for treatment with Casodex in terms of a reduction in the proportion of patients with objective disease progression or death. However, among the 3 trials, only the 95% confidence interval for the hazard ratio for Trial 24 did not cross 1.00 (Hazard ratio: 0.55 [95% CI: 0.32-0.96]). Upon request, the Sponsor provided further details regarding disease progression each of the trials (i.e., numbers of patients with [1] a positive bone scan, [2] other objective progression, and [3] death from any cause in the absence of objective progression). Review of these additional data (represented in Table 24 in non-bold text) indicated that the excess of events in the placebo-treated patients in Trial 23 was a result of (a) objective events other than positive bone scans and (b) deaths that were not due to*

prostate cancer. The data also indicated that most of the excess of events in the placebo-treated patients in Trial 24 was due to “other objective events.”

4.6.3.4 First Revision by Sponsor to Proposed Label Claims

Based in part on the information provided in the written response of 10 May 2002, the Sponsor also submitted revised wording for the Casodex 150 mg label. The revised indication (also submitted on 10 May 2002) was:

Casodex 150 mg is indicated as

- Adjuvant therapy to radical prostatectomy and radiotherapy of curative intent in patients with locally advanced non-metastatic prostate cancer who have a high risk for disease recurrence or
- Immediate treatment of non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated.

Medical Officer's Comment

- *The revised proposed indication for the adjuvant use of Casodex is more reflective of the findings from the clinical trials. The revision acknowledges that there is little, if any, evidence (based primarily on the results from Trial 23) that adjuvant use of Casodex following radical prostatectomy or radiotherapy of curative intent in patients with localized prostate cancer is of clinical benefit.*

4.6.3.5 Additional Subset Analyses to Support Immediate or Monotherapy Indication

AstraZeneca was asked to provide additional information about the disease characteristics of the watchful waiting patients in Trials 24 and 25 to allow DRUDP to assess further the relevance of these findings in non-US patients to patients in the US who would otherwise be managed by watchful waiting or surveillance. The Sponsor was asked to provide the requested data in a manner that would allow DRUDP to determine if the benefit of treatment with Casodex in the watchful waiting (immediate treatment) subgroup also was observed in patients with minimal or early disease. These data are summarized in Table 25 (Trial 24) and Table 26 (Trial 25). In these tables, patients with bone scan confirmed progression or death from any cause in the absence of progression within 2.5 years after randomization (FDA-requested endpoints) are presented in terms of baseline disease characteristics (clinical stage, Gleason category, and pre-randomization serum PSA value).

Table 25 Patients with Bone Scan Progression or Death from Any Cause within 2.5 Years of Randomization in Watchful Waiting Group (Trial 24)

Subgroup	All patients in category ²		Number (%) of patients with event ¹			
			Casodex		Placebo	
	N	%	N	%	N	%
All Patients	1294	(100)	59/628	(9.4)	89/666	(13.4)
Tumor Stage						
Localized (T1/T2)	996	(77)	35/475	(7.4)	52/521	(10.0)
Locally advanced	298	(23)	24/153	(15.7)	37/145	(25.5)
Gleason category						
Well differentiated	560	(43)	22/272	(8.1)	22/288	(7.6)
Moderately differentiated	463	(36)	19/226	(8.4)	33/237	(13.9)
Poorly differentiated	239	(19)	18/115	(15.7)	31/124	(25.0)
Prerandomization PSA						
≤ 0.2 ng/mL	8	(<1)	0/4	(0.0)	0/4	(0.0)
> 0.2 to 4 ng/mL	252	(20)	6/122	(4.9)	10/130	(7.7)
> 4 to 10 ng/mL	298	(24)	8/156	(5.1)	16/142	(11.3)
> 10 to 20 ng/mL	316	(26)	20/150	(13.3)	16/166	(9.6)
>20 ng/mL	370	(30)	20/170	(11.8)	44/200	(22.0)

1. Based on FDA-requested endpoints for disease progression.

2. Includes all patients (both those who did and did not have disease progression).

Source: Submission of 17 May 2002, Appendix 3.

Table 26 Patients with Bone Scan Progression or Death from Any Cause within 2.5 Years of Randomization in Watchful Waiting Group (Trial 25)

Subgroup	All patients in category ²		Number (%) of patients with event ¹			
			Casodex		Placebo	
	N	%	N	%	N	%
All patients	991	(100)	49/486	(10.1)	88/505	(17.4)
Tumor Stage						
Localized (T1/T2)	631	(64)	29/304	(9.5)	39/327	(11.9)
Locally advanced	360	(36)	20/182	(11.0)	49/178	(27.5)
Gleason category						
Well differentiated	462	(47)	16/229	(7.0)	24/233	(10.3)
Moderately differentiated	415	(42)	15/198	(7.6)	44/217	(20.3)
Poorly differentiated	101	(10)	17/49	(34.7)	18/52	(34.6)
Prerandomization PSA						
≤ 0.2 ng/mL	2	(<1)	1/2	(50.0)	0/0	(0.0)
> 0.2 to 4 ng/mL	98	(10)	4/39	(10.3)	3/59	(5.1)
> 4 to 10 ng/mL	209	(21)	11/111	(9.9)	10/98	(10.2)
> 10 to 20 ng/mL	237	(24)	7/125	(5.6)	12/112	(10.7)
> 20 ng/mL	434	(44)	26/206	(12.6)	61/228	(26.8)

1. Based on FDA-requested endpoints for disease progression.

2. Includes all patients (both those who did and did not have disease progression).

Source: Submission of 17 May 2002, Appendix 3.

Medical Officer's Comments

- *In each of Trials 24 and 25, approximately two thirds of the watchful waiting patients had localized disease (stage T1 or T2) as would be expected in a US population. However, the effect of treatment with Casodex in this subset was numerically small (i.e., Trial 24: 7.4% progression [Casodex group] vs. 10.0% progression [placebo group] and Trial 25: 9.5% progression [Casodex group] vs. 11.9% progression [placebo group]). In contrast, patients with locally advanced disease (stage T3 or T4) had more events and the effect of treatment with Casodex was numerically greater (e.g. Trial 24: 15.7% progression [Casodex group] vs. 25.5% progression [placebo group]). Patients with locally advanced disease are not generally managed by watchful waiting in the US.*
- *In Trials 24 and 25, 30% and 44% of patients had serum PSA values > 20 ng/mL at randomization. These values suggest more than minimal disease and it is not likely that many of these patients would be managed by watchful waiting or surveillance in the US.*
- *The majority of patients had tumor Gleason categories of well differentiated or moderately differentiated. These categories would be compatible with those likely to be observed in a US population. However, because of the lack of standardized criteria for assigning Gleason scores, they cannot be readily interpreted in these studies.*
- *A comparison of Casodex-treatment to that of placebo-treatment is probably not appropriate for estimating the likely benefit of Casodex-therapy for patients with locally advanced disease (T3/T4) and PSA values >20 ng. Such patients would most likely have received active therapy (e.g., GnRH analog therapy) in the US based on present standards of care.*

4.6.3.6 Second Revision by Sponsor to Proposed Label Claims

After receiving comments from DRUDP concerning the reasons for the non-approval of NDA 20-498/s012, AstraZeneca revised the claim for the immediate use of Casodex. The modification limited the target population to patients with *localized* disease, defined by the Sponsor as patients with T₁/T₂, N_x, M₀ prostate cancer. According to this modification, patients with locally advanced disease (i.e., T3/T4) would no longer be appropriate candidates for Casodex immediate therapy.

Medical Officer's Comments

- *The primary objective of this proposed label change was presumably to address the concerns of DRUDP. Based on the findings from Clinical Trials 306 and 307 previously submitted under NDA 20-498/s006, DRUDP was concerned that Casodex-treatment of locally advanced prostate cancer would be less effective than medical castration with a GnRH analog.*
- *To be of benefit to patients with localized non-metastatic prostate cancer who are presently managed by watchful waiting or surveillance in the US, the Sponsor will need to provide data demonstrating that prostate cancer-related morbidity or mortality in such patients occurs with a sufficiently high incidence that the potential benefits of Casodex treatment will out weight the adverse effects of treatment (e.g., gynecomastia, breast pain, and possible liver toxicity).*

- *Based on the data presented in Table 25 and Table 26, the proportion of patients with localized disease and disease progression within 2.5 years of randomization was low.*

Many elderly patients with prostate cancer die of causes unrelated to their prostate disease. The sponsor was therefore asked to provide information on the number of patients in the watchful waiting groups in Trials 24 and 25 who had objective disease progression (i.e., a positive bone scan) or death due only to prostate cancer in the absence of objective progression. This information is presented in Table 27. For patients with no prior treatment and localized disease in the placebo treatment groups, only 3.6% of patients (Trial 24) and 7.3% of patients (Trial 25) experienced disease progression.

Table 27 Patients with Bone Scan Progression or Death from Prostate Cancer within 2.5 Years of Randomization in Watchful Waiting Group (Trials 24 and 25)

Subgroup	All patients in category ²		Number (%) of patients with event ¹			
			Casodex		Placebo	
	N	%	N	%	N	%
<i>Trial 24</i>						
All patients	1294	(100)	23/628	(3.7)	48/666	(7.2)
Tumor Stage						
Localized (T1/T2)	996	(77)	10/475	(2.1)	19/521	(3.6)
Locally advanced	298	(23)	13/153	(8.5)	29/145	(20.0)
<i>Trial 25</i>						
All patients	991	(100)	22/486	(4.5)	64/505	(12.7)
Tumor Stage						
Localized (T1/T2)	631	(64)	9/304	(3.0)	24/327	(7.3)
Locally advanced	360	(36)	13/182	(7.1)	40/178	(22.5)

1. Only deaths from prostate cancer or a positive bone scan are considered to be an event.

2. Includes all patients (both those who did and did not have disease progression).

Source: Submission of 17 May 2002, Appendix 3.

Medical Officer's Comments

- *Based on the small number of events in these subgroups and the absence of any survival difference in the treatment groups, it is questionable if patients with localized disease would derive sufficient clinical benefit from Casodex treatment to justify the adverse effects of treatment. It is likely that up to 85% of Casodex-treated patients will experience gynecomastia and/or breast pain within 2 years of treatment onset (see Section 5.9.1.1 under Pharmacological Adverse Events). Although breast pain generally resolves after discontinuation of treatment, gynecomastia was reported to resolve in only 50% of patients.*
- *A better assessment of the likely benefit of Casodex treatment could be obtained if the Sponsor were to provide efficacy data based on a data cutoff more current than June 2000 (i.e., data from a more mature study).*

4.6.3.7 Additional Subset Analyses by Baseline Disease Characteristics

Although there were some differences in the inclusion and exclusion criteria of each the 3 pivotal clinical trials (see Section 4.3.3), patients with all stages of non-metastatic (M0)

prostate disease (i.e., stages T1-T4) were eligible for enrollment. In addition, patients may have undergone active therapy (radical prostatectomy or radiotherapy) or no therapy (except in Trial 23) prior to enrollment. To allow DRUDP to investigate the effects of Casodex treatment in each of these subgroups, the Sponsor was asked to provide additional descriptive subset analyses based on patient disease characteristics prior to enrollment. In these analyses, the proportions of patients with disease progression in each Trial are presented based on (1) clinical stage (T1-T4), (2) Gleason score, (3) PSA value at randomization, and (4) PSA value prior to prostatectomy or radiotherapy for adjuvant patients. Data for adjuvant patients are presented separately for the prostatectomy and radiotherapy groups in the Appendix (Appendix Tables 1a-1c, pg. 120-123). Data for the “immediate therapy patients” (i.e., watchful waiting group) are presented in Table 25 and Table 26 in the main body of this review. In these descriptive analyses, disease progression is defined as (1) a positive bone scan or (2) death from any cause in the absence of a positive bone scan, both within 2.5 years of randomization (FDA-preferred endpoints). A second set of descriptive subset analyses for adjuvant patients is presented in Appendix Tables 2a-2c (pg. 124-127). In these later analyses, disease progression is defined as (1) a positive bone scan or (2) death due to prostate cancer in the absence of a positive bone scan, both within 2.5 years of randomization (a modification of the FDA-preferred endpoints).

4.6.3.8 Central Reread of Bone Scans

The use of a binary primary efficacy endpoint, instead of a time-to-event analysis, reduced one potential source of assessment bias due to the likely unblinding of treatment assignments in some patients. Another possible source of bias resulting from this unblinding of treatment assignments concerned the reading of bone scans at the local study centers. It was possible that bone scans from patients thought to be on placebo therapy would be more likely to be read as positive than scans from patients on Casodex therapy. To investigate this possible source of bias, it was recommended by DRUDP that bone scans be reread by blinded reviewers at a central facility. In response to this request, the Sponsor designed and conducted a substudy in which all positive bone scans and a representative sample of negative scans were to be reread by at least 2 blinded reviewers at a central facility. The design and outcome of this substudy are described in detail in the separate review of Robert Yaes MD, Division of Medical Imaging and Radiopharmaceutical Drug Products (DMIRDP), FDA. The following is a brief summary of the findings from this substudy.

A total of 1,259 scans from among the 3 trials were identified for review at the central facility. Of these, 1,032 were available for review. Table 28 summarizes the comparative results from the original local read and the central reread. Scans that were available for reread were classified as positive, negative, or indeterminate. Approximately 15% of scans were not available for reread.

Table 28 Comparison of Local Read and Central Reread (Data from Trials 23, 24, and 25 Combined)

Treatment Group	Local Result	Central Reread Result			
		Number (%) of scans in each category			
		Positive	Negative	Indeterminate	Not Available
Casodex	Positive	73 (65%)	22 (19%)	5 (4%)	13 (12%)
	Negative	31 (5%)	443 (72%)	34 (6%)	107 (17%)
Placebo	Positive	144 (63%)	36 (16%)	18 (8%)	28 (12%)
	Negative	22 (4%)	359 (71%)	45 (9%)	79 (16%)

Source: Report on Bone Scan Reread Study, Table T9.2, pg. ST-66.

Medical Officer's Comments

- *The correlation between the original result and the reread was less than optimal. In this reviewer's opinion, it was surprisingly low, especially for positive scans. Excluding scans not available for reread, 73 of 100 scans locally read as positive from Casodex-treated patients were reread as positive. Twenty-two (22) and 5 were reread as negative and indeterminate, respectively. The findings were similar for scans originally read as positive from placebo-treated patients.*
- *For scans locally read as negative in Casodex-treated patients and available for central review, 443 of 508 (87%) were reread as negative. Thirty-one (31) and 34 were reread as positive and indeterminate, respectively. The findings were similar for scans originally read as negative from placebo treated patients.*
- *Although no systematic treatment-related reading bias was apparent, 27% of scans read as positive by local readers (the readings used in the Sponsor's efficacy analyses), were read as negative or indeterminate at the central reread. This lack of correlation between the initial and central readings for positive scans raises some concern about assessing the efficacy of Casodex treatment based on the relatively small differences in the numbers of non-fatal events in these immature clinical trials.*

Table 29 summarizes the comparative results from the original local read and the central reread for each trial, considering only those scans reread as positive or negative and excluding those that were reread as indeterminate or those that were not available for reread.

Table 29 Comparison of Results of Local Read and Central Reread including only Scans Reread as Positive or Negative

Trial	Treatment Group	Local Result	Central Reread Result	
			Number (%) of scans in each category	
			Positive	Negative
23	Casodex	Positive	13 (72%)	5 (23%)
		Negative	10 (6%)	150 (94%)
	Placebo	Positive	8 (67%)	4 (33%)
		Negative	7 (5%)	136 (95%)
24	Casodex	Positive	33 (69%)	15 (31%)
		Negative	12 (7%)	153 (93%)
	Placebo	Positive	70 (76%)	22 (24%)
		Negative	10 (8%)	122 (92%)
25	Casodex	Positive	27 (93%)	2 (7%)
		Negative	9 (6%)	140 (94%)
	Placebo	Positive	66 (87%)	10 (13%)
		Negative	5 (5%)	101 (95%)

Source: Report on Bone Scan Reread Study, Table T9.3, pg. ST-67 to ST-69.

Medical Officer's Comments

- *The results of the reread were consistent with there being no systematic treatment-related bias in the local readings of the bone scans between the Casodex and placebo treatment groups.*
- *The percentage of negative scans reread as positive was comparatively small relative to the percentage of positive scans reread as negative. However, because more than 90% of the bone scans across the 3 clinical trials were read locally as negative, the impact of what appears to be a small misclassification error could be substantial if it were to occur more frequently in one of the 2 treatment arms.*

4.6.3.9 Survival

At the time of the efficacy data cutoff date of 2 June 2000, the median follow-up time for patients in each treatment group was 3.0 years, which was equivalent to 12,053 and 12,033 total patient-years of follow-up for the Casodex and placebo groups, respectively. Additional data on survival were provided in the Safety Addendum Reports for each trial and the 4-Month Safety Update. The cumulative numbers and percentages of deaths due to prostate cancer or other causes in each of the trials at data cutoff dates of 2 June 2000, 23 February 2001 (Safety Addendum Reports), and 28 September 2001 (4-Month Safety Update) are listed in Table 30. At each of the data cutoff dates, there were no significant differences in the percentage of patients who had died, either of prostate cancer or of other causes, in the Casodex or placebo groups within each of the trials. There were, however, significant differences in the proportion of deaths across the trials, particularly for deaths due to prostate cancer. The percentages of patients who died from all causes was approximately 2-fold and 3-fold greater in Trial 24 and Trial 25, respectively, than in Trial 23 at each of the data cutoff times.

Table 30 Number and Percentage of Deaths in Trials 23, 24, and 25

Cause of Death	Study 23		Study 24		Study 25	
	Casodex N= 1647	Placebo N=1645	Casodex N= 1798	Placebo N=1805	Casodex N= 607	Placebo N= 611
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Prostate cancer	8 (0.5)	3 (0.2)	26 (1.4)	38 (2.1)	24 (4.0)	28 (4.6)
Other	54 (3.3)	58 (3.5)	97 (5.4)	99 (5.5)	45 (7.4)	42 (6.9)
Total¹	62 (3.8)	61 (3.7)	123 (6.8)	137 (7.6)	69 (11.4)	70 (11.5)
Prostate cancer	9 (0.6)	4 (0.2)	47 (2.6)	53 (2.9)	35 (5.8)	42 (6.9)
Other	74 (4.6)	83 (5.1)	132 (7.3)	131 (7.3)	54 (8.9)	43 (7.1)
Total²	83 (5.1)	87 (5.3)	179 (10.0)	184 (10.3)	89 (14.7)	85 (14.0)
Prostate cancer	14 (0.9)	6 (0.4)	56 (3.1)	66 (3.7)	49 (8.1)	56 (9.2)
Other	91 (5.6)	93 (5.7)	168 (9.4)	161 (9.0)	67 (11.1)	50 (8.2)
Total³	105 (6.5)	99 (6.1)	224 (12.5)	227 (12.7)	116 (19.2)	106 (17.4)

1. Data cutoff date of 2 June 2000. Data based on efficacy population.

2. Data cutoff date of 23 February 2001. Data based on safety population. (Calculated by medical reviewer).

3. Data cutoff date of 28 September 2001. Data based on safety population. (Calculated by medical reviewer).

Source: Table T5.1, ISE; Table T8.2 Safety Addendum for each of Trials 23, 24, and 25; Submission of 17 May 2002, Appendix 1.

Medical Officer's Comments

- *The proportion of patients who died from prostate cancer in the placebo treatment groups was approximately 9-fold and 23-fold greater in Trial 24 and Trial 25, respectively, compared to that in Trial 23. These observations are consistent with the higher proportions of patients with positive bone scans in Trials 24 and 25.*
- *There is no evidence that treatment with Casodex had a beneficial effect on overall survival in any of the trials based on presently available data.*
- *There is a suggestion that the percentage of deaths due to prostate cancer may be reduced in the Casodex treatment arm in Trial 25. However, there is an opposite trend in deaths due to other causes in this Trial.*

4.6.4 Secondary Efficacy Endpoints

4.6.4.1 Time to Treatment Failure

The number and percentage of patients who failed treatment in each of the trials, categorized by the reason for treatment failure, are presented in Table 31. The proportion of patients who had a treatment failure event ranged from 21.1% (Trial 23, placebo group) to 48.0% (Trial 25, placebo group). The most common reason for treatment failure in each of the trials was “withdrawal of therapy” in the absence of objective disease progression or death. Withdrawal of therapy, as the reason for treatment failure ranged from 18.5% of patients (Trial 23, placebo group) to 36.5% (Trial 23, Casodex group). In Trial 23, virtually all patients who failed treatment did so because of withdrawal of therapy in the absence of objective disease progression or death. Additional information as to the reasons for “withdrawal of therapy” in the absence of disease progression is provided in Section 5.5 (Patient Disposition).

Table 31 Reasons for Treatment Failure (Trials 23, 24, and 25)

Reason for treatment failure ¹	Number (per cent) of patients with event					
	Study 23		Study 24		Study 25	
	Casodex (N = 1647)	Placebo (N = 1645)	Casodex (N = 1798)	Placebo (N = 1805)	Casodex (N = 607)	Placebo (N = 611)
Objective disease progression	5 (0.3)	8 (0.5)	47 (2.6)	151 (8.4)	32 (5.3)	103 (16.9)
Withdrawal of therapy ²	601 (36.5)	304 (18.5)	620 (34.5)	468 (25.9)	133 (21.9)	163 (26.7)
Death	9 (0.5)	13 (0.8)	48 (2.7)	36 (2.0)	26 (4.3)	18 (2.9)
Additional systemic therapy given	3 (0.2)	4 (0.2)	12 (0.7)	25 (1.4)	3 (0.5)	7 (1.1)
No trial therapy received	20 (1.2)	18 (1.1)	8 (0.4)	10 (0.6)	2 (0.3)	2 (0.3)
Total (%) Patients	638 (38.7)	347 (21.1)	735 (40.9)	690 (38.2)	196 (32.3)	293 (48.0)

1. Categories are mutually exclusive and hierarchical; the event that occurred first was assigned as the reason for treatment failure.

2. Withdrawal of therapy in the absence of disease progression or death.

Source: Text Table 16, pg. 48, ISE.

The Sponsor's analyses of time to treatment failure are summarized in Table 32. The hazard ratios for the time to treatment failure in the Casodex versus placebo treatment groups showed statistical significance in both Trial 23 and Trial 25 (albeit in opposite directions) with no statistical significance for Trial 24.

