AstraZeneca

Date: NOV 14 2002

Karen M. Templeton-Somers, Ph.D., Executive Secretary
Oncologic Drugs Advisory Committee
Advisors and Consultants Staff
FDA, CDER, ORM
HFD-21, Room 1093
5630 Fishers Lane
Rockville, MD 20852-1734

Re: NDA 20-498/S-012
CASODEX® (bicalutamide) Tablets
Briefing Document for the December 18, 2002 Oncologic Drugs Advisory Committee (ODAC) Meeting

Dear Dr. Templeton-Somers:

AstraZeneca Pharmaceuticals LP (AstraZeneca) is herewith submitting a briefing document for CASODEX® (bicalutamide) 150 mg Tablets 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 localized non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated for the ODAC Meeting scheduled for December 18, 2002.

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Additionally, AstraZeneca will be providing the names and affiliations of the speakers and the titles of their presentations under separate cover.

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Please direct any questions or requests for additional information to me, or in my absence, to David M. Stollman, Regulatory Project Manager, at (302) 886-4695.

Sincerely,

David M Stollman for Lisa V. DeLuca

Lisa V. DeLuca, Ph.D., Director
Regulatory Affairs
Telephone: (302) 886-5594
Fax: (302) 886-2822

LVD/
Enclosure

CASODEX™ (bicalutamide) 150-mg tablets

NDA 20-498

FDA Oncologic Drug Advisory Committee Briefing Document for the use of CASODEX 150 mg in patients with localized or locally advanced nonmetastatic prostate cancer

18 December 2002

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CASODEX is used within this document to indicate both the formulated drug product as well as the unformulated drug substance bicalutamide.

Executive Summary

CASODEX early prostate cancer (EPC) program

Problem: In this year alone in the United States, prostate cancer will be diagnosed in approximately 189,000 men, and prostate-cancer-related deaths will exceed 31,000 (American Cancer Society 2002). Putatively curative or definitive treatments—radical prostatectomy and radiation therapy—are not always effective, leaving patients faced with the certain possibility of medical or surgical castration and the undesirable effects associated with the resultant androgen deprivation. Patients not suitable for definitive therapy because of age, other illness, or shortened life expectancy, and patients not willing to risk the adverse effects associated with prostatectomy or radiation, have little option but to choose medical or surgical castration or alternately a watchful waiting approach which equates to disease monitoring with intervention offered in the form of palliative treatment only after symptoms occur or PSA (prostate-specific antigen) levels suggest disease progression. In the United States, approximately 28.8% of all patients with prostate cancer chose not to elect either radical prostatectomy or radiation as their primary therapy (National Cancer Institute; Surveillance, Epidemiology, and End Results [SEER] public data base 1995-1997; Harlan 2001).

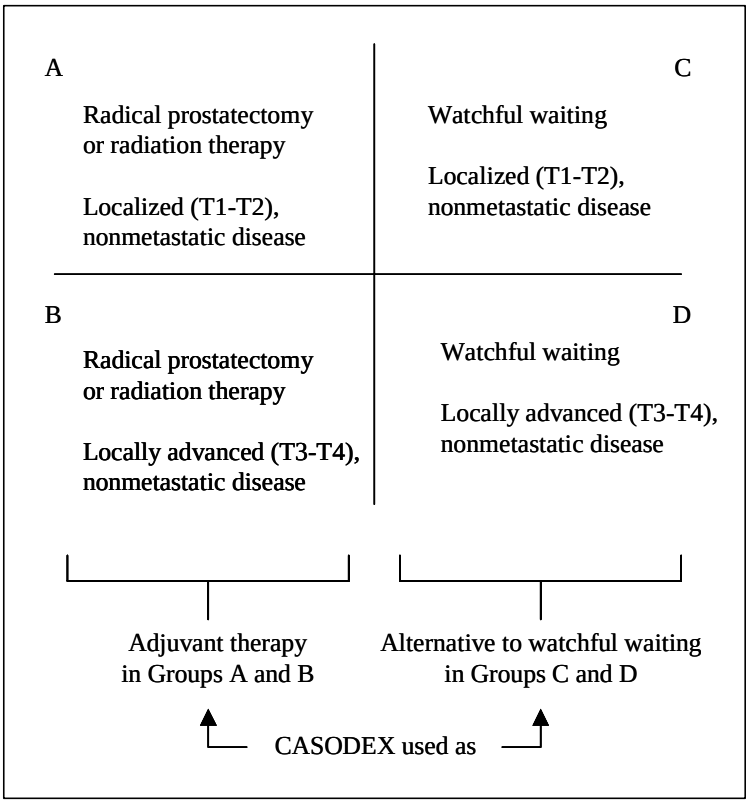
Clearly, there is a need for additional treatment options when definitive treatments fail and when definitive treatments are not indicated or desired because of adverse effects.

Hypothesis and rationale: Given the problem described, AstraZeneca Pharmaceuticals LP (AstraZeneca) decided to investigate the benefits of CASODEX™ (bicalutamide) 150 mg as (a) an adjuvant treatment to radical prostatectomy or radiation therapy and (b) an alternative treatment to watchful waiting. This program—designated the CASODEX early prostate cancer (EPC) program—enrolled a wide variety of patients with prostate cancer, including patients with localized (T1-T2) nonmetastatic (N0/NX/M0) disease and patients with locally advanced (T3-T4) nonmetastatic (N0/NX/M0) disease (Figure A).[1]

CASODEX is an oral nonsteroidal antiandrogen currently approved at the 50-mg dose for use in combination with an LHRH (luteinizing hormone-releasing hormone) analogue for the palliative treatment of advanced prostate cancer. The rationale for assessing CASODEX 150 mg in the target population was considered (a) consistent with hormone-treatment use in breast cancer, another hormone-sensitive cancer (in which sex-hormone-receptor antagonists are known to offer additional benefit to surgery) and (b) a logical extension of the accepted practice of using hormone therapy for advanced disease.

[1] TNM definitions are provided in Appendix A.

Figure A **Types of patients treated in the CASODEX EPC program, by baseline standard of care and disease stage**



Trial design: The CASODEX EPC program comprised 3 multicenter, randomized, double-blind, parallel-group, placebo-controlled Phase III trials:

- Trial 23 conducted in North America[2]
- Trial 24 conducted primarily in Europe[2]
- Trial 25 conducted in Scandinavia.[2]

All 3 trials enrolled patients who had had previous therapy of curative intent, and Trials 24 and 25 also enrolled patients engaged in watchful waiting. All patients were free from metastatic disease at trial entry as determined by bone scan. In each trial, time to objective

[2] Officially identified as Trials 7054IL/0023, 7054IL/0024, and 7054IL/0025, respectively. Trial 24 also enrolled patients from South Africa, Israel, Mexico, and Australia.

disease progression was the primary endpoint.[3] Other endpoints included survival (primary endpoint in Trials 23 and 25, secondary endpoint in Trial 24), time to PSA doubling, time to treatment failure, and tolerability. Across trials, the commonality in fundamental design features, trial objectives, and the use of identically defined endpoints enabled the planned pooled analyses of the data across the 3 trials at 2 years' minimum follow-up. A total of 8113 patients were enrolled in the CASODEX EPC program, making it the largest prostate cancer trial program ever conducted; 4052 patients were randomized to treatment with CASODEX 150 mg daily and 4061 were randomized to treatment with placebo. Enrollment was completed within 3 years.

Key efficacy findings:

- Overall (trials combined), CASODEX 150 mg reduced the risk of objective disease progression or death in the absence of progression by 42%, compared with placebo. This result was highly significantly ($p<<0.0001$) and was seen regardless of baseline standard of care, disease stage, tumor grade, or nodal status. In Trials 24 and 25, a similar highly significant ($p<<0.0001$) reduction in the risk of objective disease progression was seen.

- Trial 23 had a much lower event rate than did Trials 24 and 25 at the data cut-off date, and no difference could be demonstrated on the primary endpoint.

- Overall, CASODEX 150 mg significantly ($p<<0.0001$) reduced the risk of PSA progression (defined as doubling of PSA concentration, objective disease progression, or death). A similar highly significant ($p<<0.0001$) reduction in risk of PSA progression was seen in each of the individual trials, with risk reduced by 38% in Trial 23, 63% in Trial 24, and 76% in Trial 25.

- With a median follow-up of 3 years, it is too early to detect a survival difference between treatments. At the time of data cut-off, only 6.4% of patients had died, with less than 1.6% having died of prostate cancer.

Key safety findings:

- In the EPC program, CASODEX was shown to be safe, with the most frequently occurring adverse events—gynecomastia (67.6%) and breast pain (73.3%)—related to its endocrine actions. This event profile has been previously well described for CASODEX and related drugs. In the EPC program, gynecomastia and breast pain were considered severe in only 5.8% and 4.8% of patients, respectively. (Recent

[3] In patients with nonmetastatic prostate cancer, progression to metastatic disease represents a point when disease is no longer curable and when symptoms begin to manifest, including those related to bony metastases (eg, fractures and spinal cord compression). Therefore, increasing progression-free survival becomes an important clinical goal.

trials have shown encouraging results with the use of external beam radiation and anti-estrogens to manage gynecomastia, breast pain, or both [Sieber et al 2002, Tyrrell et al 2002].)

- Other adverse events related to the endocrine action of CASODEX included asthenia (CASODEX 10.8%, placebo 7.6%), hot flashes (CASODEX 9.1%, placebo 5.3%), alopecia (defined as a change in body hair; CASODEX 5.9%, placebo 0.8%), and weight gain (CASODEX 5.8%, placebo 2.9%).

- There was a low incidence (<5.5%) of clinically significant changes from baseline in hepatic transaminases and total bilirubin.

Submission and regulatory feedback: Data from the CASODEX EPC program were submitted to the Food and Drug Administration (FDA) as a supplemental New Drug Application (sNDA) (NDA 20-498/0012) on 20 December 2001. In recognition of an unmet medical need, the FDA granted priority review of the application on 8 January 2002, which meant that the review was targeted for completion in 6 months. During the review process, the FDA identified several issues as problematic in granting approval, and on 20 June 2002, AstraZeneca received a not-approvable letter. The FDA approval issues, listed by potential CASODEX indication, are summarized as follows:

For the potential indication of **adjuvant treatment after therapy of curative intent** (see Figure A, Groups A and B), the issue was the lack of demonstrated efficacy in the North American trial (Trial 23). Also, the FDA was unable to characterize the populations in the non-US Trials 24 and 25 who benefitted because standardized Gleason scores were lacking.[4]

For the potential indication of **immediate treatment in localized disease** (see Figure A, Group C), the issue was the need to show relevancy between the efficacy findings in non-US Trials 24 (Europe) and 25 (Scandinavia) to US patients who would otherwise be managed by watchful waiting.

For the potential indication of **immediate treatment in locally advanced disease** (see Figure A, Group D), the issue was that using immediate CASODEX monotherapy in the treatment of patients with locally advanced nonmetastatic prostate cancer might not provide a survival benefit compared with current US standard of care, as evidenced by NDA 20-498/S006 (application withdrawn on 19 Dec 2000, see Section 3.3 for details).

Purpose of the briefing document: The purpose of the full briefing document is to address these FDA-specified issues and provide in-depth trial results and discussion to support the

[4]Gleason grade or score reflects the range of differentiation among malignant cells present in a biopsy sample. See Section 1.5.2 for further explanation of Gleason scoring.

currently proposed indications (which were revised from the original indication).[5] The revised indications, which follow, now focus on 2 of 4 potential patient groups:

CASODEX 150 mg is indicated as adjuvant therapy to radical prostatectomy or radiation therapy of curative intent in patients with locally advanced, nonmetastatic prostate cancer who are at high risk of disease progression.

CASODEX 150 mg is indicated as immediate treatment of **localized** nonmetastatic prostate cancer in patients for whom therapy of curative intent is not indicated.

AstraZeneca points for discussion

In the full briefing document, AstraZeneca will show the following:

- The low event rate in Trial 23 was related to the select subset of good-prognosis patients enrolled; therefore, the lack of a demonstrated effect (on objective disease progression) cannot be interpreted as simply a lack of effect. However, for patients with localized disease who chose definitive therapy as their baseline standard of care (Figure A, Group A), adjuvant therapy with CASODEX was not shown to be needed.

- Findings for PSA progression and trends in favor of CASODEX therapy in patients characterized as high risk in Trial 23 were consistent with findings from the non-US trials. Subgroup analyses by standard prognostic factors support the adjuvant use of CASODEX 150 mg in high-risk patients for a period of at least 2 years.

- Patients with localized or locally advanced nonmetastatic prostate who benefit from CASODEX can be characterized by standard prognostic factors other than Gleason grade. As described in the literature, several nomograms can be used to predict outcome on the basis of clinical disease stage and PSA level (D'Amico et al 1998, 1999). Additionally, Gleason scoring has been associated with problems, including over and under grading, variability in interpretation, and poor reproducibility (Carlson et al 1998).

- The highly significant delay in disease progression achieved in non-US Trials 24 and 25 is applicable to US patients who are not candidates for therapy of curative intent and who would otherwise undergo watchful waiting or hormonal therapy. This point is based on findings from prostate cancer epidemiology data that identify the types of US patients who currently elect watchful waiting or use off-label

[5] The original indication was as follows: CASODEX 150 mg is indicated as immediate hormonal therapy or as adjuvant therapy to treatment of curative intent in patients with nonmetastatic disease. See Appendix B for additional discussion.

primary hormonal therapy (SEER 1995-1997, Harlan 2001). In the EPC program, subgroup analyses by baseline standard of care and standard prognostic factors support the use of CASODEX 150 mg in most watchful waiting patients until disease progression. However, the current proposed treatment indication for these patients is limited to only those patients **with localized disease**. This is in response to the FDA's concern that CASODEX 150 mg may not be better than other current options in watchful waiting patients **with locally advanced disease** (see Section 3.3 in the main document for additional details). Since patients with localized disease not undergoing radical prostatectomy or radiation therapy would receive CASODEX as their only active treatment for prostate cancer, it would be important that these patients receive CASODEX therapy until disease progression.

In considering the proposed indications for CASODEX 150 mg and the current use of prostate cancer therapies, it is important to note the accumulating experience with CASODEX as described in the literature, including data showing several advantages with CASODEX compared with medical or surgical castration, including maintenance of bone mineral density and muscle mass (vs LHRH analogues) and preservation of quality of life relative to sexual function (Iversen et al 2000, Iversen 2002, Boccardo 1999).

In conclusion, AstraZeneca will show that the overall benefit-to-risk profile established from the CASODEX EPC program, the relevant epidemiological data, and current treatment practices strongly supports approval of the revised indications for CASODEX 150 mg.

For ease of review, data in the briefing document are provided in the following 12 sections:

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1. PROSTATE CANCER: THE DISEASE

1.1 Prostate cancer in the United States

In this year alone in the United States, prostate cancer will be diagnosed in approximately 189,000 men, and prostate-cancer-related deaths will exceed 31,000 (American Cancer Society 2002). The incidence of prostate cancer is estimated at 1 in 6 men over a lifetime, and 1 in 32 will die from the disease. Although many men with prostate cancer die of other causes, the physical, psychological, and social morbidity associated with progressive prostate cancer and prostate-cancer-related death remains a major healthcare challenge. Excluding skin cancers, prostate cancer is the most common cancer in American men and the second leading cause of cancer-related death, with lung cancer being first[1] (American Cancer Society 2002).

Over the last 2 decades, there has been a large shift in the presentation of prostate cancer. Now up to 70% of men in the US present with clinically localized disease, in contrast to advanced metastatic disease, which was common in the past. Notably, clinical disease stage at presentation differs with grade of tumor. Among US men with well-differentiated tumors, more than 80% are diagnosed with localized disease, while among those with poorly or undifferentiated tumors, only 42% have localized disease (Stanford et al 1999).

Survival is related to the extent of the tumor (NCI 2002). When the cancer is confined to the prostate gland, median survival in excess of 5 years can be anticipated. However, patients with early stages of disease have relapse rates defined by factors such as pretreatment prostate-specific antigen (PSA) levels and tumor grade. Among patients with locally advanced cancer, the disease is usually not curable, and the aim is palliation and prevention of symptoms. Lastly, with spread of prostate cancer to distant organs, current therapy will not provide a cure, and many patients will suffer symptoms related to metastases (especially bone metastases). Median survival with metastatic disease is usually 1 to 3 years, and most patients with metastatic disease die from prostate cancer.

1.2 PSA

Since the late 1980s, PSA monitoring has become widespread in the early detection and management of prostate cancer. PSA is the protein product of the human kallikrein gene and is a serine protease. The standard reference range is 0.0 to 4.0 ng/ml, although a significant number of men with prostate cancer have PSA levels of <4.0 ng/ml (Hudson et al 1989). Three factors influence serum PSA levels in men with prostate cancer:

- volume of prostate cancer
- volume of benign prostatic epithelium

[1] Lung-cancer related deaths were estimated at 89,200 among US men in 2002.

- histological grade of tumor

While the usefulness of PSA as a disease marker and its correlation with survival remain controversial, PSA can be used as an indicator of disease activity (Partin et al 2002). In fact, PSA assays are FDA-approved for monitoring therapy of prostate cancer. Following radical prostatectomy and irradiation, PSA levels have been found to correlate with disease activity, with detectable postoperative PSA levels correlating with local recurrence and distant metastases. When PSA becomes detectable, levels tend to increase exponentially, making PSA doubling-time determinations particularly useful for determining risk of clinical recurrence. Many clinicians in the United States institute salvage therapy (usually hormonal) upon PSA failure, recognizing that a rising PSA level indicates a high likelihood of residual or recurrent disease.

1.3 Diagnosis of prostate cancer

Today, most US patients with prostate cancer initially present after detection of an elevated PSA level on routine screening, and usually with minimal or no findings on physical exam. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (NCI SEER) registry show that, in recent years, the rate of distant disease (M1) at presentation has fallen by 56% (from 14.9 in 100,000 in 1985 to 6.6 in 100,000 in 1995), with only about 6% of patients now presenting with distant disease (Ries et al 2002). This shift has been accompanied by a steep increase in the rate of detection of localized disease; thus, most patients diagnosed with prostate cancer in the United States today present without clinically apparent disease. Along the prostate cancer continuum (Figure 1), these patients would be those with elevated PSA or localized disease.

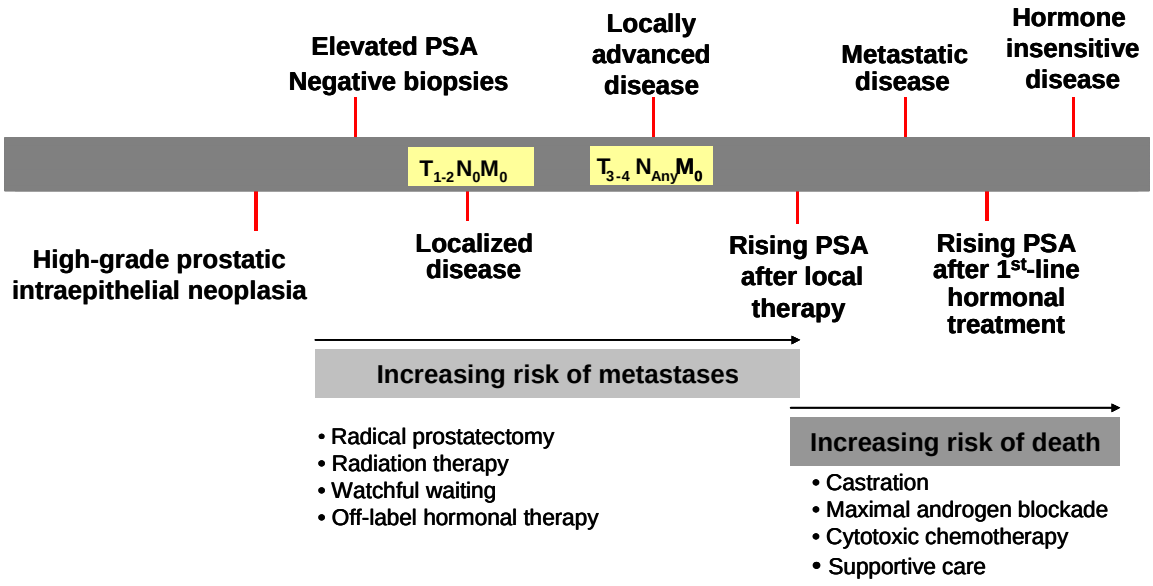

Figure 1 Prostate cancer continuum

(See Appendix A for TNM definitions.)

While the SEER data indicate that the diagnosis of prostate cancer has been accompanied by a shift towards earlier disease stages, there has been no corresponding shift toward low-grade disease. Because higher-grade tumors are associated with a worse prognosis, it is not clear that prostate cancer screening will improve mortality in patients with this disease (NCI 2002). Even with earlier diagnosis, the underlying biology of the disease still dictates outcomes after disease presentation. This has led to concerns about the adequacy of tumor control with therapies that are primarily directed towards tumor confined within the prostate. Therefore, while there has been a clear shift in the staging of disease at presentation, overall mortality has been little affected.

From a symptom perspective, clinically localized disease and locally advanced disease are usually asymptomatic, or less frequently, associated with local symptoms related to urinary obstruction. Advanced (metastatic) disease, however, is often associated with symptoms, primarily related to bony metastases (de la Monte et al 1986). Development of new treatments aimed at further reducing the risk of developing metastatic disease and its impact, therefore, remains a priority in the management of prostate cancer.

1.4 Primary treatments for early prostate cancer

Therapeutic options for managing early-stage prostate cancer range from aggressive primary therapy, including radical prostatectomy and radiation therapy, to more conservative modalities, including watchful waiting or off-label primary hormonal therapy. Leading national organizations involved in prostate cancer management have established therapeutic guidelines for the treatment for early prostate cancer, and these guidelines provide a useful starting point for understanding current US treatment practices.

Treatment guidelines for early prostate cancer from the American Urological Association (AUA 1995), NCI (2002), and National Comprehensive Cancer Network (NCCN 2002) are summarized in Table 1.[2]

[2] These guidelines are available to the public on the worldwide web using the following URLs:
AUA: https://shop.auanet.org/timssnet/products/guidelines/main_reports/pca.pdf
NCI: http://www.cancer.gov/cancerinfo/pdq/treatment/prostate/healthprofessional/
NCCN: http://www.nccn.org/physician_gls/index.html

Table 1 Treatment guidelines for early prostate cancer

Treatment	Treatment guidelines		
	AUA	NCI	NCCN
Radical prostatectomy	For patients with relatively long life expectancy, no significant surgical risk factors, and preference to undergo surgery	For patients in good health <70 y who elect surgery. Tumor confined to the prostate gland (Stages I and II)	Low risk of recurrence,[a] life expectancy >20 y; Intermediate risk,[b] life expectancy >10 y; High risk,[c] life expectancy >5 y
Irradiation	For patients with relatively long life expectancy; no significant risk factors for radiation toxicity, and a preference for radiotherapy	For patients with disease clinically confined to the prostate or surrounding tissues (Stages I, II, and III). Patients selected for brachytherapy should have low Gleason score, low PSA level, and T1 or T2 tumors	Low risk of recurrence, life expectancy >20 y Intermediate risk, life expectancy >10 y High risk, life expectancy >5 y (+ hormonal therapy)
Observation	For patients with shorter life expectancy, low-grade tumor, or both	For asymptomatic patients with advanced age or concomitant illness, especially those with low-grade and early-stage tumors	Low risk of recurrence, life expectancy <20 y Intermediate risk, life expectancy <10 y High risk, life expectancy <5 y (+ hormonal therapy)

[a] Stages T1-2a, low Gleason score (2 to 6), and PSA <10 ng/ml.
[b] Stages T2b-2c, Gleason score of 7, PSA between 10 and 20 ng/ml.
[c] Stages T3a-3b, Gleason score of 8 to 10, PSA > 20 ng/ml.
AUA American Urological Association.
NCI National Cancer Institute.
NCCN National Comprehensive Cancer Network.
NCI Stage I disease = T1a/N0/M0, tumor well differentiated.
NCI Stage II disease = T1a/N0/M0, tumor moderately differentiated, poorly differentiated, or undifferentiated; or T1b/N0/M0; or T1c/N0/M0; or T1/N0/M0; or T2/N0/M0.
NCI Stage III disease = T3/N0/M0 (see Appendix A for expanded TNM definitions).
y years.

Thus, these recently published guidelines define primary treatment options and the types of patients most likely to benefit from each option.[3] Although primary (or immediate) hormonal therapy does not appear in these recommendations, this therapy is used off-label in US practice, and there are few data to guide its use. Thus, the CASODEX early prostate cancer (EPC)

[3] The patterns of treatment used and the types of patients treated in the CASODEX early prostate cancer (EPC) program were consistent with national guidelines, as will be shown in Sections 4 and 5.

program, to be described herein, provides the largest and most comprehensive assessment of immediate hormonal therapy in patients not electing definitive therapy, as well as an assessment of adjuvant hormonal therapy in localized (T1-T2) or locally advanced (T3-T4) nonmetastatic (N0/NX/M0) prostate cancer.

1.4.1 Radical prostatectomy

US physicians have long used radical prostatectomy as primary treatment for clinically localized prostate cancer (cT1-T2/NX/M0 or Stage T2b or less).[4]. Usually surgery is reserved for patients in good health who are under the age of 70 and who elect surgical intervention. Research shows, however, that approximately 1/3 of patients with clinically localized disease treated with radical prostatectomy develop evidence of biochemical failure during long-term-follow-up (Dillioglugil et al 1997, Amling et al 2000). For patients with locally advanced disease at pathological staging, the prognosis is worse with 0% to 22% alive at 10 years following surgery (Boxer et al 1977, Elder et al 1982). Thus, a significant number of men treated with radical prostatectomy, including those thought to have organ-confined cancers, will continue to have disease progression after primary surgical therapy.

Publicly available databases and study groups (SEER, PCOS, CaPSURE, CPDR) have captured predominant treatment patterns for early prostate cancer in the United States (Stanford et al 1999, Harlan et al 2001; Koppie et al 2000, Moul et al 2001). These data show that the use of radical prostatectomy as definitive therapy for patients with clinically localized prostate cancer ranges from 30% to 48%. These findings also confirm that radical prostatectomy is generally used in men younger than 70 years.

The risks of radical prostatectomy include urinary incontinence, urethral stricture, erectile dysfunction, and morbidities associated with general anesthesia and surgery.

1.4.2 Radiation therapy

Another mode of primary therapy for clinically localized prostate cancer involves irradiation, either external-beam therapy or interstitial isotopic implantation (brachytherapy). Five-year survival with external beam irradiation is reported as 85% for patients with T1/NX tumors and as 75% for patients with T2/NX tumors (Hanks 1994, Asbell 1988). For patients with T2 tumors, there is a high local recurrence rate—15% at 5 years and 30% at 15 years. For patients with T3 and T4 tumors treated with external beam radiotherapy, local recurrence rates of 20% to 60% have been reported 10 to 15 years after therapy (Perez et al 1993, Bagshaw et al 1993, Zagars et al 1993).

