16 September 2021
EMA/613173/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Firmagon

International non-proprietary name: degarelix

Procedure No. EMEA/H/C/000986/II/0039/G

Marketing authorisation holder (MAH) Ferring Pharmaceuticals A/S

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADT androgen deprivation therapy

ANCOVA analysis of covariance

CSR clinical study report

DHT dihydrotestosterone

EAU European Association of Urology

EBRT External Beam Radiotherapy

ESMO European Society for Medical Oncology

FAS full analysis set

FSH follicle stimulating hormone

GCP good clinical practice

GS Gleason score

HT Hormone Therapy

IPPS International Prostate Symptom Score

KM Kaplan Meier

LH luteinzing hormone

LHRH Luteinzing Hormone Releasing Hormone

LUTS lower urinary tract symptoms

MAA marketing authorization application

MAH marketing authorization Holder

NCCN National Comprehensive Cancer Network

PC prostate cancer

PP per protocol

PSA prostate specific antigen

PSA-PFS prostate specific antigen-progression free survival

QoL Quality of Life

RMS Reference Member State

RT Radiotherapy

s.c. Sub-cutaneous

TVP total prostate volume

UICC Union for International Cancer Control

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Ferring Pharmaceuticals A/S submitted to the European Medicines Agency on 10 November 2020 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indications to include:

- Extension of indication to include treatment of hormone dependent advanced prostate cancer and for the treatment of high-risk localized and locally advanced hormone dependent prostate cancer in combination with radiotherapy. As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

- Extension of indication to include treatment as neo-adjuvant prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer. As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

The group of variations requested amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau

Timetable	Actual dates
Submission date	10 November 2020
Start of procedure:	26 December 2020
CHMP Rapporteur Assessment Report	19 February 2021
CHMP members comments	15 March 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 March 2021
Request for supplementary information (RSI)	25 March 2021
CHMP Rapporteur Assessment Report	25 August 2021
CHMP members comments	06 September 2021
Updated CHMP Rapporteur Assessment Report	10 September 2021
Opinion	16 September 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

This application is to extend the indication of Firmagon (Degarelix) to include the treatment of adult male patients with high-risk localized and locally advanced hormone dependent prostate cancer in combination with radiotherapy and as neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer. High-risk prostate cancer is defined by the European Association of Urology (EAU) as for Table 1 below.

State the claimed the therapeutic indication

Firmagon is already indicated for treatment of adult male patients with advanced hormone-dependent prostate cancer.

The new wording of the indication is as follow:

FIRMAGON is a gonadotrophin releasing hormone (LHRH) antagonist indicated for treatment of adult male patients with advanced hormone-dependent prostate cancer

FIRMAGON is indicated for the treatment of hormone dependent advanced prostate cancer and for the treatment of high-risk localized and locally advanced hormone dependent prostate cancer in combination with radiotherapy.

FIRMAGON is indicated as neo-adjuvant treatment prior to radiotherapy in patients with high-risk localized or locally advanced prostate cancer

Epidemiology

Worldwide, prostate cancer ranks second in cancer incidence and fifth in cancer mortality in men (Bray et al, 2018). In Europe, the estimated number of new prostate cancer cases was approximately 473,344 in 2020 and the number of deaths was approximately 108,088 in 2020 (GLOBOCAN, 2020).

Clinical presentation, diagnosis and stage/prognosis

Prostate cancer may present as localised disease, locally advanced disease or metastatic disease at initial diagnosis. Locally advanced prostate cancer represents a subpopulation of advanced prostate cancer, described as prostate cancer that has spread through the prostatic capsule to involve tissues and structures adjacent to the prostate gland, including regional lymph nodes, the urinary bladder and seminal vesicles, but not nodes and organs distant to the pelvis. In contrast, localised prostate cancer describes a condition where the neoplasm is confined within the prostate gland itself and where the prostatic capsule has not been breached by the tumour.

High-risk prostate cancer includes locally advanced prostate cancer (T3–4 N0-X M0) and high-risk localised prostate cancer (T2c N0-X M0) with either a Gleason score >7 and/or a baseline PSA of >20 ng/ml ***Table* 1**. According to the European Association of Urology (EAU), high risk prostate cancer means an increased risk of PSA failure, need for secondary therapy, metastatic progression and death from prostate cancer.

Table 1 EAU risk group for biochemical recurrence of localised and locally advanced prostate cancer

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP grade) cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

Management

There is no consensus regarding optimum management of high-risk localised prostate cancer (EAU, ESMO). However, radiotherapy associated with long-term androgen deprivation therapy is a rated recommendation for high risk localised disease.

In locally advanced disease recommend treatments are neoadjuvant androgen deprivation therapy (ADT)+ radical radiotherapy + adjuvant ADT (European Society of Medical Oncology ESMO) or external-beam radiation therapy in combination with long term androgen deprivation therapy (EAU).

2.1.2. About the product

Degarelix (FIRMAGON) is third-generation gonadotropin releasing hormone (LHRH) antagonist that competitively and reversibly binds to the pituitary gonadotropin-releasing hormone (GnRH) receptors rapidly reducing the release of the gonadotrophins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), and thereby reducing the secretion of testosterone by the testes.

Unlike GnRH agonists, GnRH antagonists do not induce a LH surge with subsequent testosterone surge/tumour stimulation and potential symptomatic flare after the initiation of treatment.

The current indication of FIRMAGON is for treatment of adult male patients with advanced hormone-dependent prostate cancer at a posology of 240 mg administered subcutaneously (sc) as starting dose followed by 80 mg sc monthly for maintenance.

The MA has been granted in Europe since February 2009.