Table 32 Analyses of Time to Treatment Failure (Trials 23, 24, and 25)

Trial	Number (%) of patients with event of treatment failure		Hazard ratio	95% confidence interval	p-value
	Casodex group	Placebo group			
23	638 (38.7)	347 (21.1)	2.083	1.827 to 2.374	<0.001
24	735 (40.9)	690 (38.2)	1.095	0.986 to 1.215	0.089
25	196 (32.3)	293 (48.0)	0.565	0.471 to 0.679	<0.001

Source: Table T6.2, ISE.

Medical Officer's Comment

- *In Trial 23, patients receiving Casodex were more likely to have a treatment failure event than those on placebo. In Trial 25, the converse was true. Patients receiving placebo in Trial 25 were more likely to have a treatment failure event than those receiving Casodex.*

4.6.4.2 Time to PSA Doubling

A PSA doubling event was the earliest of (1) a doubling of serum PSA concentrations relative to baseline, (2) objective progression of disease, or (3) death from any cause. The number and proportion of patients with a PSA doubling event in each of the trials is summarized in Table 33. In each of the trials, the proportion of patients in whom PSA doubled or with a PSA doubling event was lower in the Casodex-treated patients compared to placebo-treated patients.

Table 33 Number (%) of Patients with a PSA Doubling Event

Earliest Event ¹	Number (per cent) of patients with event					
	Study 23		Study 24		Study 25	
	Casodex (N = 1647)	Placebo (N = 1645)	Casodex (N = 1798)	Placebo (N = 1805)	Casodex (N = 607)	Placebo (N = 611)
PSA doubled	211 (12.8)	333 (20.2)	126 (7.0)	440 (24.4)	48 (7.9)	243 (39.8)
Objective progression	12 (0.7)	9 (0.5)	53 (2.9)	80 (4.4)	37 (6.1)	56 (9.2)
Death	47 (2.9)	52 (3.2)	93 (5.2)	80 (4.4)	46 (7.6)	36 (5.9)
Total (%) of patients	270 (16.4)	394 (24.0)	272 (15.1)	600 (33.2)	131 (21.6)	335 (54.8)

1. Categories are mutually exclusive and hierarchical; the event that occurred first was assigned as the reason for PSA doubling.

Source: Text Table 19, pg. 51, ISE.

Medical Officer's Comment

- *The proportion of patients in the Casodex treatment arm in Trial 23 with a PSA doubling event (16.4%) was similar to that in the Casodex treatment arm in Trial 24 (15.1%) and only somewhat lower than that in Trial 25 (21.6%). This is an unexpected finding since the proportion of patients with objective progression (Sponsor's definition of objective progression) was much lower in Trial 23 (0.7%) compared to that in Trial 24 (2.9%) and Trial 25 (6.1%).*

The results of the sponsor's analyses of time to PSA doubling (TTPSAd) are presented in Table 34. Treatment with Casodex increased the time to a PSA doubling event in each of the trials.

Table 34 Analyses of Time to a PSA Doubling Event in Trials 23, 24, and 25

Trial	Number (%) of patients with PSA doubling event				Hazard ratio	95% confidence interval	P value
	Casodex Group		Placebo Group				
	Number	(%)	Number	(%)			
23	270/1647	(16.4)	394/1645	(24.0)	0.619	0.530 to 0.722	<0.0001
24	272/1798	(15.1)	600/1805	(33.2)	0.369	0.320 to 0.426	<0.0001
25	131/607	(21.6)	335/611	(54.8)	0.243	0.197 to 0.299	<0.0001

Source: Text Table 20, pg. 54, ISE.

Medical Officer's Comment

- *The Sponsor's analysis of time to a PSA doubling event is the only analysis provided in this Application that showed a potential benefit for treatment with Casodex in Trial 23. In Trial 23, there was no evidence that Casodex treatment was of benefit compared to placebo in terms of either of the 2 primary efficacy endpoints – objective disease progression or survival (no difference from placebo) – or the secondary endpoint of time to treatment failure (Casodex was statistically inferior to placebo).*

4.7 Consultations

The findings from Clinical Trials 23, 24, and 25 were presented to the Oncology Coordinating Committee (OCC), FDA on 28 March 2002. Recommendations from the OCC regarding the approvability of Casodex 150 mg for the Sponsor's originally proposed indication included the following:

- The primary efficacy endpoint based on bone scan confirmed disease progression is acceptable to evaluate the potential clinical benefit of treatment with Casodex 150 mg.
- Demonstrating a statistically significant increase in survival is not necessary for approval if the efficacy and safety profiles are otherwise acceptable.
- Because of the lack of efficacy in the US clinical trial (Trial 23), approval can not be recommended in the absence of (a) the Sponsor conducting a trial in the US that demonstrates efficacy for the proposed indication or (2) the Sponsor providing further evidence of the relevance of the efficacy findings from Trials 24 and 25 to patients in the US with prostate cancer.

4.8 Conclusions Regarding Demonstrated Efficacy

4.8.1 Achievement of Protocol-Defined Primary Efficacy Endpoints

Time to objective disease progression (Trials 23, 24, and 25) and time to death (Trials 23 and 25 and the Sponsor's combined analysis) were the protocol-defined primary efficacy endpoints. For two of the 3 clinical trials (Trials 24 and 25), the Sponsor provided statistically significant evidence that treatment with Casodex 150 mg per day, compared to treatment with placebo, delayed disease progression as assessed by the appearance of new bone metastases or death in the absence disease progression. In Trial 23 (the only trial conducted in the US and the trial most relevant to patients in the US), there was no evidence that treatment with Casodex delayed disease progression.

There was no evidence that treatment with Casodex improved survival in any of the trials or in the combined analysis. Evidence of improved survival, however, was not anticipated by the cutoff date for efficacy data (2 June 2000) as the data were expected to be immature.

4.8.2 Support of Label Efficacy Claims

The Sponsor originally proposed the following efficacy claim:

CASODEX 150 mg tablets are indicated as immediate hormonal therapy or as adjuvant therapy to treatment of curative intent in patients with non-metastatic prostate cancer.

On 10 May 2002, the Sponsor submitted the following revised efficacy claim:

CASODEX 150 mg is indicated as (1) adjuvant therapy to radical prostatectomy and radiotherapy of curative intent in patients with locally advanced non-metastatic prostate cancer who have a high risk for disease recurrence or (2) immediate treatment of non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated.

The revised efficacy claim was submitted in response to questions submitted to the Sponsor by the Division (DRUDP) concerning the relevance of the non-US data to patients in the US, particularly in light of the negative outcome of Trial 23 (see Section 4.6.3.3). An exploratory

subset analyses submitted by the Sponsor on 10 May 2002 from Trials 24 and 25 was somewhat supportive of the revised indication. However, a similar subset analysis for Trial 23, which included only adjuvant treated patients, provided at best only minimal support for the revised indication. Other data submitted by the Sponsor on 17 May 2002 were inconclusive as to the relevance of the efficacy findings for patients in the immediate therapy groups in Trials 24 and 25 to patients in the US presently managed by watchful waiting or surveillance (see Section 4.6.3.5)

Medical Officer's Comment

- *Supplemental efficacy analyses submitted by the sponsor on 10 May 2002 and 17 May 2002 were not sufficient to support the Sponsor's proposed label indications for either adjuvant or immediate therapy with Casodex for patients with prostate cancer in the US.*

On 22 October 2002, the Sponsor revised the proposed claim for immediate treatment with Casodex. The revised claim limited immediate treatment to patients with localized (T1, T2), NX, M0 disease. This change was made, according to the Sponsor, to address concerns by DRUDP regarding the appropriateness of Casodex monotherapy for patients with locally advanced (T3, T4) disease (see Section 1.3.1).

Medical Officer's Comments

- *To be of benefit to patients with localized non-metastatic prostate cancer who are presently managed by watchful waiting or surveillance in the US, the Sponsor will need to provide data demonstrating that prostate cancer-related morbidity or mortality in such patients occurs with a sufficiently high incidence that the potential benefits of Casodex treatment will outweigh the adverse effects of treatment (e.g., gynecomastia, breast pain, and possible liver toxicity).*

4.9 Statistician's Assessment of Efficacy

The following statements are the conclusion of Dr. Hoberman's statistical review of the efficacy findings in NDA 20-498/s012. Dr. Hoberman was the primary statistical reviewer for this application.

“Each European trial provides statistically significant evidence that Casodex 150 mg delays or possibly prevents objective progression of early prostate cancer as measured by bone scans positive for metastases. However, the inclusion of disparate patient groups which received different background therapy (or lack thereof), complicates inference by inviting examination of treatment comparisons within subgroups of patients. Nevertheless, there is evidence in each European trial that patients who either underwent previous therapy (radiation and/or radical prostatectomy) or who underwent ‘watchful waiting’ derived some benefit from Casodex therapy. This evidence takes the form of (1) consistent direction of effect for Casodex in clinically relevant subgroups in both trials and of (although not rigorous statistical evidence) and (2) nominally low p-values in both trials separately comparing Casodex to placebo in each of these clinically relevant subgroups. However, based on Casodex labeling in other countries and the recent data searching by the sponsor, the revised version of the sponsor's indication now excludes patients who underwent RP with T1/T2 disease.

However, there is no evidence that Casodex would be beneficial to patients who underwent previous therapy in the US (the only class of patients who were studied in the US). Moreover, the sponsor has not provided evidence that ‘watchful waiting’ patients would benefit from Casodex 150 mg in the US. In fact, there is reason to believe that patients who got ‘watchful waiting’ in Europe are not the same patients who would receive ‘watchful waiting’ in the US. Although the sponsor claims that the patient population undergoing previous therapy in Europe and the US were quite different, adjusting for clinically relevant factors at baseline does not seem to account for the difference in incidence, a sign that baseline measurements may not be calibrated between the two regions, associations with progression are weak, and/or that there are some unrecorded factors which depressed “objectively confirmed progression” in the US. It is also possible that differences in clinical practice rendered the US study such that the prostatectomy patients were fated to get no benefit from Casodex. Only monitoring the current US trial can answer that question. Given the lack of sufficient information in the US at this time, one course is to request further data from the Trial 23 so that a decision does not rest solely on an extrapolation of results from Europe.”

4.10 Medical Reviewer’s Overall Assessment of Efficacy (Statistical and Clinical Significance)

Interpretation of the overall body of data submitted by the Sponsor in support of the efficacy of Casodex in delaying progression of disease in men with non-metastatic prostate cancer and the relevance of these data to US patients is problematic for several reasons.

1. Each of the trials enrolled patients who had undergone different therapies prior to treatment with Casodex or placebo. Each of the trials, however, was powered only to show an overall treatment effect and the protocol-defined primary efficacy analysis for each study did not address the issue of varying degrees of efficacy in the different subsets of patients based on prior therapy.
2. Although the enrollment criteria for the 3 pivotal trials were similar for the most part, there were significant differences. More importantly, review of the baseline disease characteristics of the patients enrolled into each of the 3 trials suggested that the extent or severity of disease at the time of randomization differed significantly in each of the trials.
3. The Sponsor’s protocol-defined primary efficacy assessments, endpoints, and analyses were never entirely accepted by DRUDP.
 - a. Whereas DRUDP felt that objective disease progression should be limited to the events of bone scan confirmed evidence of metastases or death in the absence of a positive bone scan, the Sponsor preferred a broader definition of objective disease progression. The Sponsor’s protocol defined events of objective disease progression included not only events confirmed by bone scan but events (both local and distant) that were documented by magnetic resonance imaging, computerized tomography, sonography, or biopsy.
 - b. The Sponsor preferred a time to event analysis in which all post-randomization “objective” events would be included in the analyses. Because of the potential for investigator assessment bias due to lack of adequate treatment blinding, DRUDP preferred an alternative binary analysis. DRUDP preferred an analysis based entirely

on the proportion of patients with bone scan confirmed progress or death within 2 years of randomization. The 2-year time point was selected because all patients were to have a protocol mandated bone scan at Year 2 if objective disease progression had not been previously documented.

4. The outcomes of the 2 non-US trials (both supportive of efficacy) differed from the outcome of the single US trial (no evidence of efficacy).

Items 1 to 3 would have been less problematic to interpretation of the overall body of efficacy data if the outcome of Trial 23 had not differed from that of Trials 24 and 25 (Item 4).

In spite of the study design issues listed above, the Sponsor has provided and statistically significant evidence in two of 3 clinical trials (Trials 24 and 25) that treatment with Casodex 150 mg per day, compared to treatment with placebo, delayed progression of prostate cancer as assessed by the appearance of new bone scan documented metastases or death in the absence of disease progression. The relevance of these findings to US patients with prostate cancer, who might receive Casodex as (1) adjuvant therapy following radical prostatectomy or radiotherapy or (2) monotherapy instead of management by watchful waiting or surveillance, is not clear.

4.10.1 Demonstrated Efficacy of Casodex in Non-US Clinical Trials (Trials 24 and 25)

Efficacy analyses of the data in each of Trials 24 and 25 provided statistically significant evidence that treatment with Casodex, compared to treatment with placebo, delayed progression of prostate cancer. Evidence of efficacy was provided using either (1) the Sponsor's preferred endpoint of all "objective progressions" or death in the absence of objective progression and a time-to-event analysis or (2) the FDA-preferred endpoint of bone scan confirmed progression or death in the absence of objective progression and a binary analysis based on events within 2.0 years (or 2.5 years) of randomization.

Although none of the trials was designed or powered to demonstrate statistically significant improvement within a subgroup, estimates of the odds ratio for each subgroup in Trials 24 and 25 with a total of at least 500 patients suggested a benefit of Casodex treatment based on the FDA-requested endpoints and analyses. For the watchful waiting subgroups in Trials 24 and 25, the estimates of the odds ratios (Casodex vs. placebo) and the associated 95% confidence intervals were 0.674 (95% CI: 0.471 to 0.964; Trial 24) and 0.498 (95% CI: 0.338 to 0.734; Trial 25). For adjuvant-treated patients in Trial 24, the estimates of the odds ratios (Casodex vs. placebo) and the associated 95% confidence intervals were 0.616 (95% CI: 0.379 to 1.003; radical prostatectomy subgroup) and 0.625 (95% CI: 0.361 to 1.081; radiotherapy subgroup). Too few adjuvant-treated patients were studied in Trial 25 to draw any conclusions about the efficacy of Casodex treatment.

4.10.2 Lack of Casodex Efficacy in US Clinical Trial (Trial 23)

Data presented by the Sponsor from Trial 23 showed no evidence of efficacy for adjuvant treatment with Casodex in patients previously treated by radical prostatectomy or radiotherapy. Patients previously managed by watchful waiting were not enrolled into Trial 23. Because the incidence of objective disease progression (i.e., positive bone scans) was very low in placebo-treated patients in Trial 23 (<1.5%), there was no opportunity for Casodex to demonstrate efficacy in the study population. The Sponsor's explanation for the

low incidence of disease progression in this Trial, relative to that in Trial 24 and Trial 25, was that patients enrolled into Trial 23 had less advanced disease at entry and had derived greater benefit from their initial therapy. To support this position, the Sponsor presented data from 2 subset analyses across the 3 trials. These subsets consisted of:

- patients who underwent prostatectomy with locally advanced disease (Stage T3/T4) and detectable postsurgical PSA levels (PSA > 0.20 ng/mL) and
- patients who underwent radiotherapy with locally advanced disease (Stage T3/T4) and elevated preradiation PSA levels (PSA > 10 ng/mL).

The subset analysis for Casodex adjuvant treatment of patients initially treated by radical prostatectomy appeared to be somewhat supportive of the Sponsor's position. Upon further review of the of the analysis for Trial 23, however, it was learned that the numeric difference in support of the efficacy of Casodex was a result primarily of (1) objective events other than bone metastases and (2) deaths unrelated to prostate cancer. The subset analysis for Casodex adjuvant treatment of patients initially treated by radiotherapy included very few patients from Trial 23 and was not supportive of the sponsor's position. Based on the results from Trial 23, it is not possible to determine which patients who are initially treated by radical prostatectomy or radiotherapy in the US might derive benefit from adjuvant treatment with Casodex.

4.10.3 Relevance of Watchful Waiting (Immediate Therapy) Subgroups in Trials 24 and 25 to Prostate Cancer Patients in the US Managed by Watchful Waiting

Patients managed by watchful waiting in the US generally are elderly men (≥ 75 years of age), have low grade (i.e., low Gleason Score), and localized (stage T1/T2) tumors with serum PSA levels < 20 ng/mL. It is anticipated that most of these men will remain free of clinically significant prostate cancer symptoms during their lifetime and will die from causes other than prostate cancer. Based on demographic data, baseline disease characteristics, and outcomes in the watchful waiting patients, it appeared that many of the patients in Trials 24 and 25 would likely have received active therapy (radiotherapy or castration [medical or surgical]) in the US in accordance with present standards of care. It cannot be determined with a reasonable level of assurance from the non-US data if patients in the US who are generally managed by watchful waiting would have experienced a sufficient number of bone scan confirmed events in the time frame of the clinical trials to have derived clinically significant benefit from Casodex monotherapy.

The originally proposed indications and the first revision of the proposed indications for Casodex 150 mg therapy indicated that the Sponsor also was seeking approval for treatment of patients with locally advanced, non-metastatic prostate cancer. This was a concern since the efficacy of Casodex monotherapy in such patients was not compared to that of castration (the generally accepted standard of care in the US) in the trials submitted in support of this application. Data previously submitted by the Sponsor from Trials 0306 and 0307 did not adequately support the Sponsor's contention that Casodex treatment and castration (medical or surgical) were equally efficacious (based on survival) for the treatment of locally advanced non-metastatic prostate cancer. Survival in the Casodex-treated MO patients, compared to that in the patients treated by castration, differed across the 2 trials. In Trial 0306 (n = 140 M0 patients), the risk of death was calculated as 36% lower in the Casodex

group while in Trial 0307 (n = 352 M0 patients), the risk of death was calculated as 25% higher in the Casodex group. This concern has been addressed in part by the Sponsor's second revision to the proposed indication for Casodex immediate therapy. The second revision states that Casodex immediate treatment is indicated for the treatment of "localized non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated."

4.10.4 Lack of Improved Survival in Casodex-Treated Patients

Treatment with Casodex had no demonstrable effect on either disease-specific or overall survival. This finding was anticipated because of the short period of patient follow up subsequent to entry into the trials (median of 3 years follow up) and immaturity of the data.

5 INTEGRATED REVIEW OF SAFETY

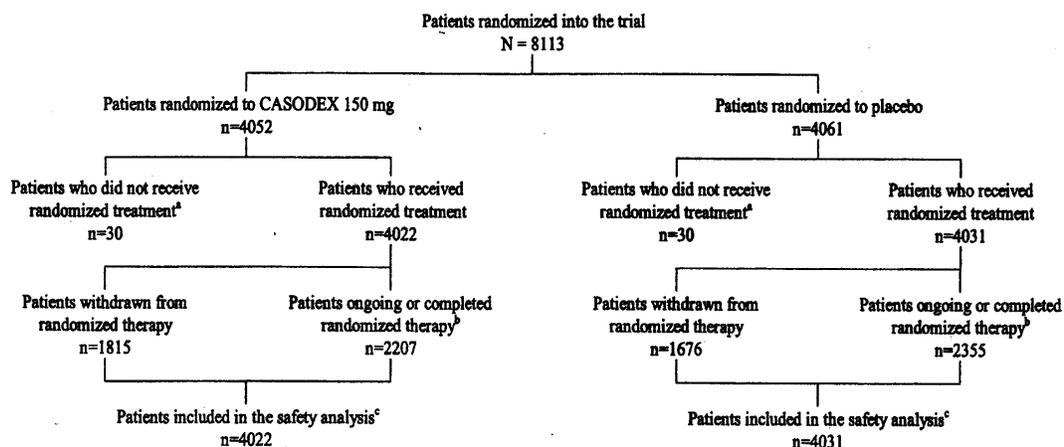
5.1 Brief Statement of Conclusions

The database from Trials 23, 24, and 25 supporting the safety of Casodex 150 mg per day was large. It included 4,022 Casodex-treated patients, representing 9,387 patient years of exposure. Overall, most patients (97.4% Casodex group, 88.2% placebo group) had at least one adverse event. The number of patients with at least 1 drug-related adverse event was approximately 3-fold higher in the Casodex group (90.5%) than the placebo group (31.4%). A greater number of patients in the Casodex group also were withdrawn from treatment because of an adverse event (27.7% compared with 9.2% of placebo-treated patients). The number of patients who had at least 1 serious adverse event was similar across the treatment groups (33.6% Casodex group, 32.5% placebo group). Much of the difference between the Casodex and placebo treatment groups in each of the categories of (1) any adverse event, (2) drug-related adverse events, and (3) adverse events leading to withdrawal was due to the pharmacological (anti-androgenic and compensatory estrogenic) actions of Casodex.

Adverse events associated with Casodex treatment can be classified for the most part into one of 2 categories: (1) those of a non-life threatening nature that are due to the pharmacological actions of Casodex and which occur with a high incidence (e.g., breast pain and gynecomastia) and (2) those that occur in a few percent of patients and which may be severe and rarely fatal (primarily hepatotoxicity). The risks of treatment with Casodex 150 mg per day appear to be justified and acceptable for patients who would derive significant benefit from treatment with Casodex.

5.2 Overview of Controlled Safety Studies (Trials 23, 24, and 25)

The sponsor submitted data from 3 randomized, double blind, placebo controlled clinical trials that enrolled men with non-metastatic prostate cancer. Enrollment criteria (with some exceptions), efficacy assessments, and safety assessments were similar across the 3 trials. Trial 23 (n = 3,254 safety patients) was conducted in North America, primarily the United States. Trial 24 (n = 3,585 safety patients) was conducted in Europe (other than Scandinavia), Israel, South Africa, Mexico, and Australia. Trial 25 (n = 1,214 safety patients) was conducted in Scandinavia. Of these patients, 4,022 received Casodex 150 mg per day and 4,031 received placebo tablets (Table 1 and Figure 2).

Figure 2 Overview of Safety Patient Population

^a Reasons for not receiving randomized treatment were as follows: bony metastases detected after informed consent given, informed consent withdrawn, starting non-randomized therapy, or other reason (not specified).

^b Patients ongoing as of data cut-off of 28 September 2001 (Trials 0024 and 0025) or completed treatment (Trial 0023).

^c Patients who did not receive any randomized trial therapy were excluded from the assessment of safety.