For patients with pretreatment PSA levels <10 ng/ml, disease-free rates at 3 to 5 years following radiation therapy range from 43% to 90% (Brawer 2002). A group at particularly high risk for failure after radiotherapy are those with pretreatment PSA levels >30 ng/ml or PSA between 10 and 30 ng/ml with tumor grades 3 or 4 (Pollack et al 1995).

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[4] See Appendix A for American Joint Committee on Cancer/International Union Against Cancer TNM staging classifications.

Studies indicate that 18% to 32% of US patients with clinically localized prostate cancer receive irradiation as their primary therapy of curative intent (Stanford et al 1999, Harlan et al 2001; Koppie et al 2000, Moul et al 2001).

The risks of radiation therapy include radiation cystitis, proctitis, enteritis, erectile dysfunction, and morbidities related to technique.

1.4.3 Nondefinitive primary therapies

Analysis of 1995 to 1997 SEER data (n=51,475) shows that 28.8% of all US patients with prostate cancer choose not to receive either radical prostatectomy or radiation therapy as initial therapy. Patients who fall into this category tend to be older and have concomitant illness, lower grade tumors, smaller tumors, or a combination of factors, all of which can influence patient decision to chose alternative therapies, including watchful waiting or off-label primary hormonal therapy (Chodak et al 1994, Carter et al 2002, Koppie et al 2000, Harlan et al 2001). The choice of watchful waiting is often made in conjunction with the desire to avoid the risks and the not-infrequent complications of surgery or radiotherapy, especially when comorbid conditions exist. This choice can be driven both by medical considerations and patient preference. Men with prostate cancer want to be involved in clinical decision making, and may rate impotence, incontinence, and the other side effects of definitive therapies differently than clinicians. Primary hormonal therapy is also chosen for many of the same reasons, but without the benefit of evidence-based data to guide such use. Maximum androgen blockade (see Section 3.1) and long-term LHRH therapy also carry significant morbidity (see Section 1.4.3.2).

1.4.3.1 Watchful waiting

For patients newly diagnosed with localized or locally advanced nonmetastatic prostate cancer, the watchful waiting approach equates to disease monitoring with intervention offered in the form of palliative treatment only after symptoms occur or PSA levels suggest disease progression. For many older men, the risk of developing hormone-resistant metastatic disease is relatively low, so the risks of aggressive primary intervention may not be balanced by sufficiently large gains in longevity. Thus with watchful waiting, physicians and patients avoid the risks of prostatectomy and radiation and may be comforted by the fact that patients are expected to outlive their disease. The downside to watchful waiting, however, is that many of these patients will suffer with progression-related symptoms even if they die from other causes.

(a) Literature findings

The watchful waiting literature continues to grow as treatment strategies evolve and longer-term follow-up becomes available. In one study among men with clinically localized prostate cancer who were managed expectantly (with watchful waiting), patients with well- and moderately differentiated tumors had a 10-year disease-specific survival rate of 87% (Chodak et al 1994). In the same study, patients with poorly differentiated tumors had a 10-year disease-specific survival rate of 34%.

A 15-year analysis among a population-based cohort of men who received no immediate therapy for newly diagnosed disease demonstrated that 6% of the patients with well-differentiated disease, 17% with moderately differentiated disease, and 56% with poorly differentiated disease died from prostate cancer (Johansson et al 1997).

Fleming et al (1993) analyzed both Medicare claims data and the literature to compare radical prostatectomy, radiotherapy, and watchful waiting (followed by hormonal therapy if disease progressed). He found the following:

- Men older than 65 with well-differentiated tumors that are clinically localized appear to have minimal risk of disease progression.

- Men aged 65 to 75 with moderately and poorly differentiated tumors have a significant risk of dying from prostate cancer; however, competing risks for death above age 70 play a more prominent role in patient survival.

- For men in their early 70s, the potential benefits of surgery or radiation therapy are sufficiently small when compared with watchful waiting so that patient preferences should dictate the optimal treatment strategy.

A recent study from a Scandinavian group compared radical prostatectomy with watchful waiting among men with early prostate cancer (Holmberg et al 2002). With a median follow-up of 6.2 years, there was a significant difference in favor of surgery for deaths due to prostate cancer, but no difference in overall mortality. Of note, though, this Scandinavian study was conducted among a largely clinically staged population who had palpable disease. In an accompanying editorial, Walsh (2002) indicates that in the United States, 75% of newly diagnosed cases have nonpalpable disease but an elevated PSA, and that watchful waiting is an appropriate option for the 10% to 20% of patients who initially present with small tumors, as well as for older patients who have a life expectancy of less than 10 years.

(b) Applicability to US patients

Because prostate cancer is slow to progress, and because patients with low risk of disease, comorbidities, or both may die of other causes before they die of prostate cancer, it is not surprising that watchful waiting is both recommended and practiced in the United States. Using the 1995 to 1997 SEER data and applying the ratio reported by Harlan et al (2001) for the proportion of patients initially treated by watchful waiting vs hormonal therapy (64%:36%), the proportion of US population with prostate cancer initially treated with watchful waiting can be estimated at approximately 18.5% (SEER 1995-1997, Harlan 2001).

Studies also show that the US watchful waiting population is generally older (70+ years) with lower clinical disease stage (T1 or T2), a Gleason score <7, and a baseline PSA <10 ng/ml (Table 2) (Potosky 2002, Koppie 2000, SEER 1995-1997). The percentage of patients who are free from secondary treatment at 2 years with watchful waiting (as primary therapy) has been described to be dependent on these same prognostic factors (Koppie 2000).

Table 2 Characteristics of US patients who choose watching waiting or do not elect surgery or radiation therapy

Characteristic	Prostate Cancer Outcomes Study[b] (Potosky 2002)	CaPSURE (Koppie 2000)	SEER (1995-1997[c])
Age	70% are ≥70 y	51% are ≥70 y	Mean: 74 y
T1/T2 stage	86%	97%	67%
Tumor grade: well or moderately differentiated[a]	70%	86%	74%[d]
PSA at diagnosis (ng/ml)	>4 to10: 45% >10: 28%	>4 to 10: 49% 10 to 20: 22%	N/A

[a] Gleason grade <7.
[b] Patients with localized disease.
[c] 1995-97 data for patients not choosing surgery or radiation therapy (n=14,816).
[d] Excludes unknowns.
NA Not available at this time.

Thus, for many patients, the choice of watchful waiting as primary therapy is consistent with recognized guidelines in relationship to baseline tumor characteristics. On the basis of the EPC trial results (to be shown), there is now the potential for an active treatment option for these men, and in particular, for those with adverse baseline factors that put them at increased risk of disease progression.

1.4.3.2 Primary hormonal therapy

Even with limited evidence guiding the use of primary hormonal therapy (medical or surgical castration) in the treatment of clinically localized prostate cancer, epidemiological databases suggest that such therapy is used in the United States in some 8% to 11% of patients with early disease (SEER 2002, Harlan et al 2001). The sequelae of castration are widely recognized (hot flashes, impotence, fatigue, osteoporosis). Despite patient acceptance, studies also show the potential for long-term sequelae, including impotence and declines in vitality (Potosky et al 2002), osteoporosis leading to bone fractures, and changes in lean body mass and fat content (Townsend et al 1997, Hatano et al 2000, Stege 2000, Stoch et al 2001, Berruti et al 2002, Mittan et al 2002). Thus, the use of medical or surgical castration for the treatment of clinically localized prostate cancer requires a careful risk-benefit assessment prior to implementation, with consideration given to patient needs.

1.5 Prognostic features of early prostate cancer

Various prognostic factors are recognized as important in determining the risk of disease progression following best efforts to control early-stage prostate cancer. Three prognostic factors, in particular, have been identified:

- T stage (AJCC system)
- biopsy Gleason sum

- pretreatment PSA level

Together, these 3 factors can be used to make reliable predictions of pathological (p) stage (Partin et al 1997). Different prognostic groups can then be developed based upon these pretreatment factors, with prognostic information derived from available literature reports (Zagars et al 1995, Zagars et al 1997, Pisansky et al 1997, Lee et al 1995, Pisansky et al 1993, Zietman et al 1994, Hanks et al 1995, Partin et al 1995, Lerner et al 1996, Zietman et al 1994, D'Amico et al 1997, D'Amico et al 1998, D'Amico et al 1999, Ragde et al 1997, Blasko et al 1995; Wallner et al 1996.)

1.5.1 Tumor staging

Tumor staging is widely used to assess ultimate outcomes, with the AJCC system being the one most widely used to do so (see Appendix A). Three main stages of prostate cancer are observed at presentation:

- Organ-confined/clinically localized disease
- Locally advanced disease, with no skeletal metastases
- Advanced disseminated disease with metastases

In this system, organ-confined/clinically localized disease is defined as T1 or T2 disease without known local regional lymph node or distant metastatic involvement. Locally advanced disease involves T3 and T4 tumors or any T stage with local regional lymph node involvement (N+). Nonregional node metastases as well as bone metastases (M1) indicate that the disease cannot be controlled locally and that the patient has incurable disease.

Using PSA-failure-free survival as an endpoint to assess the prognostic value of T stage for patients with clinically localized prostate cancer, risk categories can be developed on the basis of pretreatment clinical stage. This endpoint is often used because database-reported follow-up times in this era of PSA diagnosis are too short to determine cause-specific survival (D'Amico et al 1995). The categories are as follows:

- Low risk: greater than 85% 5-year PSA-failure-free survival—AJCC clinical stage T1c
- Intermediate risk: approximately 50% 5-year PSA-failure-free survival—AJCC clinical stage T2a
- High risk: approximately 33% 5-year PSA-failure-free survival—AJCC clinical stage T2b

The TNM staging system (essentially the same as the AJCC system) was used throughout the CASODEX EPC program, with a variety of patients at different stages of disease (T1-T4, mainly N0/NX, M0) represented across the 3 trials that comprise the program. More details of the staging demographics for each trial may be found in Section 4 of this document.

1.5.2 Histological grading of prostate cancer

The histological grading of primary prostate tumors is most often reported according to the Gleason grading system (Gleason and Mellinger 1974). This grading system is architectural in

nature, and roughly parallels the cytological grade. Since prostate cancer is usually heterogeneous, with 2 or more grades in a given cancer, Gleason chose to incorporate both a primary (most prevalent) and secondary (next most prevalent) grade in this system. The 2 grades are added to give the Gleason sum. Since 5 distinct grades or patterns are recognized, on a scale of 1 to 5 (well differentiated to poorly differentiated, respectively), the total score possibilities range from 2 (1+1) to 10 (5+5). Problems can arise when multiple grades of cancer exist within a single prostate tumor. More than 50% of prostate cancers contain at least 3 different grades (Aihara et al 1994).

Again using 5-year PSA-failure-free survival as an endpoint, prognostic groups can be developed for various pretreatment Gleason scores, as with done with T stage grouping (D'Amico 2000).

- Low risk: greater than 85% 5-year PSA-failure-free survival—biopsy Gleason score of 6 or less
- Intermediate risk: approximately 50% 5-year PSA-failure-free survival—biopsy Gleason score of 7
- High risk: approximately 33% 5-year PSA-failure-free survival—biopsy Gleason score of 8 or higher

The Gleason scoring approach is widely used; however, only a few large studies of interobserver reproducibility of Gleason grading for prostate cancer exist. In several series examining this question, both undergrading and overgrading have been found (Carlson et al 1998, Cookson et al 1997, Steinburg et al 1997). The Gleason scoring methodology is subject to considerable variability in interpretation, depending upon the sampling method used and other factors, such as the experience of pathologist.

1.5.3 Pretreatment PSA levels

Pretreatment PSA levels are used for prognostic evaluation in much the same manner as T stage and Gleason score (Partin et al 1997, D'Amico 2000). Using the same literature base mentioned for T stage and Gleason score, the same prognostic categories can be created for pretreatment PSA levels for the 5-year PSA-failure-free survival endpoint.

- Low risk: greater than 85% 5-year PSA-failure-free survival—pretreatment PSA of 10 ng/ml or less
- Intermediate risk: approximately 50% 5-year PSA-failure-free survival—pretreatment PSA between 10 and 20 ng/ml
- High risk: approximately 33% 5-year PSA-failure-free survival—pretreatment PSA greater than 20 ng/ml

Thus, pretreatment PSA levels can independently predict for the same outcomes as do Gleason sums, making this determination a suitable predictor for subsequent outcomes independent of Gleason scoring.

In terms of monitoring PSA levels following primary therapy, the likelihood of treatment failure after primary therapy can be estimated from PSA changes (Sandler et al 2000, Pound et al 1999,

Patel et al 1997, Roberts et al 2001, Lee et al 1997). These studies demonstrate that a rapid PSA doubling time (6 to 12 months) is a significant predictor of time to distant failure. Rapid rises in PSA levels often lead clinicians to institute therapy for relapsed disease, including androgen deprivation therapy. Once overt clinical progression has occurred, the patient is very likely to develop debilitating symptoms of metastatic disease, including weight loss and bone pain, and is incurable at that point. Thus, an improvement in the time to clinical disease progression is a meaningful endpoint for studies in early prostate cancer.

1.5.4 Prognostic features summary

A large body of literature clearly shows that different risk groups for subsequent disease progression can be determined based upon pretreatment prognostic factors. Each of these factors, T stage, Gleason score, and pretreatment PSA levels are individually predictive. Combined-modality staging approaches have recently been developed using these parameters. Various nomograms have been published using the combined-modality staging approach, each confirming the independent prognostic significance of T stage, Gleason score, and baseline PSA levels (Partin et al 1997, Vollmer et al 1998, D'Amico et al 1998). Thus, the use of baseline prognostic factors in the CASODEX EPC trial program, particularly T stage and pretreatment PSA levels, was suitable for determining risk of disease recurrence among the various populations enrolled.

2. HORMONAL TREATMENT IN PROSTATE CANCER

Huggins et al (1941) were the first to show that castration can achieve palliation in metastatic prostate cancer, indicating the hormonal basis for this disease. Since that initial observation, a number of hormonal manipulations have been proven to be effective in metastatic prostate cancer, including bilateral orchiectomy or LHRH agonist administration alone or in combination with nonsteroidal anti-androgens. The use of these hormonal modalities in advanced prostate cancer has followed an evolution over time similar to that which occurred with breast cancer.

Like prostate cancer, breast cancer is a hormonally based disease. The antiestrogen tamoxifen was shown to have palliative effects in metastatic breast cancer, which provided the rationale for subsequent development of antiestrogen therapy in earlier stages of disease following primary surgical therapy. Approval for this indication followed, with approval granted on the basis of a time-to-progression end point. An overview analysis of all adjuvant breast cancer studies with tamoxifen shows that at 10 years' follow-up, among women with estrogen-receptor-positive and estrogen-receptor-unknown tumors, tamoxifen reduced mortality by 26% with 5 years of adjuvant therapy (EBCTCG 1998). The proportional mortality reductions were similar for women with node-positive and node-negative disease. These benefits seemed to be largely irrespective of age, menopausal status, daily tamoxifen dose, and whether chemotherapy had been administered.

Given the hormone-responsive nature of prostate cancer, it was reasonable to postulate that the types of benefits seen in breast cancer patients could be demonstrated with adjuvant hormonal treatment in patients with nonmetastatic prostate cancer. As was the case for the breast cancer trials, emerging data from relevant prostate cancer trials suggested that early adjuvant or neoadjuvant hormonal treatment could delay progression of prostate cancer (Fair et al 1992, Loening and Narayana 1980, Zagars et al 1988). Since the CASODEX EPC program began in

1995, additional data emerged in the literature providing evidence that early hormonal treatment of prostate cancer—when the tumor volume is relatively small—can significantly delay disease progression and improve overall survival (Bolla et al 1997 [updated 2002], Messing et al 1999; Pilepich et al 1995 [updated 2001], Pilepich et al 1997, Wirth et al 1997).

These studies are summarized in Table 3 along with several other relevant studies using early hormonal therapy as adjuvant or neoadjuvant therapy for prostate cancer (Kirk et al 2000, Gransfors et al 1998, Witjes et al 1998, and Gleave et al 2000).

Table 3 Summary of trials using early hormonal therapy as adjuvant or neoadjuvant therapy for prostate cancer

Trial	N	Stage of disease	Standard care[a]	Adjuvant/ neoadjuvant[b]	Duration of randomized therapy	Average follow- up	Endpoints showing clinical benefit for hormonal therapy	p-value[a]
MRC Trial 1997	938, M0=500	T2- T4, M0 or asymptomatic M1	Delayed treatment	LHRH analogue or orchiectomy	Until progression	Minimum 31 months	Overall and progression-free survival.	≤ 0.02
Bolla et al 1997, 2002	415	T1- T4, N0-X	External radiotherapy	Adj LHRH analogue	3 years	45 months	Overall and progression-free survival.	≤ 0.001
Pilepich et al 1995, 2001	456	T2- T4, N- or N+	External radiotherapy	Flutamide and LHRH analogue	2 months before and during radiation	6.7 years	Disease-free survival Biochemical disease-free survival	0.004 <0.0001
Pilepich et al 1997	945	T1- T2, N+ or any T3	External radiotherapy	Adj LHRH analogue	Until progression	4.5 years	Relapse-, clinical-, biochemical-, and metastasis-free survival.	<0.001
Granfors et al 1998	91	T1- T4, pN0-3, M0	External radiotherapy	Adj orchiectomy	Until progression	9.3 years	Overall and progression-free survival.	≤ 0.02
Wirth et al 1997	356	pT3, pN0	Prostatectomy	Adj flutamide	Until progression	4 years	Progression- free survival	0.0023
Messing et al 1999	98	T1- T2, N+	Prostatectomy	Adj LHRH analogue or orchiectomy	Until progression	7.1 years	Overall and recurrence-free survival.	<0.01
Witjes et al 1998	402	cT2- cT3, N0, M0	Prostatectomy	Neoadj flutamide and LHRH analogue	3 months	Minimum 4 years	Down staging, no increase in time to progression or survival.	NR
Gleave et al 2001	547	cT1-cT2	Prostatectomy	Neoadj flutamide and LHRH analogue	3 months versus 8 months	Postoperative data only	Down staging; 8 months better than 3 months.	NR

[a] Received by all patients.
[b] Received by patients randomized to the adjuvant/ neoadjuvant arm only; all other patients received standard care.
[c] Represents p-values of all endpoints showing clinical benefit.
MRC Medical Research Council, LHRH Luteinizing hormone-releasing hormone, Adj Adjuvant, Neoadj Neoadjuvant, c Clinically staged, p Pathologically staged, NR Not reported.

2.1 Immediate vs deferred hormonal therapy

The first reported comparison of immediate versus delayed androgen deprivation was a study by the Medical Research Council (MRC) Prostate Cancer Working Party Investigators Group. This study evaluated immediate orchiectomy or LHRH therapy vs delay until clinical progression (MRC 1997). A total of 938 patients with T2-T4, NX, M0 tumors, as well as asymptomatic M1 disease, were enrolled. The delayed treatment group demonstrated double the rate of pathological fractures, spinal cord compression, and ureteral obstruction; 30% in the delayed group required transurethral resection of the prostate gland (TURP) for voiding symptoms, compared with 14% in the immediate treatment group. There was also an overall survival benefit for immediate treatment among all patients. For patients with M0 disease, improved disease-specific survival and overall survival were seen with immediate treatment as well. This study provided the first evidence that primary hormonal therapy could improve overall survival among men with prostate cancer, and gives a strong rationale for the usage of hormonal therapy in earlier stages of prostate cancer.

2.2 Hormonal treatment in addition to irradiation

A number of studies have demonstrated benefits for using hormonal therapy as an adjunct to radiation therapy. In RTOG 8531, 977 patients with T1-T3, N1, M0 tumors were randomized to irradiation plus goserelin acetate therapy after completion of irradiation versus irradiation followed by goserelin acetate at relapse (Pilepich et al 1997, 945 patients evaluable). There was better local control with the irradiation plus immediate goserelin acetate, as well as better survival free of distant metastases, and disease-free survival. Also, PSA relapse-free survival was improved. A survival advantage with combination treatment was apparent in the worst prognosis group with Gleason scores of 8 to 10 in the combination treatment group.

In a second study, RTOG 8610, irradiation plus short-term total androgen blockade with goserelin acetate/flutamide was compared with irradiation alone in 471 patients who had T2b-T4, N0-N1, M0 disease (Pilepich et al 2001, 456 patients evaluable). In this study, improved local control was demonstrated for the combined arm, as well as progression-free survival and the rate of distant metastases. No difference in overall survival, however, was noted. The increase in local control and decrease in distant metastases seen with this neoadjuvant hormonal therapy was most beneficial for patients whose tumors were of Gleason score 2 to 7 on subset analysis. This study led to FDA approval of goserelin acetate and flutamide in this setting.

Another trial using adjuvant hormonal therapy was conducted by the EORTC among 415 patients randomized to irradiation alone versus irradiation plus goserelin acetate (Bolla et al 1997, Bolla et al 2002). Cyproterone acetate (a nonsteroidal antiandrogen not available in the United States) was given for 1 month starting 1 week before the 1st goserelin injection. Patients with T1 and T2 tumors were eligible, but 91% had T3 and T4 disease. The authors reported a statistically significant improvement in overall survival at 5 years for the combined therapy arm (78% vs 62%), as well as improved 5-year disease-free survival for the combined therapy arm (74% vs 40%).

The MRC has reported the results from 2 large randomized trials of primary hormonal therapy in locally advanced prostate cancer. In the first study, 277 patients with locally advanced disease (T2-T4, NX, M0 tumors) were randomized to orchiectomy, irradiation, or irradiation plus orchiectomy (Fellows et al 1992). Those patients randomized to irradiation alone underwent orchiectomy at the time of clinical disease progression. Thirty-four percent had poorly differentiated cancers at presentation. With a median follow-up of more than 4 years, the incidence of distant metastases was significantly higher in the group receiving only irradiation compared with the T2 groups receiving orchiectomy ($p<0.005$). There were no differences in local progression-free survival or overall survival, however.

2.3 Hormonal therapy as adjuvant to radical prostatectomy

The major evidence for a benefit of adjuvant hormonal therapy after radical prostatectomy comes from an Eastern Cooperative Oncology Group (ECOG) study examining the role of immediate androgen deprivation therapy following radical prostatectomy and nodal dissection in patients found to have nodal metastases (Messing et al 1999). In this study, 98 men were randomly assigned to receive immediate goserelin acetate or orchiectomy, or to be followed until disease progression. With a median follow-up of 7.1 years, there was a significant survival benefit for immediate androgen deprivation therapy ($p=0.02$). Cancer-specific mortality was also favorably affected with immediate therapy. Disease-free survival was prolonged, including PSA-defined relapse. The authors concluded that immediate anti-androgen therapy after radical prostatectomy and pelvic lymphadenectomy improves survival and reduces the risk of recurrence in patients with node-positive prostate cancer.

2.4 Long-term sequelae of castration and comparative quality-of-life findings with CASODEX treatment

As medical or surgical castration has become more widely used for patients with node-positive prostate cancer, accumulated data suggest the potential for treatment-related morbidities, as described in Section 1.4.3.2. Thus, the benefits derived from medical or surgical castration need to be considered in context with potential long-term sequelae and the growing evidence that CASODEX may offer a more desirable side effect profile, as described briefly in the sections that follow (Sections 2.4.1 and 2.4.2).

2.4.1 Effects on bone mineral density and lean body mass

Since the EPC program began, trials comparing CASODEX with castration have shown advantages for CASODEX related to retention of bone mineral density and lean body mass. Mostly recently, 2 randomized trials evaluated changes in bone mineral density with either CASODEX therapy or medical castration and found significant bone mineral density losses with medical castration, while therapy with CASODEX actually preserved bone mass (Sieber et al 2002; Iversen et al 2002). Data as reported by Sieber et al (2002), who assessed treatment effects in patients with T1-4 and M0 prostate cancer, are shown in Table 4.

Table 4 Comparative effects of CASODEX on bone mineral density

Area tested	Percent change in bone mineral density from baseline at Week 96		
	CASODEX 150 mg	Medical castration	p-value (95% CI)
Lumbar spine	2.42	-5.40	<0.0001 (-10.15, -5.50)
Hip	1.13	-4.39	<0.0001 (-7.79, -3.26)

95% CI (confidence interval) for the mean difference for medical castration–CASODEX 150 mg.

2.4.2 Effects on sexual function

In another study evaluating monotherapy, CASODEX 150 mg was compared with combined androgen blockade (CAB) using flutamide plus leuprolide in patients with Stage C and D prostate cancer (Boccardo et al 1999). Treatment effects on quality of life and sexual function (libido and erectile function) were specifically elicited. Among the 220 patients enrolled, diarrhea and hot flashes were more frequent with CAB, while gynecomastia was more frequent with CASODEX. Significantly (p=0.01) more patients completely lost libido with CAB (53 of 62) than with CASODEX (34 of 57). In terms of erectile function, reduction was seen more frequently with CAB (56 of 60) than with CASODEX (36 of 52, p=0.002).

2.5 Conclusions on hormonal therapy

Androgen deprivation therapy has been shown to improve the outcome for men *with locally advanced* prostate cancer. Disease-free and overall survival rates are higher with primary androgen deprivation therapy than when androgen deprivation is delayed until clinical disease progression. Similarly, the addition of androgen deprivation to irradiation for locally advanced disease improves disease-free and overall survival compared with irradiation alone. Currently, in the United States, goserelin acetate therapy is indicated as neoadjuvant treatment to irradiation when combined with flutamide for T2b-T4 prostate cancer (starting 8 weeks before and continuing for the duration of radiation therapy). These data provided a good rationale for examining the role of anti-androgen therapy in patients with localized/locally advanced nonmetastatic prostate cancer, as was done in the CASODEX EPC program.

Moreover, the CASODEX EPC clinical program assessed the effects of CASODEX 150 mg versus placebo as adjuvant therapy to treatment of curative intent and as immediate hormonal therapy for patients who would otherwise undergo watchful waiting. Currently, no single-agent oral therapy is approved for use as an adjuvant therapy in patients with prostate cancer. However, the literature shows that primary hormonal therapy is sometimes used by US clinicians to treat patients with early prostate cancer; this is done, however, with limited evidence-based data to guide such use. The CASODEX EPC program provides the first evidence-based

rationale for the use of anti-androgen therapy to significantly alter the clinical outcomes of early prostate cancer (see Section 9 for further discussion).