Clinical results were mainly coming from a phase 3 study (Study FE 200486 CS21), an open-label, multi-centre, randomised, active comparator controlled, parallel-group phase III study. This study investigated the efficacy and safety of two different degarelix monthly dosing regimens with a starting dose of 240 mg followed by monthly sc administration of 160 mg or 80 mg, in comparison to monthly Intramuscular administration of 7.5 mg leuprorelin in patients with prostate cancer requiring androgen deprivation therapy. Degarelix was considered effective in achieving testosterone suppression below the medical castration level of 0.5 ng/ml.

The proposed dose for the claimed new indications remains unchanged.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek scientific advice.

2.1.4. General comments on compliance with GLP, GCP

The current application is based only on literature review.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

The MAH has provided literature data supporting the mechanism of synergy between androgen deprivation therapy (ADT) and radiation.

2.2.1. Ecotoxicity/environmental risk assessment

In the Environmental risk Assessment of degarelix (ERA) the market penetration factor, Fpen, was calculated based on information of patients with prostate cancer. The highest refined Fpen was that of Sweden and was calculated to be 0.25%.
As the two indications of this application concern a subset of prostate cancer patients eligible for treatment with Degarelix, a Fpen of 0.25% is applicable.
Furthermore, as the dosing route (sc), the starting dose of 240 mg/inh and the monthly maintenance dose of 80 mg/inh remain unchanged for the two indications, the predicted environmental concentrations are not regarded subject to change.
Considering the above data, degarelix is not expected to pose a risk to the environment.

2.2.2. Discussion on non-clinical aspects

Not applicable as no relevant new data were provided

2.2.3. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of degarelix.

Considering the above data, degarelix is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The current application for two new indications is based on literature review.

Tabular overview of clinical studies supporting the proposed indications are published manuscripts (Table 2)

Table 2. Overview of clinical studies

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
CS12 Van Poppel *et. al* 2008	39 sites worlwide	open-label, randomised, parallel-group, dosage finding study whose plan was to randomise a total of 180 patients into six treatment groups for 12 months	Degarelix 200mg /80mg Degarelix 200mg /120 mg Degarelix 200 mg/160 mg Degarelix 240mg /80mg Degarelix 240mg /120 mg Degarelix 240 mg/160 mg	To determine the efficacy and safety of initial doses of 200 mg or 240 mg of degarelix and thereafter monthly subcutaneous maintenance doses of 80 mg, 120 mg, or 160 mg of degarelix for the treatment of prostate cancer	Degarelix 200mg /80mg: 30/20 Degarelix 200mg /120 mg: 33/23 Degarelix 200 mg/160 mg: 32/26 Degarelix 240mg /80mg: 30/28 Degarelix 240mg /120 mg: 31/23 Degarelix 240 mg/160 mg: 31/23		Male 72 years	- histologically confirmed adenocarcinoma of the prostate (all stages), in whom endocrine treatment (except for neoadjuvant hormonal therapy) was indicated, were included -baseline serum testosterone concentration >s 2.2 ng/ml), -a PSA level of ≥ 2 ng/ml,	proportion of patients with serum testosterone ≤ 0.5 ng/ml at 1 mo and at every monthly visit up to 1 yr
CS21 Klotz *et al.* 2008	35 sites worlwide	Three-armed, randomized (1:1:1), active-controlled, open-labelled, parallelgroup phase III trial of 12 months' duration.	Degarelix 240mg/80mg s.c. Degarelix 240mg/160mg s.c. Leuprolide 7,5 mg i.m	efficacy and safety of degarelix vs leuprolide for achieving and maintaining testosterone suppression in a 1-year phase III trial	Degarelix 240/80 mg : 210/200 Degarelix 240/160 mg : 206/189 Leuprolide 7.5 mg : 204/195	02/ 2006 to 10/ 2007	Male 72 years	- histologically confirmed adenocarcinoma of the prostate (all stages), for whom endocrine treatment was indicated (except for neoadjuvant hormonal therapy), were recruited. - increasing PSA level after treatment with curative intent,	Cumulative probability of testosterone ≤ 0.5 ng/mL at any monthly measurement from 28 to 364 days
CS30 Mason *et al* . 2013	66 sites in US and europe	randomised, parallel-arm, active controlled, open-label trial randomised 3:1 to receive treatment with degarelix or goserelin for 12 weeks	Degarelix 240mg/80mg s.c Goserelin 3,6 mg + bicalutamide 50 mg from D0 to D17 Radiotherapy not described	to compare the effect of 3 month neoadjuvant therapy with degarelix versus goserelin plus bicalutamide, on total prostate volume (TPV) reduction in men with intermediate- to high-risk prostate cancer who were scheduled to undergo subsequent radiotherapy.	Degarelix n=181/164 Goserelin n=65/57		71 years	-UICC prostate cancer TNM category T2b-T4, N0, M0, Gleason score 7, or PSA 10 ng/ml; TPV >30 ml; -scheduled to undergo radical radiotherapy treatment and in whom neoadjuvant ADT was indicated	Prostate volume reduction
00006 Sun *et al.* *2019*	25 sites in China	open-label, multi-centre study in a 1:1 ratio to once-a-month subcutaneous injection of either degarelix (240/80 mg) or goserelin (3.6 mg) for 12 months	Degarelix 240mg/80mg s.c Goserelin 3.6 mg +/- bicalutamide 50 mg/day, at the discretion of the investigator	To establish non-inferiority of degarelix compared with goserelin in suppressing and maintaining castrate testosterone levels from Day 28 to Day 364 in Chinese patients with prostate cancer	Degarelix 143/123 Goserelin: 142/116	01/2013 to 05/2015	Male 74 years	-histologically confirmed adenocarcinoma of the prostate (all stages), -PSA) level 2.0 ng/mL at screening, testosterone level >1.5 ng/mL, and life expectancy of >1 year were included in this study	difference in 1-year cumulative probability of suppressing testosterone to 0.5 ng/mL
EORTC-1414	39 sites in EU	Phase IIIb randomized stratified open-label comparative 2-arm superiority study	Degarelix 240 mg/80 mg s.c. +EBRT GnRH agonists may vary + antiandrogen +EBRT EBRT total dose of 78-80 Gy, delivered as one daily fraction, five days a week, started between d1 and months 6 of the ADT The minimum duration of ADT is 18 months.	o assess if GnRH antagonists in combination with external beam radiation therapy improve progression free survival (progression that can be biological, clinical, or death) compared to GnRH agonists in combination with external beam radiation therapy.	885 participants	Start 2017 estimation of completion 2024		-PSA ≥ 10 ng/ml and two of the following 4 criteria: PSA ≥ 20 ng/ml, Gleason sum ≥ 8, cN1 (regional LN with a short axis length >10mm by CT scan or MRI) or pathologically confirmed lymph nodes (pN1), cT3-T4 (by MRI or core biopsy) (i.e. If PSA≥ 20 ng/ml then only one of the other 3 risk factors is needed) -M0 by standard imaging work-up -Testosterone ≥ 200 ng/dl	progression-free survival defined as the time in days from randomization to death, clinical or biochemical progression, whichever comes first.