5.3 Protocol Defined Safety Assessments

Safety assessments in the controlled clinical trials consisted primarily of (a) monitoring for and recording of adverse events and deaths and (b) clinical laboratory measurements for signs of liver toxicity or dysfunction. Table 4 lists the times at which the protocol-required safety assessments were to be performed.

5.3.1 Adverse Events and Survival

Collection of adverse event data

An adverse event was defined by the Sponsor as “any detrimental change in the condition of the patient unrelated to prostate cancer, irrespective of whether the investigator considered that this reported change was related to trial therapy.” Adverse events were identified by spontaneous reporting by the patient and in response to a non-leading question asked by the investigator. In addition, any clinical finding or laboratory data considered by the investigator to be clinically significant or warranting treatment also was to be reported as an adverse event. All adverse events were to be reported if (1) they had an onset date or worsened while a patients was on randomized treatment or (2) they occurred within 28 days after termination of treatment or within 28 days of the onset of initiating additional systemic therapy for prostate therapy. On occasion, serious adverse events that had an onset date outside of the 28-day follow-up period also were reported.

During the first 96 weeks after treatment onset in each of the clinical trial, patients were to be monitored for adverse events and changes in liver function every 12 weeks while receiving study drug. In Trial 23, randomized treatment was limited to 96 weeks or until disease progression, whichever occurred first. In Trials 24 and 25, treatment with study drug was to continue for at least 5 years or until disease progression. Following completion of, or withdrawal from randomized treatment, patients were to be contacted every 3-12 months to collect survival data. Progression of prostate cancer and the symptoms thereof were not routinely recorded as adverse events.

Analysis and presentation of adverse event data

All patients receiving trial therapy were included in the assessment of safety. Investigator's descriptions of adverse events were categorized using an in-house dictionary of terms, based on the Food and Drug Administration's Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) system. Consolidated COSTART terms were created to pool together common COSTART preferred terms for descriptive analyses. Adverse events were summarized by consolidated COSTART-preferred term.

Deaths were attributed to either prostate cancer alone or to other causes. In contrast to adverse event data that was limited to on-treatment events, deaths that occurred from any cause, either during or after withdrawal of trial therapy, were included in the submission.

5.3.2 Clinical Laboratory Tests

Protocol-required clinical laboratory tests were limited to the assessment of liver toxicity and liver function and consisted of (1) SGOT/AST, (2) SGPT/ALT, and (3) total bilirubin. Blood samples for these measurements were collected at screening and every 12 weeks after the start of treatment with study drug.

For the most part, all samples from the clinical trials were analyzed at a central laboratory at either AstraZeneca Pharmaceuticals, Macclesfield (Trials 24 and 25, European sites only) or Quest Diagnostics, Van Nuys, CA (Trial 23) (formerly SmithKline Beecham Diagnostics). For Trial 24, samples from Australia, Israeli, Mexican, and South African centers were sent to a local laboratory in each country.

5.3.3 Assessment of Sexual Function (Trial 25 Only)

In Trial 25, sexual function during the first 48 weeks of treatment was monitored by a patient-completed shortened version of the Golombok Rust Inventory of Sexual Satisfaction (GRISS) questionnaire. The questionnaire was completed at the baseline (pre-randomization) visit and at Weeks 12, 24, 36, and 48. The questionnaire consisted of the following 6 questions:

1. Do you have sexual intercourse more than twice a week?
2. Do you become easily sexually aroused?
3. Do you fail to get an erection?
4. Do you get an erection during foreplay with your partner?
5. Are there weeks in which you don't have sex at all?
6. Do you lose your erection during intercourse?

From the scores obtained for the 6 questions, 2 measures (domains) of sexual function were calculated: infrequency (based on the sum of the scores of Questions 1 and 5) and impotence (based on the sum of the scores of Questions 2, 3, 4 and 6).

5.4 Demographics and Other Baseline Characteristics (Safety Population)

Virtually all (>99%) of the patients randomized to treatment (the efficacy population) received one or more doses of study drug. Baseline demographic data and baseline disease characteristics for the efficacy population were reviewed earlier in Section 4.6.2. Baseline demographic data are summarized in Table 8 and baseline disease characteristics are summarized in Table 9 and Table 10.

Medical Officer's Comment

- *The Casodex and placebo treatment groups were well balanced when data from the 3 clinical trials were combined as well as when assessed within each trial. However, there were significant differences across each of the trials. These differences do not affect pooling of data across the 3 trials for safety analyses, but preclude meaningful pooling of data for efficacy analyses as discussed earlier.*

5.4.1 Exposure and Duration of Treatment in the Controlled Clinical Trials

For the controlled trials, exposure was defined as the time from starting therapy to the earlier of either withdrawal of study therapy or addition of other systemic therapy for treatment of prostate cancer. If a patient had not discontinued randomized study therapy or had not received additional systemic therapy as of the date of the safety data cutoff, the time of exposure was calculated up to the last time that the patient was known to have taken study therapy.

Table 35 presents combined patient-years of exposure in the 3 controlled trials as of the 4-Month Safety Update data cutoff date of 28 September 2001. The mean and median duration of exposure to study drug was slightly higher for placebo-treated patients than for Casodex-treated patients.

Table 35 Years of Exposure to Study Drug (Trials 23, 24, and 25 Combined)

	Years of exposure	
	Casodex (N=4022)	Placebo (N=4031)
Total patient-years	9387	9778
Mean patient years	2.33	2.43
Median patient years	1.85	1.86
Range (year)	<0.01 to 5.98	<0.01 to 5.80

N = Number of patients who received randomized treatment
Source: Safety Update, Table T2.2.1.

Table 36 summarizes exposure to treatment by duration of treatment across the 3 controlled trials. Approximately 42% of patients who received Casodex (1680/4022) and placebo (1690/4031) remained on therapy for at least 2 years. At the time of data cutoff for the

Safety Update, more than 50% of the patients in Trials 24 and 25 had received at least 3 years of Casodex therapy. Unlike Trials 24 and 25, the treatment period in Trial 23 did not extend beyond 2 years.

Table 36 Duration of Treatment (Trials 23, 24, and 25 Combined)

Duration of exposure	Number (%) of patients			
	Casodex (N=4022)		Placebo (N=4031)	
<6 months	573	(14.2)	324	(8.0)
6 months to <12 months	384	(9.5)	309	(7.7)
12 months to <18 months	230	(5.7)	217	(5.4)
18 months to <24 months	1155	(28.7)	1491	(37.0)
24 months to <36 months	248	(6.2)	303	(7.5)
36 months to <48 months	706	(17.6)	708	(17.6)
48 months +	726	(18.1)	679	(16.8)

Source: Safety Update, Table T2.1.1.

Medical Officer's Comments

- *The database supporting the safety of Casodex 150 mg per day is large. More than 4,000 patients, representing more than 9,000 patient years of exposure, were treated with Casodex 150 mg per day.*
- *Patient exposure to Casodex in the controlled clinical trials was adequate to assess the likely safety profile of Casodex 150 per day in men with prostate cancer.*

5.5 Patient Disposition

At the time of data cutoff for the ISS (23 February 2001), 1,532 of 4,022 patients (38.1%) in the Casodex-treated patients and 1,282 of 4,031 patients (31.8%) in the placebo-treated patients had withdrawn prematurely from treatment with study drug. Patient disposition in each of the clinical trials is summarized in Table 37.

In Trial 23, a total of 618 (38.0%) patients in the Casodex group and 329 (20.2%) patients in the placebo group were withdrawn from the trial. Of patients withdrawing from Casodex treatment, 31.0% withdrew due to adverse events, most notably gynecomastia and breast pain. In the placebo group, 9.0% withdrew from treatment due to adverse events. In Trial 24, 841 (47.0%) patients treated with Casodex and 801 (44.6%) patients treated with placebo were withdrawn from the trial. The most common reason for withdrawal from Casodex treatment was an adverse event (27.0% of patients compared with 9.4% of placebo-treated patients). Disease progression, either subjectively or objectively confirmed, was the most common reason for withdrawal in placebo-treated patients (12.6% compared with 3.7% of Casodex-treated patients). In Trial 25, 225 (37.2%) patients were withdrawn from Casodex treatment and 328 (53.9%) were withdrawn from placebo treatment. The most common reason for withdrawal from Casodex treatment was an adverse event (17.2% of patients compared with 7.4% of placebo-treated patients). Disease progression, either subjectively or objectively confirmed, was the most common reason for withdrawal in placebo-treated patients (32.3% compared with 10.7% of Casodex-treated patients).

Table 37 Disposition of Patients in Trials 23, 24, and 25 as of 23 February 2001

Disposition	Percentage of Patients					
	Trial 23		Trial 24		Trial 25	
	Casodex (N=1627)	Placebo (N=1627)	Casodex (N=1790)	Placebo (N=1795)	Casodex (N=605)	Placebo (N=609)
Treatment completed or ongoing ¹	62.0%	79.8%	53.0%	55.4%	62.8%	46.1%
Premature termination of treatment	38.0%	20.2%	47.0%	44.6%	37.2%	53.9%
Death	0.6%	0.8%	3.4%	2.6%	4.6%	3.3%
Disease progression ²	0.3%	0.7%	3.7%	12.6%	10.7%	32.3%
Adverse event	31.0%	9.0%	27.0%	9.4%	17.2%	7.4%
Non-compliance	0.4%	0.6%	0.8%	0.9%	0.2%	0.2%
Patient's decision	5.0%	5.4%	9.0%	7.6%	3.6%	5.3%
Investigator decision	0.6%	3.6%	--	--	--	--
Lost to follow up	--	--	0.8%	1.2%	0.2%	0.7%
Other ³	0.1%	0.1%	2.1%	10.3%	0.7%	4.8%

1. Treatment period in Trial 23 ended prior to 23 February 2001. Treatment in Trials 24 and 25 is ongoing.

2. Includes objective and subjective progression but not an increase in PSA alone.

3. Includes increase in PSA, need for other systemic therapy, and investigator's decision (Trials 24 and 25).

Source: Text Table 2, Safety Addendum Report for each of Trials 23, 24, and 25.

Medical Officer's Comments

- *In each of the clinical trials, the most common cause for premature termination of treatment with Casodex was an adverse event. Adverse events were responsible for premature termination in 31.0%, 27.0%, and 17.2% of Casodex-treated patients in Trials 23, 24, and 25, respectively. In each of the trials, the percentage of patients terminating prematurely due to an adverse event was higher in the Casodex-treated patients. In each of the trials, breast pain or gynecomastia was the most common adverse event leading to premature termination of treatment in these patients.*
- *In placebo-treated patients, the most common cause for premature termination of treatment was either an adverse event (Trial 23) or disease progression (Trial 24 and Trial 25).*

5.6 Adverse Events

In this review, adverse events for Trials 23, 24, and 25 are presented and discussed in the following manner. An overview of reported adverse events, based on the numbers of patients reporting adverse events summarized into broad categories, is first presented (Section 5.6.1). This is followed by a summary and discussion of (1) the most commonly reported adverse events (all degrees of severity and all relationships to study drugs, Section 5.6.2), (2) the most commonly reported adverse events possibly related to treatment with study drugs (Section 5.6.3), (3) adverse events that resulted in withdrawal of patients from the clinical trials (Section 5.6.4), and (4) serious adverse events reported during the treatment period (Section 5.6.5). In these trials, clinical signs or symptoms that were related to progression of prostate cancer were not considered as adverse events and were not in general reported or included in data summaries or listings.

Deaths from all causes other than prostate cancer are discussed in Section 5.7. Adverse events of particular interest (e.g., pharmacological adverse events such as gynecomastia) or

adverse events of particular concern based on the reported safety data (e.g., liver toxicity and blood dyscrasias) are reviewed separately in Section 5.9.

5.6.1 Overview of Adverse Events

Table 38 provides an overview of the proportion of patients who experienced adverse events across the 3 clinical trials during treatment with study drug. Overall, most patients (97.4% Casodex group, 88.2% placebo group) had at least one adverse event. The number of patients with at least 1 drug-related adverse event was approximately 3-fold higher in the Casodex group (90.5%) than the placebo group (31.4%). A greater number of patients in the Casodex group also were withdrawn from treatment because of an adverse event (27.7% compared with 9.2% of placebo-treated patients). The number of patients who had at least 1 serious adverse event was similar across the treatment groups (33.6% Casodex group, 32.5% placebo group). The percentage of patients with an adverse event leading to death (a non-prostate cancer related death that occurred within the treatment period) was slightly higher in the Casodex group (4.2% compared to 3.6% in placebo-treated patients).

Table 38 Overview of Adverse Events during Treatment (Trials 23, 24, and 25)

Category ¹	Number (%) of patients			
	Casodex (N=4022) ²		Placebo (N=4031)	
Patients with at least 1 adverse event	3916	(97.4)	3555	(88.2)
Drug-related adverse events	3641	(90.5)	1267	(31.4)
Adverse events leading to withdrawal	1116	(27.7)	369	(9.2)
Serious adverse events	1350	(33.6)	1310	(32.5)
Adverse events leading to death ³	168	(4.2)	145	(3.6)

1. Patients may appear in more than 1 category.

2. N = number of patients who received randomized treatment.

3. Does not include deaths attributed to prostate cancer.

Source: Safety Update. Data derived from Table T3.1.1.

Medical Officer's Comments

- *Much of the difference between the Casodex and placebo treatment groups in each of the categories of (1) patients with at least 1 adverse event, (2) drug-related adverse events, and (3) adverse events leading to withdrawal was due to the pharmacological (anti-androgenic and compensatory estrogenic) actions of Casodex, particularly breast pain and gynecomastia, as shown in the Table below.*

Category	Number (%) of patients			
	Casodex (N=4022)		Placebo (N=4031)	
<i>Any adverse event</i>				
<i>All Causes</i>	3916	(97.4)	3555	(88.2)
<i>Gynecomastia and breast pain excluded</i>	3583	(89.1)	3517	(87.2)
<i>Drug-related adverse events</i>				
<i>All Causes</i>	3641	(90.5)	1267	(31.4)
<i>Gynecomastia and breast pain excluded</i>	1700	(42.3)	962	(23.9)
<i>Adverse events leading to withdrawal</i>				
<i>All Causes</i>	1116	(27.7)	369	(9.2)
<i>Gynecomastia and breast pain excluded</i>	579	(14.4)	350	(8.7)

Source: Tables T3.1.1 and T3.1.8 from Safety Update.

Table 39 provides an overview of the proportion of patients who experienced adverse events within each of Trials 23, 24, and 25 during treatment with study drug.

Table 39 Overview of Adverse Events by Clinical Trial during Randomized Treatment

Category ¹	Percentage of Patients with Event					
	Trial 23		Trial 24		Trial 25	
	Casodex N=1627	Placebo N=1627	Casodex N=1790	Placebo N=1795	Casodex N=605	Placebo N=609
Patients with ≥ 1 adverse event	98.1	90.4	95.9	85.7	98.7	87.4
Drug related adverse event	92.8	31.8	87.5	32.0	92.7	26.3
AE leading to withdrawal	31.0	9.0	27.3	9.4	17.2	7.1
Serious adverse event	17.8	18.6	38.2	37.3	50.4	44.3
AE leading to death ²	1.2	1.5	4.7	4.3	6.9	4.4

1. Patients may appear in more than 1 category.

2. Does not include deaths attributed to prostate cancer.

N = number of patients who received randomized treatment.

Source: ISS, Table T3.1.2.

Medical Officer's Comments

- *The proportion of patients experiencing adverse events in each of the categories listed in Table 39 were similar across the 3 trials with the following exceptions:*
 - *In the Casodex-treatment groups, adverse events leading to withdrawal occurred most frequently in Trial 23 (31.0% of patients) and least frequently in Trial 25 (17.2% of patients).*
 - *The proportion of patients with serious adverse events was approximately 2-fold and 2.5-fold greater in Trials 24 and 25, respectively, compared to Trial 23.*
 - *The proportion of patients with adverse events leading to death was highest in Trial 25 and lowest in Trial 23.*

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

The majority of patients enrolled in the clinical trials had at least 1 adverse event. In the Casodex treatment group, 3,916 of 4,022 patients (97.4%) reported one or more adverse events compared with 3,555 of 4,031 patients (88.2%) in the placebo treatment group. Adverse events that occurred in 5% or more of the patients in either of the treatment groups are listed in Table 40 by decreasing incidence in the Casodex-treated patients. Adverse events more common in the Casodex-treatment group than in the placebo group included breast pain, gynecomastia, alopecia, weight gain, vasodilatation, impotence, and asthenia. The majority of these latter adverse events were considered by the investigator to be related to study drug.

Medical Officer's Comments

- *Much of difference in the proportion of patients reporting the adverse events listed in Table 40 can be attributed to the pharmacological (anti-androgenic and compensatory estrogenic) effects of treatment with Casodex.*

- *The observed incidence of non-pharmacological adverse events is not unexpected in a population of elderly men (mean age >65 years) with prostate cancer.*
- *Other adverse events of possible clinical importance that were reported with a frequency of < 5% but which occurred more frequently in Casodex-treated patients were heart failure (2.1% Casodex, 1.4% placebo) and abnormal liver function tests (3.0% Casodex; 1.5% placebo). These are reviewed and discussed later in Section 5.9.*

Table 40 Adverse Events with an Incidence \geq 5% (Combined Data from Trials 23, 24, and 25)

Adverse Event	Number of patients reporting adverse event				Relative Incidence <u>Casodex</u> placebo
	Casodex (N = 4022)		Placebo (N = 4031)		
	n ¹	(%)	n ¹	(%)	
Breast pain	2937	(73.0)	296	(7.3)	9.94
Gynecomastia	2700	(67.1)	325	(8.1)	8.33
Asthenia	427	(10.6)	303	(7.5)	1.41
Pharyngitis	415	(10.3)	441	(10.9)	0.94
Rash	390	(9.7)	324	(8.0)	1.21
Back pain	367	(9.1)	442	(11.0)	0.83
Vasodilatation	364	(9.1)	211	(5.2)	1.73
Impotence	362	(9.0)	250	(6.2)	1.45
Constipation	344	(8.6)	283	(7.0)	1.22
Arthralgia	314	(7.8)	378	(9.4)	0.83
Urinary tract infection	299	(7.4)	259	(6.4)	1.16
Flu syndrome	295	(7.3)	296	(7.3)	1.00
Abdominal pain	275	(6.8)	278	(6.9)	0.99
Hypertension	271	(6.7)	303	(7.5)	0.90
Diarrhea	263	(6.5)	268	(6.7)	0.98
Urinary incontinence	261	(6.5)	237	(5.9)	1.10
Pain	258	(6.4)	286	(7.1)	0.90
Pelvic pain	258	(6.4)	261	(6.5)	0.99
Alopecia	239	(5.9)	31	(0.8)	7.73
Urinary tract disorder	234	(5.8)	277	(6.9)	0.85
Weight gain	231	(5.7)	115	(2.9)	2.01
Edema	226	(5.6)	206	(5.1)	1.10
Hernia	195	(4.9)	242	(6.0)	0.81
Headache	191	(4.8)	204	(5.1)	0.94
Hematuria	183	(4.6)	235	(5.8)	0.78
Accidental injury	171	(4.3)	225	(5.6)	0.76

¹ Number of patients reporting the respective adverse event.
Source: Modified from Text Table 12, ISS, pg. 32.

5.6.3 Treatment-Related Adverse Events

Treatment-related adverse events were reported for 3,641 of 4,022 patients (90.5%) in the Casodex treatment group and 1,267 of 4,031 patients (31.4%) in the placebo treatment group. Treatment-related adverse events that occurred in $\geq 0.5\%$ of the patients in either of the treatment groups are listed in Table 41 by decreasing incidence in the Casodex-treated patients. Of the treatment-related adverse events listed in Table 41, 28 of 29 occurred more frequently in Casodex-treated patients. The most commonly reported treatment-related adverse events in the Casodex treatment group were breast pain (72.3% of patients), gynecomastia (66.7%), vasodilatation (8.5%), impotence (5.8%), asthenia (5.1%), alopecia (4.7%), and weight gain (4.0%).

Medical Officer's Comments

- *Among the most commonly reported treatment-related adverse events, the increased incidence in the Casodex-treated patients was most likely a consequence of the pharmacological activity of the drug. These events are discussed further in Section 5.9.1.*
- *When the adverse events of breast pain and gynecomastia were eliminated from consideration, the difference between the proportion of Casodex-treated and placebo-treated patients who experienced one or more treatment-related adverse events was reduced from 90.5% (Casodex) vs. 31.4% (placebo) to 42.3% (Casodex) vs. 23.9% (placebo).*
- *Drug-related adverse events of particular concern that occurred more frequently in the Casodex treated patients were abnormal liver function tests (Casodex group 2.5%; placebo group 1.0%) and jaundice (Casodex group 0.8%; placebo group 0.4%). These events are discussed further in Section 5.9.*

Table 41. Treatment-Related Adverse Events Occurring in $\geq 0.5\%$ of Patients (Combined Data from Trials 23, 24, and 25)

Adverse Event	Number of patients reporting adverse event				Relative Incidence
	Casodex (N = 4022)		Placebo (N = 4031)		
	n ¹	Percentage	n ¹	Percentage	Casodex placebo
Breast pain	2906	72.3%	282	7.0%	10.33
Gynecomastia	2681	66.7%	320	7.9%	8.40
Vasodilatation	342	8.5%	185	4.6%	1.85
Impotence	233	5.8%	112	2.8%	2.09
Asthenia	206	5.1%	105	2.6%	1.97
Alopecia	190	4.7%	19	0.5%	10.02
Weight gain	161	4.0%	61	1.5%	2.65
Rash	141	3.5%	66	1.6%	2.14
Libido decreased	122	3.0%	35	0.9%	3.49
Constipation	103	2.6%	49	1.2%	2.11
Diarrhea	103	2.6%	82	2.0%	1.26
Liver function tests abnormal	99	2.5%	39	1.0%	2.54
Nausea	88	2.2%	42	1.0%	2.10
Somnolence	78	1.9%	39	1.0%	2.00
Pruritus	76	1.9%	30	0.7%	2.54
Hirsutism	46	1.1%	6	0.1%	7.68
Abdominal pain	45	1.1%	24	0.6%	1.88
Dizziness	39	1.0%	18	0.4%	2.17
Headache	37	0.9%	26	0.6%	1.43
Edema	37	0.9%	13	0.3%	2.85
Sweating	36	0.9%	28	0.7%	1.29
Dyspepsia	31	0.8%	33	0.8%	0.94
Jaundice	31	0.8%	16	0.4%	1.94
Depression	29	0.7%	8	0.2%	3.63
Pelvic pain	27	0.7%	8	0.2%	3.38
Chest pain	24	0.6%	5	0.1%	4.81
Sleep disorder	24	0.6%	8	0.2%	3.01
Emotional lability	21	0.5%	2	<0.1%	10.52
Anxiety	20	0.5%	5	0.1%	4.01

¹ Number of patients reporting the event.