3. CASODEX DEVELOPMENT

3.1 Clinical pharmacology

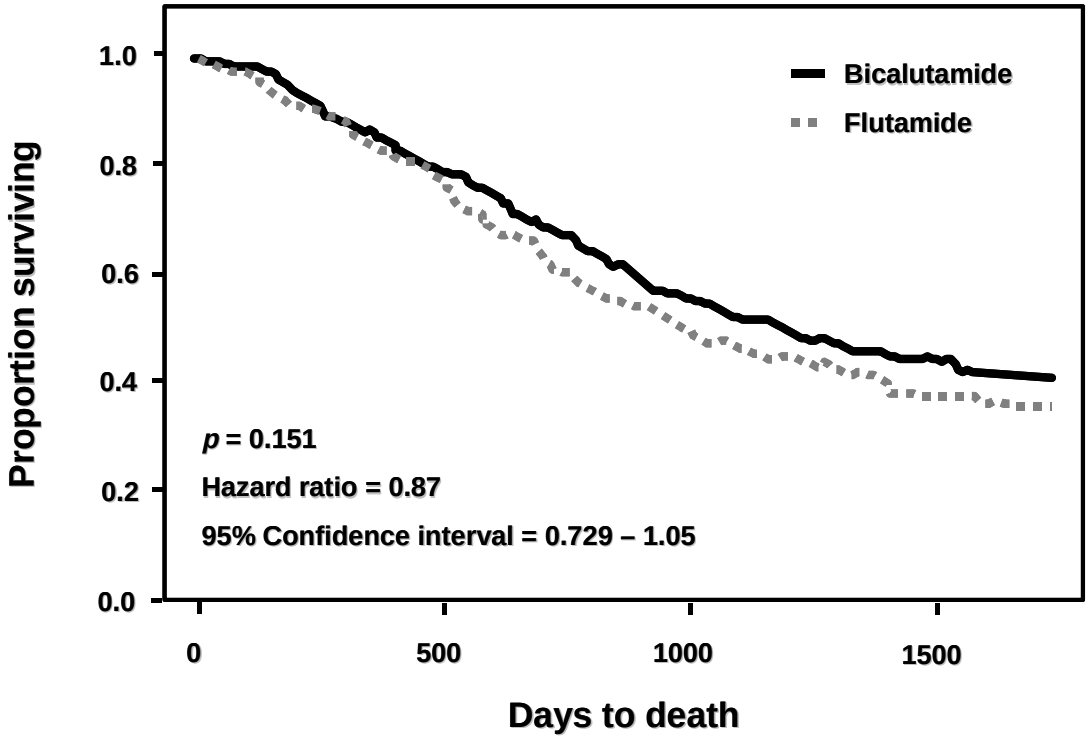
CASODEX is a nonsteroidal anti-androgen that was developed as a once daily oral therapy for the treatment of patients with prostate cancer. CASODEX blocks androgen receptors and thereby inhibits the action of androgens regardless of their source. CASODEX has no androgenic or progestational properties. It has a long plasma elimination half-life (approximately 1 week) and is effective when taken orally once daily. Increases in testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) have been observed with CASODEX administration, but these usually remain within the normal range. As noted earlier, anti-androgens are used simultaneously with LHRH analogues for the treatment of advanced prostate cancer, and this therapy is termed CAB or combined androgen blockade. CAB is based on the theory that LHRH analogues lower the level of androgens from the testes while the anti-androgen competes with any remaining circulating adrenal androgens at the level of the cellular receptors.

3.2 Current use

CASODEX 50 mg was approved for use in combination with an LHRH analogue for the palliative treatment of advanced prostate cancer in 1995.

To achieve this indication, CASODEX 50 mg once daily was studied in combination with LHRH analogues among patients with previously untreated advanced prostate cancer and was compared with LHRH therapy plus flutamide 250 mg three times daily. Overall survival was similar between the 2 groups (Figure 2) (hazard ratio=0.87 for CASODEX, 95% CI: 0.73 to 1.05). Similar results were seen for time to objective tumor progression.

Figure 2 **Comparative survival with CASODEX 50 mg plus LHRH analogue vs flutamide plus LHRH analogue**



In terms of adverse events, the incidences of diarrhea and elevated liver enzymes were greater with flutamide compared with CASODEX. The other pharmacological effects seen with both CASODEX and flutamide included hot flashes and gynecomastia. The combination of CASODEX plus LHRH therapy is now well established for the treatment of advanced prostate cancer.

3.3 Historical perspective on CASODEX monotherapy use

During the clinical development of CASODEX for the treatment of prostate cancer, monotherapy with 50 mg was investigated in the advanced disease setting. However, this dose was found to be not as effective as castration. Monotherapy trials using doses of CASODEX ranging from 10 to 200 mg daily indicated that oral doses of 100 and 150 mg reduced PSA to levels found after castration and that this effect began to plateau at the 100-mg dose (Kolvenbag and Nash 1999).

AstraZeneca undertook two pivotal monotherapy efficacy trials (Trials 306 and 307) in previously untreated patients with locally advanced (M0) and advanced (M1) prostate cancer (Iversen et al 2000). Both studies were conducted in 2 stages. In Stage 1, two blinded doses of CASODEX (100 and 150 mg) were compared with castration on a 2:2:1 randomization basis. Dose selection was based upon the fall in PSA observed at a minimum of 12 weeks' follow-up.

The PSA fall seen with 100 mg was significantly less than with castration, so the 150-mg dose was chosen for Stage 2. At an interim analysis performed in 1994, it became clear that castration was superior for M1 patients in both trials, and these patients were withdrawn from the trials. The drug safety monitoring committee (DSMC) recommended that the trials continue in M0 patients; accordingly, the trials continued in M0 patients until >50% mortality was observed, which represented a mature analysis point.

The M0 patients in these trials had locally advanced prostate cancer (T3 or T4 cancers, pretreatment PSA >20 ng/ml) and required castration therapy given the high likelihood of tumor progression in this clinical setting. Outcomes among the M0 patients in these 2 trials with a median follow-up of 6.3 years included the following:

- For the time-to-progression (TTP) and overall survival endpoints, there were statistically nonsignificant trends in favor of CASODEX in 1 trial and statistically nonsignificant trends in favor of castration in the other trial. The combined hazard ratio for the 2 trials indicated no difference between the 2 treatment groups for TTP and overall survival (HR: 1.05 for overall survival; CI: 0.81 to 1.36). Non-inferiority to castration, however, could not be ruled out for both TTP and survival.

- Quality of life evaluations were the same between bicalutamide and castration for 7 of 10 items measured, but significant differences were seen in favor of CASODEX for the items of sexual interest and physical capacity, potentially indicating a better tolerability profile for CASODEX in this population (Iversen et al 2000, Iversen 2002).

Because AstraZeneca and the FDA could not agree on the interpretation of the results from these 2 trials, the submission was withdrawn in the United States. However, a biological effect was clearly demonstrated for CASODEX 150 mg monotherapy in these studies, and this effect served as a basis for approval in more than 50 other countries, thus providing an alternative treatment to castration.

3.4 CASODEX EPC program

3.4.1 Unmet medical need in patients with early prostate cancer

As previously described, patients with early-stage disease have significant risk of relapse and subsequent death from advanced prostate cancer, dependent upon prognostic factors at disease presentation, such as tumor stage, PSA levels, and tumor grade. Despite the aggressive primary therapy commonly used in the United States (radical prostatectomy, irradiation), a medical need remains for better-tolerated adjuvant therapies to delay the onset of disease progression when primary treatment fails. In addition, there are groups of patients, primarily elderly men or those with significant comorbid conditions who are not suitable candidates for such primary therapies or who refuse surgery or radiation. Among these patients, CASODEX therapy could delay the onset of disease progression as well as the local symptoms related to disease progression within the prostate gland. Thus, the CASODEX EPC program was developed to explore the value of CASODEX in these groups of patients and to establish tolerability.

3.4.2 The EPC trials

The CASODEX EPC clinical program investigated patients with localized (T1-T2) or locally advanced (T3-T4) nonmetastatic (N0/NX/M0) prostate cancer; the only patients excluded were those with disseminated disease as identified by a positive bone scan. Patients were eligible if they previously underwent primary therapy of curative intent (radical prostatectomy or irradiation) or if they were candidates for, or already following, a watchful waiting regimen.

The objectives of the CASODEX EPC program were as follows:

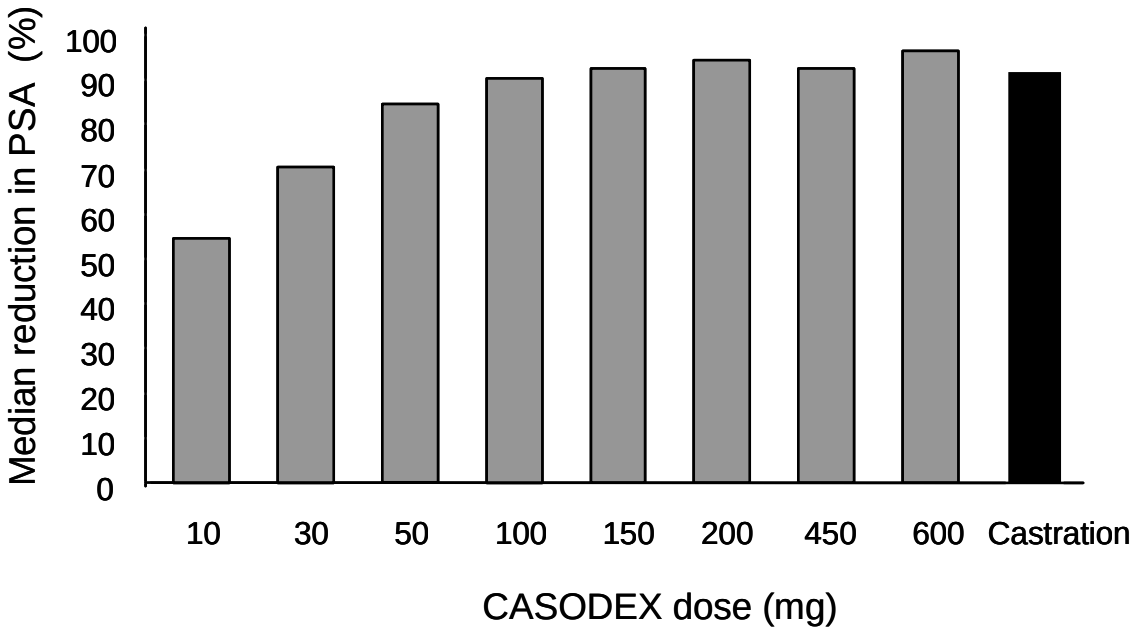
- Compare CASODEX 150 mg once daily versus placebo in terms of time to objective progression and overall survival as an adjuvant to therapy of curative intent or as immediate hormonal therapy in patients who would otherwise undergo watchful waiting
- Compare CASODEX 150 mg once daily versus placebo time to doubling of PSA concentrations and time to treatment failure in the same patient groups
- Evaluate the tolerability of CASODEX 150 mg once daily versus placebo
- As a much longer term objective, investigate the role of serum PSA as a predictor of clinical outcome

4. OVERVIEW OF THE CASODEX EPC CLINICAL TRIAL PROGRAM

4.1 Dose rationale

In CASODEX dose-ranging studies, objective response and percentage inhibition of PSA were used as measures of efficacy. When the data were evaluated, doses below 150 mg were less effective at reducing circulating PSA concentrations (Figure 3) (Kolvenbag and Nash 1999). Because no dose-related increases in adverse events were observed with CASODEX in those studies and because drug absorption starts to plateau at doses above 150 mg, the 150-mg dose was considered an appropriate dose for evaluating the efficacy and safety of CASODEX in patients targeted for enrollment in the EPC program (see Section 4.3).

Figure 3 dose-related reductions in PSA level with CASODEX



Kolvenbag GJ, Nash A. Prostate 1999;39:47-53.

Although data were emerging that suggested a benefit for the use of early hormonal therapy in prostate cancer, it was still not common practice or established policy at the time to use immediate rather than deferred therapy in patients with localized disease. Furthermore, there was no clinical consensus on the use of hormonal therapy as adjuvant to radical prostatectomy or

radiation treatment of curative intent. This allowed the use of placebo as the comparison agent in the CASODEX EPC program, thus giving AZ an opportunity to investigate the effects of CASODEX using the most robust and rigorous scientific test for assessing treatment effect, specifically, a comparison with placebo. With the proposed program, AZ could establish definitively whether early treatment with CASODEX in addition to standard care would provide a significant clinical benefit.

4.2 Primary objectives

The objectives of the CASODEX EPC were to compare CASODEX 150 mg once daily with placebo in terms of time to clinical progression, survival, and tolerability in patients with localized (T1-T2) or locally advanced (T3-T4) nonmetastatic (N0/NX/M0) prostate cancer. The types of patients sought for enrollment included patients previously treated with therapy of curative intent (either radical prostatectomy or radiotherapy) and patients eligible for watchful waiting after diagnosis.[5]

4.3 Design of program

Three pivotal Phase III trials, Trials 23, 24, and 25, comprise the CASODEX EPC program. All 3 trials are multicenter, randomized, double-blind, placebo-controlled, parallel-group trials. Patients were randomized 1:1 to treatment with CASODEX, 150 mg daily, or matching placebo. The program was designed and powered for a pooled overall analysis of the primary endpoint of time to objective progression.

All 3 trials enrolled patients who had had previous therapy of curative intent, and Trials 24 and 25 also enrolled patients who were engaged in watchful waiting. In Trial 23, patients known to have disease-positive lymph nodes were not permitted to enroll, and treatment was limited to a maximum of 2 years (Table 5). Watchful waiting patients were excluded in Trial 23 for purposes of conducting a purely adjuvant trial. Despite these differences, the commonality in fundamental design features, trial objectives, and the use of identically defined endpoints supported the planned pooled analyses of the data across the 3 trials at 2 years' minimum follow-up. It was not expected, however, that a survival benefit would be detected with this degree of follow-up.

[5] Also referred to as expectant management, conservative management, or surveillance.

Table 5 Similarities and differences in trial design: Trials 23, 24, and 25

Design element	Trial 23 (North America)	Trial 24 (Europe, South Africa, Israel, Mexico, Australia)	Trial 25 (Scandinavia)
Double-blind, placebo controlled	√	√	√
Tumor staging criteria	T1b-T4, N0-NX (N+ excluded), M0 NX only if PSA <20	T1b-T4, any N, M0	Same as 24
Intended period of randomized treatment[a]	2 years	5 years for adjuvant patients. Until progression in nonadjuvant patients	Until progression
Permitted standard care			
Radical prostatectomy, radiotherapy, or both	Yes	Yes	Yes
Watchful waiting	No	Yes	Yes
2-year bone scan to determine progression	√	√	√
Follow-up for progression and survival	√	√	√

[a] Patient recruitment began in August, September, and October of 1995 for Trials 23, 24, and 25, respectively, and closed in August 1997 for Trial 23 and June 1998 for Trials 24 and 25. Trials are ongoing, although patients in Trial 23 have completed the trial-specific treatment period of 2 years and are currently being monitored for progression and survival only.

Although there was overlap in the types of patients enrolled in the 3 trials, the differences in entry criteria and regional practices were expected to yield a group of patients with a gradient-range of prognoses (see Section 5 for demographic details). Overall, the types of patients enrolled would represent the spectrum of patients with clinically localized or locally advanced prostate cancer commonly seen in both the United States and rest of world.

4.4 Sample size, power, and statistical considerations

The overall size of the clinical program was based upon the primary endpoint of time to objective progression. Further, based upon an expected median time to objective progression of 7 years in placebo-treated patients, it was calculated that a total of 7500 patients, recruited over a 3-year period and followed for a minimum of 2 years, would be required to detect a 15% decrease in the rate of objective progression in CASODEX treated patients compared to placebo with 90% power and 2-sided 5% significance level.

To facilitate the pooling of data across trials, individual trials were designed with common objectives and identically defined endpoints, recruiting patients to ensure overlapping patient populations. The intent to pool data across trials was explicitly captured in each of the individual trial protocols and time to objective progression was the stated primary endpoint common to each trial.

In addition to the overall power requirement, individual trials were each powered on the basis of the time to objective progression endpoint, albeit to detect larger differences than could be detected in a pooled analysis. The assumption regarding the expected event rate in placebo treated patients, ie, a median time to progression of 7 years was common to all three trials; median follow-up at the time of the first analysis was expected within each trial to be approximately 3.5 years.

An analysis plan was developed for the pooled analysis and was shared with FDA prior to the 1st analysis (see Section 9). Analysis plans for the individual trials were also developed and were derived from the plan for the pooled analysis.

4.5 Efficacy endpoints

4.5.1 Primary

The primary endpoints for the CASODEX EPC program were discussed with regulatory authorities and agreed at the outset of the program, with time to progression (TTP) chosen as the common primary endpoint for each of the 3 trials.[6] A potential for bias due to endocrine-related adverse events was recognized (see Section 6.7 for details) and discussed with the FDA at the outset, as well as at various times during the conduct of the trial program. To address this, AstraZeneca designed the trials so that bone scans were required every 2 years for patients without progression who were still undergoing treatment with randomized therapy, thus minimizing the potential for acquisition bias. It should be noted, however, that bone scans are not obtained every 2 years as part of standard clinical practice; in the United States, treatment changes generally occur on the basis of clinical or biochemical progression. Thus, data in this briefing document are presented first according to the protocoled endpoint of TTP, with bone scan data included as supportive information.

In addition to TTP, survival was designated as a primary endpoint for the overall analysis, albeit one that would not be mature until much later in the program.[7] Although follow-up for each trial is ongoing to determine survival differences between CASODEX and placebo, no survival differences at the current 3-year median follow-up were expected.

4.5.1.1 TTP

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 disease progression) and, as such, measured the progression-free survival interval. Changes in serum PSA alone were not

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[6] Time to disease recurrence was used as an endpoint for FDA registration of both NOLVADEX™ (tamoxifen) and ARIMIDEX™ (anastrozole) for the adjuvant treatment of breast cancer.

[7] In Trials 23 and 25, survival was also designated a primary endpoint. In Trial 24, survival was designated a secondary endpoint.

considered to be evidence of objective progression. Objective progression was defined as the first occurrence of disease progression confirmed by one of the following methods: bone scan imaging, X-ray, MRI (magnetic resonance imaging) scan, CT (computed tomography) scan, ultrasound, or biopsy, or as death from any cause prior to progression.

4.5.1.2 Bone-scan confirmed progression

Any patient who had a positive bone scan or who died for any reason (in the absence of bone-scan-confirmed progression) at, or at any time before, the nominal 2-year (± 6 months) bone scan was categorized as having bone-scan-confirmed disease progression. All other patients were categorized as not having evidence of bone-scan-confirmed progression.

4.5.1.3 Overall survival (time to death)

Time to death was defined as the number of days between randomization and the documented date of the patient's death from any cause.

4.5.2 Secondary efficacy endpoints

4.5.2.1 Time to PSA doubling

PSA progression was assessed by changes in PSA, as measured by time to PSA doubling (PSAdt). PSAdt was therefore defined as the number of days from the date of randomization until the earliest of the following times:

- PSA sample time at which PSA had doubled compared with the value recorded immediately prior to randomization
- time of objective progression (in the absence of PSA doubling)
- time of death (in the absence of either objective progression or PSA doubling)

4.5.2.2 Time to treatment failure

Time to treatment failure (TTF) was a secondary efficacy endpoint and was defined as the number of days between the date of randomization and the date of the first of the following events:

- death from any cause
- objective progression of disease
- withdrawal of trial therapy (for any reason including adverse events)
- administration of an additional systemic therapy or radiotherapy for prostate cancer

4.6 Data safety monitoring committee (DSMC)

An independent DSMC, consisting of expert urologists and a statistician experienced in the design and analysis of prostate cancer trials, was established for the EPC program. The role of the DSMC was to provide AstraZeneca with ongoing guidance and recommendations for actions with respect to the management of patients within the EPC program based upon regular review of efficacy and safety data. Thus, input from the DMSC could influence the direction of the trial program.

As part of their responsibilities, the DSMC met approximately yearly to review the accumulating safety data. Demography was presented by treatment group, with 1 group labeled A and the other, B. Nonpharmacological adverse events, deaths, withdrawals due to adverse events, and liver function test data were reviewed on a trial basis without breakdown by treatment group and on an overall basis by treatment groups A and B. Pharmacological adverse events were reviewed with the blind unbroken.

The DSMC also met following the first analysis of efficacy data to review results (see Section 8 for additional details).

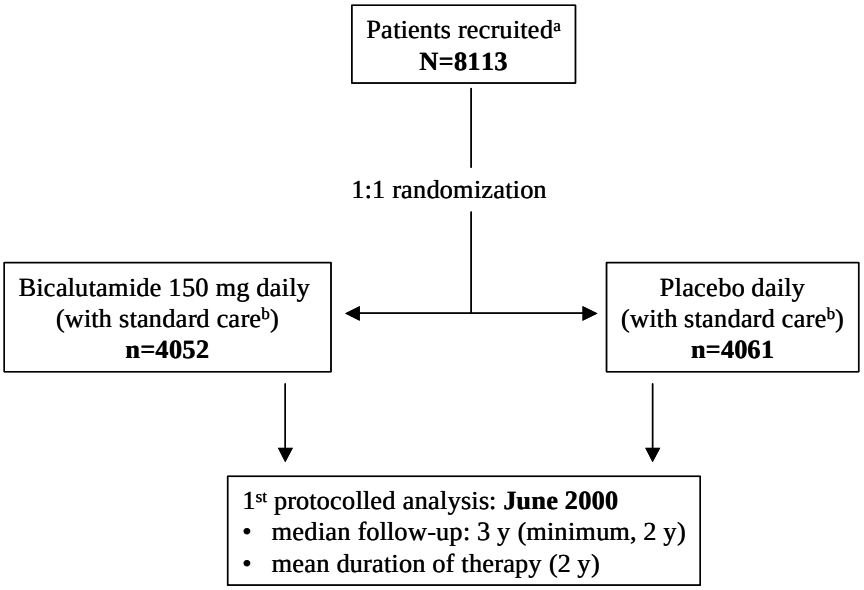
When necessary, recommendations for action were made to both AstraZeneca and the 4 principal investigators who comprised the steering committee. The role and remit of the DSMC was documented and archived.

5. DEMOGRAPHY AND DISEASE CHARACTERISTICS

5.1 Overview of the EPC program

The EPC program recruited 8113 men with localized or locally advanced nonmetastatic prostate cancer (Figure 4).

Figure 4 EPC program: recruitment and randomization



[a]Aug 1995 to July 1998.
[b]Radical prostatectomy, radiation therapy, or watchful waiting.

5.1.1 All trials

The EPC program comprised a population (Table 6) of mostly white men with a mean age of 67 years and a mean weight of 81 kg. At trial entry, 55% of patients had undergone radical prostatectomy, 17% had received radiation therapy, and 28% were candidates for or already undergoing watchful waiting (Table 7). A total of 67% of patients presented with stage T1 or T2 disease, 44% had moderately differentiated tumors, and less than 2% had known node-positive disease (Table 7). This patient profile, relative to disease stage and tumor differentiation, is similar to that reported in the SEER registry for US patients presenting with prostate cancer.

When patients were considered by treatment group (CASODEX vs placebo) across trials, baseline demographic data were well balanced in terms of age, age distribution and race, and key prognostic factors, such as stage, grade, nodal status, and PSA (Tables 6 and 7).

Table 6 Baseline demographic characteristics: overall and by trial

Demographic characteristic	Combined data		Trial 23		Trial 24		Trial 25	
	CASODEX (n=4052)	Placebo (n=4061)	CASODEX (n=1647)	Placebo (n=1645)	CASODEX (n=1798)	Placebo (n=1805)	CASODEX (n=607)	Placebo (n=611)
Age, y								
Mean	66.9	66.9	64.5	64.4	68.6	68.7	68.5	68.5
Range	42 to 93	38 to 93	42 to 85	38 to 83	42 to 93	46 to 93	46 to 87	52 to 77
Age distribution, % of patients								
<55 y	6	5	9	9	3	3	2	1
55 to <65 y	28	28	37	37	24	24	16	19
65 to <75 y	54	54	47	48	52	52	78	77
≥75 y	12	13	6	6	21	22	4	4
Race, n (%)								
White	91.0	91.3	83.1	84.6	95.3	94.7	99.8	99.3
Black[a]	5.1	4.9	11.6	11.4	0.9	0.7	0	0
Other[b]	3.8	3.8	5.3	4.0	3.7	4.6	0.2	0.7

[a] Includes Afro-Caribbean.
[b] Includes Asian, Oriental, Hispanic, and mixed race.
n number of patients randomized.
y years.

Table 7 Baseline disease characteristics: overall and by trial

Disease characteristic	Combined data		Trial 23		Trial 24		Trial 25	
(% of patients)	CASODEX (n=4052)	Placebo (n=4061)	CASODEX (n=1647)	Placebo (n=1645)	CASODEX (n=1798)	Placebo (n=1805)	CASODEX (n=607)	Placebo (n=611)
Tumor stage: T category (%)[a]								
T1	18.2	18.5	9.6	9.7	25.5	25.2	19.8	22.4
T2	48.6	49.6	62.7	63.2	38.8	41.1	39.7	38.1
T3	31.7	30.3	27.4	26.9	33.2	31.2	38.9	37.0
T4	1.5	1.6	0.2	0.2	2.6	2.5	1.5	2.3
TX	<0.1	<0.1	0	0	0	0	0.2	0.2
Gleason score (%)								
Well differentiated (2, 3, 4)	21.8	22.3	4.2	4.8	31.0	31.2	42.7	43.2
Moderately differentiated (5, 6)	44.0	44.7	47.9	48.5	40.5	41.1	43.7	45.2
Poorly differentiated (7, 8, 9, 10)	33.1	32.2	47.9	46.7	26.7	26.1	11.9	11.1
Not known	1.1	0.8	0	0	1.8	1.6	1.8	0.5
Lymph node category (%)								
N–	59.7	58.7	72.0	71.2	61.3	60.4	21.7	20.0
N+	1.9	1.8	0.1	0	2.6	2.7	4.6	4.3
NX	38.4	39.4	27.9	28.8	36.0	36.9	73.6	75.8
Previous therapy of curative intent (%)[b]								
Radical prostatectomy[c]	55.2	54.6	80.3	80.5	46.4	45.0	13.0	13.1
Radiotherapy only[d]	17.3	16.5	19.7	19.5	18.6	18.0	6.4	4.3
Watchful waiting	27.5	28.8	0	0	34.9	36.9	80.1	82.7
Other[e]	0.1	<0.1	0	0	0	0.1	0.5	0

[a] Represents a mixture of clinically or pathologically staged specimens.
[b] Mutually exclusive categories.
[c] Includes radical prostatectomy with radiotherapy.
[d] Includes brachytherapy.
[e] Includes cryotherapy/cryosurgery.
TX/NX tumor stage/lymph nodes not assessable.
N– No regional lymph node metastasis.
N+ includes categories N1, N2, and N3 (metastasis in lymph node [local or regional]).
n number of patients randomized.

5.1.2 Individual trials

Within individual trials, baseline demographic and disease characteristics were also well balanced between treatment groups (Tables 6 and 7). Between trials, though, some differences were observed (Table 8).