2.3.2. Pharmacokinetics

No new pharmacokinetics data have been submitted in this application.
The scheme of administration remains unchanged for the claimed indications (starting dose of 240 mg followed by monthly doses of 80mg sub-cutaneous).

2.3.3. Pharmacodynamics

Not applicable. No pharmacodynamics data have been submitted in this application.

2.3.4. PK/PD modelling

Not applicable. No pharmacodynamics data have been submitted in this application.

2.3.5. Discussion on clinical Pharmacology

Not applicable

2.3.6. Conclusions on clinical pharmacology

Not Applicable

2.4. Clinical efficacy

This extension of indication is justified based on:

1) the recommendations of ESMO, EAU and National Comprehensive Cancer Network (NCCN) guidelines 2020 for androgen suppression in patients with high-risk prostate cancer.

2) the mechanism of action of the androgen suppression by LHRH antagonist compared to LHRH agonist Although the initial effect of LHRH agonists and antagonists is different, the downstream effect of both treatments is to decrease testosterone level.

3) the non-inferiority of degarelix vs a LHRH agonist on suppression of testosterone which already has been assessed in the initial MAA (see SmPC 5.1 and CS21, Klotz *et al*.). This study was designed to compare the efficacy and safety of degarelix versus leuprorelin in achieving and maintaining testosterone suppression in a 1-year trial involving patients with all stages prostate cancer. Among the patients included, an average of 1/3 had localized disease and 1/3 had locally advanced disease in each group.

4) the marketing authorization of LHRH agonists with the claimed indications presented below.

PAMORELIN LA® (triptorelin) DE/H/0566/001

PAMORELIN LA 22.5 mg is indicated in the treatment of high-risk localised or locally advanced hormone-dependent prostate cancer in combination with radiotherapy.

In section 4.2, it is specified that in high-risk localised or 'locally advanced hormone-dependent prostate cancer as concomitant to and following radiation therapy' clinical data have shown that radiotherapy followed by long-term androgen deprivation therapy is preferable to radiotherapy followed by short-term androgen deprivation therapy.

ELIGARD® (leuprorelin) DE/H/0508/002

ELIGARD is indicated for the treatment of hormone dependent advanced prostate cancer and for the treatment of high-risk localized and locally advanced hormone dependent prostate cancer in combination with radiotherapy. ELIGARD 22.5 mg may be used as neoadjuvant or adjuvant therapy in combination with radiotherapy in high-risk localized and locally advanced prostate cancer.

GOSERELIN ALVOGEN® (goserelin) PT/H/1276/001

GOSERELIN ALVOGEN is indicated as adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer where goserelin has demonstrated improved disease-free survival and overall survival (see section 5.1).

As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer where goserelin has demonstrated improved disease-free survival.

2.4.1. Dose response study(ies)

No new dose responses studies were submitted with this application. The posology for the claimed indications (degarelix 240 mg administered subcutaneously as starting dose followed by 80 mg sc monthly for maintenance) is the dose authorised for the other indication.

2.4.2. Main studies

The MAH provided references to 5 studies assessing degarelix (Table1). Of these 5 studies, three are considered as main studies supporting the claimed indications.

- **Study 00006:** Efficacy and safety of degarelix in patients with prostate cancer: Results from a phase 3 study in China Sun Y, et.al. Asian Journal of Urology 2019
- **Study CS30:** Neoadjuvant androgen deprivation therapy for prostate volume reduction, lower urinary tract symptom relief and quality of life improvement in men with intermediate -to high-risk prostate cancer: A randomized non-inferiority trial of degarelix versus goserelin plus bicalutamide. Mason M, et.al. Clinical Oncology 2013; 25:190-196
- **Study EORTC-1414**: Trial Comparing Irradiation Plus Long Term Adjuvant Androgen Deprivation With LHRH Antagonist Versus LHRH Agonist Plus Flare Protection in Patients With Very High Risk Localized or Locally Advanced Prostate Cancer (PEGASUS)-EORTC-1414 A Joint Study of the EORTC ROG and GUCG. This is an ongoing study.

Study 00006: Efficacy and safety of degarelix in patients with prostate cancer: Results from a phase 3 study in China Sun Y, et.al.. Asian Journal of Urology 2019

Methods

Study participants

This Chinese study enrolled male ≥18 years of age with a histologically confirmed adenocarcinoma of the prostate (all stages), prostate-specific antigen (PSA) level ≥2.0 ng/mL at screening, testosterone level >1.5 ng/mL, and life expectancy of >1 year.