Source: Modified from ISS, Text Table 16, pg. 40.

5.6.4 Adverse Events Resulting in Patient Withdrawal

Adverse events resulting in patient withdrawal were reported for 1,116 of 4,022 patients (27.7%) in the Casodex treatment group and 369 of 4,031 patients (9.2%) in the placebo treatment group. Adverse events resulting in patient withdrawal that occurred in $\geq 0.3\%$ of patients in either of the treatment groups are listed in Table 42 by decreasing incidence in the Casodex-treated patients. The most frequently reported adverse events leading to withdrawal

in the Casodex-treated patients were breast pain (12.5% of patients), gynecomastia (10.6%), asthenia (1.4%), abnormal liver function tests (1.2%), vasodilatation (0.9%), and impotence (0.7%).

Table 42 Adverse Events with an Incidence \geq 0.3% Leading to Withdrawal (Combined Data from Trials 23, 24, and 25)

Adverse Event	Number of patients reporting adverse event				Relative Incidence
	Casodex (N = 4022)		Placebo (N = 4031)		
	n ¹	Percentage	n ¹	Percentage	Casodex placebo
Breast pain	504	12.5%	15	0.4%	33.68
Gynecomastia	425	10.6%	16	0.4%	26.62
Asthenia	56	1.4%	18	0.5%	3.12
Liver function tests abnormal	47	1.2%	18	0.5%	2.62
Vasodilatation	36	0.9%	14	0.4%	2.58
Impotence	29	0.7%	6	0.2%	4.84
Myocardial infarction	27	0.7%	33	0.8%	0.82
Nausea	26	0.7%	14	0.4%	1.86
Rash	26	0.7%	14	0.4%	1.86
Libido decreased	25	0.6%	9	0.2%	2.78
Abdominal pain	23	0.6%	14	0.4%	1.65
Gastrointestinal carcinoma	22	0.6%	18	0.5%	1.22
Weight gain	22	0.6%	6	0.2%	3.67
Diarrhea	21	0.5%	20	0.5%	1.05
Somnolence	20	0.5%	5	0.1%	4.01
Heart failure	17	0.4%	3	0.1%	5.68
Jaundice	17	0.4%	6	0.2%	2.84
Carcinoma of lung	17	0.4%	20	0.5%	0.85
Depression	15	0.4%	6	0.2%	2.51
Cerebrovascular accident	14	0.4%	30	0.7%	0.47
Constipation	14	0.4%	6	0.2%	2.34
Dizziness	14	0.4%	10	0.3%	1.40
Heart arrest	13	0.3%	6	0.2%	2.17
Pruritus	13	0.3%	3	0.1%	4.34
Headache	11	0.3%	4	0.1%	2.76
Chest pain	10	0.3%	4	0.1%	2.51
Angina pectoris	10	0.3%	8	0.2%	1.25
Anxiety	10	0.3%	3	0.1%	3.34
Dyspnea	10	0.3%	6	0.2%	1.67
Pneumonia	5	0.1%	11	0.3%	0.46

Source: Safety Update, Text Table 20, pg. 47.

Medical Officer's Comments

- *When the adverse events of breast pain and gynecomastia were eliminated from consideration, the difference between the proportion of Casodex-treated and placebo-treated patients who experienced one or more adverse events leading to withdrawal was reduced from 27.7% (Casodex) vs. 9.2% (placebo) to 14.4% (Casodex) vs. 8.7% (placebo).*
- *Of the 23 adverse events listed in Table 42 that were not likely to be a direct result of the pharmacological activity of Casodex, 18 of the 23 events occurred in a higher proportion of Casodex-treated patients than placebo-treated patients (events with a relative incidence ≥ 1.2 [Casodex vs. placebo]).*
- *Adverse events of particular concern, with an incidence at least 2-fold greater in Casodex-treated patients, that lead to withdrawal of treatment involved the cardiovascular system and liver toxicity. These adverse events and their relative incidence (Casodex/placebo) included heart failure (5.68), heart arrest (2.17), abnormal liver function tests (2.62), and jaundice (2.84). Cardiovascular adverse events and liver toxicity are reviewed in Section 5.9.*

5.6.5 Serious Adverse Events during the Treatment Period

Adverse events classified as serious were reported for 1,350 of 4,022 patients (33.6%) in the Casodex treatment group and 1,310 of 4,031 patients (32.5%) in the placebo treatment group. Serious adverse events that occurred in $\geq 0.5\%$ of the patients during the treatment period in either of the treatment groups are listed in Table 43, arranged by decreasing incidence in the Casodex-treated patients.

Medical Officer's Comments

- *Serious adverse events were reported by approximately equal proportions of patients in the 2 treatment groups.*
- *The types of reported serious adverse events were generally similar across the 2 treatment groups. Among the adverse events listed in Table 43, there were 16 instances in which the incidence of the adverse event in the Casodex group exceeded that in the placebo group by at least 20% (relative incidence >1.2). Conversely, there were 16 instances in which the incidence of the adverse event in the placebo group exceeded that in the Casodex group by at least 20% (relative incidence Casodex/placebo ≤ 0.83).*
- *Several serious cardiac-related adverse events were reported in a slightly higher proportion of Casodex-treated patients (heart failure: 1.5% vs. 0.9%; heart arrest: 0.5% vs. 0.2%; chest pain: 1.4% vs. 0.7%). However, other serious cardiac-related adverse events were reported in a slightly higher proportion of placebo-treated patients (myocardial infarct: 1.8% [Casodex] vs. 2.4% [placebo]; myocardial ischemia: 1.3% [Casodex] vs. 1.6%[placebo]). Cardiac-related adverse events are discussed further in Section 5.9.*
- *In general, the majority of the serious adverse events reported are compatible with the age and disease status of an elderly population of men with prostate cancer.*

Table 43 Serious Adverse Events with Incidence $\geq 0.5\%$ during Treatment Period

Adverse Event	Number of patients reporting adverse event				Relative Incidence <u>Casodex</u> placebo
	Casodex (N = 4022)		Placebo (N = 4031)		
	n ¹	Percentage	n ¹	Percentage	
Gynecomastia	109	2.7%	1	<0.1%	109.24
Urinary tract disorder	103	2.6%	109	2.7%	0.95
Hernia	87	2.2%	108	2.7%	0.81
Myocardial infarct	72	1.8%	97	2.4%	0.74
Angina pectoris	71	1.8%	66	1.6%	1.08
Heart failure	61	1.5%	36	0.9%	1.70
Pneumonia	60	1.5%	61	1.5%	0.99
Chest pain	56	1.4%	29	0.7%	1.94
Myocardial ischemia	54	1.3%	64	1.6%	0.85
Infection	52	1.3%	30	0.7%	1.74
Gastrointestinal carcinoma	45	1.1%	37	0.9%	1.22
Accidental injury	41	1.0%	65	1.6%	0.63
Urinary retention	38	0.9%	68	1.7%	0.56
Cerebrovascular accident	37	0.9%	71	1.8%	0.52
Dyspnea	33	0.8%	39	1.0%	0.85
Breast pain	30	0.7%	1	<0.1%	30.07
Abdominal pain	29	0.7%	19	0.5%	1.53
Urinary tract infection	29	0.7%	21	0.5%	1.38
Cardiovascular disorder	28	0.7%	37	0.9%	0.76
Skin carcinoma	28	0.7%	24	0.6%	1.17
Arthritis	26	0.6%	19	0.5%	1.37
Arthrosis	26	0.6%	25	0.6%	1.04
Atrial arrhythmia	25	0.6%	35	0.9%	0.72
Cholelithiasis	25	0.6%	11	0.3%	2.28
Carcinoma of lung	23	0.6%	27	0.7%	0.85
Hematuria	23	0.6%	33	0.8%	0.70
Anemia	22	0.5%	16	0.4%	1.38
Cholecystitis	20	0.5%	15	0.4%	1.34
Kidney calculus	20	0.5%	31	0.8%	0.65
Urinary incontinence	20	0.5%	11	0.3%	1.82
Pain	19	0.5%	15	0.4%	1.27
Heart arrest	19	0.5%	7	0.2%	2.72
Cataract specified	19	0.5%	32	0.8%	0.60
Back pain	18	0.4%	21	0.5%	0.86
Syncope	18	0.4%	14	0.3%	1.29
Hypertension	15	0.4%	24	0.6%	0.63
Sepsis	13	0.3%	19	0.5%	0.69
Rectal hemorrhage	13	0.3%	19	0.5%	0.69
Pathological fracture	13	0.3%	21	0.5%	0.62
Vascular disorder	11	0.3%	27	0.7%	0.41
Urination impaired	7	0.2%	19	0.5%	0.37

Source: Safety Update, Text Table 22, pg. 51, and Table T5.2.3.

5.7 Deaths

The number (and percentage) of patients in each treatment group who died in Trials 23, 24, and 25 (data combined across trials) are listed in Table 44. As of the data cutoff date for the Safety Update (28 September 2001), 445 of 4,022 patients (11.1%) who received Casodex and 432 of 4,031 patients (10.7%) who received placebo had died. The majority of deaths in each of the treatment groups was due to reasons other than prostate cancer.

Table 44 Number and Percentage of Deaths in Trials 23, 24, and 25 (Combined Data)

Category	Number (%) of patients			
	Casodex (N=4022)		Placebo (N=4031)	
Total deaths (number [%]) ¹	445	(11.1)	432	(10.7)
Deaths due to prostate cancer alone	119	(3.0)	128	(3.2)
Deaths not due to prostate cancer	326	(8.1)	304	(7.5)
Deaths due to adverse events ²	177	(4.4)	150	(3.7)
Deaths due to drug-related adverse event	7	(0.2)	1	(<0.1)
Deaths outside of treatment period	149	(3.7)	154	(3.8)

N = number of patients who received randomized treatment.

¹ Two patients who received no therapy also died.

² Includes deaths during the treatment period and deaths due to an adverse event that started during the treatment period.

Source: Data derived from Tables T4.1 and T4.5 of Safety Update.

Medical Officer's Comment

- *The number of patients who were reported to have died due to prostate cancer alone was slightly higher in the placebo group. Conversely, the number of patients who were reported to have died due to causes other than prostate cancer was slightly higher in the Casodex group. The small numeric excess of deaths not due to prostate cancer appear to have occurred during the treatment period (i.e., deaths listed by the Sponsor as "deaths due to adverse events."*

The number (and percentage) of patients in each treatment group who died in each of Trials 23, 24, and 25 are listed in Table 45. Within each of the trials, the number of deaths in the Casodex and placebo treatment groups were similar. However, the proportions of patients who died from prostate cancer or other causes varied across the 3 trials. Total deaths across the trials ranged from approximately 6% (Trial 23) to 18% (Trial 25).

Table 45 Number and percentages of Deaths in Each of Trials 23, 24, and 25

Cause of Death	Study 23		Study 24		Study 25	
	Casodex N= 1647	Placebo N=1645	Casodex N= 1798	Placebo N=1805	Casodex N= 607	Placebo N= 611
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Prostate cancer	14 (0.9)	6 (0.4)	56 (3.1)	66 (3.7)	49 (8.1)	56 (9.2)
Other	91 (5.6)	93 (5.7)	168 (9.4)	161 (9.0)	67 (11.1)	50 (8.2)
Total	105 (6.5)	99 (6.1)	224 (12.5)	227 (12.7)	116 (19.2)	106 (17.4)

Sources: Safety Update (SAS files) and submission of 17 May 2002.

Medical Officer's Comments

- *The proportion of patients who died of prostate cancer in the placebo treatment groups showed considerable variation across the 3 trials and was approximately 9-fold and 23-fold greater in Trial 24 and Trial 25, respectively, than in Trial 23.*
- *More patients also died of causes unrelated to prostate cancer in each of Trials 24 and 25 than in Trial 23. The proportions of patients who died of causes other than prostate cancer were slightly less than 2-fold greater in each of Trials 24 and 25 compared to Trial 23.*

There were 8 instances in which a death was considered by the investigator to be possibly related to treatment with study drug (Table 46). Seven (7) of these 8 deaths occurred in patients treated with Casodex.

Table 46 Primary Causes of Death due to Drug-Related Adverse Events

Body system Consolidated COSTART term	Number (%) of patients who died	
	Casodex (N=4022)	Placebo (N=4031)
Cardiovascular system		
Cerebrovascular accident	1 (<0.1)	0
Myocardial infarction	1 (<0.1)	0
Myocardial ischemia	1 (<0.1)	0
Pulmonary embolus	1 (<0.1)	0
Digestive system		
Pancreas disorder	1 (<0.1)	0
Hemic/lymphatic system		
Blood dyscrasia	2 (0.1)	0
Urogenital system		
Kidney failure	0	1 (<0.1)
Total	7 (0.2)	1 (<0.1)

Source: Safety Update, Text Table 18, pg. 43.

Medical Officer's Comments

- *The observed imbalance in drug-related deaths should be viewed with reservation. Therapy in the clinical trials was not completely blinded due to the high incidence of pharmacological adverse events. It is unlikely that investigators would attribute a non-prostate cancer death to "placebo therapy."*
- *Cardiac adverse events and acute myelogenous leukemia or myelodysplasia syndrome are reviewed in Section 5.9.4 and Section 5.9.5.2.*

The number (and percentage) of patients whose primary cause of death was classified within each of the COSTART body systems are listed in Table 47. Deaths are further classified in terms of time of occurrence, i.e., during treatment with study drug or posttreatment. Patients whose primary cause of death was prostate cancer are not included in the Table. The body systems associated with the highest number of total deaths (those occurring either during or following treatment) in the Casodex treated patients were cardiovascular (n=143), respiratory

(n=62), digestive (n=42) and body as a whole (n=42). These 4 body systems accounted for 289 of 326 (88.7%) of the non-prostate cancer deaths. Total deaths in the placebo treated patients followed a similar pattern with the cardiovascular (n=122), respiratory (n=72), digestive (n=36) and body as a whole (n=44) body systems accounting for 274 of 304 (90.1%) of deaths.

Table 47 Number (%) of Patients with Primary Cause of Death Classified by COSTART Body System Term and Treatment Period (All Trials)

Body System	Treatment Period	Number (%) of patients with cause of death ¹				Relative Incidence <u>Casodex</u> placebo
		Casodex (N = 4022)		Placebo (N = 4031)		
		n	Percentage	n	Percentage	
Body as a whole	During Treatment	18	0.45	11	0.27	1.64
	Post Treatment	24	0.60	33	0.82	0.73
	<i>Total</i>	42	1.04	44	1.09	0.96
Cardiovascular	During Treatment	77	1.91	66	1.64	1.17
	Post Treatment	66	1.64	56	1.39	1.18
	<i>Total</i>	143	3.56	122	3.03	1.17
Digestive	During Treatment	24	0.60	17	0.42	1.41
	Post Treatment	18	0.45	19	0.47	0.95
	<i>Total</i>	42	1.04	36	0.89	1.17
Endocrine	Post Treatment	1	0.02	1	0.02	1.00
	<i>Total</i>	1	0.02	1	0.02	1.00
Hematopoietic/ lymphatic	During Treatment	10	0.25	4	0.10	2.51
	Post Treatment	3	0.07	2	0.05	1.50
	<i>Total</i>	13	0.32	6	0.15	2.17
Metabolic and nutritional	During Treatment	2	0.05	2	0.05	1.00
	Post Treatment	1	0.02	2	0.05	0.50
	<i>Total</i>	3	0.07	4	0.10	0.75
Musculoskeletal	During Treatment	0	0.00	2	0.05	0.00
	Post Treatment	1	0.02	1	0.02	1.00
	<i>Total</i>	1	0.02	3	0.07	0.33
Nervous	During Treatment	4	0.10	4	0.10	1.00
	Post Treatment	3	0.07	3	0.07	1.00
	<i>Total</i>	7	0.17	7	0.17	1.00
Respiratory	During Treatment	29	0.72	36	0.89	0.81
	Post Treatment	33	0.82	36	0.89	0.92
	<i>Total</i>	62	1.54	72	1.79	0.86
Skin/appendages	During Treatment	1	0.02	2	0.05	0.50
	Post Treatment	1	0.02	0	0.00	NC
	<i>Total</i>	2	0.05	2	0.05	1.00
Urogenital	During Treatment	3	0.07	2	0.05	1.50
	Post Treatment	4	0.10	5	0.12	0.80
	<i>Total</i>	7	0.17	7	0.17	1.00

¹ Patients whose primary cause of death was prostate cancer are NOT included in the listing.
Source: Safety Update, Table T4.4.

Medical Officer's Comment

- *A greater percentage of patients treated with Casodex, compared to placebo-treated patients, died of primary causes that linked to the hematopoietic/lymphatic (0.32% vs. 0.15%; relative incidence 2.17), cardiovascular (3.56% vs. 3.03%; relative incidence 1.17), and digestive (1.04% vs. 0.89%; relative incidence 1.17) body systems. For the most part, these imbalances were a result of increased numbers of deaths that occurred during the period of treatment with study drug and not during the post treatment period.*

The primary causes of death (other than that of prostate cancer) and the number (%) of patients who died of these causes during the treatment period are listed by COSTART body system and COSTART preferred term in Table 48. Cardiovascular events were the major cause of death with 77 cases reported in Casodex-treated patients and 66 cases reported in placebo-treated patients (relative incidence, Casodex/placebo: 1.17). Of the cardiac-related deaths in Casodex-treated patients, deaths due to myocardial infarction (n=24), heart failure (n=15), and heart arrest (n=12) were the most commonly reported events. In the placebo-treated patients, deaths due to myocardial infarction, heart failure, and heart arrest were reported for 31, 1, and 5 patients, respectively.

Deaths that linked to the respiratory system were the second most frequent in both treatment groups, occurring in 29 Casodex-treated and 36 placebo-treated patients.

Deaths that linked to the digestive system were the third most frequent, affecting 24 Casodex-treated patients and 17 placebo-treated patients (relative incidence, Casodex/placebo: 1.41). Among this group, gastrointestinal carcinoma was the most common single cause of death, affecting 18 Casodex-treated patients and 10 placebo-treated patients.

Medical Officer's Comments

- *As would be expected in a population of elderly men, cardiovascular events were the major cause of death unrelated to prostate cancer in both treatment groups. There was an excess of cardiovascular deaths due to myocardial infarction, heart failure, and heart arrest in the Casodex-treated patients (n=51) compared to the number of similarly classified deaths in the placebo-treated patients (n=37). This imbalance was partially offset by other causes of cardiovascular death in the placebo-treated patients and is discussed further in Section 5.9.4.1.*
- *The imbalance in deaths related to the digestive system (greater in Casodex-treated patients) was due largely to the increased number of patients who died from a gastrointestinal malignancy in the Casodex-treated patients (n=18) compared to the number of similar deaths in the placebo-treated patients (n=10).*
- *Deaths that linked to the hematopoietic/lymphatic body were 2.5-fold more common in Casodex-treated patients. These are discussed in Section 5.9.5.2.*

Table 48 Primary Causes of Death (Other than Prostate Cancer) during the Treatment Period (Trials 23, 24, and 25 Combined)

Body System Cause of Death (COSTART term)	Number (%) of patients with cause of death				Relative Incidence <u>Casodex</u> placebo
	Casodex (N = 4022)		Placebo (N = 4031)		
	n	Percentage	n	Percentage	
Body as a whole	18	0.45	11	0.27	1.64
Accidental injury	2	0.05	2	0.05	1.00
Ascites	1	0.02	0	0.00	NC ²
Carcinoma	2	0.05	1	0.02	2.00
Death ¹	7	0.17	0	0.00	NC
Gangrene	1	0.02	0	0.00	NC
Neoplasm	1	0.02	3	0.07	0.33
Peritonitis	0	0.00	1	0.02	0.00
Sarcoma	2	0.05	1	0.02	2.00
Sepsis	1	0.02	1	0.02	1.00
Suicide	1	0.02	2	0.05	0.50
Cardiovascular	77	1.91	66	1.64	1.17
Arrhythmia	0	0.00	2	0.05	0.00
Arteriosclerosis	2	0.05	0	0.00	NC
Cardiomegaly	1	0.02	0	0.00	NC
Cardiomyopathy	1	0.02	2	0.05	0.50
Cardiovascular disorder	2	0.05	2	0.05	1.00
Cerebrovascular accident	11	0.27	15	0.37	0.73
Embolus	0	0.00	1	0.02	0.00
Heart arrest	12	0.30	5	0.12	2.41
Heart failure	15	0.37	1	0.02	15.03
Intracranial hemorrhage	1	0.02	0	0.00	NC
Myocardial infarction	24	0.60	31	0.77	0.78
Myocardial ischemia	4	0.10	5	0.12	0.80
Pulmonary embolus	4	0.10	2	0.05	2.00
Digestive	24	0.60	17	0.42	1.41
Cirrhosis of liver	0	0.00	1	0.02	0.00
Gastrointestinal carcinoma	18	0.45	10	0.25	1.80
Gastrointestinal hemorrhage	1	0.02	2	0.05	0.50
GI neoplasia	2	0.05	1	0.02	2.00
Hepatoma	1	0.02	2	0.05	0.50
Intestinal obstruction	1	0.02	0	0.00	NC
Pancreas disorder	1	0.02	0	0.00	NC
Rectal hemorrhage	0	0.00	1	0.02	0.00

¹ Not otherwise specified.² Not calculated.

(Continued)

Source: Safety Update. Text Table 17, pg. 39 and Table T4.3.