Table 8 Differences in disease characteristics across trials

Category (% of patients)	Trial 23 (North America) (n=3292)	Trial 24 (Europe, South Africa, Israel, Mexico, Australia) (n=3603)	Trial 25 (Scandinavia) (n=1218)
Prior radical prostatectomy (RP)	80.4	45.7	13.1
RP and nondetectable PSA levels	86%[a]	70%[a]	22%[a]
Prior radiotherapy (RT)	19.6	18.3	13.1
RT and clinically localized disease[b]	98%[b]	62%[b]	34%[b]
Managed by watchful waiting	0	35.9	81.3
Known, node-positive disease	<0.05	2.6	4.4
Node status unknown	28	37	75
Tumor grade poorly differentiated	47.3	26.5	11.5

[a] Denominator is all patients with radical prostatectomy and nonmissing postsurgical PSA levels: n=2628 in Trial 23; n=1528 in Trial 24, and n=156 in Trial 25.
[b] Denominator is all patients previously treated with radiation therapy: n=645 in Trial 23; n=660 in Trial 24, and n=65 in Trial 25.
PSA prostate-specific antigen.

While the characteristics of the individual trial populations overlapped, the demography data across trials reveal the gradient-range of prognoses expected given the individual trial entry criteria. Notwithstanding the greater proportion of patients with poorly differentiated tumors in Trial 23, Trial 23 enrolled more patients with predominantly good-prognosis characteristics, Trial 25 enrolled more patients with predominantly poor-prognosis characteristics, and Trial 24 enrolled a more prognosis-balanced population. The phenomenon seen in Trial 23 relative to tumor grade was attributed to the fact that more than 80% of patients had tumor grade interpreted from surgical specimens, rather than from biopsy specimens as is typical in rest-of-world countries, ie, specimen grading lends itself to higher grading compared with biopsy grading.

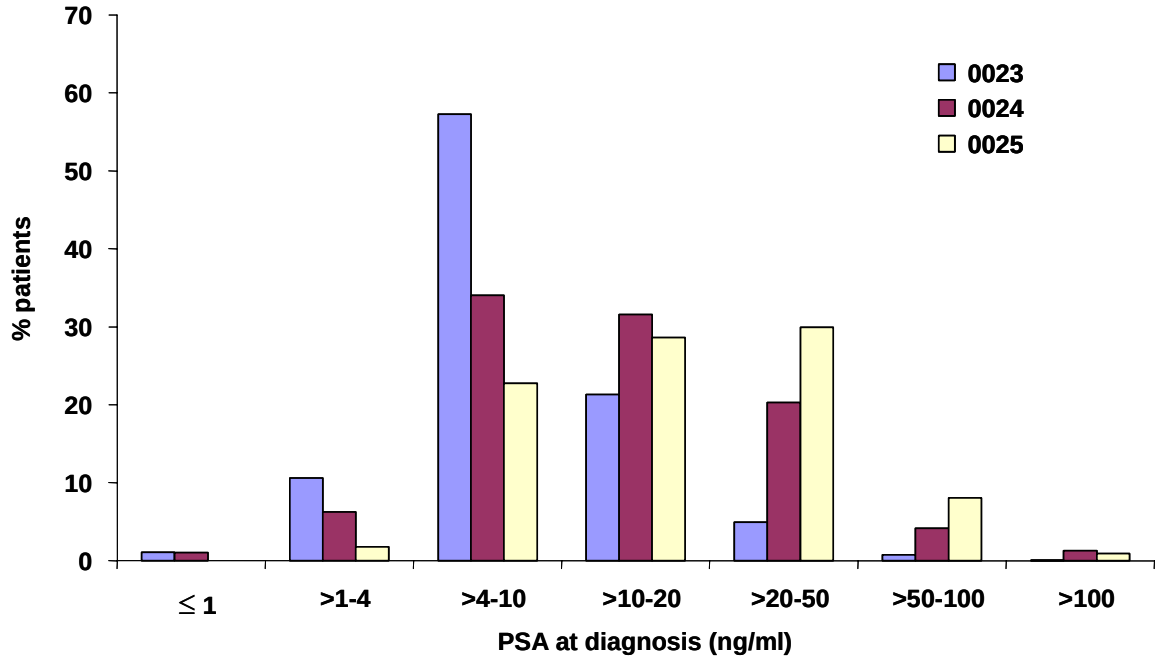
Differences between trials in PSA levels at diagnosis and randomization also demonstrate the differing prognoses among patients from the different treatment regions (Table 9). Differences in PSA distribution at diagnosis are shown in Figure 5 for patients treated with radical prostatectomy or radiation therapy. Notably, 75% of patients in Trial 23 had PSA levels of <10 ng/ml at diagnosis, which contrasts considerably with the 40% in Trial 24 and the 25% in Trial 25 who had PSA levels of <10 ng/ml at diagnosis.

Table 9 Regional variations in PSA (ng/ml) at diagnosis and randomization

PSA (ng/ml)	Trial 23	Trial 24	Trial 25
At diagnosis (median)	7.1	11.7	16.1
With radical prostatectomy	6.9	10.4	14.4
With radiotherapy	8.1	16.2	29.4
With watchful waiting	N/A	11.4	17.2
At randomization (median)			
With radical prostatectomy	BLQ	BLQ	1.2
With radiotherapy	3.0	3.4	8.2

N/A Not applicable.
BLQ Below the limit of quantification.

Figure 5 Distribution of PSA at diagnosis in patients treated with prostatectomy or radiation



6. EFFICACY RESULTS

6.1 Follow-up

The data cut-off date for assessing efficacy in this submission was 2 June 2000. As a result, median follow-up was 3 years, with a total follow-up of 24,086 patient years.

6.2 Objective disease progression

Progression rates across trials and for the individual trials are presented in Table 10 and summarized in the sections that follow. Kaplan-Meier probabilities for TTP (progression-free survival) are presented in Figures 6 and 7 (combined and individual trial data, respectively), and analyses results follow.

6.2.1 Trials combined

Overall, a smaller proportion of patients randomized to CASODEX 150 mg had objectively confirmed disease progression compared with patients randomized to placebo: 9.0% vs 13.8%, respectively.

6.2.2 Individual trials

In Trials 24 and 25, similar patterns were seen. In Trial 24, 10.1% of patients in the CASODEX group compared with 16.2% in the placebo group had objectively confirmed disease progression. In Trial 25, corresponding percentages were 16.3% for patients in the CASODEX group compared with 29.3% for patients in the placebo group.

In Trial 23, rates of progression were low in both treatment groups: in 5.0% of CASODEX-treated patients and 5.3% of placebo-treated patients.

Overall, daily treatment with CASODEX 150 mg resulted in a highly significant ($p<<0.0001$) 42% reduction in the risk of objection disease progression or death in the absence of progression, compared with placebo.

Table 10 Summary of patients with disease progression

Type of progression	Number (%) of patients							
	Combined data		Trial 23		Trial 24		Trial 25	
	CASODEX (n=4052)	Placebo (n=4061)	CASODEX (n=1647)	Placebo (n=1645)	CASODEX (n=1798)	Placebo (n=1805)	CASODEX (n=607)	Placebo (n=611)
Objective[a]								
Death[bc]	196 (4.8)	191 (4.7)	52 (3.2)	55 (3.3)	96 (5.3)	92 (5.1)	48 (7.9)	44 (7.2)
Bone scan[bd]	113 (2.8)	226 (5.6)	21 (1.3)	15 (0.9)	60 (3.3)	116 (6.4)	32 (5.3)	95 (15.5)
Other[be]	54 (1.3)	142 (3.5)	10 (0.6)	17 (1.0)	25 (1.4)	85 (4.7)	19 (3.1)	40 (6.5)
Total	**363 (9.0)**	**559 (13.8)**	**83 (5.0)**	**87 (5.3)**	**181 (10.1)**	**293 (16.2)**	**99 (16.3)**	**179 (29.3)**
Nonobjective[f]	17 (0.4)	84 (2.1)	0	0	5 (0.3)	31 (1.7)	12 (2.0)	53 (8.7)

[a] Includes death in the absence of objective progression.
[b] Categories are mutually exclusive.
[c] In the absence of objective progression.
[d] Bone-scan-confirmed progression.
[e] Other objectively confirmed progression, eg, magnetic resonance imaging, computerized tomography, biopsy.
[f] Patients with positive subjective assessments but no positive objective confirmation of progression. Patients with subjective disease progression alone were not included in the statistical analyses.

Figure 6 Kaplan-Meier plot for time to progression: combined data (EPC program)

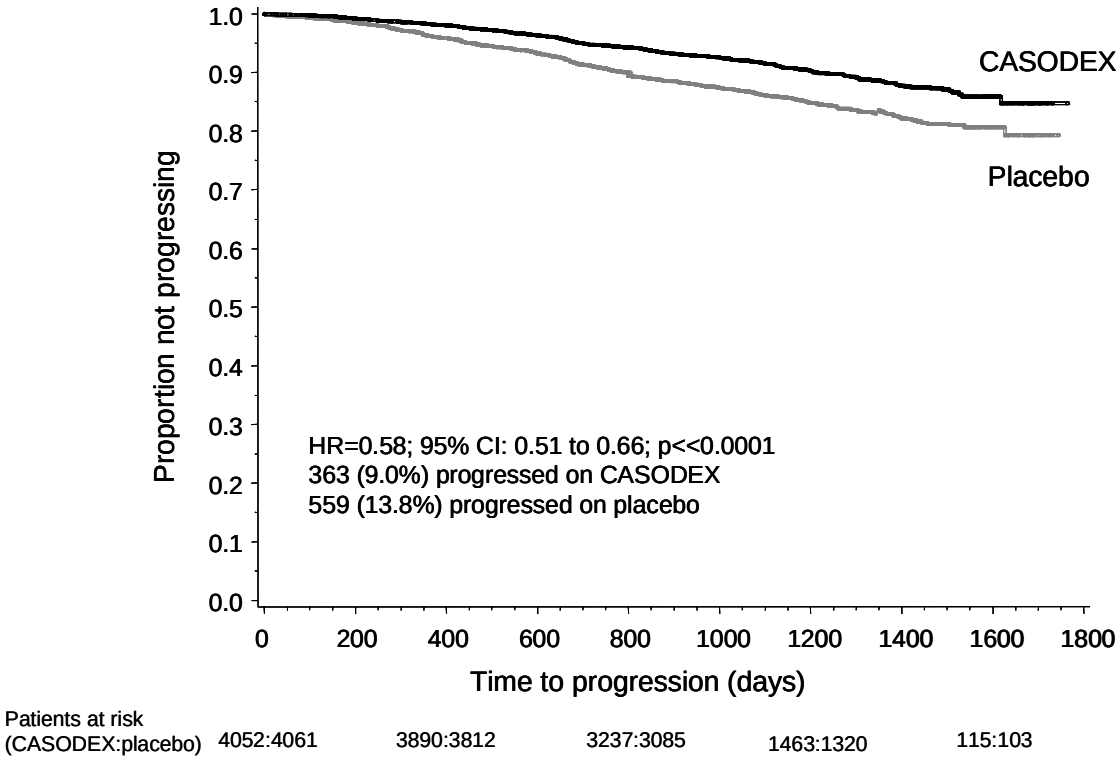
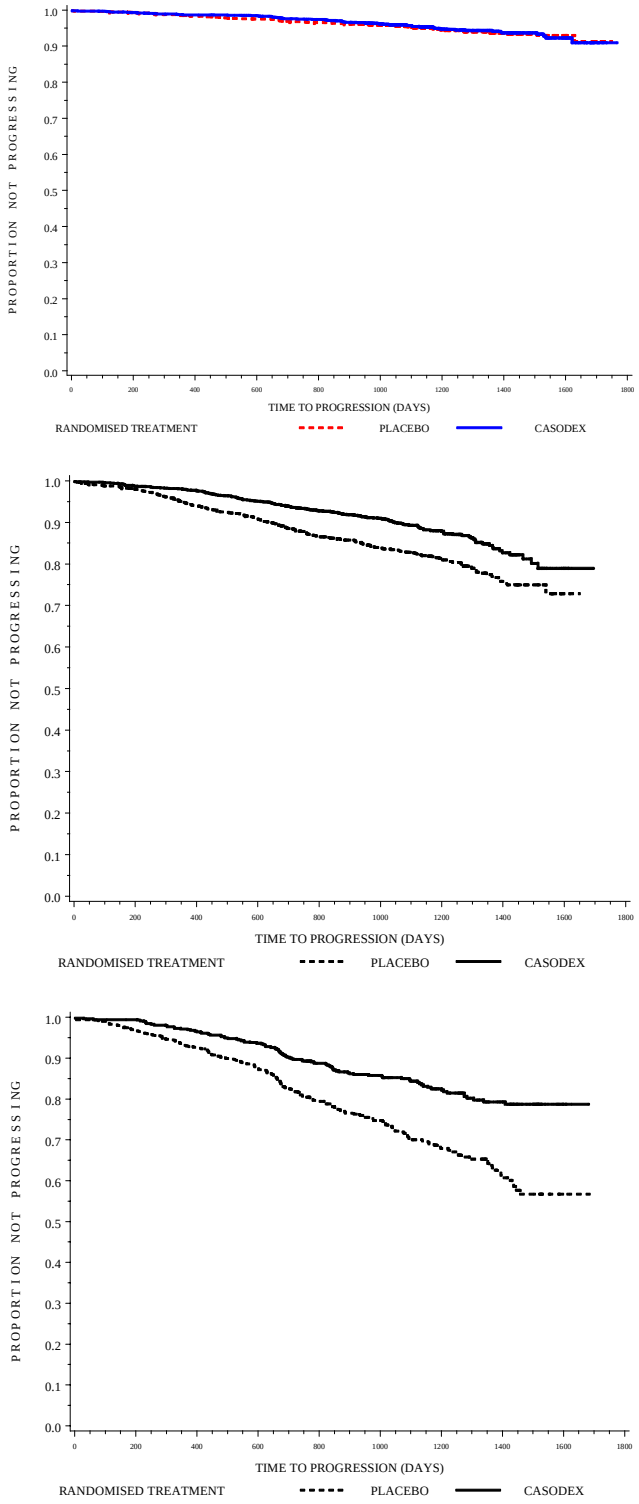


Figure 7 **Kaplan-Meier plots for time to progression in the individual trials: Trials 23, 24, and 25, respectively**



Overall, daily treatment with CASODEX 150 mg resulted in a highly significant (p<<0.0001) 42% reduction in the risk of objection disease progression or death in the absence of progression, compared with placebo (Table 11). A similar finding for CASODEX was seen in both Trials 24 (HR: 0.57) and 25 (HR: 0.43), each of which showed significant (p<0.0001) reduction in the risk of progression or death in the absence of progression in patients treated with CASODEX 150 mg, compared with placebo (Table 11, Figure 8)

Although the TTP analysis for Trial 23 did not show a statistical difference between treatments, the reason for this is related to the very small proportion of patients in both treatment groups who had disease progression. Currently, there is less than 25% power to detect the treatment effect identified from the power calculation for this trial (ie, a reduction in the risk of progression of >18%).

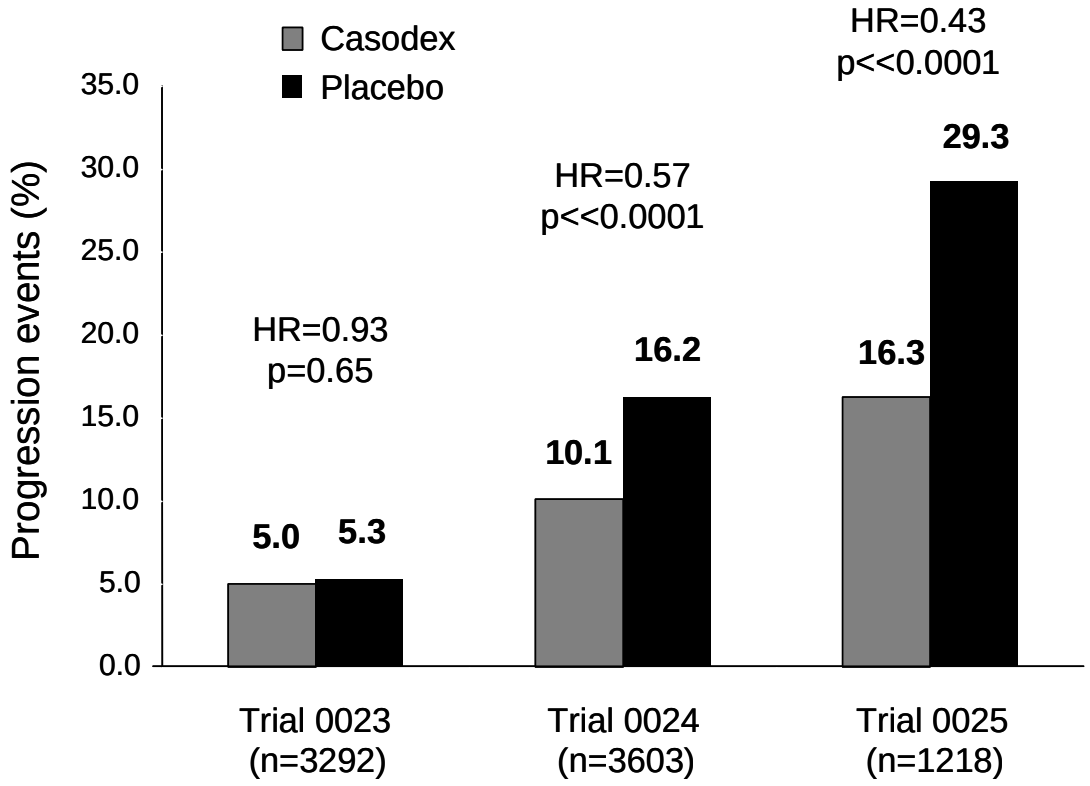
Table 11 Analyses of time to objective progression: combined and individual trial data

Trial number	Events (%) in the CASODEX group[a]		Events (%) in the placebo group[a]		Hazard ratio	95% confidence interval	p-value
Combined data	363/4052	(9.0)	559/4061	(13.8)	0.581	0.509 to 0.663	<<0.0001
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

[a] Events are objectively confirmed progressions or death in the absence of progression in all trials.

The overall reduction in risk equates to a 46% increase in the progression-free survival interval over the follow-up period (Collett 1994, Kalbfleisch and Prentice 1980, Byar 1982). This can be expressed as follows: the estimated time taken for 10% of CASODEX-treated patients to progress was 1 year longer than that for placebo-treated patients.

Figure 8 Objective disease progression by trial



HR Hazard ratio

6.3 Supplementary analysis of bone-scan-confirmed progression

Overall, a smaller proportion (5.3%) of patients randomized to CASODEX, compared with patients randomized to placebo (7.9%), had bone-scan-confirmed disease progression or had died in the absence of such progression in the nominal 0- to 2-year (±6 month) interval (Table 12). Similar patterns were seen in Trials 24 and 25 (Table 12).

In the overall analysis, the incidence of bone-scan-confirmed progression in the nominal 0- to 2-year interval after randomization or death in the absence of such progression was significantly ($p<<0.0001$) lower (37%) in the CASODEX group, compared with that in the placebo group (odds ratio estimate, 0.633; 95% confidence interval, 0.527 to 0.761). Per FDA requests, analyses that combined data from Trials 24 and 25 and additional analyses that considered only positive bone-scan outcomes in the time window of 2 years ± 6 months also showed significant treatment effects favoring CASODEX.

Table 12 Bone-scan-confirmed progression or death[a] over the 2-year interval[b] following randomization in the EPC program

Event	Number (%) of patients							
	Combined (N=8113)		Trial 23 (n=3292)		Trial 24 (n=3603)		Trial 25 (n=1218)	
	CASODEX (n=4052)	Placebo (n=4061)	CASODEX (n=1647)	Placebo (n=1645)	CASODEX (n=1798)	Placebo (n=1805)	CASODEX (n=607)	Placebo (n=611)
Progression per bone-scan	78 (1.9)	181 (4.5)	14 (0.9)	11 (0.7)	42 (2 3)	98 (5.4)	22 (3.6)	72 (11.8)
Death[a]	136 (3.4)	140 (3.4)	25 (1.5)	37 (2.2)	70 (3.9)	70 (3.9)	41 (6.8)	33 (5.4)
Total	214 (5.3)	321 (7.9)	39 (2.4)	38 (2.9)	112 (6.2)	168 (9.3)	63 (10.4)	105 (17.2)

[a] In the absence of a positive bone scan.
[b] ±6 months.
n Number of patients randomized.

The overall incidence of bone-scan-confirmed progression in the nominal 0- to 2-year interval after randomization or death in the absence of such progression was significantly ($p<0.0001$) lower (37%) in the CASODEX group, compared with the placebo group.

6.4 Time to progression: analysis by patient subgroups

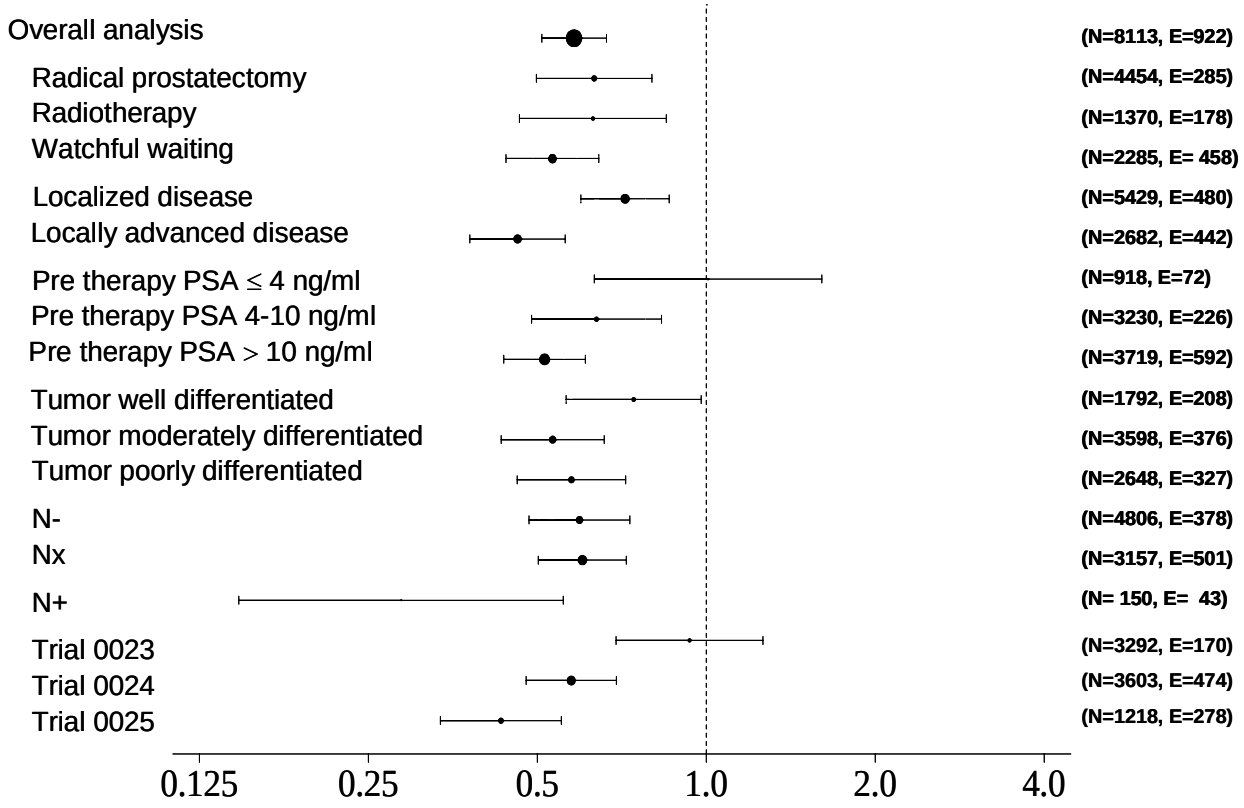
To examine whether the overall TTP effect with CASODEX was driven by one particular patient subgroup, exploratory analyses were conducted to examine TTP on the basis of prior therapy (curative intent or watchful waiting); disease stage (localized or locally advanced); PSA level at randomization; Gleason score; node status; and trial (see Section 6.4.1). Subgroup analyses were also performed for all patients by standard care at baseline in which the same factors used in the overall subgroup analyses were examined (see Section 6.4.2). For patients who had prior treatment with radical prostatectomy or radiation therapy, posttreatment PSA levels were included as variables. In another analysis, treatment effect by baseline standard of care was examined by risk of disease progression (low or high) on the basis of grouped baseline characteristics.

To better understand the observed treatment effects and possibly identify which factors were most prognostic for objective disease progression, AstraZeneca also performed multivariate analyses of TTP by standard care, using a Cox regression model that considered the following disease and patient characteristics: disease stage; Gleason grade; PSA levels before randomization (continuous) and after curative intent therapy (detectable/nondetectable); age, and randomized treatment.

6.4.1 Overview of subgroup analyses

The overall results of the subgroup analyses are shown graphically in Figure 9.

Figure 9 Overall subgroup analyses: hazard ratios and 95% confidence intervals for proportional risk reduction in time to progression



The size of the hazard ratio circle is proportional to the number of events (E) in the analysis.

The results of these analyses show that the beneficial TTP effect achieved with CASODEX was seen across a multitude of prognostic factors and that no one particular subgroup of patients drove the effect. Graphical presentations of the overall subgroup analyses for each trial are provided in Appendix C. Patterns in Trials 24 and 25 were similar to the pattern seen in the overall analysis across trials.

The results of the subgroup analyses on combined data show that the beneficial TTP effect achieved with CASODEX was seen across a multitude of prognostic factors and that no one particular subgroup of patients drove the effect.