The key exclusion criteria were previous or current hormonal treatment for prostate cancer (surgical castration or other hormonal manipulation, including LHRH receptor agonists, LHRH receptor antagonists, anti-androgens, estrogens, megestrol acetate, and ketoconazole).

Patients having undergone prostatectomy, radiotherapy or cryotherapy with curative intention neoadjuvant/adjuvant hormonal therapy for a maximum duration of 6 months was accepted if this treatment had been terminated at least 6 months prior to the screening visit. Other key exclusion criteria were history of any serious or significant health condition, undergoing treatment with 5-alpha reductase inhibitor and/or treatment with any investigational drug within 28 days before enrolling into the study.

Treatments

Patients received a once-a-month treatment with degarelix or goserelin with 28-day intervals between injections. Degarelix was administered as a deep subcutaneous (sc) injection in the abdominal region, at a starting dose of 240 mg (40 mg/mL) at Day 0, followed by 12 monthly (28- day intervals) maintenance doses of 80 mg (20 mg/mL).

Goserelin (Zoladex 3.6 mg) was administered sc into the anterior abdominal wall as 12 monthly (28-day intervals) doses. Patients could also receive anti-androgen treatment, bicalutamide 50 mg/day, starting with the first goserelin dose, and for a maximum of 28 days as flare protection, at the discretion of the investigator

Objectives

To establish non-inferiority of degarelix compared with goserelin in suppressing and maintaining castrate testosterone levels from Day 28 to Day 364 in Chinese patients with prostate cancer.

Outcomes/endpoints

The primary endpoint of the study was the difference in the cumulative probability of testosterone at castrate level (≤0.5 ng/mL) from Day 28 to Day 364 between patients treated with the degarelix and goserelin. Secondary endpoints were cumulative probabilities of testosterone at castrate level from Day 56 to Day 364, no PSA failure, PSA-progression-free survival (PSA-PFS), and PFS. PSA failure was defined as two consecutive assessments at least 2 weeks apart with an increase of 50% and at least 5 ng/mL increase compared to nadir. PSA-PFS was defined as PSA failure or death from any cause, whichever is first. PFS was defined as PSA failure, death from any cause, or introduction of additional therapy related to prostate cancer, whichever is first. Also evaluated was proportion of patients with testosterone levels _0.5 ng/mL at Day 3, and at each subsequent visit, serum levels of testosterone and PSA over time; and percentage change in PSA from baseline to Day 28. Changes in health-related quality of life (HRQoL) were measured by European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and lower urinary tract symptoms (LUTS) were measured by International Prostate Symptom Score (IPSS).

Safety was evaluated by recording adverse events (AEs), and other laboratory parameters. The AEs were presented by Medical Dictionary for Regulatory Activities.

Sample size

Of the 322 patients screened, 285 patients were randomized (143: Degarelix; 142: Goserelin, ITT analysis set), and 239 patients completed the study (123: Degarelix; 116: Goserelin).

Randomisation

Patients were randomised 1:1 to either degarelix or goserelin, stratified by the use of 5-alpha reductase inhibitors in the previous 12 months.

Blinding (masking)

Not applicable, this was an open-label trial.

Statistical methods

Primary endpoint:

The 1-year cumulative probability of testosterone levels below castrate level (≤0.5 ng/mL) was estimated using the Kaplan-Meier (KM) method using testosterone measurements every 4 weeks (at Day 28 to Day 364). The standard error (SE) of the mean of this estimate was based on Greenwood's formula. The two-sided 95% confidence interval (CI) for the suppression probability was based on the log-log transformation, Greenwood's formula, and asymptotic maximum likelihood theory. The two-sided 95% CI of the difference between degarelix and goserelin in cumulative suppression rate probabilities from Day 28 to Day 364 was constructed using the pooled SEs. If the lower limit of this CI was >-10%, the non-inferiority of degarelix to goserelin was confirmed. However, if the lower limit of this CI was >0%, superiority could have been declared. In case of failure to calculate the CIs and SEs while achieving a 0% or a 100% response rate, CIs were calculated using the Clopper-Pearson interval, (0, 3.69/N) for 0% observed responders, and (1-3.69/N, 1) for 100% responders, where N is the number of completers and 3.69=- lnα=2 with α=0.05. When estimating the SE of the KM estimate in the case of a 0% or a 100% response, the SE of the mean of the KM estimate was set to 1/2 x3/N, where 3/N corresponds to the one-sided 95% Clopper-Pearson CI with a 0% or 100% response.

Secondary endpoints:

The median percentage change from baseline to Day 28 in PSA was presented for both treatment groups, and comparisons between the treatment groups were made using the Wilcoxon test (α=0.05, two-sided). Cumulative probabilities of no PSA failure, PSA-PFS and PFS were also estimated using the KM method.