Table 47 Primary Cause of Death (other than Prostate Cancer) during the Treatment Period (Trials 23, 24, and 25 Combined)

Body System Cause of Death (COSTART term)	Number (%) of patients with cause of death				Relative Incidence <u>Casodex</u> placebo
	Casodex (N = 4022)		Placebo (N = 4031)		
	n	Percentage	n	Percentage	
Hematopoietic/lymphatic	10	0.25	4	0.10	2.50
Acute leukemia	2	0.05	1	0.02	2.00
Blood dyscrasia	2	0.05	0	0.00	NC ²
Chronic myelocytic leukemia	1	0.02	1	0.02	1.00
Leukemia	1	0.02	0	0.00	NC
Lymphoma like reaction	4	0.10	1	0.02	4.01
Myeloma	0	0.00	1	0.02	0.00
Metabolic and nutritional	2	0.05	2	0.05	1.00
Hypoxia	1	0.02	0	0.00	NC
Uremia	0	0.00	1	0.02	0.00
Weight loss	1	0.02	1	0.02	1.00
Musculoskeletal		0.00		0.00	NC
Muscle atrophy	0	0.00	2	0.05	0.00
Nervous	4	0.10	4	0.10	1.00
CNS neoplasia	1	0.02	3	0.07	0.33
Dementia	2	0.05	0	0.00	NC
Extrapyramidal syndrome	0	0.00	1	0.02	0.00
Meningitis	1	0.02	0	0.00	NC
Respiratory	29	0.72	36	0.89	0.81
Apnea	3	0.07	4	0.10	0.75
Bronchitis	1	0.02	2	0.05	0.50
Carcinoma of larynx	0	0.00	1	0.02	0.00
Carcinoma of lung	16	0.40	14	0.35	1.15
Emphysema	1	0.02	2	0.05	0.50
Lung disorder	2	0.05	3	0.07	0.67
Pneumonia	4	0.10	10	0.25	0.40
Respiratory disorder	2	0.05	0	0.00	NC
Skin/appendages	1	0.02	2	0.05	0.50
Skin carcinoma	0	0.00	2	0.05	0.00
Skin melanoma	1	0.02	0	0.00	NC
Urogenital	3	0.07	2	0.05	1.50
Bladder carcinoma	2	0.05	1	0.02	2.00
Kidney failure	1	0.02	1	0.02	1.00

² Not calculated.

Source: Safety Update. Text Table 17, pg. 39 and Table T4.3.

5.8 Laboratory Assessments

Protocol required laboratory assessments for safety were limited to measurements of hepatic toxicity (ALT/SGPT, AST/SGOT) or hepatic function (total bilirubin). Laboratory data for these assessments (referred to as LFTs in this review) are presented as follows:

- Mean values and mean changes from baseline values for each laboratory test at selected protocol-designated assessment times.
- Percentages of patients with laboratory values that shifted from within the normal range at baseline to above the normal range at selected protocol-designated assessment times.
- Clinically relevant laboratory values (values outside of the normal range that were considered to be of particular concern, based on the Sponsor's predefined criteria) that were observed during treatment.

5.8.1 Mean LFT Values and Mean Changes from Baseline Values

Data for mean serum ALT values and mean of the percent changes from baseline at 12-week intervals during the first year of treatment and every 24 weeks thereafter through Week 144 in the Casodex-and placebo-treatment groups are presented in Table 49. At baseline, the treatment groups in each of the trials were well matched for mean and median serum hepatic biochemistry values. During the first 6 months of treatment, mean ALT values and the means of the changes from baseline were numerically higher in the Casodex-treated patients. Thereafter, mean serum ALT values and mean changes from baseline in the Casodex-treated patients were comparable to or lower than those observed in the placebo-treated patients.

Table 49 Mean Serum ALT Values (U/L) and Mean of Percent Changes from Baseline during Treatment (Data Combined from Trials 23, 24, and 25)

Study Week	Casodex (N=4022) ¹			Placebo (N=4031)	
	n ²	Mean ALT (U/L)	Mean of % change from baseline	Mean ALT (U/L)	Mean of % change from baseline
Baseline	3942	21.5		21.2	
12	3817	22.8	25.9%	20.5	6.7%
24	3589	22.4	22.8%	20.7	9.0%
36	3422	20.8	14.7%	20.8	9.6%
48	3256	19.1	5.6%	20.9	10.5%
72	3001	18.5	1.2%	20.9	12.5%
96	2905	18.0	-2.5%	21.8	16.9%
120	1811 ³	19.0	-1.5%	22.1	16.1%
144	1580	18.6	-2.8%	23.0	15.6%

¹ Number of patients who received at least one dose of study drug.

² Number of patients upon which mean absolute values in Casodex treatment group are based. The number of observations at each assessment time is lower for the category of "mean of % change from baseline."

³ Decreased number of patients after Week 96 largely a result of maximum 2-year treatment period in Trial 23. Source: Table T7.2, ISS and Table 2, Appendix B of 3 May 2002 Submission.

Medical Officer's Comments

- *AST values (i.e., mean serum values and mean changes from baseline) in the Casodex- and placebo-treated patients showed a pattern of relative changes similar to that for ALT values.*
- *There were no notable differences in mean serum bilirubin values or mean changes from baseline in the Casodex-treated patients compared to the placebo-treated patients.*
- *In summary, although there were instances of large, clinically significant changes in LFT values in individual patients in both treatment groups, changes in mean and median serum values for ALT, AST, and total bilirubin were relatively small and did not appear to be of clinical significance.*

5.8.2 Shifts in LFT Laboratory Values to Above the Normal Range

The number and proportion of Casodex- and placebo-treated patients with a normal ALT value at baseline and an ALT value above the normal range at representative protocol-designated clinical visits are listed in Table 50 for each of the 3 clinical trials. Similar data for changes in bilirubin values in each of the trials are listed in Table 51.

Table 50 ALT Shifts from Within the Normal Range at Baseline to Above the Normal Range (High) during Treatment in Each of Trials 23, 24, and 25

Study Week	Number (%) of patients with shift to above the normal range											
	Trial 23				Trial 24				Trial 25			
	Casodex N=1627		Placebo N=1627		Casodex N=1790		Placebo N=1795		Casodex N=605		Placebo N=609	
	n	(%) ²	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
12	38	(2.6)	23	(1.5)	32	(2.2)	8	(0.5)	24	(4.3)	5	(0.9)
24	48	(3.6)	16	(1.1)	39	(2.7)	14	(0.9)	24	(4.4)	5	(0.9)
36	24	(2.0)	18	(1.3)	26	(1.8)	9	(0.6)	23	(4.3)	4	(0.8)
48	14	(1.2)	15	(1.1)	22	(1.6)	14	(1.0)	13	(2.5)	2	(0.4)
72	8	(0.8)	26	(2.0)	15	(1.2)	17	(1.3)	6	(1.2)	1	(0.2)
96	8	(0.9)	26	(2.1)	15	(1.2)	18	(1.5)	5	(1.0)	7	(1.6)
120	-- ¹		--		18	(1.5)	18	(1.5)	5	(1.1)	2	(0.5)
144	--		--		18	(1.7)	20	(2.0)	1	(0.2)	9	(2.6)

1. Treatment period was limited to 96 weeks.

2. Percentages based on both number of values above the normal range and the total number of samples evaluate at each of the respective study weeks.

Source: Safety Addendum for each of Trials 23, 24, and 25. Table T9.2.2.

Medical Officer's Comments

- *In both treatment groups, the proportion of patients who shifted to above the normal range for serum ALT values was relatively small and did not exceed 4.4% (Casodex-treatment group, Trial 25). However, a greater proportion of patients in the Casodex treatment groups shifted to above the normal range, most noticeable during the first 36 weeks (Trial 23), first 48 weeks (Trial 24), and first 72 weeks (Trial 25) of treatment.*

- *The largest numeric disparity between the Casodex and placebo treatment groups was observed in Trial 25.*
- *Changes in AST values (not listed) were similar to those observed for ALT values.*

Table 51 Bilirubin Shifts from Within the Normal Range at Baseline to Above the Normal Range (High) during Treatment in each of Trials 23, 24, and 25

Study Week	Number (%) of patients with shift											
	Trial 23		Trial 24		Trial 25							
	Casodex N=1627	Placebo N=1627	Casodex N=1790	Placebo N=1795	Casodex N=605	Placebo N=609						
	n	(%) ²	n	(%)	n	(%)	n	(%)				
12	27	(1.8)	30	(1.9)	24	(1.7)	31	(2.2)	4	(0.7)	8	(1.5)
24	28	(2.0)	30	(2.0)	13	(1.0)	24	(1.8)	5	(1.0)	2	(0.4)
36	21	(1.7)	28	(1.9)	14	(1.1)	28	(2.2)	5	(1.0)	4	(0.8)
48	21	(1.8)	26	(1.9)	11	(0.9)	18	(1.4)	4	(0.8)	1	(0.2)
72	20	(1.9)	27	(2.1)	15	(1.3)	20	(1.7)	3	(0.6)	4	(0.9)
96	18	(1.9)	21	(1.7)	9	(0.8)	20	(1.8)	4	(0.9)	2	(0.5)
120	-- ¹		--		9	(0.8)	18	(1.7)	2	(0.5)	1	(0.3)
144	--		--		17	(1.8)	11	(1.2)	2	(0.5)	2	(0.6)

1. Treatment period was limited to 96 weeks.

2. Percentages based on both number of values above the normal range and the total number of samples evaluate at each of the respective study weeks.

Source: Safety Addendum for each of Trials 23, 24, and 25, Table T9.2.1.

Medical Officer's Comment

- *In both treatment groups, the proportion of patients who shifted to above the normal range for serum total bilirubin values was relatively small and did not exceed 2.2% at any specific assessment time. Within each trial, the proportion of patients in the Casodex and placebo treatment groups who shifted to above the normal range appeared to be comparable during the 96-week and 144-week treatment periods represented in the above Table.*

5.8.3 Clinically Relevant Changes in LFT Laboratory Values

Definitions for clinically relevant changes in hepatic laboratory values (changes that were considered to be of particular concern) were established by the Sponsor. For ALT and AST values, a clinically relevant change was defined as an increase of (1) greater than or equal to 3 times the upper reference range for that laboratory variable or (2) greater than or equal to twice the upper reference range for that laboratory variable on 2 or more consecutive occasions. For total bilirubin values, a clinically relevant change was defined as an increase from the pre-randomization value by greater than or equal to 100% of the upper reference range for that laboratory variable.

The number and percentage of patients with one or more clinically relevant changes in each of ALT, AST, or total bilirubin values in Trials 23, 24, and 25 (combined analysis) are listed in Table 52. For each biochemistry variable, data are presented separately for patients who had normal or abnormal baseline values. Among patients with normal baseline values, a higher proportion of Casodex-treated patients showed clinically relevant changes from

baseline for AST (1.7%), ALT (1.6%), and bilirubin (0.8%) than placebo-treated patients (0.7%, 0.4%, and 0.5%, respectively).

Table 52 Clinically Relevant Changes in ALT, AST, and Total Bilirubin Values during Treatment in Trials 23, 24, and 25 (Combined Analysis)

Parameter	Baseline Value ¹	Casodex (N=4022)			Placebo (N=4031)		
		Baseline	Patients with clinically relevant change		Baseline	Patients with clinically relevant change	
		N ²	n ³	(%)	N ²	n ³	(%)
AST	Normal	3745	65	(1.7)	3770	27	(0.7)
	Abnormal	100	3	(3.0)	93	4	(4.3)
ALT	Normal	3660	60	(1.6)	3685	13	(0.4)
	Abnormal	186	9	(4.8)	179	8	(4.5)
Total bilirubin	Normal	3530	29	(0.8)	3558	18	(0.5)
	Abnormal	314	7	(2.2)	305	1	(0.3)

¹ Baseline value: normal = within reference range; abnormal = outside reference range

² N = number of patients with a baseline value and at least one non-missing laboratory assessment post dose.

³ n = number of patients with a clinically relevant change in the laboratory value.

Source: ISS, Text Table 24, pg. 62.

Medical Officer's Comments

- *The number of patients with normal baseline values that had clinically relevant changes in hepatic biochemistry values was generally very low. However, more patients treated with Casodex had clinically relevant changes from a baseline value of normal than placebo-treated patients.*
- *In patients with abnormal baseline ALT or AST values, the proportion with clinically relevant changes during treatment was similar in both treatment groups. However, for patients with an abnormal bilirubin value at baseline, the proportion of patients with a clinically relevant change during treatment was greater in Casodex-treated patients.*

The number of patients with resolution of their clinically relevant change(s) in ALT, AST, or total bilirubin, either within the treatment or post treatment period, is listed in Table 53. Resolution is presented either as (1) return of the parameters to within the normal range or (2) parameter no longer clinically relevant but not within the normal range.

Table 53 Resolution of Clinically Relevant Changes in ALT, AST, and Total Bilirubin Values in Trials 23, 23, and 25 (Combined Analyses)

Status of clinically relevant (CR) change	AST		ALT		Bilirubin	
	Casodex N=68 ¹	Placebo N=31	Casodex N=69	Placebo N=21	Casodex N=36	Placebo N=19
Time of Resolution	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Parameter within normal range						
Within treatment period	18 (26)	12 (39)	21 (30)	7 (33)	11 (31)	5 (26)
Post treatment period	23 (34)	7 (23)	23 (33)	5 (24)	3 (8)	0 (0)
Parameter no longer CR						
Within treatment period	5 (7)	3 (10)	4 (6)	1 (5)	3 (8)	8 (42)
Post treatment period	2 (3)	0 (0)	1 (1)	0 (0)	5 (14)	0 (0)
Not resolved	3 (4)	4 (13)	5 (7)	4 (19)	1 (3)	0 (0)
No further information	17 (25)	5 (16)	15 (22)	4 (19)	13 (36)	6 (32)

¹ Total number of patients with the clinically relevant change.

Source: ISS, Tables T7.5.1, T7.5.2, and T7.5.3.

Medical Officer's Comments

- *For those patients with follow up laboratory data (64-75% of patients in the Casodex group), more than 90% had resolution (complete or partial) of their clinically relevant changes. Among Casodex-treated patients with follow up data, 4% (AST), 7% (AST), and 3% (bilirubin) showed no improvement.*
- *Overall, these changes in hepatic laboratory values do not raise concerns of sufficient magnitude to preclude the use of Casodex in the proposed population (men with prostate cancer) and are adequately addressed in proposed labeling. Previous labeling appears to have provided adequate guidance to physicians for the safe use of Casodex 50 mg per day in men with prostate cancer, based on post marketing safety reports.*
- *The potential clinical significance of these changes in biochemistry measurements of hepatic toxicity or function is discussed further in Section 5.9.3.*

5.8.4 Non-hepatic Laboratory Safety Assessments

Protocol required laboratory assessments for safety were limited to measurements of hepatic toxicity (ALT/SGPT, AST/SGOT) and hepatic function (total bilirubin). Androgens are known to affect erythropoiesis; consequently, an increase in the number of Casodex-treated patients, relative to placebo-treated patients, who experienced reduced concentrations of hemoglobin and anemia, was not unexpected. Since collection of hematological laboratory data was not a component of these clinical trials, assessment of the effect of Casodex on blood indices in these clinical trials is limited to reports of hematological adverse events (see Table 54). A higher proportion of Casodex-treated patients reported an adverse event classified as anemia or erythrocyte disorder (2.9% vs. 1.9%). Adverse events of these types classified as serious also occurred more frequently in Casodex-treated patients (25 of 4022, 0.62%) than in placebo-treated patients (19 of 4031, 0.47%).

Table 54 Adverse Events Reported as Anemia or Erythrocyte Disorder during the Treatment Period (Combined Data from Trials 23, 24, and 25)

Treatment group	Number (%) of patients							
	All Adverse events ¹		Deaths		Withdrawals ²		Serious Adverse Events ³	
	n	%	n	%	n	%	n	%
Casodex (N=4022)	115	(2.9)	0	--	4	(0.10)	25	(0.62)
Placebo (N=4031)	77	(1.9)	0	--	2	(0.05)	19	(0.47)

1. All adverse events reported as anemia or erythrocyte disorder.

2. All withdrawals due to an adverse event reported as anemia or erythrocyte disorder.

3. All serious adverse events reported as anemia or erythrocyte disorder.

Source: ISS, Table T12.2

Medical Officer's Comment

- *The differences in the proportion of Casodex-treated and placebo-treated patients who experienced adverse events classified as anemia or erythrocyte disorders was to be expected. The magnitude of the differences, particularly for serious adverse events, was very small.*

5.9 Safety Issues of Special Interest or Concern

5.9.1 Pharmacological Adverse Events

Adverse events that may have been a result of the anti-androgenic or compensatory estrogenic activity of Casodex (i.e., pharmacological adverse events) and the number of patients who experienced them are summarized in Table 55. All occurred more frequently in Casodex-treated patients than in placebo-treated patients. The most frequently reported adverse events, occurring in 73% and 67% of patients in the Casodex group were breast pain and gynecomastia, respectively. Other adverse events occurring in 5-10% of Casodex treated patients were vasodilatation, impotence, and alopecia.

Table 55 Pharmacological-Related (Anti-androgenic and Estrogenic) Adverse Events (Combined Data from Trials 23, 24, and 25)

Adverse Event	Number (%) of patients			
	Casodex (N=4022)		Placebo (N=4031)	
	n	%	n	%
Breast pain	2937	73.0%	296	7.3%
Gynecomastia	2700	67.1%	325	8.1%
Vasodilatation	364	9.1%	211	5.2%
Impotence	362	9.0%	250	6.2%
Alopecia	239	5.9%	31	0.8%
Libido decreased	145	3.6%	45	1.1%

Source: Modified from ISS, Text Table 30, pg. 74.

Medical Officer's Comment

- *The high incidence of gynecomastia and breast pain may be a direct consequence of the anti-androgenic activity of Casodex, a consequence of the compensatory increase in serum concentrations of estradiol that are observed during treatment with Casodex, or a combination of both.*

5.9.1.1 Gynecomastia and Breast Pain during the Treatment Period

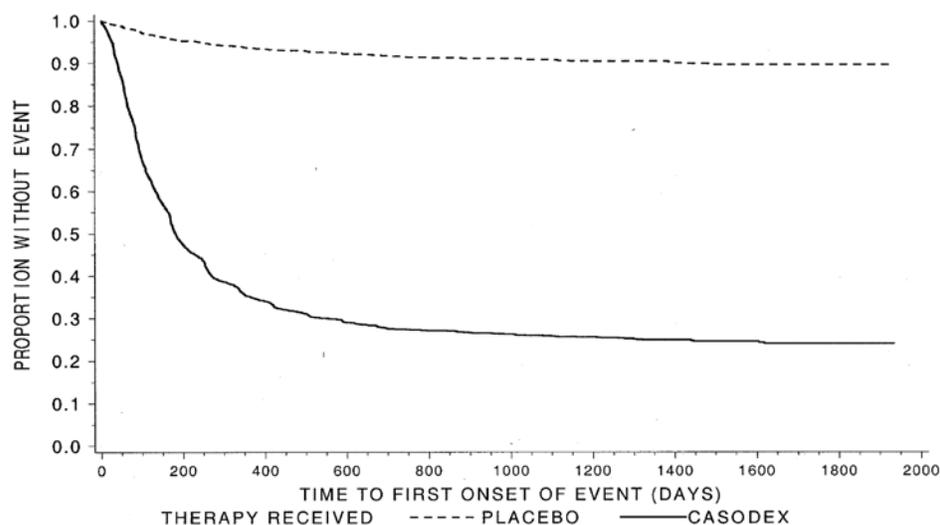
Most Casodex-treated patients (86.2%) reported gynecomastia or breast pain. Of these, 649/4022 (16.1%) patients withdrew from Casodex therapy. A total of 345/4,022 (8.6%) of these patients reported severe gynecomastia or severe breast pain. In the placebo-treated patients, only 12.4% patients reported gynecomastia or breast pain, and only 0.6% withdrew from treatment because of these adverse events (Table 56).

Table 56 Incidence of and Withdrawals due to Gynecomastia and Breast Pain within the Treatment Period (Combined Data from Trials 23, 24, and 25)

Category	Number (%) of patients			
	Casodex		Placebo	
	(N=4022)		(N=4031)	
	n	(%)	n	(%)
Number of patients with:				
Gynecomastia alone	2700	(67.1)	325	(8.1)
Male breast pain alone	2937	(73.0)	296	(7.3)
Both gynecomastia and male breast pain	2170	(54.0)	120	(3.0)
<i>Either gynecomastia or male breast pain</i>	3467	(86.2)	501	(12.4)
Number of patients with withdrawal due to:				
Gynecomastia	418	(10.4)	15	(0.4)
Male breast pain	498	(12.4)	15	(0.4)
Both gynecomastia and male breast pain	267	(6.6)	5	(0.1)
<i>Either gynecomastia or male breast pain</i>	649	(16.1)	25	(0.6)

Source: Text Table 31, pg. 75 of the ISS.

The time to occurrence of gynecomastia was estimated from Kaplan-Meier plots (Figure 3). More than 50% of Casodex-treated patients who developed gynecomastia did so within 200 days of treatment onset. Most who developed gynecomastia did so within 24 months of starting treatment.

Figure 3 Time to First Occurrence of Gynecomastia within the Treatment Period

Source: Figure 2, pg 76 of the ISS.

Table 57 summarizes the percentage of patients with gynecomastia and/or breast pain within the treatment period and the percentage of patients who withdrew because of these adverse events in each of Trials 23, 24, and 25. The percentage of Casodex-treated patients reporting gynecomastia was highest in Trial 23 (72.6%) and lowest in Trial 25 (55%). The percentage of Casodex-treated patients reporting either gynecomastia or breast pain differed slightly across the 3 trials and ranged from 90.1% (Trial 23) to 82.9% (Trial 24). The percentage of patients reporting either of these adverse events was considerably lower in the placebo treatment groups and ranged from 16.1% (Trial 23) to 6.6% (Trial 25). The percentage of Casodex-treated patients who withdrew from treatment because of either gynecomastia or breast pain also was highest in Trial 23 (20.0%) and lowest in Trial 25 (4.5%). Less than 1% of patients in any of the placebo groups withdrew because of either gynecomastia or breast pain.