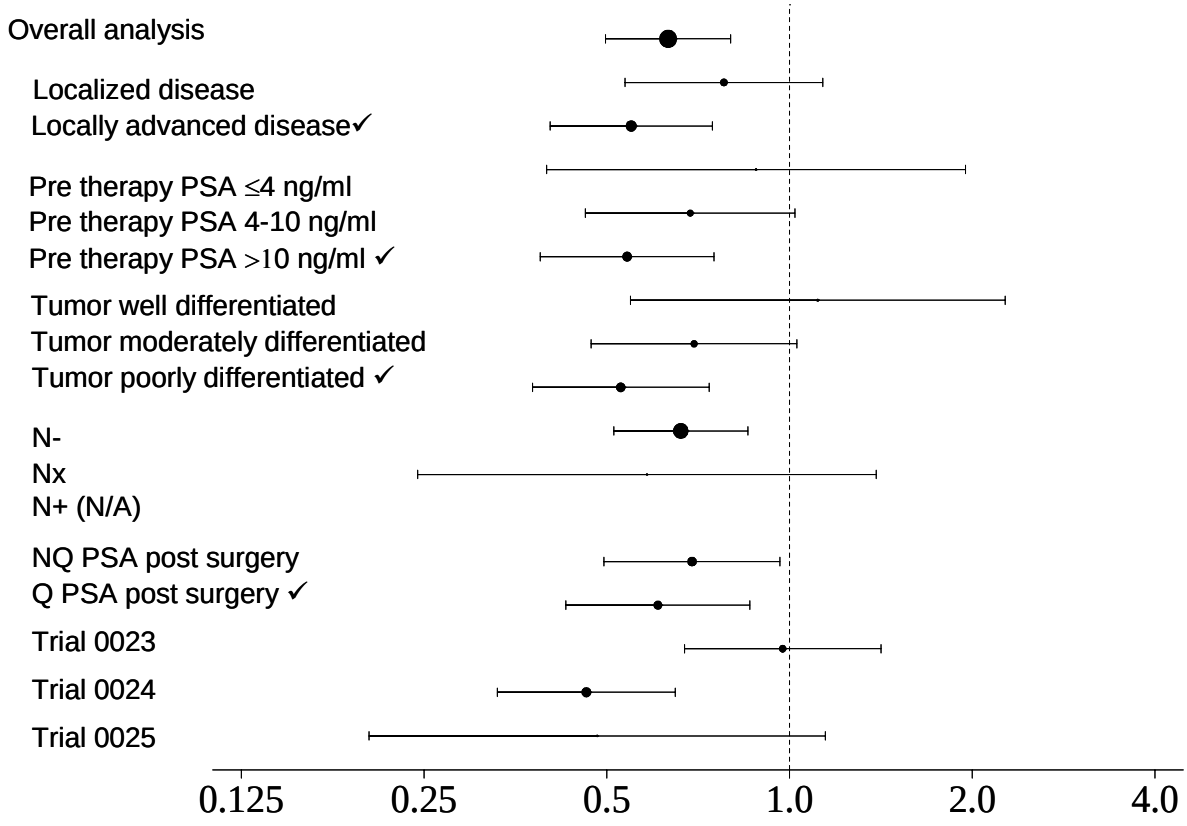
6.4.2 Subgroup analyses of TTP by baseline standard of care

6.4.2.1 Radical prostatectomy

The results of the exploratory TTP analyses for patients in the radical prostatectomy group are shown in Figure 10. This analysis was based on 285 events across trials.

In this group of patients, a TTP benefit was most evident in high-risk patients, ie, those with locally advanced disease, pretherapy PSA levels greater than 4 ng/ml, tumors moderately to poorly differentiated, and quantifiable PSA levels after surgery. The results of the multivariate analysis for this group of patients showed that the most important prognostic factors were, in order, PSA after surgery ($p<<0.0001$), disease stage ($p<0.0001$), randomized treatment ($p<0.001$), PSA before surgery ($p=0.01$), age (not significant [NS]), and then grade (NS).

Figure 10 Subgroup analyses for radical prostatectomy patients: hazard ratios and 95% confidence intervals for proportional risk reduction in time to progression



The size of the hazard ratio circle is proportional to the number of events included in the analysis.
N/A Not applicable (<20 events; therefore, no corresponding data line). NQ Not quantifiable. Q Quantifiable.
✓ Disease characteristics discussed in conjunction with proposed adjuvant therapy indication (see Section 11).

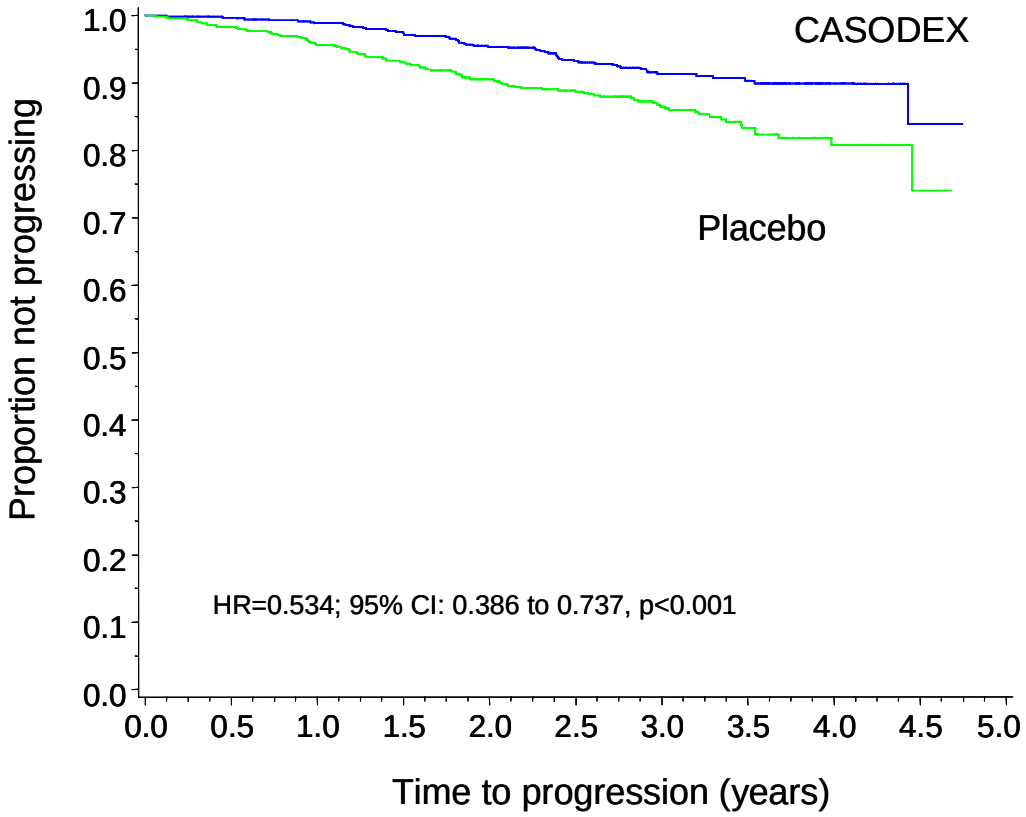
When treatment effect was examined by risk of disease progression (high or low) among radical prostatectomy patients, a significant 47% reduction in the risk of progression was seen for high-risk patients treated with CASODEX (Table 13, Figure 11). The factors that defined high-risk patients were locally advanced disease and any one of the following: baseline PSA >10 ng/ml, quantifiable postsurgical PSA levels, or Gleason sum ≥7. All other patients were categorized as low risk.

Table 13 Analyses of TTP in patients treated with radical prostatectomy, by risk of disease progression

Risk category	Events (%) in the CASODEX group[a]		Events (%) in the placebo group[a]		Hazard ratio	95% confidence interval	p-value
High risk[a]	59/722	(8.2)	100/702	(14.2)	0.534	0.386 to 0.737	<0.001
Low risk[b]	56/1514	(3.7)	70/1516	(4.6)	0.796	0.559 to 1.132	0.204

[a] High risk defined as locally advanced disease and any one of the following: baseline (presurgery) PSA >10 ng/ml, quantifiable postsurgical PSA, or Gleason sum of 7 or greater.
[b] Low risk defined as all other patients.

Figure 11 Kaplan-Meier plot for time to progression in radical prostatectomy patients at high risk of disease progression



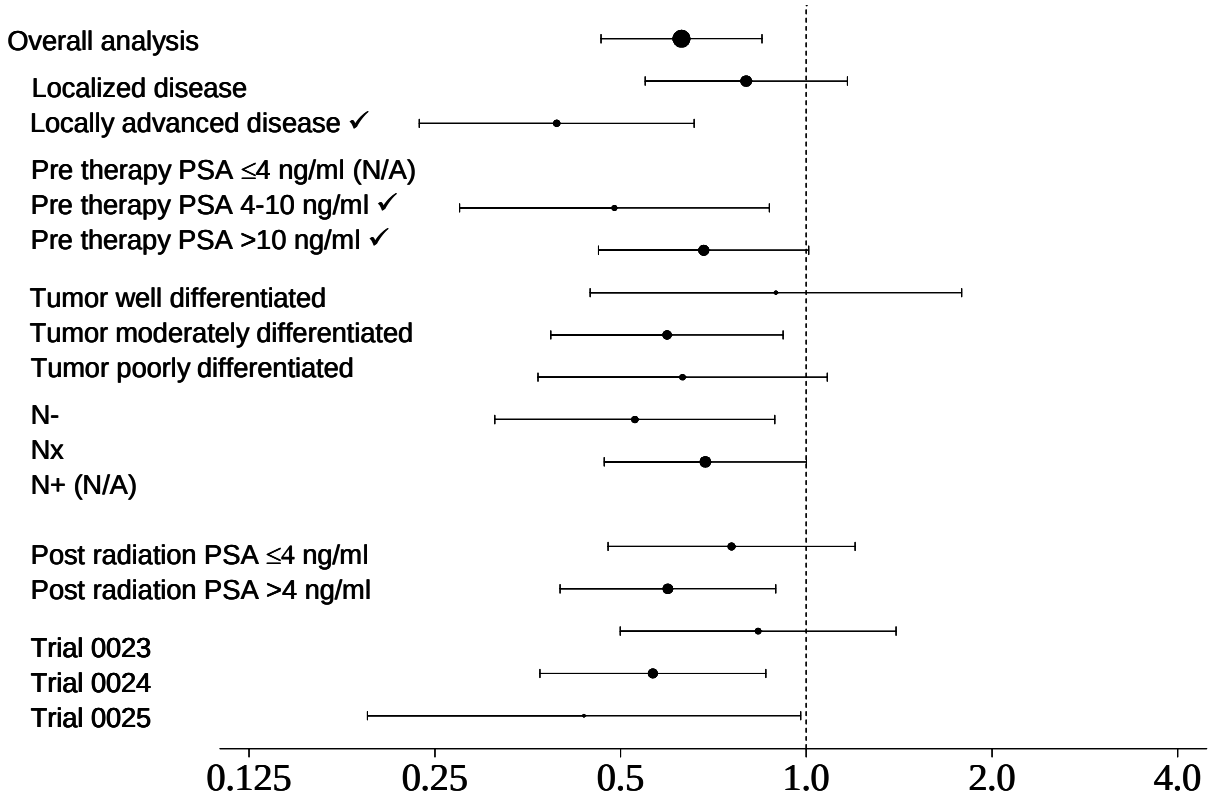
HR Hazard ratio; CI Confidence interval

6.4.2.2 Radiation therapy

The results of the exploratory TTP analyses for patients in the radiation therapy group are shown in Figure 12. This analysis was based on 178 events across trials.

In this group of patients (the smallest standard-care subgroup), a TTP benefit was again most evident in high-risk patients, ie, those with locally advanced disease, pretherapy PSA levels greater than 4 ng/ml, tumors moderately to poorly differentiated, and postradiation PSA levels. The results of the multivariate analysis for this group of patients showed that the most important prognostic factors were, in order, disease stage ($p<0.0001$), PSA prior to radiation therapy ($p<0.01$), randomized treatment ($p<0.01$), grade (NS), PSA after radiation therapy (NS), and age (NS).

Figure 12 Subgroup analyses for radiation therapy patients: hazard ratios and 95% confidence intervals for proportional risk reduction in time to progression



The size of the hazard ratio circle is proportional to the number of events included in the analysis.
N/A Not applicable (<20 events; therefore, no corresponding data line).
✓ Disease characteristics discussed in conjunction with proposed adjuvant therapy indication (see Section 11).

When treatment effect was examined by risk of disease progression (high or low) among patients treated with radiation therapy, a significant 61% reduction in the risk of progression was seen for

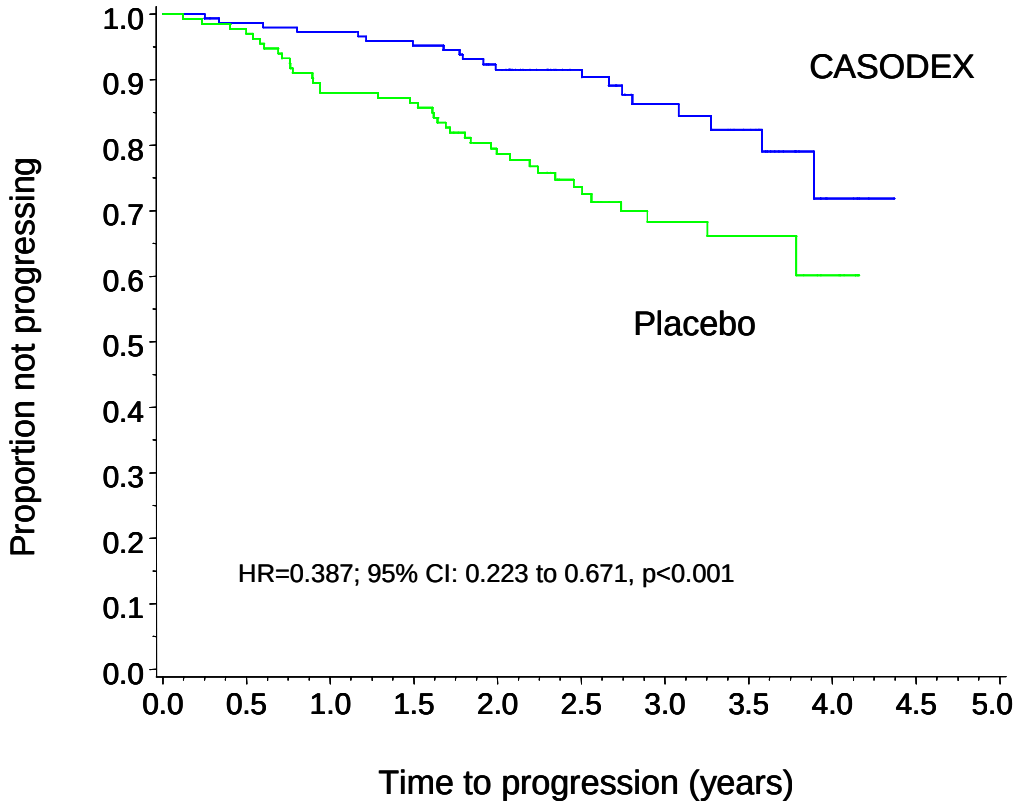
high-risk patients treated with CASODEX (Table 14, Figure 13). The factors that defined high-risk patients were locally advanced disease and preradiation PSA >4 ng/ml. All other patients were categorized as low risk.

Table 14 Analyses of TTP in patients treated with radiation therapy, by risk of disease progression

Risk category	Events (%) in the CASODEX group[a]		Events (%) in the placebo group[a]		Hazard ratio	95% confidence interval	p-value
High risk[a]	20/148	(13.5)	39/134	(29.1)	0.387	0.223 to 0.670	<0.001
Low risk[b]	55/551	(10.0)	64/537	(11.9)	0.781	0.543 to 1.124	0.183

[a] High risk defined as locally advanced disease and baseline (preradiation) PSA >4 ng/ml.
[b] Low risk defined as all other patients.

Figure 13 Kaplan-Meier plot for time to progression in radiation therapy patients at high risk of disease progression



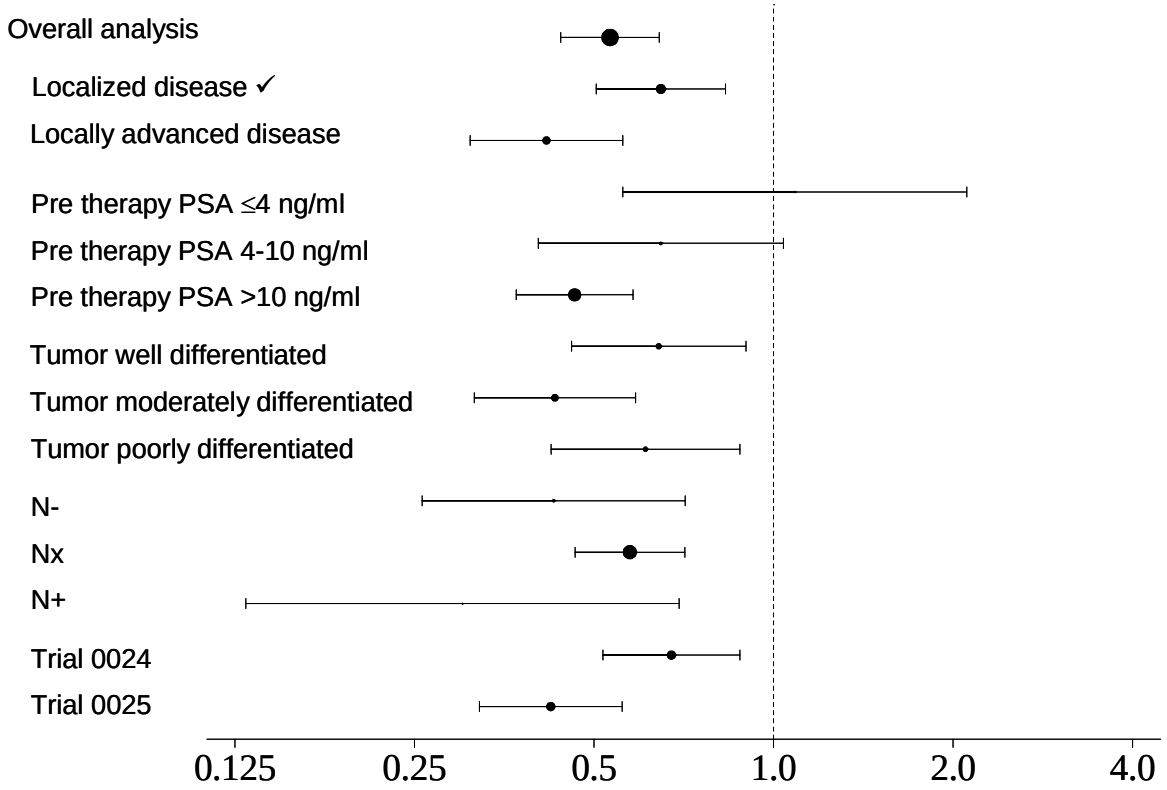
HR Hazard ratio; CI Confidence interval

6.4.2.3 Watchful waiting

The results of the exploratory TTP analyses for patients in the watchful waiting group are shown in Figure 14. This analysis was based on 458 events across Trials 24 and 25.

Hazard ratios and 95% CI show that the reduced risk of disease progression in this patient subgroup by prognostic factor is consistent with the risk reduction seen in the overall subgroup analyses.

Figure 14 Subgroup analyses for patients in the watchful waiting group: hazard ratios and 95% confidence intervals for proportional risk reduction in time to progression



The size of the hazard ratio circle is proportional to the number of events included in the analysis.
✓ Disease characteristic discussed in conjunction with proposed immediate therapy indication (see Section 11).

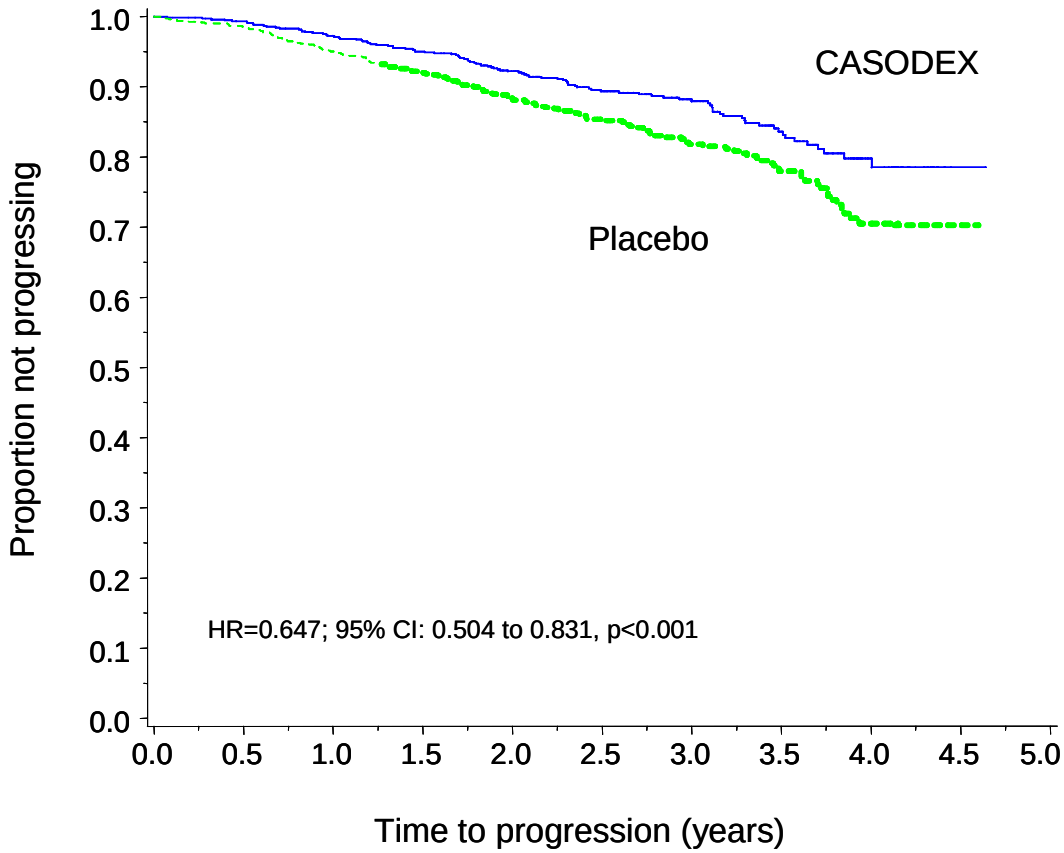
When treatment effect was examined by risk of disease progression (high or low) among patients in the watchful waiting group, significant reductions in the risk of progression were seen with CASODEX (Table 15) regardless of risk (low or high): 35% in low-risk patients (Figure 15) and 59% in high-risk patients. The factor that defined high-risk patients was locally advanced disease. All other patients were categorized as low risk.

Table 15 Analyses of TTP in patients in the watchful waiting group, by risk of disease progression

Risk category	Events (%) in the CASODEX group[a]		Events (%) in the placebo group[a]		Hazard ratio	95% confidence interval	p-value
High risk[a]	69/335	(20.6)	132/322	(41.0)	0.409	0.305 to 0.549	<0.001
Low risk[b]	103/779	(13.2)	154/849	(18.1)	0.647	0.504 to 0.831	<0.001

[a] High risk defined as locally advanced.
[b] Low risk defined as all other patients.

Figure 15 Kaplan-Meier plots for time to progression: patients in the watchful waiting group at low risk of disease progression



HR Hazard ratio; CI Confidence interval

6.4.3 Conclusions from the subgroup analysis

Close examination of the TTP data reveal that the overall treatment effect is robust, with reductions in risk of progression seen across a range of important prognostic factors, including each of the primary treatment modalities used. Further examination of data by primary treatment modality shows that the treatment effect was most strongly associated with the following groups of patients:

- patients with locally advanced disease at high risk of disease progression after radical prostatectomy or radiation therapy of curative intent (Figures 10 to 13)
- patients with localized or locally advanced nonmetastatic prostate cancer who chose watchful waiting as their initial primary care (Figures 14 and 15)

Examination of TTP data by primary treatment modality shows that the treatment effect with CASODEX was most strongly associated with the following groups of patients:

- patients with locally advanced disease at high risk of disease progression after radical prostatectomy or radiation therapy of curative intent
- patients with localized or locally advanced nonmetastatic prostate cancer who chose watchful waiting as their initial primary care

6.5 PSA progression

To assess the effects of CASODEX on changes in serum PSA, an analysis of PSA progression was performed.

The numbers and proportion of patients with PSA progression, defined as doubling of PSA (PSAdt), objective progression, or death, are given in Table 13 for the trials combined and the individual trials. Overall, a greater proportion of patients randomized to placebo (32.7%), compared with those randomized to CASODEX 150 mg (16.6%), had a PSA doubling event. The same effect was seen in each trial (Table 16).

Table 16 Patients with PSA doubling events

Earliest event[a]	Number (%) of patients															
	Combined data				Trial 23				Trial 24				Trial 25			
	CASODEX (n=4052)		Placebo (n=4061)		CASODEX (n=1647)		Placebo (n=1645)		CASODEX (n=1798)		Placebo (n=1805)		CASODEX (n=607)		Placebo (n=611)	
PSA doubled	385	(9.5)	1016	(25.0)	211	(12.8)	333	(20.2)	126	(7.0)	440	(24.4)	48	(7.9)	243	(39.8)
Objective progression	102	(2.5)	145	(3.6)	12	(0.7)	9	(0.5)	53	(2.9)	80	(4.4)	37	(6.1)	56	(9.2)
Death	186	(4.6)	168	(4.1)	47	(2.9)	52	(3.2)	93	(5.2)	80	(4.4)	46	(7.6)	36	(5.9)
Total	673	(16.6)	1329	(32.7)	270	(16.4)	394	(24.0)	272	(15.1)	600	(33.2)	131	(21.6)	335	(54.8)

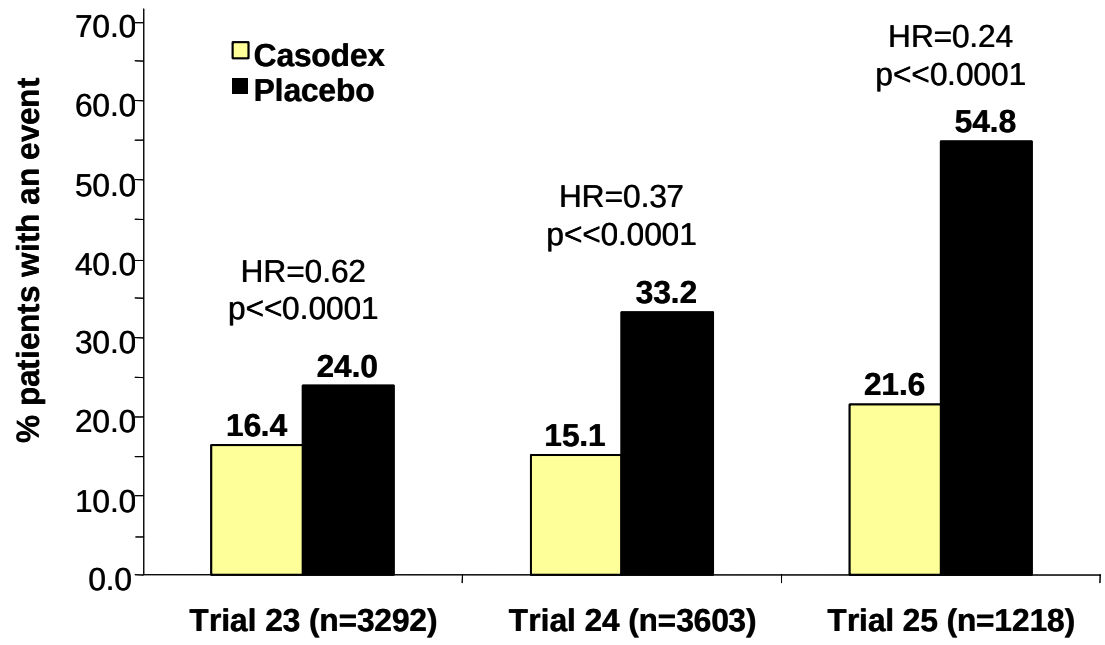
[a] Categories are mutually exclusive and hierarchical; the event that occurred first was assigned as the reason for PSA doubling.
n Number of patients randomized.

Across trials, the risk of PSA progression was significantly (p<<0.0001) reduced with CASODEX by 59% (95% CI: 0.38 to 0.45), compared with placebo.