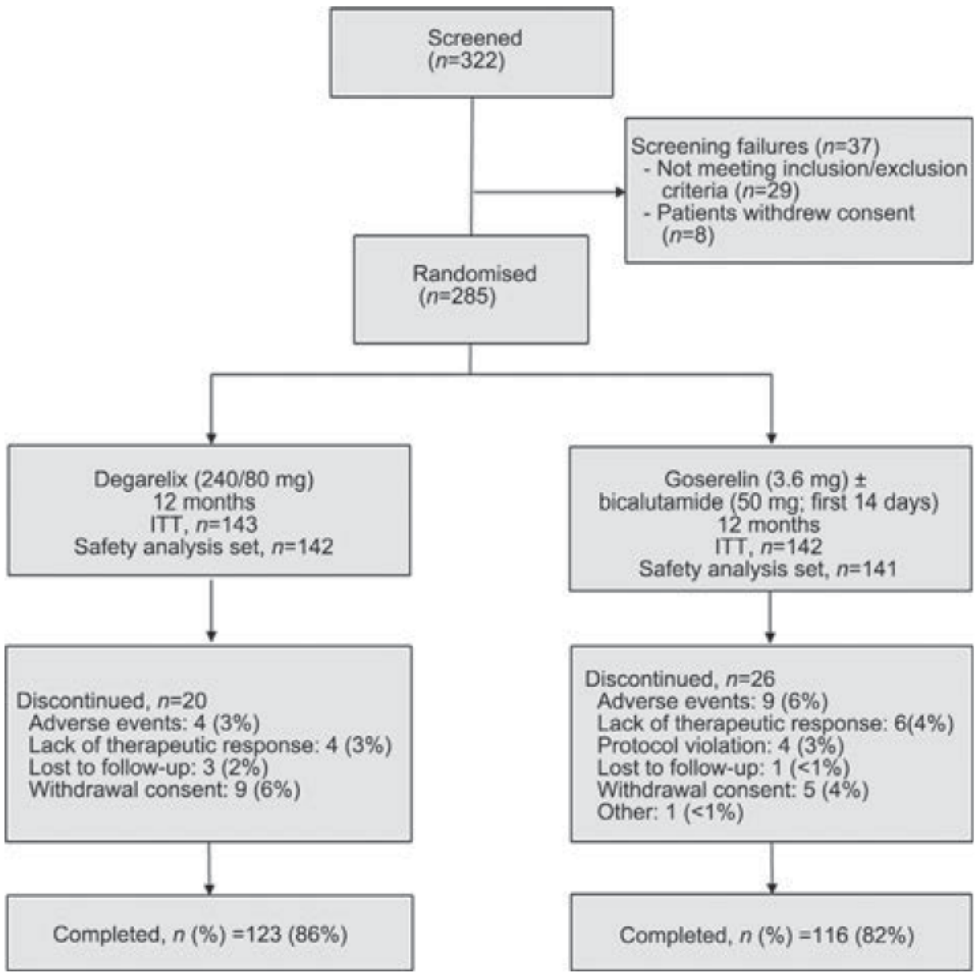
Categorical data were summarized as counts and percentages, while descriptive statistics were presented for continuous data; the data were tabulated by treatment group and visit. For laboratory efficacy parameters (testosterone and PSA) with reported values below the lower limit of quantification (LLOQ), a value of 1/2 LLOQ was used in the calculations. Drop-outs were accounted for by the KM approach, as censored observations. Drop-outs were censored at the time of their last testosterone assessment; missing values after Day 28 were imputed as ≤0.5 ng/mL provided all other testosterone assessment were less than 0.5 ng/mL, including missing values at Day 364. If one or both values before and after the missing value was greater than 0.5 ng/mL, the patient was considered an endpoint failure at the first assessment above 0.5 ng/mL.

For the secondary endpoints related to PSA, there was an additional analyses according to whether or not the patient was previously treated with a 5-alpha reductase inhibitor. The KM analysis of cumulative probability of no PSA failure was performed for the subgroups defined by the previous inhibitor use.

Results

Participant flow

Participant flow diagram of study and patient disposition



Conduct of the study

The study was approved by the Independent Ethics Committee of People's Hospital of Peking University (No. 43 [2013]) and was conducted in accordance with the Declaration of Helsinki and its amendments, International Council on Harmonisation-Good Clinical Practice Guidelines and in compliance with the approved protocol and applicable regulatory requirements. All patients provided written informed consents before enrolment.

Baseline data

	Degarelix (*N*=142)	Goserelin (*N*=141)
Median age (range), year	75 (52–86)	73 (47–91)
Median baseline BMI (range), kg/m^2	23.3 (16.9–34.9)	22.7 (14.5–32.6)
Median testosterone (range), ng/mL	4.6 (1.3–9.6)	4.6 (1.7–11.2)
Median PSA (range), ng/mL	89.4 (2.4–8 000)	131 (2.6–8 000)
5-alpha reductase therapy, *n* (%)	23 (16)	17 (12)
Disease stage, *n* (%)		
Localised	35 (25)	33 (23)
Locally advanced	13 (9)	17 (12)
Metastatic	89 (63)	85 (60)
Not classifiable[a]	5 (4)	6 (4)
Gleason score (at diagnosis), *n* (%)		
2–4	1 (<1)	1 (<1)
5–6	17 (12)	16 (11)
7–10	124 (87)	124 (88)
Median time since diagnosis (range), day	14 (4–3 012)	14 (6–1 133)

BMI, body mass index; PSA, prostate-specific antigen.
[a] Not classifiable was chosen when an investigator could not medically conclude that a patient's prostate cancer was definitely localised, locally advanced or metastatic.

Numbers analysed

The number of patients analysed for efficacy in the ITT population were 143 for degarelix and 142 patients for goserelin ± bicalutamide.

The number of patients included in the Safety analysis set were 142 for degarelix and 141 patients for goserelin ± bicalutamide.

Outcomes and estimation

Degarelix was non-inferior to goserelin in achieving and maintaining serum testosterone suppression at castrate levels from Day 28 to Day 364 Figure 1. The difference between the two treatment groups was 3.6% (95% CI: -1.5%, 8.7%), and the lower limit of the CI (for the difference in probability) was higher than the pre-defined threshold of >-10%.