Medical Officer's Comments

- *Gynecomastia and/or breast pain are by far the most frequently reported adverse events in men treated with Casodex, occurring in 86% of patients in the combined trials. In 8.6% of the patients, these adverse events were reported as severe. Across the 3 trials, 16.1% of Casodex-treated patients withdrew because of these adverse events.*
- *Patients in Trial 23 (primarily US patients) tolerated gynecomastia and/or breast pain least well. Twenty (20) percent of Casodex-treated patients in Trial 23 withdrew from treatment because of these adverse events while only 4.5% of Casodex-treated patients in Trial 25 withdrew for this reason. The high withdrawal rate because of gynecomastia and/or breast pain was clearly related to treatment with Casodex per se and not study participation in general in that < 1% of patients in the placebo group in Trial 23 withdrew because of these adverse events.*

- *The Sponsor performed subset analyses to determine if there were any associations other than Casodex that were related to the development of gynecomastia or breast pain. According to the Sponsor, there was no obvious relationship between age, race (Trial 23 only), tumor stage, weight, or body mass index and the incidence of gynecomastia or breast pain.*
- *In Trial 25, some patients were offered breast irradiation prior to initiation of randomized therapy; however, the number of patients was too small to draw any conclusions about the benefit of the procedure.*

Table 57 Incidence of and Withdrawals due to Gynecomastia and Breast Pain within the Treatment Period in Each of Trials 23, 24, and 25

Category	Number (per cent) of patients with event					
	Study 23		Study 24		Study 25	
	Casodex (N = 1627)	Placebo (N = 1627)	Casodex (N = 1790)	Placebo (N = 1795)	Casodex (N = 605)	Placebo (N = 609)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<i>Number of patients with adverse event</i>						
Gynecomastia	1182 (72.6)	165 (10.1)	1185 (66.2)	141 (7.9)	333 (55.0)	19 (3.1)
Breast pain	1390 (85.4)	173 (10.6)	1173 (65.5)	98 (5.5)	374 (61.8)	25 (4.1)
Either gynecomastia or breast pain	1466 (90.1)	262 (16.1)	1484 (82.9)	199 (11.1)	517 (85.5)	40 (6.6)
<i>Number of patients withdrawing because of adverse event</i>						
Gynecomastia	190 (11.7)	6 (0.4)	212 (11.8)	8 (0.4)	16 (2.6)	1 (0.2)
Breast pain	285 (17.5)	8 (0.5)	195 (10.9)	7 (0.4)	18 (3.0)	0 (0.0)
Either gynecomastia or breast pain	326 (20.0)	12 (0.7)	296 (16.5)	12 (0.7)	27 (4.5)	1 (0.2)

Source: ISS, Tables 9.3.2 and 9.3.3

5.9.1.2 Resolution of Breast Pain and Gynecomastia after Withdrawal of Treatment

Approximately 10% of all patients who withdrew from trial therapy with ongoing gynecomastia or breast pain did not have any follow-up information. For Casodex-treated patients who had gynecomastia ongoing at the time of withdrawal and had at least 1 follow-up assessment as of the 23 February 2001 data cutoff, 50.7% had resolution of their gynecomastia (Table 58). The median time from withdrawal of trial therapy to resolution of gynecomastia was approximately 101 weeks. According to the Sponsor, the time to resolution of gynecomastia appeared to be longer with increasing duration of trial therapy.

For Casodex-treated patients who had breast pain ongoing at the time of withdrawal and had at least 1 follow-up assessment, 92.2% of patients had resolution of breast pain by the date of data cutoff. The median time from withdrawal of trial therapy to resolution of breast pain was approximately 24 weeks.

Table 58 Percentage of Patients with Resolution of Gynecomastia and Breast Pain after Withdrawal of Treatment

Category	Number (%) of patients Casodex (N=4022) ¹	
	n ²	(%)
Gynecomastia:		
Patients with event ongoing at withdrawal and follow up information	1572	(100.0)
Patients with event ongoing at withdrawal and follow up information and resolution	787	(50.7)
Breast pain		
Patients with event ongoing at withdrawal and follow up information	1729	(100.0)
Patients with event ongoing at withdrawal and follow up information and resolution	1595	(92.2)

1. Total number of patients treated with Casodex.

2. Number of patients with condition.

Source: ISS, Summary Table T9.2.2.

Medical Officer's Comments

- *The high percentage of patients who developed gynecomastia during treatment (67%) and persistence of gynecomastia after discontinuation of Casodex treatment are significant problems and of concern. According to the Sponsor, only 50.7% of Casodex-treated patients with post treatment follow up data had resolution of gynecomastia by the date of data cutoff. For many men, particularly those with localized prostate disease who had undergone radical prostatectomy or radiation therapy of curative intent, permanent gynecomastia may be a significant quality of life consideration.*
- *GnRH analogs were not compared to Casodex in the clinical trials included in this submission. However, in a prior submission (NDA 20-498/s006), GnRH analogs were shown to be at least as effective as Casodex in terms of a survival endpoint in men with locally advanced non-metastatic prostate cancer and superior to Casodex in men with metastatic (M1) prostate cancer. In the present application, the Sponsor argues that Casodex is likely to be better tolerated than GnRH analogs that induce a complete medical castration and more severe symptoms of androgen deprivation. GnRH analogs, however, do not induce gynecomastia or breast pain. It is therefore unclear as to which therapy would be associated with a better quality of life, particularly if long-term survival is anticipated.*

5.9.2 Sexual Dysfunction

In Trial 25, sexual function was assessed during the first 48 weeks of treatment by a patient-completed shortened version of the GRISS questionnaire. The questionnaire was completed and the responses were collected at baseline and then at 12-week intervals until Week 48. Maintenance of sexual function based on the GRISS questionnaire relative to baseline during the first 48 weeks of treatment is summarized in Table 59. Maintenance of sexual function was considered to be no loss of potency or frequency. The findings summarized in Table 59 indicate that Casodex therapy was associated with a reduction in the frequency of sexual

intercourse and an increase in impotence compared to treatment with placebo. At Week 48, 31.4% of Casodex-treated patients and 47.6% of placebo-treated patients were assessed as having had no significant change in sexual frequency. Also at Week 48, 34.9% of Casodex-treated patients and 53.4% of placebo-treated patients were assessed as having had no significant change in sexual potency.

Table 59 Maintenance of Sexual Function Relative to Baseline

Sexual function domain	Weeks post-randomization			
	Wk 12	Wk 24	Wk 36	Wk 48
	Percentage of patients who maintained baseline function			
Frequency				
Casodex	44.9%	41.9%	36.1%	31.4%
Placebo	61.5%	55.1%	47.1%	47.6%
Potency				
Casodex	49.8%	43.7%	39.7%	34.9%
Placebo	62.1%	58.4%	60.1%	53.4%

Source: Table 25, pg. 65, ISS.

Medical Officer's Comments

- *It is of interest that almost 40% of patients were assessed as having had a decrease in either sexual frequency or potency at 12 weeks after the onset of placebo therapy.*
- *Changes in sexual function based on the GRISS questionnaire were qualitatively consistent with the pattern of adverse events for decreased libido and impotence reported in Trial 25. Based on reported adverse events, Casodex-treated patients had higher rates of decreased libido (23/605 [3.8%]) and impotence (97/605 [16.0%]) than placebo-treated patients (decreased libido: 7/609 [1.2%] and impotence: 41/609 [6.7%]). These adverse events, however, appear to have been underreported since the proportion of patients with decreased sexual function based on the GRISS questionnaire was much higher.*

5.9.3 Liver Toxicity

5.9.3.1 Abnormal Liver Function Test (LFT) Values Reported as Adverse Events

Laboratory values outside of the normal range were not to be routinely reported as adverse events unless the investigator believed that they were clinically significant or required clinical intervention. The number and proportion of patients for whom an increase in serum concentrations of ALT, AST, or total bilirubin were reported as an adverse event in each of the trials is listed in Table 60. Across the 3 trials, 138 of 4022 (3.4%) patients in the Casodex group and 94 of 4031 (2.3%) patients in the placebo group had one or more increased liver function test values reported as an adverse event. In each of the trials, the proportion of patients with a LFT-related adverse event (any type) was numerically higher in the Casodex treatment group.

Table 60 Number (%) of Patients with Increased Liver Function Test Values Reported as Adverse Events (Trials 23, 24, and 25)

Test Reported as Adverse Event	Number (per cent) of patients with event					
	Study 23		Study 24		Study 25	
	Casodex (N = 1627)	Placebo (N = 1627)	Casodex (N = 1790)	Placebo (N = 1795)	Casodex (N = 605)	Placebo (N = 609)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any Increased Test ¹	68 (4.2)	60 (3.7)	50 (2.8)	14 (0.8)	20 (3.3)	6 (1.0)
Increased ALT	52 (3.2)	44 (2.7)	41 (2.3)	11 (0.6)	19 (3.1)	2 (0.3)
Increased AST	43 (2.6)	25 (1.5)	39 (2.2)	12 (0.7)	18 (3.0)	3 (0.5)
Increased bilirubin	20 (1.2)	19 (1.2)	8 (0.4)	3 (0.2)	4 (0.7)	3 (0.5)

1. Total number (%) of patients with an increased ALT, AST, or bilirubin value reported as an adverse event.

Source: Table 12, Safety Addendum Trial 23; Table 1 and Table 2 (Pg. 7) of submission of May 3, 2002.

Medical Officer's Comments

- *For each of the 3 tests of liver toxicity or liver function, higher numbers of adverse events were reported for Casodex-treated patients in each of the trials with 2 exceptions (bilirubin values in Trials 23 and 25). The absolute differences between the proportion of Casodex-treated and placebo-treated patients were in general small, particularly in Trial 23 (“any increased tests”) and in all trials for “increased bilirubin.”*
- *Clinically relevant changes in LFT values and their likely clinical significance were previously reviewed (see Table 52 and Table 53).*

5.9.3.2 Hepatic-related Adverse Events during the Treatment Period

All adverse events. A total of 220 (5.3%) of Casodex-treated patients and 139 (3.3%) placebo-treated patients had at least one hepatic-related adverse event. Table 61 summarizes all hepatic-related adverse events reported during the treatment period in Trials 23, 24, and 25 combined. In this Table, the category of Abnormal Liver Function Test includes the COSTART preferred terms of “liver function tests abnormal, AST/SGOT increased, and ALT/SGPT increased.” The category of jaundice includes the COSTART preferred terms of “cholestatic jaundice, jaundice, bilirubinemia, and gamma glutamyl transpeptidase increased.” The incidence of hepatic-related adverse events was numerically greater in the Casodex group for 7 of the 10 categories represented in Table 61. However, only 3 categories of hepatic-related adverse events were reported by 1% or more of the patients in either treatment group. These were abnormal liver function test (3.0% Casodex group; 1.6% placebo group), jaundice (1.0% Casodex group, 0.7% placebo group), and cholelithiasis (1.0% Casodex group, 0.7% placebo group).

Serious adverse events other than deaths. The most frequently reported serious hepatic-related adverse events were cholelithiasis (0.6% Casodex-treated patients, 0.3% placebo-treated patients) and cholecystitis (0.5% Casodex-treated patients; 0.4% placebo-treated patients). Other categories in which the incidence of serious hepatic-related adverse events exceeded 0.1% in Casodex-treated patients were abnormal liver function tests (0.3%) and jaundice (0.2%).

Table 61 Hepatic-related Adverse Events during Treatment (Trials 23, 24, and 25)

Adverse Event Treatment group	Number (%) of patients ^{1,2}							
	All Adverse events ³		Deaths ³		Withdrawals ³		Serious Adverse Events ³	
	n	%	n	%	n	%	n	%
Abnormal Liver Function Test ⁴								
Casodex	120	(3.0)	0		47	(1.2)	10	(0.3)
Placebo	63	(1.6)	0		18	(0.5)	0	
Jaundice ⁵								
Casodex	42	(1.0)	0		17	(0.4)	6	(0.2)
Placebo	30	(0.7)	0		6	(0.2)	1	(<0.1)
Cholelithiasis								
Casodex	40	(1.0)	0		1	(<0.1)	23	(0.6)
Placebo	28	(0.7)	0		1	(<0.1)	10	(0.3)
Cholecystitis								
Casodex	22	(0.6)	0		1	(<0.1)	20	(0.5)
Placebo	16	(0.4)	0		1	(<0.1)	14	(0.4)
Hepatitis								
Casodex	8	(0.2)	0		4	(0.1)	4	(0.1)
Placebo	1	(<0.1)	0		0		0	
Hepatic Neoplasia								
Casodex	6	(0.2)	1	(<0.1)	1	(<0.1)	3	(0.1)
Placebo	5	(0.1)	0		1	(<0.1)	4	(0.1)
Biliary Pain								
Casodex	3	(0.1)	0		0		0	
Placebo	2	(0.1)	0		0		1	(<0.1)
Cirrhosis of Liver								
Casodex	1	(<0.1)	0		0		0	
Placebo	1	(<0.1)	1	(<0.1)	1	(<0.1)	1	(<0.1)
Liver Fatty Deposit								
Casodex	1	(<0.1)	0		0		0	
Placebo	6	(0.2)	0		0		0	
Hepatomegaly								
Casodex	0		0		0		0	
Placebo	3	(0.1)	0		1	(<0.1)	0	

1. Individual patients may have had more than 1 event and may be represented in > 1 category.

2. 220 of 4022 (5.3%) Casodex-treated patients and 139 of 4031 (3.3%) placebo-treated patients experienced one or more hepatic adverse events during treatment.

3. Includes all adverse events, deaths, withdrawals, or serious adverse events in the respective category.

4. Includes COSTART preferred terms of "liver function tests abnormal, SGOT increased, and SGPT increased."

5. Includes COSTART preferred terms of "cholestatic jaundice, jaundice, bilirubinemia, and gamma glutamyl transpeptidase increased."

Source: Safety Update, Table T8.1.

Medical Officer's Comments

- *The majority of adverse events related to increased AST and ALT values appeared to have occurred within the first year of trial therapy in both treatment groups.*

- *The incidences of abnormal LFTs and jaundice that led to withdrawal were higher in Casodex-treated patients (1.2% and 0.4%, respectively) than placebo-treated patients (0.5% and 0.2%, respectively). Of the patients with abnormal liver function tests, 10 cases in Casodex-treated patients and 0 cases (none) in the placebo-treated patients were classified as serious.*

5.9.3.3 Deaths Related to Hepatic Failure or Primary Hepatic Neoplasms

Deaths classified as related to hepatic failure or primary hepatic neoplasms that occurred either during the treatment period or during the post treatment follow up period are listed in Table 62. Five (5) Casodex-treated patients and 6 placebo-treated patients were reported to have died from one of these causes. One of the deaths in the placebo group may have been associated with metastatic cancer to the liver and not due to a primary hepatic tumor. One case in the Casodex treatment group was classified by the investigator as possibly related to treatment with study drug.

Table 62 Deaths Related to Hepatic Failure or Primary Hepatic Neoplasms

Trial No.	Patient No.	Age	Cause of Death (Actual Wording of Investigator)	Length of Tx (Days)	Study Day of Death	Comment	
CASODEX							
	23	---	61	Hepatic Coma ¹	673	1641	
	24	---	76	Hepatocarcinoma	1713	1858	Poss. related to Tx per Investigator
	24	---	75	Hepatic Cancer Death	1702	1749	
	24	---	57	Liver Failure	1268	1389	Pt received open label Casodex ²
	25	---	67	Hepatocellular Cancer ¹	248	1849	
PLACEBO							
	23	---	62	End Stage Liver Disease ¹	505	547	
	23	---	56	End-Stage Cirrhosis (Liver)	361	1729	
	24	---	72	Hepatic Cancer ¹	646	787	
	25	---	71	Cirrhases Hepates ¹	371	974	
	25	---	71	Carcinoma Hepatocellulare	194	194	
	25	---	71	Carcinoma Of Liver	1326	1326	May be metastatic cancer to liver

1. Patient narrative not provided for review.

2. Patient assigned to placebo treatment. Received open label Casodex after code break.

Source: Prepared by medical reviewer from Sponsor's SAS transport file for all deaths and Table G2, both in Safety Update.

Medical Officer's Comments

- *The distribution and causes of hepatic-related deaths appeared to be similar in the Casodex and placebo treatment groups.*
- *There were 2 and 3 deaths in the Casodex and placebo treatment groups, respectively that were related to hepatic failure that was not associated with a primary hepatic tumor. Deaths due to a primary hepatic tumor were reported for 2 and 2 or 3 patients in the Casodex and placebo treatment groups, respectively.*

Medical Officer's Summary Comments Regarding Hepatotoxicity

- *The potential for drug-induced liver toxicity with all nonsteroidal anti-androgens is a concern, particularly if they are intended for long-term use. The safety data provided in this supplemental NDA includes 9,387 and 9,778 total patient-years of treatment in the Casodex and placebo treatment groups. This is an adequate sample size to assess the likely toxicity of Casodex 150 mg per day in men with localized and locally advanced non-metastatic cancer of the prostate. Since the 3 clinical trials that were conducted in support of this supplemental NDA were placebo controlled, safety comparisons across treatment groups are particularly useful.*
- *The safety data provided in NDA 20-498/s012 indicate that treatment with Casodex is associated with an increase in the incidence of liver toxicity compared to treatment with placebo. The increase in liver-related toxicity is manifested primarily by an increase in the proportion of patients with an increase in serum transaminases and to a lesser extent an increase in serum total bilirubin levels. Patients withdrawals due to increased serum ALT or AST values and increased bilirubin values were higher in Casodex-treated patients (1.2% and 0.4%, respectively) than in placebo-treated patients (0.5% and 0.2%, respectively). Similarly, adverse events classified as serious due to increased serum ALT or AST values and increased bilirubin values were more frequent in Casodex-treated patients (0.3% and 0.2%, respectively) than in placebo-treated patients (0.0% and <0.1%, respectively). However, the number of patients reported to have died from hepatic failure or a primary hepatic neoplasm was similar in the 2 treatment groups (5 of 4,022 Casodex-treated patients and 5 or 6 of 4,031 placebo-treated patients.*
- *The current labeling for Casodex 50 mg and the proposed labeling for Casodex 150 mg indicate (under Warnings Section) that “serum transaminase levels should be measured prior to starting treatment with CASODEX, at regular intervals for the first 4 months of treatment, and periodically thereafter. If clinical symptoms or signs suggestive of liver dysfunction occur, (e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, “flu-like” symptoms, dark urine, jaundice, or upper right quadrant tenderness), serum transaminases, in particular the serum ALT, should be measured immediately. If at any time a patient has jaundice, or the ALT level rises above 2 times the upper limit of normal, CASODEX should be discontinued, with appropriate follow-up of liver function.”*
- *The Sponsor also provided an analysis of liver toxicity for both flutamide and Casodex (50 mg per day) based on US post marketing safety data. According to the Sponsor, the incidence of significant flutamide-related hepatotoxicity has been estimated to be 2.5 per 100,000 prescriptions in the US (Wysowski 1996⁵) against a background incidence in a similar US population of 0.2 per 100,000 prescriptions in patients not exposed to drugs. Using the same criteria as Wysowski (cases from the USA only and number of prescriptions filled in the US), the Sponsor claims that the incidence of significant hepatic toxicity for Casodex using those US post-marketing cases considered by AstraZeneca Pharmaceuticals to be even possibly related to Casodex was 0.1 per 100,000 prescriptions. The estimated number of prescriptions for Casodex in the US since launch to May 2000 was 1,714,000 per the Sponsor. It is possible, however, that hepatotoxicity will be increased in patients receiving 150 mg Casodex per day compared to those receiving 50 mg per day.*

5.9.4 Cardiovascular Morbidity and Mortality

5.9.4.1 Cardiovascular Adverse Events during the Treatment Period

Serious cardiovascular adverse events were reported less frequently in Casodex-treated patients (351 of 4,022 patients [8.73%]) than placebo-treated patients (386 of 4,031 patients [9.58%]) (Table 5.4, submission of 3 May 2002). As noted earlier in this review, however, some types of serious cardiovascular adverse events and deaths due to cardiovascular causes (both based on COSTART preferred terms) were reported more frequently in Casodex-treated patients. Serious cardiovascular adverse events reported for $\geq 0.2\%$ of patients in either treatment group are listed in Table 63. Events are listed by decreasing incidence in the Casodex-treated patients. Cardiac events of note that occurred more frequently in Casodex-treated patients (relative incidence of ≥ 1.2 , Casodex/placebo) included heart failure, heart arrest, syncope, and arrhythmia. Cardiac events that occurred more frequently in placebo-treated patients (relative incidence of ≤ 0.85 included myocardial infarction, myocardial ischemia, and atrial arrhythmia.

Table 63 Serious Cardiovascular Adverse Events with Incidence $\geq 0.2\%$ during Treatment Period (Combined Data from Trials 23, 24, and 25)

Adverse Event	Number of patients reporting adverse event				Relative Incidence
	Casodex (N = 4022)		Placebo (N = 4031)		
	n	Percentage	n	Percentage	Casodex placebo
Myocardial infarct	72	1.8%	97	2.4%	0.74
Angina pectoris	71	1.8%	66	1.6%	1.08
Heart failure	61	1.5%	36	0.9%	1.70
Chest pain	56	1.4%	29	0.7%	1.94
Myocardial ischemia	54	1.3%	64	1.6%	0.85
Cerebrovascular accident	37	0.9%	71	1.8%	0.52
Cardiovascular disorder	28	0.7%	37	0.9%	0.76
Atrial arrhythmia	25	0.6%	35	0.9%	0.72
Heart arrest	19	0.5%	7	0.2%	2.72
Syncope	18	0.4%	14	0.3%	1.29
Cerebral Ischemia	16	0.4%	17	0.4%	0.94
Hypertension	15	0.4%	24	0.6%	0.63
Arrhythmia	15	0.4%	11	0.3%	1.37
Vascular disorder	11	0.3%	27	0.7%	0.41
Carotid occlusion	11	0.3%	14	0.4%	0.97
Arteriosclerosis	9	0.2%	8	0.2%	1.13
Thrombosis	5	0.1%	9	0.2%	0.56

Source: Safety Update, Text Table 22, pg. 51, and Table T5.2.3.

5.9.4.2 Cardiovascular Mortality

Cardiovascular-related events were the most common single cause of death (other than prostate cancer), both during and following treatment with study drug. The numbers (%) of patients whose primary cause of death was classified as cardiovascular-related are listed in

Table 64. A numerically greater proportion of Casodex-treated patients was classified as having died of a cardiovascular event, either during or following treatment. Overall, the primary cause of death was considered to be cardiovascular-related in 143 of 4,022 (3.56%) of Casodex-treated patients and 122 of 4,031 (3.03%) of placebo-treated patients.

Table 64 Patients with a Cardiovascular-related Primary Cause of Death (Combined Data from Trials 23, 24, and 25)

Treatment Period	Number (%) of patients				Relative Incidence <u>Casodex</u> placebo
	Casodex (N = 4022)		Placebo (N = 4031)		
	n	Percentage	n	Percentage	
During Treatment	77	1.91%	66	1.64%	1.17
Post Treatment	66	1.64%	56	1.39%	1.18
Total	143	3.56	122	3.03	1.17

Source: Safety Update, Table T4.3.