On a trial basis, CASODEX 150 mg also significantly (p<<0.0001) reduced the risk of PSA progression, by 38% in Trial 23, 63% in Trial 24, and 76% in Trial 25 (Figure 16).

For Trials 24 and 25, the significant reduction in PSA progression was highly consistent with the significant delay in disease progression.

Figure 16 Patients with PSA doubling event, by trial



HR Hazard ratio.

Daily treatment with CASODEX 150 significantly (p<<0.0001) reduced the risk of PSA progression, by 59% overall and by 38%, 63%, and 76% in Trials 23, 24, and 25, respectively, compared with placebo.

6.6 Overall survival

At the data cut-off 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.

The overall incidence of death was similar across the treatment groups, and this was also true whether death was the result of prostate cancer or due to other causes (Table 17). After approximately 3 years of follow-up, deaths from causes unrelated to prostate cancer prevailed. A similar pattern was seen in each of the individual trials (Table 17). (See Section 6.10 for a brief summary of additional planned analyses.)

Table 17 Number and percentage of deaths: overall and by trial

Category	Number (%) of patients			
	CASODEX 150 mg		Placebo	
Overall	(n=4052)		(n=4061)	
Total deaths[a]	254	(6.3)	268	(6.6)
from prostate cancer	58	(1.4)	69	(1.7)
from other causes	196	(4.8)	199	(4.9)
Deaths in Trial 23	(n=1647)		(n=1645)	
Total death	62	(3.8)	61	(3.7)
from prostate cancer	8	(0.5)	3	(0.2)
from other causes	54	(3.3)	58	(3.5)
Deaths in Trial 24	(n=1798)		(n=1805)	
Total death	123	(6.8)	137	(7.6)
from prostate cancer	26	(1.4)	38	(2.1)
from other causes	97	(5.4)	99	(5.5)
Deaths in Trial 25	(n=607)		(n=611)	
Total death	69	(11.4)	70	(11.5)
from prostate cancer	24	(4.0)	28	(4.6)
from other causes	45	(7.4)	42	(6.9)

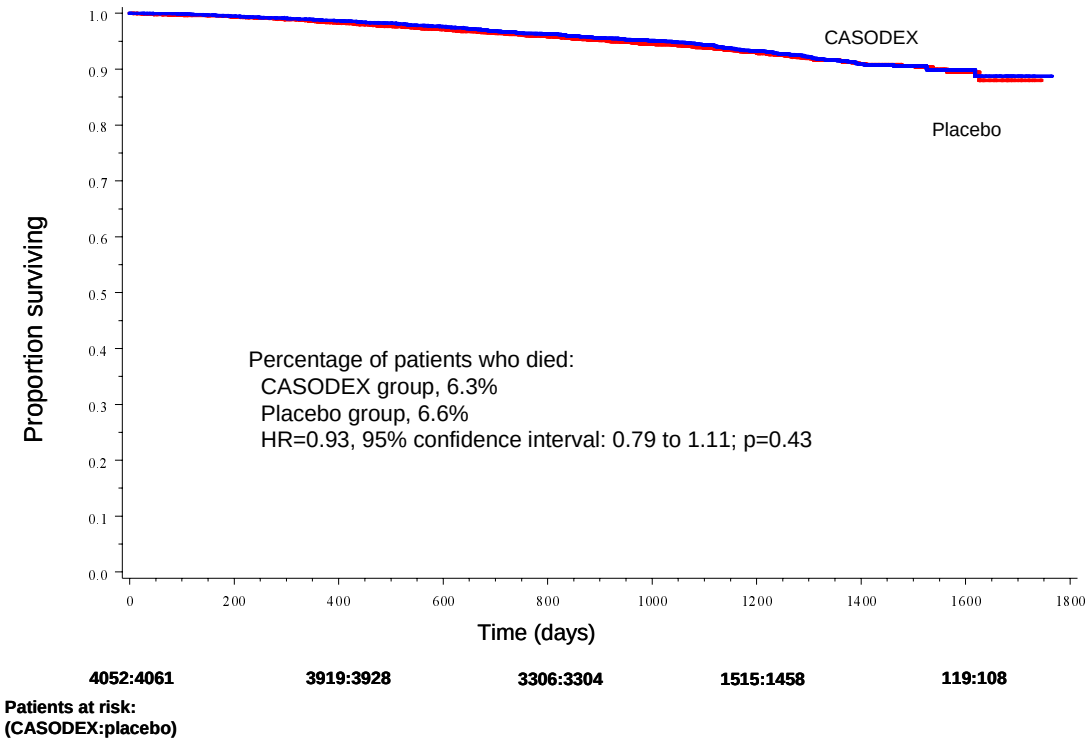
[a] Includes deaths following progression.
n Number of patients randomized.

In the combined analysis of overall survival, no significant difference was observed between the treatment groups (Table 18, Figure 17). Given the immaturity of the data, ie, less than 1.6% of deaths attributed to prostate cancer and an overall mortality rate of 6.4%, the inability to detect a survival difference at 3 years' follow-up was not unexpected.

Table 18 Analysis of time to death: combined data

Trials analyzed	Events (%) in the CASODEX group		Events (%) in the placebo group		Hazard ratio	95% confidence interval	p-value
Combined data	254	(6.3)	268	(6.6)	0.933	0.785 to 1.107	0.426

Figure 17 Kaplan-Meier probability of survival across trials



With a median follow-up of 3 years, it is too early to detect a survival difference between treatments. At the time of data cut-off, only 6.4% of patients had died, with less than 1.6% having died of prostate cancer.

6.7 Potential for biases in the assessment of disease progression

Throughout the EPC program, the FDA raised concerns regarding the potential for bias in the assessment of objective disease progression, namely, that the pharmacological effects (ie, gynecomastia) of an active anti-androgen could cause the investigator to become aware of the trial treatment allocated to individual patients. Further, it was thought that the routine use, by treating physicians, of PSA as a marker of underlying disease could result in fewer progressions being detected in CASODEX-treated patients, or initiate earlier and more frequent assessments of progression in placebo-treated patients. Therefore, the EPC program was designed so that all patients who had not shown objective disease progression would have bone scans every 2 years while remaining on randomized therapy. In this way, any progressions that might have been missed because of the factors described above would be captured, thereby minimizing the potential for bias.

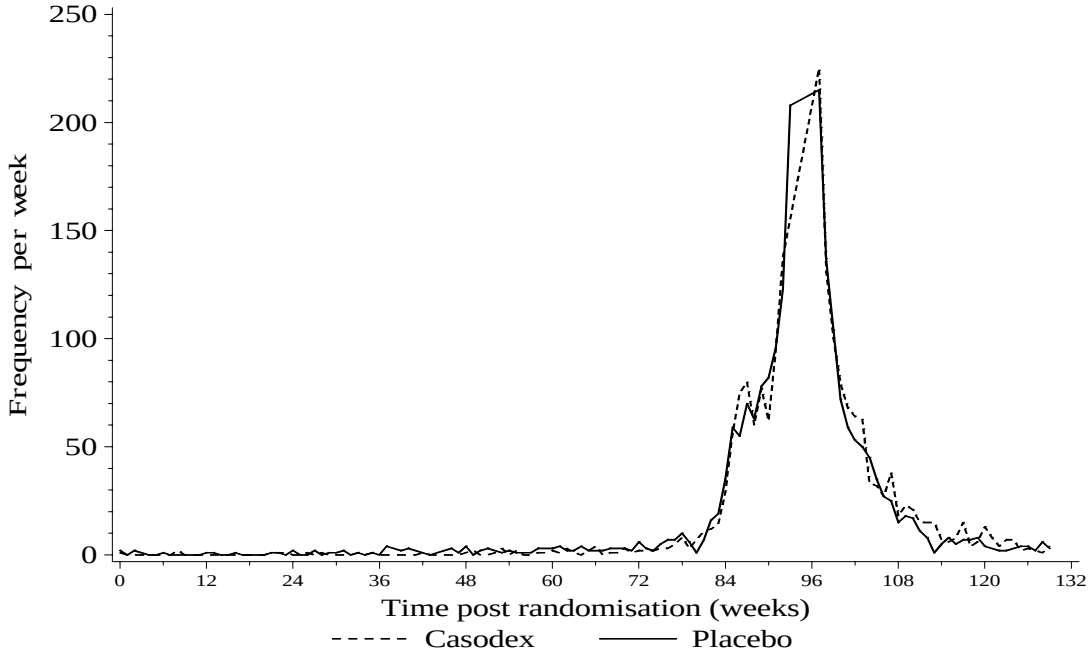
6.7.1 Timing of the scheduled 2-year bone scan and frequency of other assessments for disease results

If bias had been introduced into the primary analysis due to issues with PSA rises and adverse events of known pharmacological effect, a differential pattern in the timing of progression assessments between randomized treatment groups could be expected.

Among patients eligible for 2-year bone-scans (ie, excluding those who had either an earlier positive scan or died before the scheduled 2-year time point), the majority in both treatment groups had their scans performed at the scheduled 2-year time point: CASODEX-treated patients, 89.3% [3481of 3898]; placebo-treated patients, 87.4% [3363 of 3848]) (Figure 18). Between treatment groups, there was no difference in the number of scans performed. Additionally, the median timing of scans was in line with the scheduled 96-week time point: 95.7 weeks for both treatment groups (with 5% and 95% percentiles of 86.6 and 109.6 weeks, respectively, for CASODEX and 86.4 and 106.9 weeks, respectively, for placebo). The large proportion of patients having timely scans at 2 years and the similarity between the 2 treatment groups in the timing of assessments showed that bias was not introduced relative to the timing of bone scans. In all, there was no evidence of any difference between the treatment groups in the frequency and timing of assessment for disease progression.

There was no evidence of any difference between the treatment groups in the frequency and timing of assessment for disease progression.

Figure 18 Timing of bone-scans performed during 0 to 2 years (+6 months) after randomization



6.7.2 Central retrospective re-read of bone scans

To ensure that the bone scan process itself was not biased, the FDA also requested that a sample of bone scans be subjected to a retrospective, central re-read by a panel of blinded, independent experts. This re-read was completed by 3 US-based expert readers for all patients with bone-scan-confirmed progression and for a random sample of patients without objective evidence of disease progression. The sample was weighted by trial and by underlying therapy to ensure equal precision in the estimation of reclassification rates. An analysis plan was developed for the evaluation of the re-read outcome prior to completion of the re-read exercise and unblinding of the resultant data.

The conclusions from the central re-read of bone scans were as follows:

- There was no treatment-related bias in the local determination of disease progression, as confirmed by the FDA, and the treatment effect remained significantly in favor of CASODEX.
- There was a high overall agreement (93%) between the first read and re-read of bone scan data.
- There was no evidence of bias between treatment groups in the rates at which outcomes were reclassified.

- When progression rates were recalculated after reclassification, the treatment effect remained significantly in favor of CASODEX-treated patients.

6.8 TTF

TTF, a secondary endpoint in the EPC program (see Section 4.5.2.2), is a heterogeneous endpoint that captures, for each patient, the 1st event that resulted in the discontinuation of randomized therapy as the primary treatment for prostate cancer. As such, it measures the time from randomization to withdrawal of therapy or to the introduction of additional therapies for the treatment of prostate cancer and so reflects a hybrid of efficacy deficits and tolerability issues.

For this endpoint, a significant qualitative treatment-by-trial interaction was identified (ie, treatment effects were significantly in opposing directions). Therefore, it was not possible (according to a priori statistical methods defined in the trial protocols) to pool the TTF data from each trial into a combined analysis. Treatment failure reasons are summarized in Table 19, by trial.

Table 19 Summary of treatment failure reasons, by individual trial

Reason for treatment failure[a]	Number (%) of patients											
	Trial 23				Trial 24				Trial 25			
	CASODEX (n=1647)		Placebo (n=1645)		CASODEX (n=1798)		Placebo (n=1805)		CASODEX (n=607)		Placebo (N=611)	
No trial therapy received[b]	20	(1.2)	18	(1.1)	8	(0.4)	10	(0.6)	2	(0.3)	2	(0.3)
Death	9	(0.5)	13	(0.8)	48	(2.7)	36	(2.0)	26	(4.3)	18	(2.9)
Objective disease progression	5	(0.3)	8	(0.5)	47	(2.6)	151	(8.4)	**32**	**(5.3)**	**103**	**(16.9)**
Therapy withdrawn	601	(36.5)	304	(18.5)	620	(34.5)	468	(25.9)	133	(21.9)	163	(26.7)
Adverse event	**505**	**(84.0)**	**147**	**(48.4)**	435	(70.2)	135	(28.8)	95	(71.4)	37	(22.7)
Trial noncompliance	4	(0.7)	6	(2.0)	10	(1.6)	12	(2.6)	1	(0.8)	0	
Patient decision[c]	82	(13.6)	88	(28.9)	135	(21.8)	116	(24.8)	20	(15.0)	27	(16.6
Lost to follow-up	0		0		10	(1.6)	21	(4.5)	1	(0.8)	4	(2.5
Other[d]	10	(1.7)	63	(20.7)	30	(4.8)	184	(39.3)	16	(12.0)	95	(58.3
Systemic therapy or radiotherapy added	3	(0.2)	4	(0.2)	12	(0.7)	25	(1.4)	3	(0.5)	7	(1.1)
Total	638	(38.7)	347	(21.1)	735	(40.9)	690	(38.2)	196	(32.3)	293	(48.0)

[a] Categories are mutually exclusive and hierarchical; the event that occurred first was assigned as the reason for treatment failure.
[b] Patients were randomized to treatment but never actually started treatment.
[c] Patient unwilling or unable to continue.
[d] Includes investigator decision, rise in PSA level, receipt of additional curative treatment, and various other reasons.
n Number of patients randomized.

Analyses of TTF showed significant differences ($p<0.001$) between treatment groups in Trial 25 (which favored CASODEX) and Trial 23 (which favored placebo) and no significant difference ($p=0.089$) between treatment groups in Trial 24. In Trial 25, in patients with more advanced disease, this outcome was influenced primarily by the greater proportion of placebo-treated patients who withdrew because of progression (Table 19) and was consistent with the trial-specific TTP benefit seen for CASODEX (see Section 6.2). In Trial 23, in patients with less advanced disease, the difference between treatment groups was influenced primarily by the greater proportion of CASODEX-treated patients who withdrew because of adverse events (Table 19), primarily gynecomastia and breast pain.[8] This outcome was consistent with the greater incidence of withdrawals related to the pharmacological effects of CASODEX (see Section 7.6.1), and may reflect patient reluctance to tolerate adverse events after undergoing putatively curative primary therapy. In Trial 23, at data cut-off, withdrawals due to adverse events outnumbered withdrawals due to progressive disease. In Trial 24, withdrawals due to progression on placebo were somewhat counterbalanced by withdrawals due to adverse effects in the CASODEX group.

Since the TTF endpoint treats all withdrawals as equal—whether related to efficacy, tolerability, or patient perception of benefit—and since withdrawals from therapy due to pharmacological effects (gynecomastia and breast pain) may not equate with those related to objective disease progression, the main interpretation of the efficacy from the CASODEX EPC program should be based on the findings for the primary TTP endpoint (as determined in the TTP analysis), which were significant despite withdrawals.

[8] For all trials, adverse events leading to withdrawal included all fatal adverse events.

6.9 Efficacy summary and conclusion

CASODEX 150 mg was evaluated as adjuvant therapy to radical prostatectomy and radiation therapy and as alternate therapy to watchful waiting in patients with localized or locally advanced nonmetastatic prostate cancer. Data were generated as planned from 3 randomized, double-blind, placebo-controlled, multicenter, clinical trials that comprised the EPC program.

Reduced risk of objective disease progression (from Sections 6.2 through 6.4)

Daily treatment with 150 mg of CASODEX resulted in the following beneficial effects as related to time to objective disease progression or TTP:

- Overall, a significantly ($p<0.0001$) prolonged TTP (progression-free survival) compared with placebo; alternately, a 42% reduction in risk of objective disease progression
  - A similar, highly significant effect in 2 individual trials: Trials 24 and 25.
- A TTP benefit regardless of prior therapy at baseline, disease stage, tumor differentiation (grade), or nodal status and when pretherapy PSA level was >4 ng/ml
- For patients treated adjuvantly after radical prostatectomy, greatest benefit among patients at highest risk of disease recurrence—those with locally advanced disease, pretherapy PSA levels greater than 4 ng/ml, tumors moderately to poorly differentiated, or quantifiable PSA levels after surgery
- For patients treated adjuvantly after radiation therapy, greatest benefit among patients at highest risk of disease recurrence—those with locally advanced disease, pretherapy PSA levels greater than 4 ng/ml, tumors moderately to poorly differentiated, or detectable postradiation PSA
- For watchful waiting patients, an overall TTP benefit (consistent with the overall treatment effect) and a TTP benefit in nearly all subgroups of patients examined, compared with placebo-treated patients.

Among patients who progressed, the majority had disease progression confirmed by bone scan or died before objective confirmation. The beneficial TTP effect seen with CASODEX was confirmed in a separate analysis of bone-scan-confirmed progression that included deaths in the absence of such progression in the 2-year (± 6-month) treatment interval after randomization. A subsequent central review of bone scans showed no evidence of acquisition bias, thereby supporting the TTP outcome.

The low rate of disease progression in Trial 23 reflects patient and disease characteristics at trial entry, as emphasized by low PSA levels at diagnosis and randomization. In that trial only, the

low rate of progression in both the CASODEX and placebo groups prevents detection of the expected treatment effect with adequate power.

Although watchful waiting patients were only enrolled in the non-US trials (Trials 24 and 25), the types of patients treated with CASODEX had characteristics similar to US patients who elect watchful waiting (Harlan 2001). These are described in further detail in Section 11. Since no evidence exists to suggest that prostate cancer behaves differently in different parts of the world, the findings in the EPC program should be relevant to comparable patients in the United States.

Reduced risk of PSA progression (from Section 6.5)

Daily treatment with 150 mg of CASODEX resulted in the following beneficial effects as related to PSA progression:

- Overall, a significant reduction (59%) in the risk of PSA progression ($p<<0.000l$)
  - A similar, highly significant effect in each of the 3 individual trials, with risk reduced by 38%, 63%, and 76% in Trials 23, 24, and 25, respectively

These data offer supportive evidence of a biological effect across a group of patients that together are highly representative of the types of patients who present with nonmetastatic prostate cancer in the United States (Stanford et al 1999).

Implications for survival (from Section 6.6)

With the current median follow-up of 3 years, survival data are immature and a survival benefit cannot be concluded at this time.

6.10 Additional efficacy analyses

The next formal assessment of efficacy data is planned after 1200 deaths have accrued. Formal requests for additional efficacy data from various regulatory authorities, in conjunction with ongoing worldwide submissions, made it necessary to superficially interrogate the data set used for the 4-month safety update for additional efficacy data (data cut-off of 28 September 2001). These additional data, which represented another 15 months of follow-up, continued to support the conclusions contained in the original sNDA. The number of progression events in Trial 23 remained low in both treatment groups, a further reflection of the predominantly good-prognosis patients enrolled; consequently, differences between treatments are unlikely to emerge prior to the next formal analysis. Even with the additional follow-up, it was still too early to expect emerging differences in survival and none were seen.

7. TOLERABILITY

Exposure and tolerability data are provided as of 28 September 2001 whereas efficacy data are provided as of 2 June 2000. Therefore, there are differences between death data provided in this section (for safety purposes) and survival data provided in Section 6 (for efficacy purposes).

Since CASODEX was first approved in 1995, nearly 7 years of marketing experience has accumulated and the worldwide safety database continues to show that CASEODEX is a safe drug. The safety profile established from the EPC program continues to provide evidence of this, as will be shown with the data that follow.

7.1 Exposure

In the EPC program, the mean duration of exposure to trial therapy was 2.33 patient-years for the CASODEX treatment group and 2.43 patient-years for the placebo-treatment group. The total patient-years of exposure were 9387 and 9778 for the CASODEX- and placebo-treatment groups, respectively.

7.2 Adverse events in the controlled trials

7.2.1 Overview of adverse events in the controlled trials

The majority of patients had at least 1 adverse event, with adverse events determined by spontaneous reporting.[9] The difference in the incidence of adverse events between the treatment groups can largely be attributed to gynecomastia and male breast pain, known pharmacological effects of CASODEX. The observed high incidence of adverse events was not unexpected in the population studied (elderly men with prostate cancer).

The safety analysis includes only those patients who received trial medication and, therefore, excludes 60 patients who were randomized, but did not receive therapy.

7.2.2 Incidence of adverse events in the controlled trials

Table 20 shows adverse events, reported by body system, that occurred with an incidence of at least 5%.

The most frequently occurring adverse events in the CASODEX group were those related to its endocrine actions, primarily gynecomastia (67.6%) and breast pain (73.3%).

[9] At each visit, patients were asked, "Has anything bothered you since your last visit?"

Table 20 Number of patients with adverse events occurring with an incidence of at least 5% in the controlled trials

Body system[a] and consolidated COSTART term[b]	Number (%) of patients with an adverse event			
	CASODEX (n=4022)		Placebo (n=4031)	
Body as a whole	**1988**	**(49.4)**	**2060**	**(51.1)**
Abdominal pain	285	(7.1)	288	(7.1)
Accidental injury	178	(4.4)	246	(6.1)
Asthenia	433	(10.8)	307	(7.6)
Back pain	387	(9.6)	456	(11.3)
Flu syndrome	301	(7.5)	304	(7.5)
Headache	194	(4.8)	208	(5.2)
Hernia	206	(5.1)	252	(6.3)
Infection	217	(5.4)	205	(5.1)
Pain	268	(6.7)	298	(7.4)
Pelvic pain	264	(6.6)	269	(6.7)
Cardiovascular system	**1190**	**(29.6)**	**1153**	**(28.6)**
Hypertension	300	(7.5)	321	(8.0)
Hot flashes	366	(9.1)	213	(5.3)
Digestive system	**1510**	**(37.5)**	**1396**	**(34.6)**
Constipation	353	(8.8)	297	(7.4)
Diarrhea	267	(6.6)	275	(6.8)
Endocrine system[c]	102	(2.5)	109	(2.7)
Hemic/lymphatic system[c]	206	(5.1)	170	(4.2)
Metabolic/nutritional system	**794**	**(19.7)**	**677**	**(16.8)**
Edema	237	(5.9)	213	(5.3)
Weight gain	232	(5.8)	117	(2.9)
Musculoskeletal system	**823**	**(20.5)**	**943**	**(23.4)**
Arthralgia	329	(8.2)	387	(9.6)
Nervous system[c]	1069	(26.6)	881	(21.9)
Respiratory system	**1097**	**(27.3)**	**1137**	**(28.2)**
Pharyngitis	426	(10.6)	450	(11.2)
Skin/appendages	**1028**	**(25.6)**	**758**	**(18.8)**
Alopecia	239	(5.9)	32	(0.8)
Rash	395	(9.8)	331	(8.2)
Special senses[c]	319	(7.9)	370	(9.2)
Urogenital system	**3640**	**(90.5)**	**1823**	**(45.2)**
Gynecomastia	2717	(67.6)	333	(8.3)
Hematuria	191	(4.8)	248	(6.2)
Impotence	365	(9.1)	254	(6.3)
Breast pain	2948	(73.3)	307	(7.6)
Urinary incontinence	272	(6.8)	244	(6.1)
Urinary tract disorder	240	(6.0)	284	(7.1)
Urinary tract infection	312	(7.8)	269	(6.7)

[a] Numbers given per body system represent the total number of patients with adverse events in that category.
[b] A patient may have had more than 1 adverse event.
[c] Body system included for completion but no one adverse event related to that system occurred in at least 5% of patients.
n Number of patients who received randomized treatment.
COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.

The most frequently occurring adverse events in the CASODEX group were those related to its endocrine actions, primarily gynecomastia (67.6%) and male breast pain (73.3%), which are discussed in more detail in Section 7.5.1.

Other adverse events related to the endocrine action of CASODEX included asthenia (CASODEX 10.8%, placebo 7.6%), hot flashes (CASODEX 9.1%, placebo 5.3%), alopecia (defined as a change in body hair; CASODEX 5.9%, placebo 0.8%), and weight gain (CASODEX 5.8%, placebo 2.9%). The majority of these adverse events were considered by the investigator to be related to study drug. There was a low incidence (<5.5%) of clinically significant changes from baseline in AST, ALT, and total bilirubin, but no clinical significant changes in mean or median values (see Section 7.6.2 for further details). The incidences of other non-endocrine-related adverse events did not raise specific safety concerns (see Section 7.6.3 for discussion on second cancers).

7.3 Deaths

All patients were followed-up until death irrespective of when they stopped taking CASODEX or placebo, or withdrew from the trial.

At the data cut-off date, 445 (11.1%) of 4022 patients randomized to CASODEX and 432 (10.7%) of 4031 patients randomized to placebo had died (Table 21). The majority of deaths were due to reasons other than prostate cancer. The number of patients reported to have died from prostate cancer alone was similar between groups. A total of 177 (4.4%) patients in the CASODEX group and 150 (3.7%) patients in the placebo group died due to an adverse event.

Table 21 Number and percentage of patients who died in the EPC program

Category	Number (%) of patients			
	CASODEX 150 mg		Placebo	
Overall	(n=4022)		(n=4031)	
Total deaths	445	(11.1)	432	(10.7)
From prostate cancer	119	(3.0)	128	(3.2)
From other causes	326	(8.1)	304	(7.5)
Adverse-event related	177	(4.4)	150	(3.7)
Non-adverse-event related	149	(3.7)	154	(3.8)

n numbers of patients who received randomized treatment.

Cardiovascular events were the major cause of death, with 78 events reported for CASODEX-treated patients and 67 events reported for placebo-treated patients (overall incidence of 1.9% and 1.7%, respectively).

As expected in a population of elderly males, cardiovascular events were the major cause of death, with 78 cases reported for CASODEX-treated patients and 67 cases reported for placebo-treated patients. Of these, deaths were due to myocardial infarction in 24 patients treated with CASODEX versus 31 treated with placebo and to heart arrest in 12 CASODEX-treated patients versus 5 placebo-treated patients). Heart failure, including congestive heart failure, was the cause of death in 15 CASODEX-treated patients and 1 placebo-treated patient. Twelve deaths due to cerebrovascular accident were reported in the CASODEX group and 15 were reported in the placebo group. Four of these deaths were thought to have a causal relationship with CASODEX (1 cerebrovascular accident, 1 myocardial infarction, 1 myocardial ischemia, 1 embolus).

Deaths due to respiratory events occurred in 31 CASODEX-treated patients and 37 placebo-treated patients. Pneumonia was the cause of death in 4 patients treated with CASODEX and 10 patients treated with placebo.

Deaths due to hemic/lymphatic system events occurred in 11 CASODEX-treated patients and 4 placebo-treated patients. Second cancers relating to these types of events are discussed more fully in Section 7.6.3.

Other cancers were also commonly reported as the primary cause of death. None of these deaths due to other cancers is thought to have a causal relationship with either CASODEX or placebo treatment. Other adverse events leading to death occurred in only 1 or 2 patients in each treatment group and are well distributed across body systems.