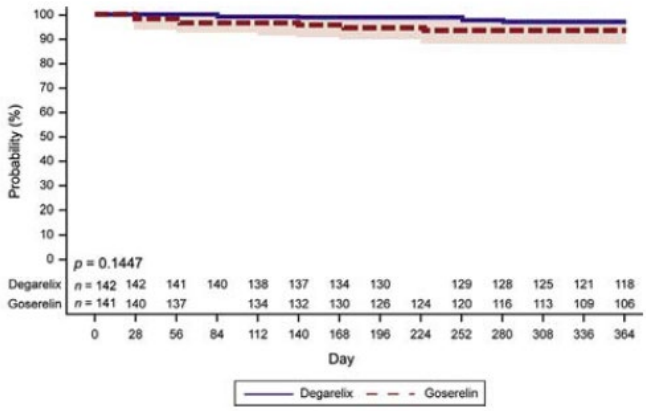


Figure 1 *Cumulative probability of testosterone at castrate level (≤0.5ng/mL) from Day 28 to Day 364.*

The individual cumulative probabilities of maintaining castrate testosterone levels over a period of 1 year was 97.0% (95% CI: 92.3%, 98.9%) for degarelix and 93.4% (95% CI: 87.7%, 96.5%) for goserelin. The sensitivity analysis in patients who did not receive a previous treatment with 5-alpha reductase inhibitor demonstrated non-inferiority of degarelix to goserelin. However, in the subgroup previously treated with 5-alpha reductase inhibitor, the point estimate of the difference in suppression rates was -4.5%, but due to the low number of patients (n=40), non-inferiority could not be demonstrated. The cumulative probability of achieving and maintaining serum testosterone suppression at castrate levels from Day 56 to Day 364 was also comparable between degarelix and goserelin (97.0% [95% CI: 92.3%, 98.9%] and 95.5% [95% CI: 90.2%, 97.9%], respectively).

Testosterone levels were rapidly suppressed to castrate levels with degarelix (0.25 ng/mL) at Day 3 compared with goserelin (p<0.0001), and 96% of patients achieved castrate levels of testosterone in the degarelix group compared to none in the goserelin group (p<0.0001). The time concentration curve of testosterone with respect to degarelix and goserelin is presented in Figure 2. In the goserelin group, there was a 53% increase in the testosterone levels from the baseline to Day 3 (4.58 ng/mL and 7.31 ng/mL). After Day 3, the proportion of patients achieving testosterone castrate levels was similar in both groups, though median testosterone levels were higher in the goserelin group as compared with the degarelix group (0.05 ng/mL [range, 0.05-0.38 ng/mL] and 0.112 ng/mL [range, 0.05-9.92 ng/mL], respectively). Median levels of testosterone remained suppressed for both degarelix and goserelin groups until the end of the study on Day 364. Similar results were observed in the PP analysis set.

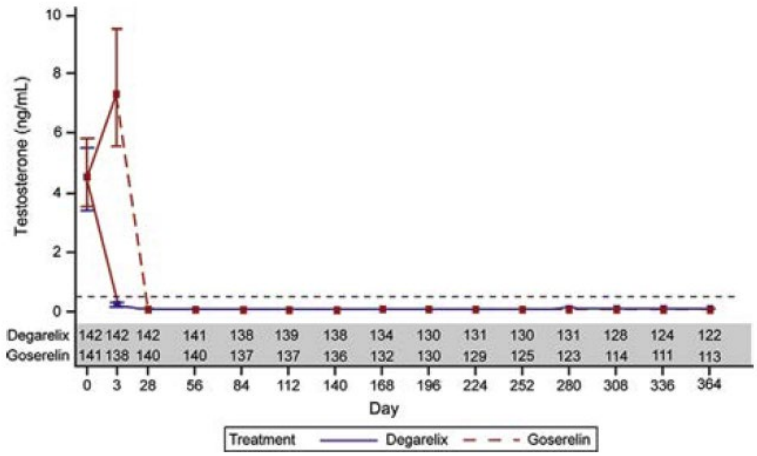


Figure 2 *Time concentration curve of testosterone: Median values (interquartile range)*

Treatment with degarelix resulted in a rapid and more profound PSA suppression from baseline to Day 3 versus goserelin group (22.20% versus 8.65% reduction in PSA).

By Day 28, the treatment groups had a 91% reduction from baseline in PSA levels, which continued to be similar throughout the treatment period in the two treatment groups Figure 3. A previous treatment/no treatment with 5-alpha reductase inhibitor did not impact the PSA reduction. PSA failure occurred more frequently in patients with a high PSA level at baseline, and those with metastatic disease. On the other hand, patients previously treated with 5-alpha reductase inhibitor had a lower PSA failure rate. The cumulative probability of PSA-PFS at Day 364 was significantly higher for degarelix as compared with goserelin (p=0.038).

Furthermore, the cumulative probability of PFS showed a favourable trend for degarelix in terms of disease control Table 3.

Table 3 *Estimate of disease progression at Day364-full analysis set.*

	Degarelix ($n=142$)	Goserelin ($n=141$)	p-Value
No PSA failure	82.8 (75.2—88.2)	73.4 (64.9—80.1)	0.062
PSA-PFS	82.3 (74.7—87.7)	71.7 (63.2—78.5)	0.038
PFS	81.5 (73.9—87.1)	71.7 (63.2—78.5)	0.058

PFS, progression free survival; PSA, prostate-specific antigen.