The primary causes of cardiovascular-related deaths in each of the treatment groups, both during and following treatment, are listed in Table 65. The most common causes of deaths (treatment and post treatment periods combined) in the Casodex-treated patients were myocardial infarction (n=42), cerebrovascular accident (n=25), heart arrest (n=23), and heart failure (n=21). In the placebo-treated patients, the most common causes of death were myocardial infarction (n=52), cerebrovascular accident (n=22), and heart arrest (n=12).

Medical Officer's Comments

- *Overall, there were 21 more deaths attributed to cardiovascular causes in the Casodex-treated patients than in the placebo treated patients. This difference can be accounted for almost entirely by the excess number of deaths due to heart arrest ($\Delta = 11$) and heart failure ($\Delta = 16$) in the Casodex-treated patient partially offset by an excess number of deaths due to myocardial infarction ($\Delta = 10$) in the placebo-treated patients.*
- *The Sponsor states the following in their analysis of cardiac-related deaths in the Integrated Summary of Efficacy.*
 - *“Across all 3 controlled studies, only 5 patients (3 CASODEX, 2 placebo) experienced heart arrest in association with a cardiac condition which was not pre-existing at trial entry. These numbers of heart arrest events are too small to causally implicate CASODEX.”*
 - *“CASODEX does not cause heart failure in animals. Only 2 patients had unconfounded cases of heart failure (1 of which was deemed related to trial therapy by the investigator), a finding not unexpected in an elderly male population of 4,022 patients treated with CASODEX.”*

Table 65 Primary Causes of Cardiovascular Deaths with Incidence $\geq 0.05\%$ (Combined Data from Trials 23, 24, and 25)

Cause of Death (COSTART term)	Number (%) of patients with cause of death				Relative Incidence $\frac{\text{Casodex}}{\text{placebo}}$
	Casodex (N = 4022)		Placebo (N = 4031)		
	n	Percentage	n	Percentage	
Arrhythmia					
On treatment	0	0.00	2	0.05	0.00
Post treatment	0	0.00	0	0.00	NC ¹
Total	0	0.00	2	0.05	0.00
Arteriosclerosis					
On treatment	2	0.05	0	0.00	NC
Post treatment	5	0.12	3	0.07	1.67
Total	7	0.17	3	0.07	2.34
Cardiomyopathy					
On treatment	1	0.02	2	0.05	0.50
Post treatment	0	0.00	2	0.05	0.00
Total	1	0.02	4	0.10	0.25
Cardiovascular disorder					
On treatment	2	0.05	2	0.05	1.00
Post treatment	2	0.05	2	0.05	1.00
Total	4	0.10	4	0.10	1.00
Cerebrovascular accident					
On treatment	11	0.27	15	0.37	0.73
Post treatment	14	0.35	7	0.17	2.00
Total	25	0.62	22	0.55	1.14
Heart arrest					
On treatment	12	0.30	5	0.12	2.41
Post treatment	11	0.27	7	0.17	1.57
Total	23	0.57	12	0.30	1.92
Heart failure					
On treatment	15	0.37	1	0.02	15.03
Post treatment	6	0.15	4	0.10	1.50
Total	21	0.52	5	0.12	4.21
Myocardial infarction					
On treatment	24	0.60	31	0.77	0.78
Post treatment	18	0.45	21	0.52	0.86
Total	42	1.04	52	1.29	0.81
Myocardial ischemia					
On treatment	4	0.10	5	0.12	0.80
Post treatment	4	0.20	3	0.07	1.33
Total	8	0.20	8	0.20	1.00
Pulmonary embolus					
On treatment	4	0.10	2	0.05	2.00
Post treatment	1	0.12	4	0.10	0.25
Total	5	0.12	6	0.15	0.84

1. Unable to calculated as no events occurred in placebo group.

Source: Safety Update, Table T4.3.

5.9.5 Second Tumors

The proportion of patients with solid second tumors during the treatment period was similar in both treatment groups (312 of 4,022 [7.76%] Casodex-treated patients; 315 of 4,031 [7.81%] placebo-treated patients). Solid second tumors reported as an adverse event in $\geq 0.2\%$ of patients during the treatment period are summarized by body system and COSTART preferred term in Table 66. The most common solid tumors in both treatment groups were neoplasm (body as a whole), skin cancer, GI neoplasia, gastrointestinal carcinoma, and carcinoma of the lung.

Table 66 Solid Tumors Reported as Adverse Events within the Treatment Period in $\geq 0.2\%$ Patients (Data Combined for Trials 23, 24, and 25)

COSTART body system	COSTART preferred term	Number (%) of patients with event			
		Casodex (N=4022)		Placebo (N=4031)	
		No. Pt	Percent	No. Pt	Percent
Body as a whole	Adenoma	9	0.22	14	0.35
	Carcinoma	17	0.42	11	0.27
	Neoplasm	67	1.67	60	1.49
Digestive	Gastrointestinal carcinoma	48	1.19	39	0.97
	Gastrointestinal neoplasm	65	1.62	75	1.86
Respiratory	Carcinoma of lung	24	0.60	28	0.69
Skin	Skin cancer	58	1.44	61	1.51
	Skin melanoma	9	0.22	9	0.22
Urogenital system	Bladder carcinoma	13	0.32	9	0.22
	Bladder neoplasm	9	0.22	7	0.17

Source: SAS File aeaf1 (calculated by medical reviewer) and Table T14.4, both from Safety Update.

Medical Officer's Comments

- *Tumors listed as carcinoma under “body system as a whole” included a diverse number of tumor types for which descriptions were often vague, thus making more precise classification impossible in many instances. Included in this category were 5 cases of renal cell carcinoma or renal cancer (3 and 2 cases in the Casodex and placebo groups, respectively). Tumors listed as neoplasm under “body system as a whole” were predominantly benign neoplasms, often lipomas or merely described as ‘lumps.’*
- *Tumors classified under the digestive body system included a greater number of tumors classified as gastrointestinal carcinoma in the Casodex-treated patients (n=48) than in placebo-treated patients (n=39). Conversely, tumors classified as gastrointestinal neoplasm were more common the placebo-treated patients (n=75) than in the Casodex-treated patients (n=65).*

5.9.5.1 Gastrointestinal Tumors

The Sponsor provided a more detailed analysis of the incidence of gastrointestinal tumors based on a somewhat broader review of the data from the 3 clinical trials. The result of this analysis is presented in Table 67.

Table 67 Incidence of Gastrointestinal Tumors (Trials 23, 24, and 25)

Gastrointestinal tumor site	Number of patients with event		
	Casodex (N=4022)	Placebo (N=4031)	Incidence ratio ¹
Colorectal	30	27	1.11
Colon	21	23	0.91
Rectal	9	4	2.25
CUP-abdominal ²	3	2	1.50
Esophageal	5	3	1.67
Gastric	5	7	0.71
Hepatic	4	2	2.00
Mouth	1	2	0.50
Pancreatic	5	5	1.00
Parotid	1	0	
Small intestine	2	1	2.00
Total	56	49	1.14

¹ Casodex/placebo

² CUP = cancer unknown primary

Source: Text Table 36 of Safety Update, pg. 80.

Medical Officer's Comments

- *Although the number of patients with a gastrointestinal tumor continued to be numerically higher in the Casodex-treated patients, the difference was relatively small (56 of 4,022 [1.4%] Casodex-treated patients; 49 of 4,031 [1.2%] placebo-treated patients).*

5.9.5.2 Myelodysplasia and Leukemia

There was an increase in the number of Casodex-treated patients who developed myelodysplasia syndrome or leukemia. The patients who were identified by the Sponsor as having developed myelodysplasia syndrome or leukemia or whose underlying cause of death was related to these disorders are listed in Table 68. Twelve (12) Casodex-treated patients and 5 placebo-treated patients are represented in the Table (relative incidence Casodex/placebo = 2.4). Of these patients, 8 of 12 Casodex-treated patients and 4 of 5 placebo-treated patients have died as a direct or indirect result of their underlying hematologic disorder.

Table 68 Patients Who Developed Myelodysplasia Syndrome or Leukemia

Patient number	Age at Study Entry	Diagnosis ¹	Duration of Treatment (Days)	Time to Diagnosis (Days)	Death (Y/N)
Casodex treatment group					
----	72	AML	321	1012	N
----	56	MDS	126	139	N
----	60	AML	666	1167	Y
----	68	MDS	658	496	Y
----	65	AML	283	1444	N
----	82	MDS	581	627	Y
----	70	AML	90	166	Y
----	74	AML	482	483	Y
----	64	AML	1084	1019	Y
----	73	MDS	1096	1024	N
----	74	MDS	90	113	Y
----	65	AML	1190	1168	Y
Placebo treatment group					
----	59	MDS	92	1012	Y
----	76	MDS	755	1335	Y
----	75	MDS	1776	1248	Y
----	66 ²	AML	1090	1139	N
----	72	AML	1253	1037	Y

1 AML = acute myelogenous leukemia; MDS = myelodysplasia syndrome.

2 This patient was withdrawn from placebo therapy and began open-label treatment with Casodex. AML was diagnosed 6-7 weeks after starting Casodex.

Source: Text Table 35, pg. 78, of Safety Update.

Medical Officer's Comments

- *The basis for this numeric imbalance is unclear. Based on the preclinical toxicology of Casodex, one would not anticipate that treatment with this drug would cause the development of either myelodysplasia syndrome or leukemia.*
- *The numeric imbalance (12 of 4022 Casodex-treated patients [0.30%]; and 5 of 4031 placebo-treated patients [0.12%]) was not statistically significant (p -value = 0.24, Fisher's exact test for a 2-sided hypothesis, FDA calculation).*
- *The significance of this numeric imbalance and its possible relationship to treatment with Casodex are not known at this time.*

5.10 Adequacy of Patient Exposure and Safety Assessments

The safety database for this application was large and included 4022 Casodex-treated patients and 4031 placebo-treated patients. At the time of the data cutoff for the Safety Update, total exposure to study drug was 9,387 patient-years in the Casodex treatment group and 9,778 patient-years in the placebo treatment group. Total patient exposure to Casodex and safety monitoring in Trials 23, 24, and 25 was adequate to assess the likely safety profile of Casodex 150 per day in men with prostate cancer.

6 DOSING REGIMEN

6.1 Dosing Regimen

The proposed dosing-regimen is Casodex 150 mg per day for at least 2 years or until disease progression. The proposed dose appears to be appropriate based on dose-ranging data provided in an earlier submission (NDA 20-498/s006). The basis for the recommendation that treatment should continue for at least 2 years is unclear since the protocols for Trial 24 and Trial 25 recommended that treatment should continue for at least 5 years or until disease progression.

6.2 Effects of Renal or Hepatic Impairment on Casodex Pharmacokinetics

According to the Sponsor, renal impairment (as measured by creatinine clearance) had no significant effect on the elimination of total bicalutamide or the active R-enantiomer in doses up to 450 mg.

Casodex is extensively metabolized by the liver. Limited data in subjects with severe hepatic impairment suggest that excretion of Casodex may be delayed and could lead to further accumulation.

7 CONCLUSIONS AND RECOMMENDATIONS

7.1 Conclusions

7.1.1 Benefits of Treatment with Casodex

The Sponsor has provided statistically significant findings from 2 non-US clinical trials in men with non-metastatic prostate cancer (Clinical Trials 24 and 25) that treatment with Casodex 150 mg per day, compared to treatment with placebo, delayed progression of disease. Progression of disease was defined as (a) the appearance of new bone scan confirmed metastases, (b) other objectively confirmed progression of prostate cancer (as documented by magnetic resonance imaging, computerized tomography, sonography, or biopsy), or (c) death due to any cause in the absence of objectively documented progression of prostate cancer. In these trials, Casodex was studied as (1) adjuvant therapy in men previously treated by radical prostatectomy or radiotherapy or (2) immediate therapy (monotherapy) in patients who otherwise were to be managed by watchful waiting. In a third trial (Trial 23) that was conducted primarily within the US, there was no evidence that treatment with Casodex delayed disease progression. In this trial, Casodex was studied only as an adjuvant therapy following radical prostatectomy or radiotherapy. The relevance of the findings in the 2 non-US trials for men with prostate cancer in the US who might be treated with Casodex adjuvant therapy or Casodex monotherapy is uncertain at this time.

The actual reduction in the incidence of (a) objective disease progression (based only on new bone scan confirmed metastases) and (b) death from any cause in the absence of disease progression within 2.5 years after entry into Trial 24 or Trial 25 was modest. In Trial 24, the proportion of patients with objective disease progression within 2.5 years of study entry decreased from 9.3% (placebo group) to 6.2% (Casodex group). In Trial 25, the proportion of patients with objective disease progression within 2.5 years of study entry decreased from 17.2% (placebo group) to 10.4% (Casodex group). Based on the information presented by

the Sponsor, the short term clinical significance of this decrease in disease progression in Casodex-treated patients is not known as quality of life data (e.g., the proportion of symptomatic versus asymptomatic bone metastases) and other assessments of quality of life were not provided.

The long-term clinical benefit of treatment with Casodex is unknown. There was no evidence of increased disease-specific survival or overall survival for Casodex-treated men in any of the 3 clinical trials. Median follow up time for disease progression was approximately 3 years, a short period for assessing the long-term benefits of a medical therapy for men with non-metastatic prostate cancer. It is possible, but entirely unproved at this time, that treatment with Casodex might improve disease-specific survival compared to placebo treatment.

Medical therapy for early or locally advanced, non-metastatic prostate cancer. No medical therapy is presently approved by the FDA as monotherapy for early or locally advanced, non-metastatic prostate cancer. However, the present standard of care for patients with locally advanced, non-metastatic prostate cancer generally includes androgen deprivation therapy by medical or surgical castration.

Casodex adjuvant therapy or Casodex monotherapy for men with non-metastatic prostate cancer may be equivalent to, but not superior to, treatment with a GnRH analog in terms of reducing disease progression. Both classes of drug (nonsteroidal anti-androgens and GnRH analogs) are thought to be effective in the management of prostate cancer by reducing androgen stimulation of cancer cells. However, nonsteroidal anti-androgens compared to GnRH analogs are likely to be less effective *in vivo* in blocking the effects of testosterone as there is a compensatory increase in serum testosterone concentrations during treatment with nonsteroidal anti-androgens. In some situation, (e.g., men with metastatic prostate cancer), this difference in pharmacological activity has important clinical consequences such as reduced survival as was shown in Trials 0306 and 0307 (NDA 20-498/s006) for patients with stage M1 disease. In other situations, efficacy may be similar and the difference in side effect profiles may be an important consideration in the choice of drug. Men treated with a GnRH analog are likely to have more severe and more frequent vasomotor symptoms (e.g., hot flashes), bone loss, and possibly more sexual dysfunction (impotence and decreased libido). Conversely, a very high proportion of men receiving 150 mg Casodex per day will develop gynecomastia and/or breast pain and are at a slightly greater risk for clinically significant hepatotoxicity.

7.1.2 Risks of Treatment with Casodex

Adverse events associated with Casodex treatment can be classified for the most part into one of 2 categories:

- Those of a non-life threatening nature that are due to the pharmacological actions of Casodex and which occur with a high incidence (i.e., gynecomastia and breast pain)
- Those that occur in a few percent of patients and which may be severe or life threatening (primarily hepatotoxicity)

Gynecomastia and Breast Pain. In Trials 23, 24, and 25, gynecomastia alone was reported in 67.1% and 8.1% of Casodex-treated and placebo-treated patients, respectively.

Gynecomastia or breast pain was reported to occur in 86.2% and 12.4% of Casodex-treated

and placebo-treated patients, respectively. Breast pain was reversible in > 90% of patients after cessation of Casodex therapy. Gynecomastia, however, resolved in only 50% of patients with at least 1 or more follow up visits.

Hepatotoxicity. The safety data provided in NDA 20-498/s012 indicate that treatment with Casodex is associated with an increase in the incidence of liver toxicity compared to treatment with placebo. Liver-related toxicity is manifested primarily by an increase in the proportion of Casodex-treated patients with elevated serum transaminase levels, and to a lesser, elevated serum total bilirubin levels. Patient withdrawals due to increased serum ALT or AST values or increased bilirubin values were higher in Casodex-treated patients (1.2% and 0.4%, respectively) than in placebo-treated patients (0.5% and 0.2%, respectively). Similarly, adverse events due to increased serum ALT or AST values or increased bilirubin values classified as serious were more frequent in Casodex-treated patients (0.3% and 0.2%, respectively) than in placebo-treated patients (0.0% and <0.1%, respectively). However, the number of patients reported to have died from hepatic failure or a primary hepatic neoplasm was similar in the 2 treatment groups (5 of 4,022 Casodex-treated patients and 5 or 6 of 4,031 placebo-treated patients).

The current labeling for Casodex 50 mg and the proposed labeling for Casodex 150 mg state under the Warnings Section that “serum transaminase levels should be measured prior to starting treatment with CASODEX, at regular intervals for the first 4 months of treatment, and periodically thereafter....If at any time a patient has jaundice, or the ALT level rises above 2 times the upper limit of normal, CASODEX should be discontinued.”

The risk of serious hepatotoxicity in Casodex-treated patients with prostate cancer does not appear to be sufficient to preclude approval of the drug if the benefits of therapy are clinically and statistically significant.

7.1.3 Summary of Risk-Benefit Analysis

The relevance of the findings in Trials 24 and 25 supporting the efficacy of adjuvant treatment and monotherapy with Casodex 150 mg per day to men with prostate cancer in the US is uncertain. Based on the data submitted by the Sponsor, patients similar to those enrolled in Trial 23 who are initially treated by radical prostatectomy or radiotherapy, would derive no benefit from Casodex adjuvant therapy. Such patients exhibited too few events of disease progression to warrant treatment with Casodex. Whether patients who would be treated by Casodex monotherapy, instead of watchful waiting in accordance with current medical practices in the US, would derive significant benefit also is uncertain. A watchful waiting subgroup was not included in Trial 23. Review of the baseline disease characteristics of the watchful waiting subgroups in Trials 24 and 25 indicated that many of these patients had more advanced prostate cancer than patients likely to be managed by watchful waiting alone in the US. The Sponsor has not show that patients presently managed by watchful waiting in the US would experience disease progression of sufficient magnitude to warrant treatment with Casodex and the side effects associated with such treatment. The Sponsor also has not shown that patients with locally advanced, non-metastatic prostate cancer treated by Casodex monotherapy would derive comparable benefit as patients treated by medical or surgical castration, the present standard of care in the US. Data previously submitted by the Sponsor from Trials 0306 and 0307 did not adequately support the Sponsor’s contention that Casodex treatment and castration (medical or surgical) were equally efficacious (based on

survival) for the treatment of locally advanced non-metastatic prostate cancer. Patients with locally advanced prostate cancer who are treated with Casodex monotherapy may be at a slight survival disadvantage compared to men treated by medical or surgical castration.

In summary, the risks of treatment with Casodex 150 mg per day are justified and acceptable for patients who would derive significant clinical benefit from treatment. Such patients may be similar to those enrolled in Trials 24 and 25. However, based on data submitted to date by the Sponsor, it is not clear as to which patients in the US would derive significant clinical benefit from either adjuvant therapy or immediate monotherapy with Casodex. In the absence of such data, the risks of Casodex treatment for men in the US with non-metastatic prostate cancer are not warranted.

7.2 Recommendations

7.2.1 Recommendations Regarding Approvability (Based on Indications Submitted on 10 May 2002)

Indication No. 1: “CASODEX 150 mg is indicated as adjuvant therapy to radical prostatectomy and radiotherapy of curative intent in patients with locally advanced non-metastatic prostate cancer who have a high risk for disease recurrence.”

- *Approval for Indication No. 1 is not recommended at this time*

The Sponsor has not provided sufficient evidence (1) of efficacy for the adjuvant use of Casodex in men with prostate cancer initially treated by radical prostatectomy or radiotherapy in the US and (2) that the findings in Trials 24 and 25 are relevant to prostate cancer patients in the US. In particular, the data in the present application do not identify the subset of men with prostate cancer in the US who are most likely to benefit from Casodex adjuvant therapy.

Indication No. 2: “CASODEX 150 mg is indicated as immediate treatment of non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated.”

- *Approval for Indication No. 2 is not recommended at this time.*

The proposed indication does not adequately identify the population of prostate cancer patients in the US who might derive sufficient benefit from Casodex monotherapy to warrant the risks of treatment.

For local or early disease. The Sponsor has not provided sufficient evidence that the findings in Trials 24 and 25 are relevant to prostate cancer patients in the US who are currently managed by watchful waiting. In addition, the Sponsor will need to provide data demonstrating that prostate cancer-related morbidity or mortality in patients with localized prostate cancer occurs with a sufficiently high incidence that the potential benefits of Casodex treatment will outweigh the adverse effects of treatment (e.g., gynecomastia, breast pain, and possible liver toxicity).

For locally advanced disease. Trials 24 and 25 were not conducted in accordance with present standards of care for patients with locally advanced, non-metastatic prostate cancer in the US. Since the comparator in these trials was placebo and not active therapy (i.e., medical or surgical castration), it is not possible to adequately address the efficacy of Casodex monotherapy. This is a critical issue since survival may be shortened in patients with locally

advanced prostate cancer treated with Casodex monotherapy instead of by medical or surgical castration (the present standard of care in the US for such patients).

This concern has been addressed in part by the Sponsor's second revision to the proposed indication for Casodex immediate therapy that was submitted on 22 October 2002. The second revision states that Casodex immediate treatment is indicated for the treatment of "localized non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated."