7.4 Withdrawals

7.4.1 Overview of withdrawals because of adverse events

Overall, 1116 (27.7%) CASODEX-treated patients and 369 (9.2%) placebo-treated patients were withdrawn because of adverse events (including death) in the EPC program. This clinically significant difference reflected the high incidence of withdrawals due to gynecomastia or breast pain in patients treated with CASODEX. When gynecomastia and breast pain events were excluded from this analysis, the incidences of AE-related withdrawals between treatment groups were more closely aligned (14.4% with CASODEX vs 8.7% with placebo). Comparatively across individual trials, a higher proportion of patients withdrew from CASODEX therapy due to adverse events in Trial 23 (31.0%, 505 of 1627 patients) than in Trial 24 (28.0%, 501 of 1790 patients) or Trial 25 (18.2%, 110 of 605), with the main difference again reflecting the higher rate of withdrawal due to gynecomastia and male breast pain. There were no differences in withdrawal rates between trials for placebo-treated patients (range, 7.4% to 9.9%)

Table 22 summarizes those adverse events that led to withdrawal in at least 0.5% of patients (either treatment group). Only 4 adverse events led to withdrawal in more than 1% of patients (either treatment group): breast pain, gynecomastia, asthenia, and elevated hepatic transaminases (abnormal liver function tests).

Table 22 Adverse events that led to withdrawal from treatment and occurred in at least 0.5% of patients in either treatment group

Body system[a] and consolidated COSTART term	Number (%) of patients[b] with adverse events leading to withdrawal			
	CASODEX 150 mg (n=4022)		Placebo (n=4031)	
Body as a whole	**148**	**(3.7)**	**74**	**(1.8)**
Abdominal pain	23	(0.6)	14	(0.4)
Asthenia	56	(1.4)	18	(0.5)
Cardiovascular system	**145**	**(3.6)**	**129**	**(3.2)**
Cerebrovascular accident	14	(0.4)	30	(0.7)
Myocardial infarction	27	(0.7)	33	(0.8)
Hot flashes	36	(0.9)	14	(0.4)
Digestive system	**182**	**(4.5)**	**104**	**(2.6)**
Diarrhea	21	(0.5)	20	(0.5)
Gastrointestinal carcinoma	22	(0.6)	18	(0.5)
Liver function tests abnormal	47	(1.2)	18	(0.5)
Nausea	26	(0.7)	14	(0.4)
Endocrine[c]	2	(0.1)	3	(0.1)
Hemic/lymphatic[c]	17	(0.4)	11	(0.3)
Metabolic and nutritional disorders	**35**	**(0.9)**	**13**	**(0.3)**
Weight gain	22	(0.6)	6	(0.2)
Musculoskeletal system	11	(0.3)	9	(0.2)
Nervous system	**118**	**(2.9)**	**57**	**(1.4)**
Libido decreased	25	(0.6)	9	(0.2)
Somnolence	20	(0.5)	5	(0.1)
Respiratory system	**48**	**(1.2)**	**56**	**(1.4)**
Carcinoma of lung	17	(0.4)	20	(0.5)
Skin and other appendages	**54**	**(1.3)**	**28**	**(0.7)**
Rash	26	(0.7)	14	(0.4)
Special senses[c]	9	(0.2)	7	(0.2)
Urogenital system	**690**	**(17.2)**	**52**	**(1.3)**
Gynecomastia	425	(10.6)[d]	16	(0.4)
Impotence	29	(0.7)	6	(0.2)
Breast pain	504	(12.5)[d]	15	(0.4)

[a] Numbers given per body system represent the total number of patients with adverse events leading to withdrawal in that category.
[b] A patient may have been withdrawn because of more than 1 adverse event.
[c] Body system included for completion but no single event in that category resulted in withdrawal of at least 0.3% patients.
[d] The percentage of CASODEX-treated patients who withdrew with either gynecomastia or breast pain was 16.3% (compared with 0.6% with placebo).
n Number of patients who received randomized treatment.
COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.

As expected from the pharmacological action of nonsteroidal anti-androgens, an excess of withdrawals due to gynecomastia and breast pain led to more withdrawals in CASODEX-treated patients overall relative to placebo-treated patients. Gynecomastia and breast pain are discussed in more detail in Section 7.6.1.

7.5 Serious adverse events

A comparable proportion of patients in each treatment group had serious adverse events[10]: CASODEX-treated patients, 33.6% (1350 of 4022) and placebo-treated patients, 32.5% (1310 of 4031). These events generally reflected the age and disease status of the patient population. No single serious adverse event occurred in more than 3% of patients. Those that occurred in at least 2% of patients (either treatment group [CASODEX vs placebo]) included hernia (2.2% vs 2.7%), myocardial infarction (1.8% vs 2.4%), gynecomastia (2.7% vs <0.1%), and urinary tract disorder (2.6% vs 2.7%).

A comparable proportion of patients in each treatment group had serious adverse events: 34% with CASODEX and 33% with placebo. No single serious adverse event occurred in more than 3% of patients.

[10] For regulatory purposes, a serious adverse event was one that was fatal or life-threatening; caused or prolonged hospitalization; resulted in disability or incapacity; was a cancer (other than prostate cancer or it metastases); was a congenital abnormality; or was an overdose.

7.6 Topics of specific interest: tolerability and safety

7.6.1 Gynecomastia and male breast pain

Given the high incidence of gynecomastia and breast pain, these data were examined in more detail. Further information is presented on incidence rates, severity, onset, and resolution rates following withdrawal of randomized therapy.

7.6.1.1 Incidence, withdrawal rates, and severity

The incidences of gynecomastia and breast pain are summarized in Table 23, along with resultant withdrawal rates.

Table 23 Incidence of and withdrawals due to gynecomastia and breast pain

Category	Number (%) of patients			
	CASODEX (n=4022)		Placebo (n=4031)	
Adverse event				
Gynecomastia	2717	(67.6)	333	(8.3)
Breast pain	2948	(73.3)	307	(7.6)
Adverse event-related withdrawal				
Gynecomastia	425	(10.6)	16	(0.4)
Breast pain	504	(12.5)	15	(0.4)
Either gynecomastia or breast pain	656	(16.3)	26	(0.6)

As described earlier, a greater proportion of CASODEX-treated patients had gynecomastia or breast pain, compared with placebo-treated patients, and a greater number of CASODEX-treated patients withdrew from therapy as a result of these events. Among CASODEX-treated patients, gynecomastia and breast pain were rated as severe in only 5.8% and 4.8%, respectively. A higher incidence of CASODEX-treated patients younger than 65 years withdrew from trial therapy due to gynecomastia or breast pain compared with patients 65 years or older.

There was no obvious effect on the incidence of gynecomastia or breast pain adverse events in relation to age, race (Trial 23 only), tumor stage, weight, or body mass index. Despite the high incidence, other characterizations suggested reasonable tolerance; the reported rates of serious gynecomastia and breast pain were low (2.7% and 0.8%, respectively).

7.6.1.2 Onset and resolution

Approximately 70% of patients reported gynecomastia within 24 months of starting treatment with CASODEX. Breast pain was reported within the same period of time in approximately 75% of CASODEX-treated patients.

The continued presence of gynecomastia and breast pain in patients with at least 1 follow-up visit, as of the 28 September 2001 cut-off date, was recorded along with the number of patients known to have had resolution of these events. Approximately 10% of all patients who withdrew from trial therapy with known ongoing gynecomastia or breast pain did not have any follow-up information.

For patients with gynecomastia ongoing at the time of withdrawal, approximately 47% of CASODEX-treated patients had resolution on the basis of Kaplan-Meier estimates at 96 weeks compared with approximately 63% of patients in the placebo group. Median time to resolution after treatment withdrawal was approximately 122 weeks in the CASODEX group and 49 weeks in the placebo group.

For patients with breast pain ongoing at the time of withdrawal, more than 90% of patients in both treatment groups had resolution at 96 weeks on the basis of Kaplan-Meier estimates. Median time to resolution after treatment withdrawal was approximately 16 weeks in the CASODEX group and 13 weeks in the placebo group.

Recent trials have shown encouraging results with the use of external beam radiation and anti-estrogens to manage gynecomastia, breast pain, or both (Sieber et al 2002, Tyrrell et al 2002).

7.6.2 Sexual function

In Trial 25 only, the GRISS questionnaire was used to assess sexual interest relative to patient responses to questions of infrequency of sexual activity and impotence. Since the majority of patients (>80%) were engaged in watchful waiting, they did not enter the trial with the physical complications that can follow from radical prostatectomy or radiotherapy and cause impotence.

After nearly 1.5 years of treatment, approximately 50% of patients treated with placebo were able to maintain sexual function at the same level as that assessed at baseline (47.4% frequency, 53.3% potency). The proportion of CASODEX-treated patients who were able to do the same was considerable at 31.4% relative to frequency and 34.9% relative to potency. Although the incidences of decreased libido and impotence reported as adverse events in Trial 25 were slighter greater among patients treated with CASODEX (3.8% and 16.0%, respectively, vs 1.1% and 6.7%, respectively, with placebo), these events appeared to be underreported in both treatment groups because of the proportion of patients who reported that sexual function was not maintained (per GRISS questionnaire).

For younger men and men who value continued sexual activity despite increasing age, a reduction in libido may be cause for concern. The overall low reported incidence of decreased libido in the EPC program (CASODEX, 3.6%; placebo, 1.1%) suggests that with CASODEX, there is a high likelihood, compared with placebo, that libido can be maintained. When the adverse event of impotence was considered across trials, the rate for the CASODEX group (9.1%) was only slightly greater than that for the placebo group (6.3%); however, underreporting may have occurred since patients were not directly questioned about sexual

side effects. In approximately 35% and 55% of CASODEX and placebo-treated patients, respectively, impotence was not considered drug related.

7.6.3 Hepatic biochemistry

The potential for drug-induced liver toxicity with CASODEX has been the subject of ongoing review as the drug is intended for long-term use and other nonsteroidal anti-androgens are associated with significant hepatotoxicity. Distinguishing drug-related hepatotoxicity can be difficult in patients with cancer that may metastasize to the liver or require cytotoxic therapy, or in patients who have concurrent illness or take concomitant therapy that may have hepatic effects. The current labeling for CASODEX 50 mg provides guidance (under Warnings) for when transaminase levels should be measured and when CASODEX should be discontinued.

In the EPC program, there were no clinically significant changes in median or median values for total bilirubin, alanine aminotransferase, or aspartate aminotransferase in any treatment group up to 96 weeks of drug administration, the point at which summary statistics can still be considerable reliable. Small percentages of patients in both treatment groups had clinically relevant changes in 1 or more variables, with these changes slightly more frequent in CASODEX-treated patients (Table 24). In patients who entered the trial program with abnormal LFTs, their risk of having abnormal LFTs thereafter was not increased with CASODEX therapy, relative to placebo therapy.

Table 24 Clinically relevant changes in hepatic biochemistry variables in the EPC program

Parameter	Baseline[a] finding	CASODEX 150 mg (N=4022)			Placebo (N=4031)		
		No. with CR changes	N	(%)	No. with CR changes	N	%
AST	Normal	67	3744	(1.8)	30	3770	(0.8)
	Abnormal	3	100	(3.0)	4	94	(4.3)
ALT	Normal	61	3659	(1.7)	15	3686	(0.4)
	Abnormal	10	186	(5.4)	8	179	(4.5)
Total bilirubin	Normal	37	3529	(1.0)	22	3558	(0.6)
	Abnormal	8	314	(2.6)	5	306	(1.6)

[a] Prerandomization.
Normal Within the reference range.
Abnormal Outside the reference range.
CR Clinically relevant.
CR for AST/ALT: increase to a value ≥ 3 times the upper reference range value or ≥ twice the upper reference range value on 2 or more consecutive occasions; CR for total bilirubin: an increase from baseline value of ≥ 100% the upper reference range value.

7.6.4 Second cancers

Preclinical data do not suggest a causal role for bicalutamide in second cancers. CASODEX is not mutagenic, clastogenic, or leukemogenic. The only tumors observed in animals following bicalutamide exposure were the MFO-induced (species-specific) and uterine adenocarcinomas—both irrelevant to this population. However, there was a recognizable background incidence of non-prostate cancers in the population studied; therefore, the frequency and nature of these second cancers were reviewed.

The incidence of second cancers was low and comparable for both treatment groups across the controlled trials. There was a spread of types of second cancers reported but the incidences of each type were generally low. Overall, the most common second cancers were neoplasm (body as a whole), skin carcinoma, gastrointestinal carcinoma, GI neoplasia, and carcinoma of the lung. These incidences are expected given the population studied. The proportion of solid tumors was similar in both treatment groups (7.6%, 304/4022 CASODEX-treated patients; 7.4%, 297/4031 placebo-treated patients). The number of hematologic/lymphatic malignancies was small and approximately equal in both treatment groups, with the exception of AML or MDS.

7.6.4.1 Acute myelogenous leukemia or myelodysplasia

In the EPC program, 12 cases of AML and/or MDS were reported in patients treated with CASODEX and 4 cases of AML and/or MDS, in placebo-treated patients.[11] Because of this numerical difference, the role of CASODEX in these cases was investigated further.

In animals, CASODEX exposure did not lead to acute leukemia or MDS. CASODEX may affect bone marrow and erythropoiesis through a hormonally mediated mechanism as an inhibitor of androgens. However, there are no known effects of androgens on myeloid or megakaryocytic lines, nor are there any examples of increased hematologic malignancies in states of male hyper or hypogonadism.

The median latency of time to onset is 4 years for AML and 3 to 3.5 years for MDS after exposure to leukemogenic stimuli such as chemotherapy, radiation, or solvents (Rosenbloom et al 1992, Pui et al 1991, Ratain et al 1987, Rinsky et al 1981, Aksoy et al 1985). In the controlled trials, a specific date of diagnosis was determined for each case of AML and MDS. Of the 12 CASODEX-treated patients who developed AML or MDS, 3 patients had a time to onset of less than 6 months, 3 patients had a time to onset of 6 months to 2 years, and 3 had a time

[11] One CASODEX-treated patient was originally randomized to treatment with placebo in the EPC program but withdrew and began open-label treatment with CASODEX. Within 2 months of starting open-label therapy, he was hospitalized with AML; the investigator assessed the AML as not related to bicalutamide.

to onset of between 2 and 3 years. The remaining 3 patients in the CASODEX group had a time to onset between 3 and 4 years, which is in line with the latency observed after exposure. The placebo group had 2 patients who had a time to onset between 3 to 4 years.

In the EPC population of 8113 patients, 8 combined cases of AML and MDS would be expected on the basis of a 0.1% prevalence for patients over 65 years of age (Copplestone et al 1986). Review of all available data suggests that a causal relationship between CASODEX and AML/MDS is unlikely.

7.6.4.2 Conclusion on second cancers

Cumulative information from worldwide experience with CASODEX; preclinical CASODEX data that show no mutagenic or clastogenic activity in either in vitro or in vivo animal systems; and epidemiology literature suggest that a causal relationship between CASODEX and second cancers is unlikely.

7.7 Safety summary and conclusion

Overall, more than 85% of patients per treatment group reported at least 1 adverse event: 97.4% in the CASODEX group and 88.2% in the placebo group. The biggest differences between treatment groups were the expected higher incidences of gynecomastia (67.6%) and breast pain (73.3%) among CASODEX-treated patients (compared with 8.3% and 7.6%, respectively, in placebo-treated patients). These known pharmacological effects of CASODEX also contributed to treatment group imbalances with respect to overall incidences of drug-related adverse events (CASODEX, 90.5%; placebo, 31.4%) and adverse events leading to treatment withdrawal (CASODEX, 27.7%; placebo, 9.2%). Gynecomastia and male breast pain were generally classified as mild or moderate, with events assessed as severe in only 5.8% and 4.8% of patients, respectively. Other pharmacologically predictable events, including asthenia, weight gain, depression, decreased libido, somnolence, and impotence, were much less influential in causing withdrawal, but when withdrawals occurred, incidences attributed to CASODEX were not substantially higher than incidences attributed to placebo.

In both treatment groups, the numbers of patients with clinically relevant changes in hepatic biochemistry variables were generally low (<2.0% when baseline values were normal; <5.5% when baseline values were abnormal). However, regardless of baseline values, changes generally resolved either spontaneously during treatment or following cessation of therapy.

No evidence to date suggests a causal relationship between CASODEX and second cancers.

Except for gynecomastia and male breast pain, the tolerability profile is consistent with the current CASODEX prescribing information and indicates a favorable safety profile for the treatment of patients with early prostate cancer.

8. DSMC REVIEW

The data from the 2-year minimum follow-up analysis were reviewed by the DSMC in a grouped, but blinded fashion (randomized treatment groups were labeled 'A' and 'B'; pharmacological adverse event data were grouped as 'C' and 'D'). The result, relative to the primary endpoint of time to objective progression, was considered to potentially represent a clinical benefit for patients. The blind was therefore broken by the DSMC due to statistically significant differences in time to objective progression in Trials 24 and 25. The review of the safety data did not raise any concerns with the DSMC. AstraZeneca and the principal investigators acted upon these findings and took the decision to share the data with the trials' investigational review boards and ethics committees, trial patients, and the public. All patients have therefore been informed of these results, and all patients continue to be followed under the trial protocols.

9. ROLE FOR CASODEX

Approximately 29% of all US patients with prostate cancer chose not to elect either radical prostatectomy or radiation therapy as their primary treatment (SEER 1995-1995), with about 18.5% choosing watchful waiting. Reasons for this vary from absolute medical contraindication for surgery or radiation to patient preference for watchful waiting (which may reflect patient desire to avoid the not-infrequent complications of surgery or radiation). Current guidelines from the NCI, AUA, and NCCN recognize watchful waiting as an alternative to definitive primary treatment and further identify the types of patients most suitable for this approach. For patients who struggle with the concept of watchful waiting—the idea of postponing treatment until symptoms develop or PSA rises—the next-step treatment option is androgen deprivation. This is currently achieved either pharmacologically with LHRH agonists or with surgical castration, options that both have widely recognized medical sequelae, some with long-term implication (as described in Section 2.4). Additionally, LHRH agonists must be administered by injection, and surgical castration has inherent surgical risks.

The patients who comprise this group could potentially benefit with additional treatment options, as could the considerable proportion of patients at risk for biochemical failure or local disease recurrence after definitive primary therapies (see Sections 1.4.1 and 1.4.2).

The CASODEX EPC program has shown that CASODEX 150 mg, when administered orally on a daily basis, provides such a benefit by reducing the risk of disease progression in a variety of patients with localized or locally advanced nonmetastatic prostate cancer. Overall, greatest benefit was seen in those with high risk of disease progression after definitive therapy and those who elect watchful waiting as their primary standard of care. In essence, the EPC program has shown that CASODEX does have a role in treating localized or locally advanced nonmetastatic prostate cancer.

The emerging benefits of CASODEX-based androgen deprivation, compared with androgen deprivation by other methods, are further reasons to consider CASODEX 150 mg as a

treatment option in the target population. These benefits, in context with the tolerability profile established for CASODEX 150 mg in the EPC program, provide a better understanding of the CASODEX risk-to-benefit paradigm and support its expanded use.

The changing prostate-cancer knowledge base remains a backdrop against which treatment options and strategies must be evaluated. The option of using CASODEX as adjuvant therapy in high-risk patients or as an alternative to watchful waiting fits into the current web of approved treatment strategies for reasons of efficacy, when compared with placebo; for reasons of potential benefit, when compared with medical or surgical castration; and for reasons of demonstrated tolerability.

10. SUBMISSION, REGULATORY FEEDBACK, AND ASTRAZENECA POINTS FOR DISCUSSION

10.1 Submission

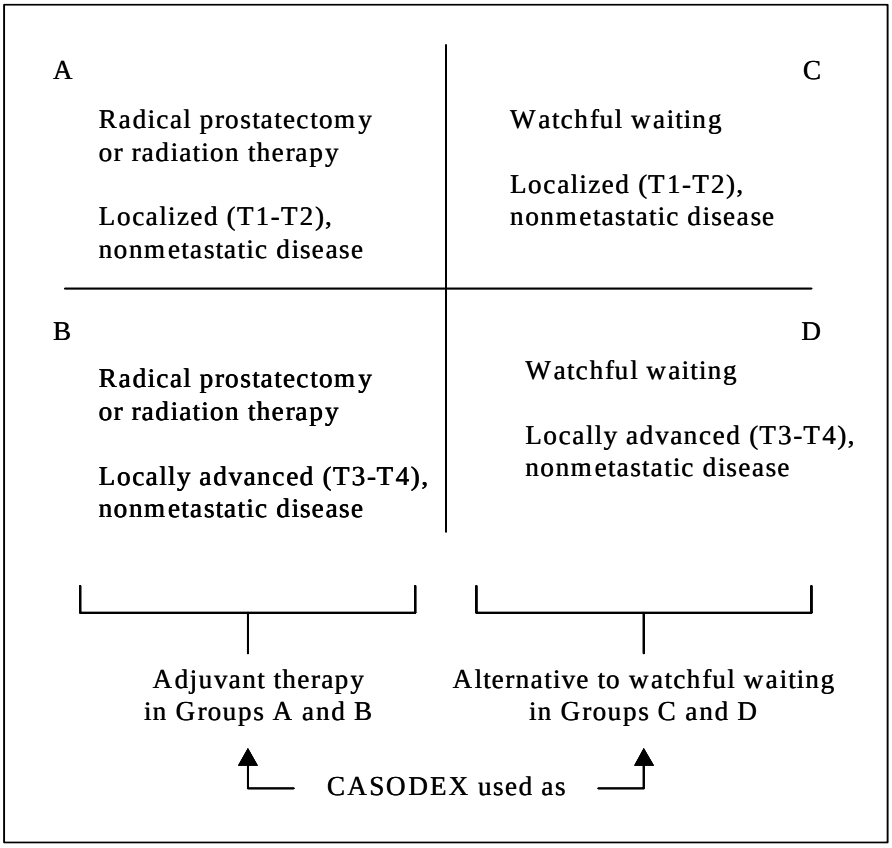
In planning and conducting the CASODEX EPC program, AstraZeneca had numerous contacts with the Food and Drug Administration (FDA) to discuss and clarify various aspects of the program, including trial design, endpoints, statistical issues, and requests for additional data and analyses. The main issues for discussion included the use of time to progression as an endpoint and the potential unblinding due to gynecomastia and PSA changes in the CASODEX group. Additionally, there were regulatory concerns that bias was introduced in the evaluation of bone scans by center-affiliated radiologists, who may have had access to additional patient data. A brief summary of FDA-AstraZeneca interactions and decisions are provided in Appendix B.

Data from the CASODEX EPC program were submitted to the FDA as a supplemental New Drug Application (sNDA) (NDA 20-498/0012) on 20 December 2001. In recognition of an unmet medical need, the FDA granted priority review of the application on 8 January 2002, which meant that the review was targeted for completion in 6 months. The sNDA contained data and analyses results to address aforementioned concerns, including subgroup analyses by therapy and disease stage, a central re-evaluation of bone scan outcomes, and supplementary analyses of bone-scan-confirmed progression events over a 0- to 2-year interval following randomization. The original proposed indication was as follows:

Original indication: CASODEX 150 mg is indicated as immediate hormonal therapy or as adjuvant therapy to treatment of curative intent in patients with nonmetastatic disease.

Approval of this indication would have permitted the use of CASODEX 150 mg in the types of patients treated in the EPC program (Figure 19).

Figure 19 Types of patients treated in the CASODEX EPC program, by baseline standard of care and disease stage



10.2 Feedback and points for discussion

Following an FDA-AstraZeneca teleconference on 25 April 2002 to discuss the relevance of the program results to the US population (see Appendix B for additional details), AstraZeneca revised their original single indication to the following 2 indications:

CASODEX 150 mg is indicated as adjuvant therapy to radical prostatectomy or radiation therapy of curative intent in patients with locally advanced, nonmetastatic prostate cancer who are at high risk of disease progression.

CASODEX 150 mg is indicated as immediate treatment of nonmetastatic prostate cancer in patients for whom therapy of curative intent is not indicated.

On 20 June 2002, AstraZeneca received a not-approvable letter from the FDA, who listed obstacles to approval by 3 potential CASODEX indications: adjuvant treatment after therapy of curative intent, immediate treatment in **localized** disease, and immediate treatment in

locally advanced disease. These obstacles are summarized as follows, by potential CASODEX indication.

Potential indication: Adjuvant treatment after therapy of curative intent

- There was a lack of demonstrated efficacy when used as adjuvant therapy in patients in North American Trial 23, and there was an absence of demonstrated efficacy in high-risk patients in North America Trial 23.

- The FDA was unable to characterize the populations in the non-US Trials 24 (Europe) and 25 (Scandinavia) who benefitted because of a lack of standardized Gleason scores.[12]

AstraZeneca points for discussion (expanded in Section 11):

The low event rate in Trial 23 was related to the select subset of good-prognosis patients enrolled; therefore, the lack of demonstrated effect in US patients does not alter the relevancy of the beneficial effect achieved with CASODEX in similar patients in the other 2 trials.

The findings for PSA progression and trends in favor of CASODEX therapy in patients characterized as high risk are consistent with findings from the non-US trials.

Patients with localized or locally advanced nonmetastatic prostate cancer who benefit from CASODEX can be characterized by standard prognostic factors other than Gleason grade. (See Section 1.5.2 for an explanation of the Gleason grading system.)

Potential indication: Immediate treatment in localized disease (ie, the use of CASODEX as an alternative to watchful waiting in patients with localized disease)

- The relevance of the efficacy findings in non-US Trials 24 (Europe) and 25 (Scandinavia) to US patients who would otherwise be managed by watchful waiting was not shown.

AstraZeneca point for discussion (expanded in Section 11):

The highly significant delay in disease progression achieved in non-US Trials 24 and 25 is applicable to US patients with localized disease who are not candidates for therapy of curative intent on the basis of the types of patients treated with watchful waiting in the United States.

[12]Gleason grade or score reflects the range of differentiation among malignant cells present in a biopsy sample. See Section 1.5.2 for further explanation of Gleason scoring.

Potential indication: Immediate treatment in locally advanced disease

- Patients with locally advanced nonmetastatic prostate cancer treated with immediate CASODEX monotherapy may incur a survival disadvantage compared with patients who are treated with current US standard of care, as evidenced by NDA 20-498/S006 (application withdrawn on 19 Dec 2000 [see Section 3.3 for details]). Therefore, the comparison of CASODEX with placebo on the effects of efficacy and survival in this population is not sufficient.

AstraZeneca point for discussion:

In response to the FDA's concern about the use of CASODEX 150 mg as immediate treatment in watchful waiting patients **with locally advanced disease,** AstraZeneca will not pursue this indication at this time. This decision is the result of previous discussions with the FDA in relationship to earlier monotherapy trials in which CASODEX was compared with castration in patients with locally advanced (M0) or advanced (M1) disease (and mean PSA >20 ng/ml) who were eligible for immediate castration (see Section 3.3 for additional details). For those trials, AstraZeneca and the FDA could not agree on the interpretation of trial results and AstraZeneca is not contesting the FDA view that LHRH therapy may be a better choice for these patients, even though, in the EPC trial, a significant effect was seen when CASODEX when used as immediate therapy in patients with locally advanced disease.