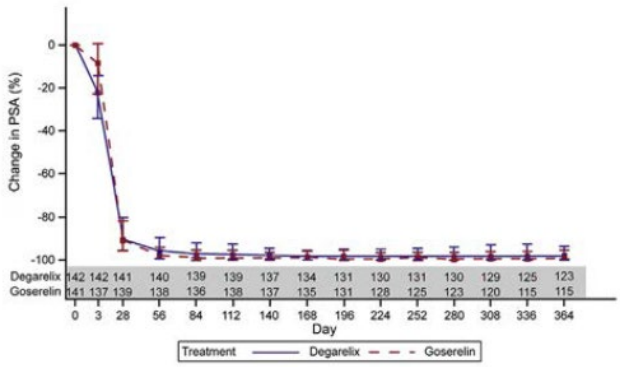


***Figure* 3** *Percentage change from base*line in PSA: Median *values (interquartile range). PSA, prostate-specific antigen.*

Study CS30: Neoadjuvant androgen deprivation therapy for prostate volume reduction, lower urinary tract symptom relief and quality of life improvement in men with intermediate -to high-risk prostate cancer: A randomized non-inferiority trial of degarelix versus goserelin plus bicalutamide. Mason M, et.al. Clinical Oncology 2013; 25:190-196

Methods

The trial was a randomized, parallel-arm, active controlled, open-label trial

Study participants

Main inclusion criteria included prostate cancer TNM category T2b-T4, N0, M0, Gleason score ≥7, or PSA ≥10 ng/ml; total prostate volume (TPV) >30 ml; scheduled to undergo radical radiotherapy treatment and in whom neoadjuvant ADT was indicated.

Major exclusion criteria included treatment for prostate cancer or transurethral resection of the prostate; use of a urethral catheter; treatment with a 5-alpha reductase inhibitor (finasteride or dutasteride) in the past 12 and 16 weeks, respectively; or treatment with an alpha-adrenoceptor blocker in the past 4 weeks.

Treatments

In the degarelix group, a starting dose of 240 mg (40 mg/ml) was given on day 0. The second and third doses (maintenance doses) of 80 mg (20 mg/ml) were given on days 28 and 56, respectively.

In the control arm, once-daily treatment with bicalutamide 50 mg as anti-androgen flare protection was initiated on day 0 and this treatment continued for 17 days. On day 3, the first goserelin implant (3.6 mg) was administered and the second and third doses were given on days 31 and 59, respectively.

Objectives and Outcomes/endpoints

The primary objective was to demonstrate that the mean percentage reduction in prostate volume with degarelix is non-inferior to goserelin plus bicalutamide, based on Transrectal Ultrasound (TRUS) at 12 weeks compared to baseline. Secondary objectives included the effect on lower urinary tract symptom (LUTS) relief, changes of quality of life related to urinary symptoms, testosterone control, PSA control, oestradiol levels, safety of degarelix and goserelin plus bicalutamide treatments.

The primary endpoint was the mean percentage reduction in prostate volume at 12 weeks as compared to baseline. Secondary endpoints were: reduction in IPSS from baseline at 4, 8, and 12 weeks, change in serum testosterone concentration at 4, 8, and 12 weeks as compared to baseline, change in serum PSA concentration at 4, 8, and 12 weeks as compared to baseline, change in serum oestradiol concentration at 4, 8, and 12 weeks as compared to baseline, quality of life evaluation at 4, 8, and 12 weeks compared to baseline.

Sample size

The number of patients was 240, 160 in degarelix arm and n=80 in goserelin arm

Randomisation

Eligible patients were randomised in a 3:1 ratio to receive treatment with degarelix or goserelin for 12 weeks

Blinding (masking)

Not applicable, this was an open label study

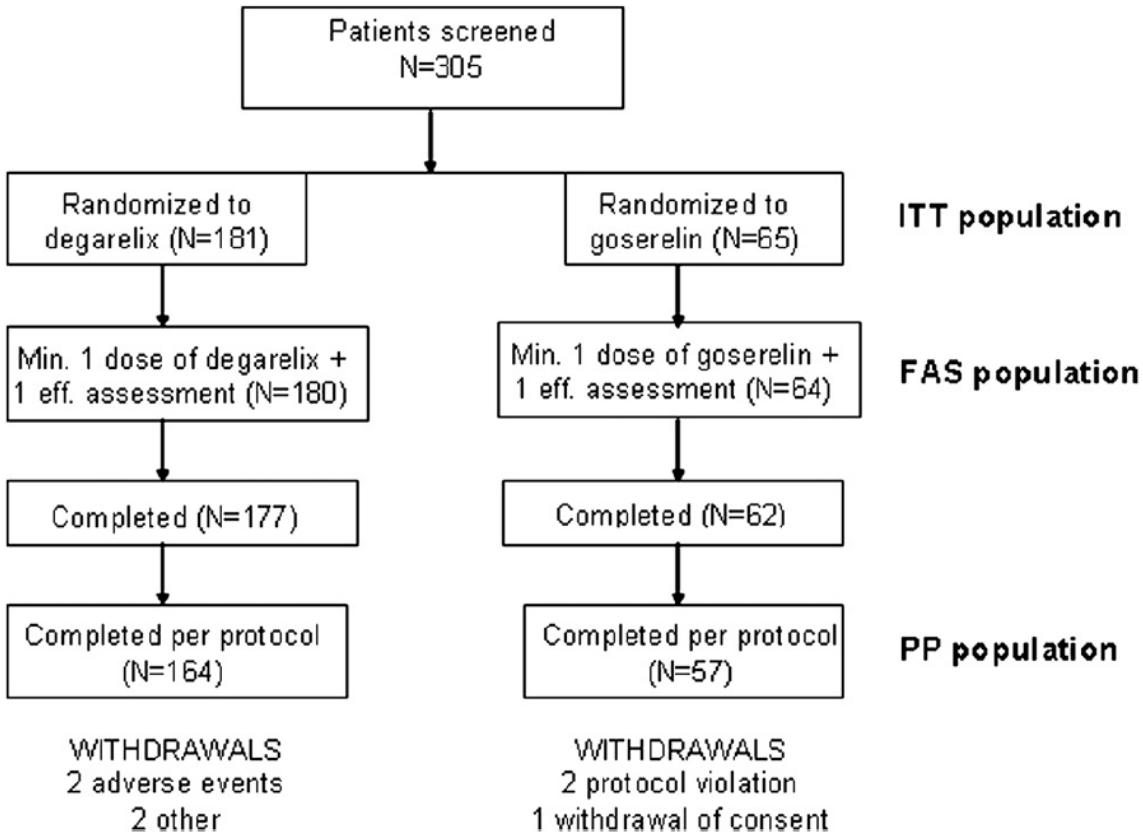
Statistical methods

Patients who received at least one dose of the investigational drug and had at least one efficacy assessment were included in the full analysis set (FAS). The per-protocol population was obtained by