8 REFERENCES

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Appendix
(Supplemental Efficacy Analyses)

Supplemental Efficacy Analyses (Set No. 1)

- Proportion of Patients with (1) Bone Scan Documented Progression or (2) Death from Any Cause in the Absence of Progress within 2.5 Years of Randomization as a Function of Baseline Disease Characteristics

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Appendix Table 1a. Proportion of Patients with (1) Bone Scan Documented Progression or (2) Death from Any Cause in the Absence of Progress within 2.5 Years of Randomization as a Function of Baseline Disease Characteristics (Trial 23)

Subgroup	N (%)	Events (%) in CASODEX arm	Events (%) in placebo arm
All adjuvant patients	3292 (100.0)	39/1647 (2.4)	48/1645 (2.9)
Radical Prostatectomy patients	2647 (80.4)	26/1322 (2.0)	30/1325 (2.3)
by tumour stage ^b			
• localised	1759 (53.4)	15/874 (1.7)	17/885 (1.9)
• locally advanced	888 (27.0)	11/448 (2.5)	13/440 (3.0)
by Gleason score			
• well	69 (2.1)	2/34 (5.9)	0/35 (0.0)
• moderate	1205 (36.6)	4/591 (0.7)	12/614 (2.0)
• poor	1373 (41.7)	20/697 (2.9)	18/676 (2.7)
by category of pre-procedure PSA (µg/l)			
• 0 to 4	317 (9.6)	4/157 (2.5)	3/160 (1.9)
• >4 to 10	1545 (46.9)	13/765 (1.7)	14/780 (1.8)
• >10 to 20	520 (15.8)	3/266 (1.1)	10/254 (3.9)
• >20	162 (4.9)	5/80 (6.3)	1/82 (1.2)
by category of pre-randomisation PSA (µg/l)			
• ND: 0 to 0.2	2273 (69.0)	17/1136 (1.5)	21/1137 (1.8)
• Detectable: >0.2	355 (10.8)	8/176 (4.5)	9/179 (5.0)
• >0.2 to 4	330 (93.0 ^c)	5/162 (3.1)	9/168 (5.4)
• >4 to 10	19 (5.4 ^c)	2/10 (20.0)	0/9 (0.0)
• >10 to 20	6 (1.7 ^c)	1/4 (25.0)	0/2 (0.0)
• >20	0 (0.0 ^c)	0/0	0/0
Radiotherapy patients	645 (19.6)	13/325 (4.0)	18/320 (5.6)
by tumour stage ^b			
• localised	632 (19.2)	12/317 (3.8)	17/315 (5.4)
• locally advanced	13 (0.4)	1/8 (12.5)	1/5 (20.0)
by Gleason score			
• well	79 (2.4)	0/35 (0.0)	1/44 (2.3)
• moderate	382 (11.6)	6/198 (3.0)	9/184 (4.9)
• poor	184 (5.6)	7/92 (7.6)	8/92 (8.7)
by category of pre-procedure PSA (µg/l)			
• 0 to 4	68 (2.1)	3/39 (7.7)	2/29 (6.9)
• >4 to 10	339 (10.3)	5/167 (3.0)	9/172 (5.2)
• >10 to 20	181 (5.5)	4/91 (4.4)	4/90 (4.4)
• >20	27 (0.8)	1/13 (7.7)	1/14 (7.1)
by category of pre-randomisation PSA (µg/l)			
• ND: 0 to 0.2	84 (2.6)	4/46 (8.7)	2/38 (5.3)
• Detectable: >0.2	556 (16.9)	9/277 (3.2)	16/279 (5.7)
• >0.2 to 4	305 (54.9 ^c)	6/154 (3.9)	8/151 (5.3)
• >4 to 10	183 (32.9 ^c)	3/93 (3.2)	7/90 (7.8)
• >10 to 20	58 (10.4 ^c)	0/25 (0.0)	0/33 (0.0)
• >20	10 (1.8 ^c)	0/5 (0.0)	1/5 (20.0)

^a Bone scan confirmed progression or death in the absence of progression occurring within 2.5 years of randomisation

^b Patients with locally advanced disease are categorised as T3, T4, TX or N+ ; all other patients are considered to have localised disease

^c Percentage of the total number detectable ND = Not Detectable

Appendix Table 1b. Proportion of Patients with (1) Bone Scan Documented Progression or (2) Death from Any Cause in the Absence of Progress within 2.5 Years of Randomization as a Function of Baseline Disease Characteristics (Trial 24)

Subgroup	N (%)	Events (%) in CASODEX arm	Events (%) in placebo arm
All adjuvant patients	2308 (100.0)	53/1170 (4.5)	79/1138 (6.9)
Radical Prostatectomy patients	1648 (71.4)	29/835 (3.5)	43/813 (5.3)
by tumour stage ^b			
• localised	919 (39.8)	9/461 (2.0)	13/458 (2.8)
• locally advanced	729 (31.6)	20/374 (5.3)	30/355 (8.5)
by Gleason score			
• well	347 (15.0)	2/166 (1.2)	5/181 (2.8)
• moderate	727 (31.5)	15/375 (4.0)	12/352 (3.4)
• poor	545 (23.6)	12/285 (4.2)	25/270 (9.3)
by category of pre-procedure PSA (µg/l)			
• 0 to 4	131 (5.7)	3/66 (4.5)	3/65 (4.6)
• >4 to 10	638 (27.6)	7/307 (2.3)	8/331 (2.4)
• >10 to 20	524 (22.7)	7/270 (2.6)	17/254 (6.7)
• >20	325 (14.1)	11/177 (6.2)	13/148 (8.8)
by category of pre-randomisation PSA (µg/l)			
• ND: 0 to 0.2	1073 (46.5)	10/540 (1.9)	21/533 (3.9)
• Detectable: >0.2	455 (19.7)	18/230 (7.8)	21/225 (9.3)
• >0.2 to 4	415 (91.2 ^c)	15/213 (7.0)	17/202 (8.4)
• >4 to 10	29 (6.4 ^c)	3/14 (21.4)	4/15 (26.7)
• >10 to 20	4 (0.9 ^c)	0/1 (0.0)	0/3 (0.0)
• >20	7 (1.5 ^c)	0/2 (0.0)	0/5 (0.0)
Radiotherapy patients	660 (28.5)	24/335 (7.2)	36/325 (11.1)
by tumour stage ^b			
• localised	411 (17.8)	14/206 (6.8)	16/205 (7.8)
• locally advanced	249 (10.8)	10/129 (7.8)	20/120 (16.7)
by Gleason score			
• well	214 (9.3)	7/119 (5.9)	5/95 (5.3)
• moderate	279 (12.1)	9/127 (7.1)	18/152 (11.8)
• poor	157 (6.8)	8/80 (10.0)	13/77 (16.9)
by category of pre-procedure PSA (µg/l)			
• 0 to 4	36 (1.6)	0/17 (0.0)	1/19 (5.3)
• >4 to 10	147 (6.4)	5/78 (6.4)	9/69 (13.0)
• >10 to 20	204 (8.8)	6/100 (6.0)	9/104 (8.7)
• >20	268 (11.6)	13/137 (9.5)	17/131 (13.0)
by category of pre-randomisation PSA (µg/l)			
• ND: 0 to 0.2	55 (2.4)	2/29 (6.9)	4/27 (14.8)
• Detectable: >0.2	583 (25.3)	22/301 (7.3)	30/282 (10.6)
• >0.2 to 4	303 (52.0 ^c)	8/160 (5.0)	12/143 (8.4)
• >4 to 10	152 (26.1 ^c)	4/81 (4.9)	7/71 (9.9)
• >10 to 20	86 (14.8 ^c)	5/41 (12.2)	6/45 (13.3)
• >20	42 (7.2 ^c)	5/19 (26.3)	5/23 (21.7)

^a Bone scan confirmed progression or death in the absence of progression occurring within 2.5 years of randomisation

^b Patients with locally advanced disease are categorised as T3, T4, TX or N+ ; all other patients are considered to have localised disease

^c Percentage of the total number detectable ND = Not Detectable

Appendix Table 1c. Proportion of Patients with (1) Bone Scan Documented Progression or (2) Death from Any Cause in the Absence of Progress within 2.5 Years of Randomization as a Function of Baseline Disease Characteristics (Trial 25)

Subgroup	N (%)	Events (%) in CASODEX arm	Events (%) in placebo arm
All adjuvant patients	224 (100.0)	13/118 (11.0)	17/106 (16.0)
Radical Prostatectomy patients	159 (71.0)	6/79 (7.6)	8/80 (10.0)
by tumour stage ^b			
• localised	56 (25.0)	2/30 (6.7)	2/26 (7.7)
• locally advanced	103 (46.0)	4/49 (8.2)	6/54 (11.1)
by Gleason score			
• well	40 (17.9)	3/18 (16.7)	0/22 (0.0)
• moderate	88 (39.3)	3/43 (7.0)	6/45 (13.3)
• poor	31 (13.8)	0/18 (0.0)	2/13 (15.4)
by category of pre-procedure PSA (µg/l)			
• 0 to 4	3 (1.3)	0/2 (0.0)	1/1 (100.0)
• >4 to 10	46 (20.5)	2/23 (8.7)	4/23 (17.4)
• >10 to 20	54 (24.1)	1/27 (3.7)	2/27 (7.4)
• >20	51 (22.8)	2/25 (8.0)	1/26 (3.8)
by category of pre-randomisation PSA (µg/l)			
• ND: 0 to 0.2	34 (15.2)	2/18 (11.1)	0/16 (0.0)
• Detectable: >0.2	122 (54.5)	4/60 (6.7)	8/62 (12.9)
• >0.2 to 4	102 (83.6 ^c)	4/50 (8.0)	7/52 (13.5)
• >4 to 10	12 (9.8 ^c)	0/6 (0.0)	1/6 (16.7)
• >10 to 20	3 (2.5 ^c)	0/2 (0.0)	0/1 (0.0)
• >20	5 (4.1 ^c)	0/2 (0.0)	0/3 (0.0)
Radiotherapy patients	65 (29.0)	7/39 (17.9)	9/26 (34.6)
by tumour stage ^b			
• localised	22 (9.8)	4/15 (26.7)	2/7 (28.6)
• locally advanced	43 (19.2)	3/24 (12.5)	7/19 (36.8)
by Gleason score			
• well	21 (9.4)	3/12 (25.0)	3/9 (33.3)
• moderate	36 (16.1)	4/22 (18.2)	3/14 (21.4)
• poor	7 (3.1)	0/4 (0.0)	3/3 (100.0)
by category of pre-procedure PSA (µg/l)			
• 0 to 4	1 (0.4)	0/1 (0.0)	0/0
• >4 to 10	5 (2.2)	0/1 (0.0)	2/4 (50.0)
• >10 to 20	10 (4.5)	0/7 (0.0)	0/3 (0.0)
• >20	36 (16.1)	4/21 (19.0)	7/15 (46.7)
by category of pre-randomisation PSA (µg/l)			
• ND: 0 to 0.2	0 (0.0)	0/0	0/0
• Detectable: >0.2	64 (28.6)	7/39 (17.9)	8/25 (0.3)
• >0.2 to 4	17 (26.6 ^c)	0/12 (0.0)	0/5 (0.0)
• >4 to 10	20 (31.3 ^c)	2/11 (18.2)	3/9 (33.3)
• >10 to 20	11 (17.2 ^c)	2/7 (28.6)	1/4 (25.0)
• >20	16 (25.0 ^c)	3/9 (33.3)	4/7 (57.1)

* Bone scan confirmed progression or death in the absence of progression occurring within 2.5 years of randomisation

^b Patients with locally advanced disease are categorised as T3, T4, TX or N+ ; all other patients are considered to have localised disease

^c Percentage of the total number detectable ND = Not Detectable

Supplemental Efficacy Analyses (Set No. 2)

- Proportion of Patients with (1) Bone Scan Documented Progression or (2) Death only from Prostate Cancer in the Absence of Progress within 2.5 Years of Randomization as a Function of Baseline Disease Characteristics

Appendix Table 2a. Trial 23125

Appendix Table 2b. Trial 24126

Appendix Table 2c. Trial 25127

Appendix Table 2a Proportion of Patients with (1) Bone Scan Documented Progression or (2) Death only from Prostate Cancer in the Absence of Progress within 2.5 Years of Randomization as a Function of Baseline Disease Characteristics (Trial 23)

Subgroup	N (%)	Events (%) in CASODEX arm	Events (%) in placebo arm
All adjuvant patients	3292 (100.0)	17/1647 (1.0)	11/1645 (0.7)
Radical Prostatectomy patients	2647 (80.4)	12/1322 (0.9)	8/1325 (0.6)
by tumour stage ^b			
• localised	1759 (53.4)	6/874 (0.7)	2/885 (0.2)
• locally advanced	888 (27.0)	6/448 (1.3)	6/440 (1.4)
by Gleason score			
• well	69 (2.1)	0/34 (0.0)	0/35 (0.0)
• moderate	1205 (36.6)	1/591 (0.2)	1/614 (0.2)
• poor	1373 (41.7)	11/697 (1.6)	7/676 (1.0)
by category of pre-procedure PSA (µg/l)			
• 0 to 4	317 (9.6)	1/157 (0.6)	0/160 (0.0)
• >4 to 10	1545 (46.9)	7/765 (0.9)	4/780 (0.5)
• >10 to 20	520 (15.8)	1/266 (0.4)	3/254 (1.2)
• >20	162 (4.9)	2/80 (2.5)	0/82 (0.0)
by category of pre-randomisation PSA (µg/l)			
• ND: 0 to 0.2	2273 (69.0)	4/1136 (0.4)	5/1137 (0.4)
• Detectable: >0.2	355 (10.8)		
• >0.2 to 4	330 (93.0 ^c)	5/162 (3.1)	3/168 (1.8)
• >4 to 10	19 (5.4 ^c)	1/10 (10.0)	0/9 (0.0)
• >10 to 20	6 (1.7 ^c)	1/4 (25.0)	0/2 (0.0)
• >20	0 (0.0 ^c)	0/0	0/0
Radiotherapy patients	645 (19.6)	5/325 (1.5)	3/320 (0.9)
by tumour stage ^b			
• localised	632 (19.2)	5/317 (1.6)	3/315 (1.0)
• locally advanced	13 (0.4)	0/8 (0.0)	0/5 (0.0)
by Gleason score			
• well	79 (2.4)	0/35 (0.0)	0/44 (0.0)
• moderate	382 (11.6)	0/198 (0.0)	0/184 (0.0)
• poor	184 (5.6)	5/92 (5.4)	3/92 (3.3)
by category of pre-procedure PSA (µg/l)			
• 0 to 4	68 (2.1)	1/39 (2.6)	1/29 (3.4)
• >4 to 10	339 (10.3)	2/167 (1.2)	0/172 (0.0)
• >10 to 20	181 (5.5)	2/91 (2.2)	2/90 (2.2)
• >20	27 (0.8)	0/13 (0.0)	0/14 (0.0)
by category of pre-randomisation PSA (µg/l)			
• ND: 0 to 0.2	84 (2.6)	1/46 (2.2)	0/38 (0.0)
• Detectable: >0.2	556 (16.9)		
• >0.2 to 4	305 (54.9 ^c)	1/154 (0.6)	1/151 (0.7)
• >4 to 10	183 (32.9 ^c)	3/93 (3.2)	2/90 (2.2)
• >10 to 20	58 (10.4 ^c)	0/25 (0.0)	0/33 (0.0)
• >20	10 (1.8 ^c)	0/5 (0.0)	0/5 (0.0)

^a Bone scan confirmed progression or death due to prostate cancer in the absence of progression occurring within 2.5 years of randomisation

^b Patients with locally advanced disease are categorised as T3, T4, TX or N+ ; all other patients are considered to have localised disease

^c Percentage of the total number detectable ND = Not Detectable

Appendix Table 2b Proportion of Patients with (1) Bone Scan Documented Progression or (2) Death only from Prostate Cancer in the Absence of Progress within 2.5 Years of Randomization as a Function of Baseline Disease Characteristics (Trial 24)

Subgroup	N (%)	Events (%) in CASODEX arm	Events (%) in placebo arm
All adjuvant patients	2308 (100.0)	26/1170 (2.2)	58/1138 (5.1)
Radical Prostatectomy patients	1648 (71.4)	14/835 (1.7)	29/813 (3.6)
by tumour stage ^b			
• localised	919 (39.8)	3/461 (0.7)	7/458 (1.5)
• locally advanced	729 (31.6)	11/374 (2.9)	22/355 (6.2)
by Gleason score			
• well	347 (15.0)	1/166 (0.6)	2/181 (1.1)
• moderate	727 (31.5)	5/375 (1.3)	7/352 (2.0)
• poor	545 (23.6)	8/285 (2.8)	20/270 (7.4)
by category of pre-procedure PSA (µg/l)			
• 0 to 4	131 (5.7)	0/66 (0.0)	1/65 (1.5)
• >4 to 10	638 (27.6)	2/307 (0.7)	5/331 (1.5)
• >10 to 20	524 (22.7)	3/270 (1.1)	11/254 (4.3)
• >20	325 (14.1)	8/177 (4.5)	10/148 (6.8)
by category of pre-randomisation PSA (µg/l)			
• ND: 0 to 0.2	1073 (46.5)	4/540 (0.7)	12/533 (2.3)
• Detectable: >0.2	455 (19.7)		
• >0.2 to 4	415 (91.2 ^c)	7/213 (3.3)	13/202 (6.4)
• >4 to 10	29 (6.4 ^c)	3/14 (21.4)	3/15 (20.0)
• >10 to 20	4 (0.9 ^c)	0/1 (0.0)	0/3 (0.0)
• >20	7 (1.5 ^c)	0/2 (0.0)	0/5 (0.0)
Radiotherapy patients	660 (28.5)	12/335 (3.6)	29/325 (8.9)
by tumour stage ^b			
• localised	411 (17.8)	6/206 (2.9)	11/205 (5.4)
• locally advanced	249 (10.8)	6/129 (4.7)	18/120 (15.0)
by Gleason score			
• well	214 (9.3)	2/119 (1.7)	3/95 (3.2)
• moderate	279 (12.1)	4/127 (3.1)	14/152 (9.2)
• poor	157 (6.8)	6/80 (7.5)	12/77 (15.6)
by category of pre-procedure PSA (µg/l)			
• 0 to 4	36 (1.6)	0/17 (0.0)	1/19 (5.3)
• >4 to 10	147 (6.4)	0/78 (0.0)	6/69 (8.7)
• >10 to 20	204 (8.8)	2/100 (2.0)	6/104 (5.8)
• >20	268 (11.6)	10/137 (7.3)	16/131 (12.2)
by category of pre-randomisation PSA (µg/l)			
• ND: 0 to 0.2	55 (2.4)	2/29 (6.9)	1/27 (3.7)
• Detectable: >0.2	583 (25.3)		
• >0.2 to 4	303 (52.0 ^c)	1/160 (0.6)	8/143 (5.6)
• >4 to 10	152 (26.1 ^c)	0/81 (0.0)	7/71 (9.9)
• >10 to 20	86 (14.8 ^c)	4/41 (9.8)	6/45 (13.3)
• >20	42 (7.2 ^c)	5/19 (26.3)	5/23 (21.7)

* Bone scan confirmed progression or death due to prostate cancer in the absence of progression occurring within 2.5 years of randomisation

^b Patients with locally advanced disease are categorised as T3, T4, TX or N+; all other patients are considered to have localised disease

^c Percentage of the total number detectable ND = Not Detectable

Appendix Table 2c Proportion of Patients with (1) Bone Scan Documented Progression or (2) Death only from Prostate Cancer in the Absence of Progress within 2.5 Years of Randomization as a Function of Baseline Disease Characteristics (Trial 25)

Subgroup	N (%)	Events (%) in CASODEX arm	Events (%) in placebo arm
All adjuvant patients	224 (100.0)	6/118 (5.1)	14/106 (13.2)
Radical Prostatectomy patients	159 (71.0)	1/79 (1.3)	7/80 (8.8)
by tumour stage ^b			
• localised	56 (25.0)	0/30 (0.0)	2/26 (7.7)
• locally advanced	103 (46.0)	1/49 (2.0)	5/54 (9.3)
by Gleason score			
• well	40 (17.9)	1/18 (5.6)	0/22 (0.0)
• moderate	88 (39.3)	0/43 (0.0)	5/45 (11.1)
• poor	31 (13.8)	0/18 (0.0)	2/13 (15.4)
by category of pre-procedure PSA (µg/l)			
• 0 to 4	3 (1.3)	0/2 (0.0)	1/1 (100.0)
• >4 to 10	46 (20.5)	1/23 (4.3)	3/23 (13.0)
• >10 to 20	54 (24.1)	0/27 (0.0)	2/27 (7.4)
• >20	51 (22.8)	0/25 (0.0)	1/26 (3.8)
by category of pre-randomisation PSA (µg/l)			
• ND: 0 to 0.2	34 (15.2)	0/18 (0.0)	0/16 (0.0)
• Detectable: >0.2	122 (54.5)		
• >0.2 to 4	102 (83.6 ^c)	1/50 (2.0)	6/52 (11.5)
• >4 to 10	12 (9.8 ^c)	0/6 (0.0)	1/6 (16.7)
• >10 to 20	3 (2.5 ^c)	0/2 (0.0)	0/1 (0.0)
• >20	5 (4.1 ^c)	0/2 (0.0)	0/3 (0.0)
Radiotherapy patients	65 (29.0)	5/39 (12.8)	7/26 (26.9)
by tumour stage ^b			
• localised	22 (9.8)	2/15 (13.3)	2/7 (28.6)
• locally advanced	43 (19.2)	3/24 (12.5)	5/19 (26.3)
by Gleason score			
• well	21 (9.4)	2/12 (16.7)	1/9 (11.1)
• moderate	36 (16.1)	3/22 (13.6)	3/14 (21.4)
• poor	7 (3.1)	0/4 (0.0)	3/3 (100.0)
by category of pre-procedure PSA (µg/l)			
• 0 to 4	1 (0.4)	0/1 (0.0)	0/0
• >4 to 10	5 (2.2)	0/1 (0.0)	2/4 (50.0)
• >10 to 20	10 (4.5)	0/7 (0.0)	0/3 (0.0)
• >20	36 (16.1)	2/21 (9.5)	5/15 (33.3)
by category of pre-randomisation PSA (µg/l)			
• ND: 0 to 0.2	0 (0.0)	0/0	0/0
• Detectable: >0.2	64 (28.6)		
• >0.2 to 4	17 (26.6 ^c)	0/12 (0.0)	0/5 (0.0)
• >4 to 10	20 (31.3 ^c)	1/11 (9.1)	1/9 (11.1)
• >10 to 20	11 (17.2 ^c)	1/7 (14.3)	1/4 (25.0)
• >20	16 (25.0 ^c)	3/9 (33.3)	4/7 (57.1)

^a Bone scan confirmed progression or death due to prostate cancer in the absence of progression occurring within 2.5 years of randomisation

^b Patients with locally advanced disease are categorised as T3, T4, TX or N+ ; all other patients are considered to have localised disease

^c Percentage of the total number detectable ND = Not Detectable