11. DISCUSSION AND CONCLUSION

11.1 Discussion

11.1.1 Prostate cancer and the CASODEX EPC program

Early prostate cancer is the most commonly diagnosed malignancy in US men. While many men will remain free of their disease after primary definitive therapy—radical prostatectomy or radiation therapy—a substantial number remain at high risk for disease progression. In addition, there are groups of patients for whom the adverse risks of definitive therapy are considered too great; therefore, these patients are managed by watchful waiting, or alternately turn to off-label hormonal therapy. Such patients are generally considered to be at low risk for disease progression, but as indicated in the literature, disease progression to metastatic disease does occur (see Section 1.4.1).

Progression to metastatic disease in prostate cancer is associated with significant morbidity. Bone metastases are the most common expression of disease progression and are frequently associated with pain, hypercalcemia, pathological fracture, and spinal cord compression. Therefore, new treatments that can delay or prevent progression of prostate cancer have the potential to significantly impact patients' lives, especially if treatments are relatively well tolerated and free of potentially fatal adverse effects.

Over 8000 men with nonmetastatic prostate cancer were treated and evaluated in the CASODEX EPC program, making it the largest program to evaluate hormonal treatment in

this population. The culmination of this effort is the provision of data showing clear value for CASODEX therapy in early-stage disease, and in particular, showing that CASODEX 150 mg significantly delays time to disease progression, compared with placebo. This is a clinically important finding as it relates to delaying the onset of symptoms of metastatic disease and delaying the time at which the disease becomes incurable.

11.1.2 AstraZeneca responses to FDA

In AstraZeneca's investigation of CASODEX therapy as adjuvant therapy for radical prostatectomy or radiation therapy, or as an alternative to watchful waiting, AstraZeneca executed the trials and reported the data as planned and as discussed with the FDA. AstraZeneca believes that the data provided in this briefing document meet the regulatory requirement of substantial evidence of clinical benefit, as shown by positive outcomes not only in the combined analysis but in 2 of 3 adequate and well-controlled clinical trials. Further, AstraZeneca believes that CASODEX 150 mg should be approved for use according to the following proposed indications (see Groups B and C in Figure 19):

CASODEX 150 mg is indicated as adjuvant therapy to radical prostatectomy or radiation therapy of curative intent in patients with locally advanced, nonmetastatic prostate cancer who are at high risk of disease progression.

CASODEX 150 mg is indicated as immediate treatment of **localized** nonmetastatic prostate cancer in patients for whom therapy of curative intent is not indicated.

Finally, AstraZeneca believes that the issues raised by the FDA should not be obstacles to approval for reasons provided in the discussion sections that follow.

FDA issue: The adjuvant therapy indication is not approvable because of the lack of demonstrated efficacy of CASODEX as adjuvant therapy for patients in US Trial 23.

AstraZeneca response: With a progression rate of only 5% (both treatment groups) in Trial 23, currently, there is less than 25% power to detect the treatment effect identified from the power calculation for this trial (ie, a reduction in the risk of progression of >18%).

The low event rate in Trial 23 is consistent with the overall good prognostic characteristics of the patient population enrolled, as emphasized by the range of low PSA levels at diagnoses and randomization (see Section 5.1.2). The fact that PSA progression was significantly and favorably influenced by CASODEX therapy suggests a positive biological effect on the disease in these patients.

AstraZeneca nonetheless accepts that the efficacy of CASODEX was not demonstrated at this point in the lower-risk Trial 23 patients.

However, the same is not true for high-risk patients, and consequently AstraZeneca believes that CASODEX 150 mg has a role as adjuvant treatment in patients at high risk for disease progression after primary definitive treatment (Group B in Figure 19). This indication is

supported by the combined data shown in Section 6.4.2.1 and Figures 10 and 11 for patients previously treated with radical prostatectomy and in Section 6.4.2.2 and Figures 12 and 13 for patients previously treated with radiation therapy. In both Figures 10 and 12, hazard ratios are consistently below 1 for patients at highest risk of disease progression. Data from the EPC program support the adjuvant use of CASODEX 150 mg for a period of at least 2 years.

FDA issue: Patients who benefited from CASODEX adjuvant treatment in Trials 24 and 25 could not be characterized because of lack of standardized Gleason scores.

AstraZeneca response: AstraZeneca acknowledges the lack of standardization (local vs central) in tumor grading within and across the 3 trials, in part, a reflection of practice differences between countries.

However, a large body of external evidence exists that characterizes the relevance and relative importance of the various prognostic factors for patients with early prostate cancer. These data show that Gleason sum does not outweigh the prognostic ability of PSA level or T stage. In published nomograms that predict outcome after radical prostatectomy, disease stage and preoperative PSA are shown to be more important predictive factors than Gleason sum in multivariate analyses (D'Amico et al 1998, Graefen et al 1999). In published nomograms that predict outcome after radiation therapy, clinical disease stage (T3-T4) and PSA level (>20 ng/ml preradiation) are shown to be the more important predictive factors. Gleason sum adds to the predictability, but is generally the least predictive in multivariate analyses (D'Amico et al 1999, Zagars et al 1997, Pisansky et al 1997). Importantly, these models show that the benefit of CASODEX therapy can be validated on the basis of disease stage and baseline PSA levels.

Significant variations in interpretation of Gleason scores are described in the literature, which further support the use of other prognostic factors in characterizing patient outcome. In the CASODEX EPC program, the lack of standardized Gleason grading does not change the fact that CASODEX significantly delayed TTP (ie, increased progression-free survival). Additionally, the process of randomization makes any errors in grading prior to randomization irrelevant to the treatment effect.

Thus, AstraZeneca believes that patients who benefit from CASODEX can be adequately described on the basis of PSA at diagnosis and tumor stage, and that it is unlikely that a centralized review of Gleason grades would improve on this.

FDA issue: The relevance of the efficacy findings in Trials 24 and 25 to patients in the US who would otherwise be managed by watchful waiting according to present standards of care has not been demonstrated.

AstraZeneca response: Data gathered from US epidemiological databases and literature show that nearly 19% of US patients with prostate cancer choose watchful waiting as their primary standard of care and another 9% choose off-label hormonal therapy (SEER 1995-1997, Harlan 2001). When the characteristics of US watchful waiting patients are compared with the characteristics of the watchful waiting patients from Trials 24 and 25, similarities are seen (Table 25).

Table 25 Comparison of CASODEX EPC watchful waiting patients with US patients who choose watching waiting or do not elect surgery or radiation therapy

	CASODEX EPC Program Trials 24 and 25	Prostate Cancer Outcomes Study (Potosky 2002)[b]	CaPSURE (Koppie 2000)	SEER (1995-1997)[c]
Mean age (y)	71.7	70% are ≥70 y	51% are ≥70 y	Mean: 74 y
T1/T2 stage	70%	86%	97%	67%
Tumor grade: well or moderately differentiated[a]	83%	70%	86%	74%[d]
PSA at diagnosis (ng/ml)[d]	>4 to 10: 23% >10: 61%	>4 to 10: 45% >10: 28%	>4 to 10: 49% 10 to 20: 22%	N/A

[a] Gleason grade <7.
[b] Patients with localized disease.
[c] 1995-97 data for patients not choosing surgery or radiation therapy (n=14,816).
[d] Excludes unknowns.
NA Not available at this time.

In the EPC program, daily treatment with CASODEX 150 mg, compared with placebo, provided a clear overall TTP benefit among watchful waiting patients, as well as a consistent benefit when these patients were considered by various baseline prognostic factors, as shown in Section 6.4.2.3 and Figures 14 and 15.

Patients who elect watchful waiting are, in essence, receiving no therapy, and as a result, their prostate cancer will continue along a natural course of disease progression. Because there is no evidence that untreated prostate cancer behaves differently in US patients relative to patients elsewhere in the world, the beneficial effects of CASODEX seen in Trials 24 and 25 are directly applicable to the various stages of untreated prostate cancer seen in US watchful waiting patients. Data from the EPC program support the use of CASODEX 150 mg in these patients until disease progression.

On the basis of SEER data (1995-1997) (Table 25), patient similarities can also be seen among the overall group of US patient who choose either watchful waiting or off-label hormonal therapy (as primary therapy) and the types of watchful waiting patients who benefited with CASODEX therapy in the EPC program.

11.2 Conclusion

The major finding of the CASODEX EPC program is that, with a median follow-up of 3.0 years, CASODEX 150 mg significantly ($p<<0.0001$) reduced the risk of objective disease progression by 42%, compared with placebo, in patients with localized or locally advanced nonmetastatic prostate cancer. In these types of patients, future disease progression or recurrence represents a point when disease is no longer curable and when major symptoms will begin to manifest. Therefore, delaying disease progression (or increasing progression-free survival) becomes an important clinical goal.

The robustness of the TTP analysis result was demonstrated by the fact that the individual analyses results from Trials 24 and 25 were also highly statistically significant. Although the North American trial (Trial 23) did not demonstrate a statistically significant TTP effect, this does not alter the relevancy of the beneficial effect achieved with CASODEX in patients in the other 2 trials. Trials 24 and 25 included substantial numbers of patients whose baseline characteristics are typical of important subgroups of US patients for whom CASODEX would offer an important treatment option.

From the subgroup analyses, those patients who would benefit most, and who thus provide the basis for the final proposed indications, are those with locally advanced disease at high risk of disease progression following radical prostatectomy or radiation therapy and those with localized disease who would otherwise undergo watching waiting. (Watchful waiting patients with locally advanced disease are excluded for reasons described in Section 10.2.)

For patients at high risk of progression following prostatectomy or radiation therapy, there are currently few treatment options, and many patients seek and accept treatment choices, despite the paucity of evidence to support such use—as shown by the large number of patients who receive LHRH agonist therapy for non-FDA approved indications—and despite the risk of significant morbidity. This trial program provides a wealth of data to support the use of CASODEX in many of those patients.

Along with the beneficial findings of efficacy, the EPC program showed that the major tolerability issue with CASODEX was the incidence of gynecomastia and breast pain. While generally mild or moderate, these effects are sometimes troublesome and may affect patient willingness to continue therapy. However, these effects are not life threatening and are part of the risk-benefit analysis that patients and physicians would need to make prior choosing CASODEX150 mg monotherapy. As patients come to understand the potential adverse effects and long-term sequelae of castration, they may be more accepting of CASODEX-based androgen deprivation given that CASODEX has been shown to preserve bone mineral density, lean body mass, and several aspects of sexual function (see Section 2.4).

In conclusion, data from the CASODEX EPC program strongly support the approval of the following CASODEX 150 mg indications:

CASODEX 150 mg is indicated as adjuvant therapy to radical prostatectomy or radiation therapy of curative intent in patients with locally advanced, nonmetastatic prostate cancer who are at high risk of disease progression.

CASODEX 150 mg is indicated as immediate treatment of **localized** nonmetastatic prostate cancer in patients for whom therapy of curative intent is not indicated.

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Appendix A: 1997 AJCC/International Union Against Cancer TNM Staging Classification

Stage	Definition
Primary tumor, clinical (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor not palpable or visible by imaging T1a: Tumor incidental histologic finding in 5% or less of tissue resected T1b: Tumor incidental histologic finding in more than 5% of tissue resected T1c: Tumor identified by needle biopsy (e.g. because of elevated prostate specific antigen levels)
T2	Tumor confined to the prostate T2a: Tumor involves one lobe T2b: Tumor involves both lobes
T3	Tumor extends through the prostate capsule T3a: Extracapsular extension (unilateral or bilateral) T3b: Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than the seminal vesicle(s) structures: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall
Primary tumor, pathologic (pT)	
pT2	Organ confined pT2a: Unilateral pT2b: Bilateral
pT3	Extraprostatic extension pT3a: Extraprostatic extension pT3b: Seminal vesicle invasion
pT4	Invasion of bladder, rectum
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in regional lymph node(s)
Distant metastases (M)	
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases M1a: Nonregional lymph node(s) M1b: Bone(s) M1c: Other site(s)

Appendix B: Dialogue with the FDA: a brief history

In planning and conducting the CASODEX EPC program, AstraZeneca had numerous contacts with the FDA to discuss and clarify various aspects of the program, including trial design, endpoints, statistical issues, and request for additional data and analyses. These interactions are summarized herein.

At the End-of-Phase II meeting on 7 June 1995, the Agency concurred with the overall design of the clinical trial program, but raised concerns about the potential for unblinding due to gynecomastia and PSA changes in the CASODEX group. AstraZeneca recognized these issues as well and had designed the trials so that all patients who had not previously shown objective disease progression were scheduled to have bone scans every 2 years, thus minimizing the potential for acquisition bias. During the meetings, the following points were agreed upon:

- A meta-analysis for survival was acceptable.
- If a time-to-progression (TTP) endpoint was the only endpoint, 2 trials would be required.

In addition, the FDA recognized that data on individual trials might be immature at the time of a submission.

(The trials proceeded as planned and approximately 3 years later, in June 1998, patient enrollment was completed.)

In May 1999, an advisory meeting was held with the Division of Reproductive and Urologic Drug Products (DRUDP). AstraZeneca provided an update on the EPC program and sought advice as to the acceptability of using a single meta-analysis for a TTP endpoint as the basis for regulatory approval. Recent government initiatives for cancer drugs and lagging event rates were cited as the impetus for providing a revised statistical approach.

During the meeting, the Agency reiterated its concerns that PSA changes and gynecomastia could potentially unblind the treatment and reconfirmed that a meta-analysis of a survival endpoint for the 3 trials was acceptable. The Agency also maintained the position that 2 trials would be needed to support the TTP endpoint for approval.

On 16 August 1999, a teleconference was held with DRUDP to further discuss issues raised during the May 1999 meeting. A briefing document was submitted prior to the meeting and contained, per Agency request, estimated times for achieving the following:

- A meta-analysis for survival
- Two of three trials for TTP

During this teleconference, the Agency again raised concerns for potential unblinding citing PSA and gynecomastia as key factors. Further and unexpectedly, the Agency reversed an earlier decision and stated the following:

- Two trials supporting a TTP endpoint are no longer considered supportive of approval for this indication; DRUDP prefers a survival endpoint, using a meta-analysis.

  – This conclusion was made following consultation with Dr. Barry Kramer, Deputy Division Director for the Cancer Prevention Division at the National Institutes of Health, with consideration especially given to the impact of the measurement of PSA values on the trial endpoints, the change in use and relevance of PSA, and the possible unblinding due to gynecomastia.

As a result of this action, AstraZeneca and DRUDP held a pre-Dispute Resolution meeting on 9 September 1999 to discuss the Agency's shift in position regarding the validity of a TTP endpoint. Following presentation and discussion, the following decision were made:

- Because the possible bias due to PSA levels and gynecomastia still existed as a major review concern, AstraZeneca would perform further analyses to address the impact of these issues on study results.

- A supplement with a pooled analysis of a binary disease progression endpoint (IE, an analysis of bone-scan-confirmed progression, or death from any cause in the absence of progression, over the first 2 years after randomization) across all three trials would be an acceptable option.

In a follow-up teleconference the next day (10 September 1999), the Agency requested that a detailed description of the evaluation of the bone scans be specified (AZ was directed to the Draft Guidance for the Development of Medical Imaging Drugs). The agency also suggested that because of differences in treatment durations and patient populations (among the 3 trials), AstraZeneca should consider combining only Trials 0024 and 0025. The take-away action was that AstraZeneca would submit a statistical plan to the FDA before submitting the sNDA.

On 22 December 1999, AstraZeneca met with DRUDP to discuss the statistical plan and reach agreement on the combination of trials for meta-analysis. During the meeting, the FDA stated the following:

- Combination of Trials 0024 and 0025 is acceptable for the binary meta-analysis of the [bone-scan] primary endpoint.

- Use of a binary outcome regarding evidence of disease progression is acceptable; DRUDP recommends, however, that the primary endpoint for evidence of progression be limited to new bone metastases seen on bone scan or death during the first 2 years; MRI and CT scans and physical exams are subject to bias; all patients had bone scans within 2 years of study initiation.

- Based on the discussions with DRUDP, AstraZeneca amended the analyses plan to include the binary analysis, submitted the plan for review, and provided the resultant data within the sNDA.

A pre-sNDA meeting was conducted on 13 November 2000. Included among the FDA's comments during the meeting were the following:

- FDA previously agreed to allow pooling of all three trials (0023, 0024, 0025) for the survival endpoint only; pooling of data from Trials 0024 and 0025 can be done for the endpoint of new metastases on 2-year bone scan or death (the primary endpoint); the time-to-progression analysis will be considered exploratory

- A qualitative subgroup analysis by previous therapy and by cancer stage should be provided in the sNDA.

  - AstraZeneca performed the requested analysis and included the data within the sNDA submission.

- The Division of Medical Imaging and Radiopharmaceutical Drug Products (DMIRDP) recommended that, minimally, a random sample of the bone scans be re-read in a blinded fashion by a central site; DMIRDP was concerned that bias was introduced by the inclusion of the clinical history on the scans as well as by the use of community-based radiologists with access to the patient's previous radiologic studies.

  - Following this request, numerous interactions occurred between AstraZeneca and DRUDP regarding the necessity of a bone scan central re-read and the scope of the activity that would be required.

  - Ultimately, AstraZeneca responded by conducting a central re-read and submitting the report within the sNDA.

  - During a 19 March 2001 teleconference, AstraZeneca requested that DRUDP consult the Division of Oncologic Drug Products regarding the EPC program

The sNDA was filed on 20 December 2001 and was subsequently granted priority review status. During the review, AstraZeneca responded to several requests for additional information, including multiple subgroup analysis.

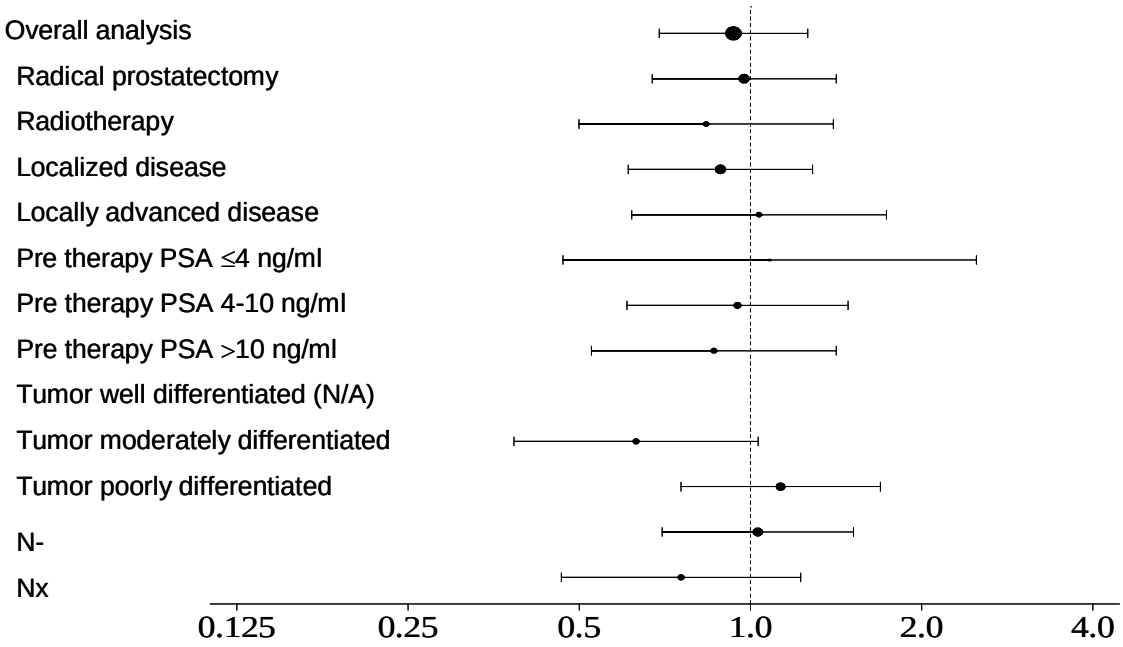
A teleconference was conducted on 25 April 2002 to discuss the relevancy of the program to the US patient population. During the teleconference, the FDA informed AstraZeneca that the reviewing Division did not believe that any bias had been introduced in the local assessment of bone scans and that bias was no longer an issue. At the request of the Agency, AstraZeneca provided a written response to the questions raised during the teleconference and, additionally, provided a revised label on the basis of the preceding discussions.

On 20 June 2002, the FDA issued a not-approvable letter to AstraZeneca for the sNDA.

This letter is summarized in the briefing document's Executive Summary and in Section 10 of the briefing document itself.

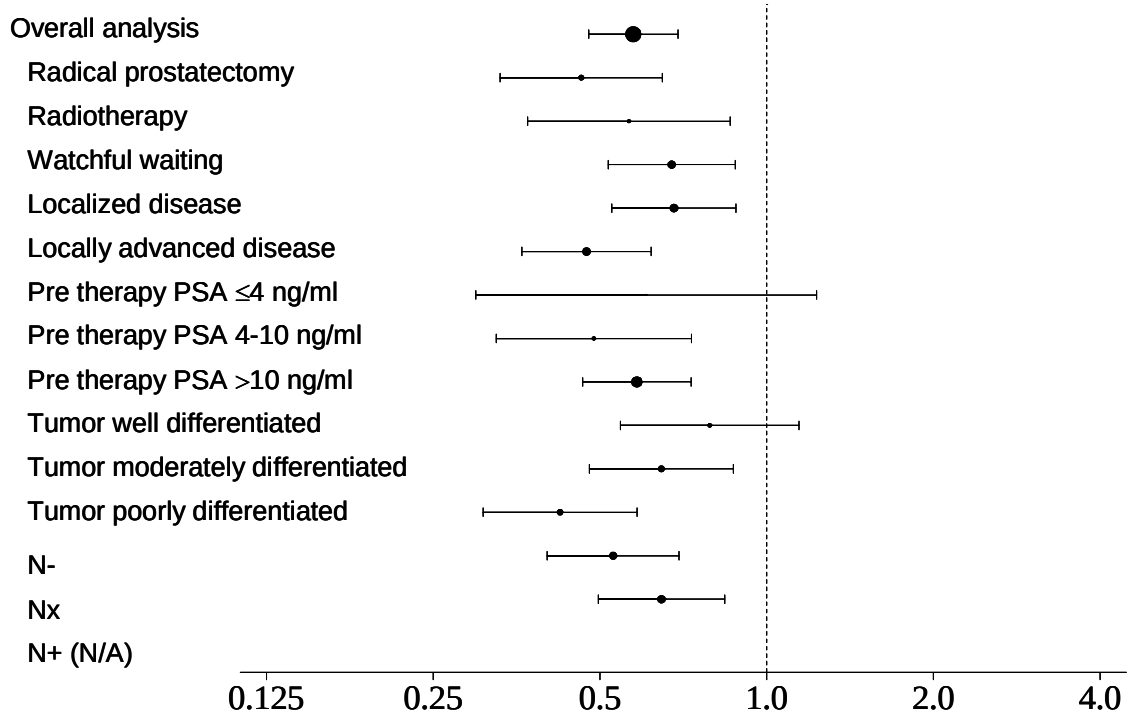
Appendix C Subgroup analyses for time to progression, by trial

Figure A-1 Trial 0023 subgroup analyses: hazard ratios and 95% confidence intervals for proportional risk reduction in time to progression



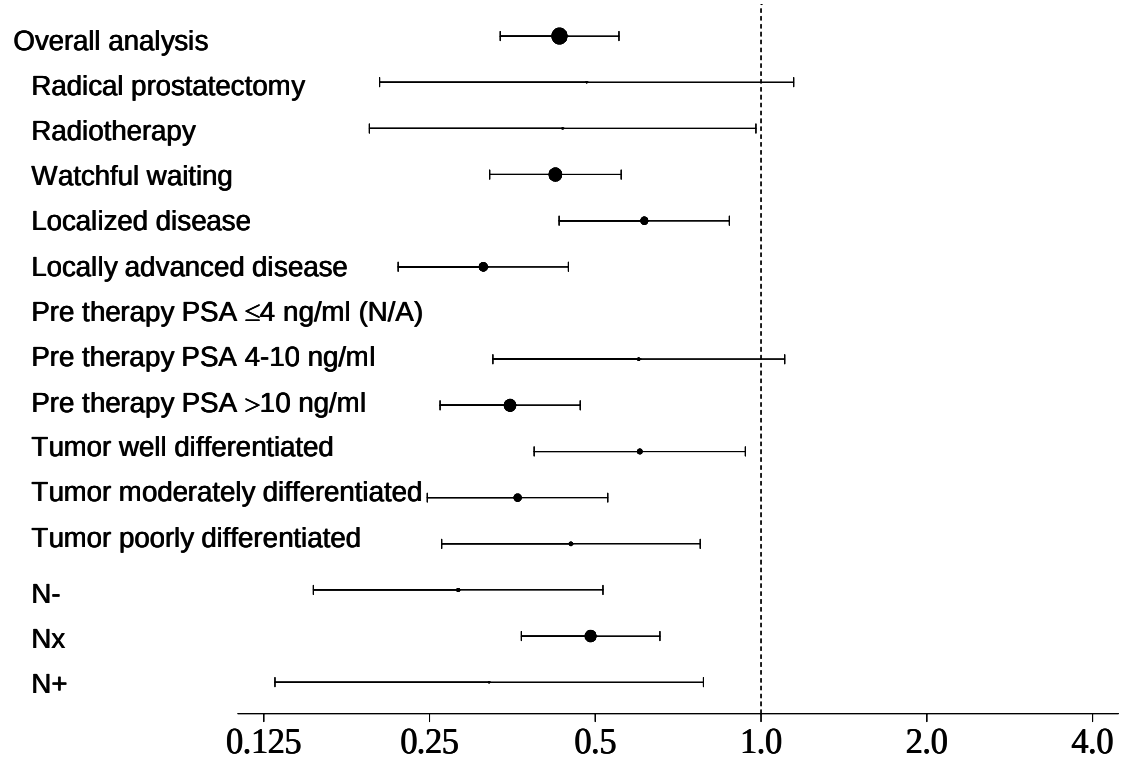
N/A Not applicable (<20 events; therefore, no corresponding data line).
The size of the hazard ratio circle is proportional to the number of events included in the analysis.

Figure A-2 Trial 0024 subgroup analyses: hazard ratios and 95% confidence intervals for proportional risk reduction in time to progression



N/A Not applicable (<20 events; therefore, no corresponding data line).
The size of the hazard ratio circle is proportional to the number of events included in the analysis.

Figure A-3 Trial 0025 subgroup analyses: hazard ratios and 95% confidence intervals for proportional risk reduction in time to progression



N/A Not applicable (<20 events; therefore, no corresponding data line).
The size of the hazard ratio circle is proportional to the number of events included in the analysis.