excluding patients who fulfilled any pre-set criteria for exclusion from the per-protocol analysis set. The primary efficacy measure was the mean percentage reduction in TPV from baseline at week 12. Changes were analyzed by analysis of covariance (ANCOVA) for both the FAS and per-protocol populations. Non inferiority was established if the treatment difference in adjusted mean percentage reduction was significantly greater than Δ=-10 points in both the FAS and per-protocol analysis sets (two-sided at α= 0.05 level). Changes in IPSS from baseline were analysed by ANCOVA. Changes in quality of life due to urinary symptoms were analyzed by polytomous regression. In total, 228 (171 degarelix and 57 goserelin) patients were required in order to show non-inferiority with 90% probability (assuming a standard deviation of the change from baseline of 20 percentage points at week 12). An additional 5% of anticipated protocol violators were added to arrive at the total of 240 patients.

Results

Participant flow



Baseline data

Table 4 *Baseline characteristic of the trial population [mean± standard deviation or median with range (minimum-maximum)]*

Baseline characteristics	Degarelix	Goserelin/ bicalutamide
Full analysis set	180	64
Age (years)	70.6 (6.37)	70.8 (5.96)
Weight (kg)	83.6 (14.2)	80.9 (12.4)
Body mass index (kg/m^2)	27.8 (3.99)	26.8 (3.69)
Time since prostate cancer diagnosis (days)	75 (14–1378)	72 (17–1526)
Tumour stage*		
Localised	111 (62%)	41 (64%)
Locally advanced	63 (35%)	20 (31%)
Not classifiable	6 (3%)	3 (5%)
T1/2a	5 (83%)	1 (33%)
T3/4	1 (17%)	1 (33%)
TX		1 (33%)
Gleason score		
2–6	41 (23%)	12 (19%)
7	97 (54%)	42 (66%)
8–10	42 (23%)	10 (16%)
ECOG score		
Fully active	154 (86%)	58 (91%)
Restricted, but ambulatory	21 (12%)	6 (9%)
Ambulatory, unable to work	5 (3%)	0
Capable of only limited self-care	0	0
Total prostate volume (ml)	50.9 (20.3)	52.5 (18.8)
IPSS	9.5 (6.71)	8.5 (6.30)
IPSS quality of life	2.27 (1.63)	1.94 (1.56)
Mean PSA (ng/ml)	17.4 (30.1)	13.4 (12.9)
Median PSA	10.0 (2.5–339)	9.75 (2.9–80)
Mean testosterone (ng/ml)	4.18 (1.72)	4.45 (1.49)
Median testosterone	3.92 (0.58–11.2)	4.42 (0.19–8.16)

ECOG, Eastern Cooperative Oncology Group; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen.
* Localised = T1 or T2 and (NX or N0) and M0; locally advanced = T3 or T4 and (NX or N0) and M0 or (N1 & M0).

Numbers analysed

The FAS population was of 180 patients in degarelix group and of 64 patients in goserelin+bicalutamide group while PP population was of 164 patients in degarelix group and of 57 patients in goserelin+bicalutamide group.

Outcomes and estimation

Mean Percentage Change in Total Prostate Volume (TPV)

TPV decreased significantly from baseline to week 12 in both treatment groups with mean (± standard deviation) percentage changes of -36.0 ± 14.5% and -35.3 ± 16.7% for degarelix and goserelin, respectively, for the FAS and -36.2 ±14.5% and -35.4 ±16.9% for degarelix and goserelin, respectively, for the per-protocol analysis set Figure 4.

The adjusted differences between treatment groups were -0.3% (95% confidence interval -4.74; 4.14%) for the FAS and -0.27% (95% confidence interval -5.05; 4.52%) for the per-protocol analysis set. The upper limits of the two-sided 95% confidence interval for the adjusted mean differences were thus below the non-inferiority margin of 10, and non-inferiority was considered to have been established.

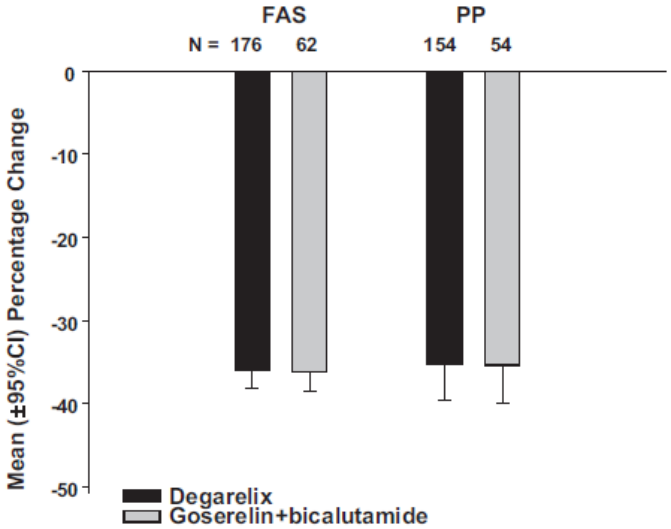


Figure 4. Mean percentage change (±95% confident interval) in prostate volume measured with transrectal ultrasound at 12 weeks compared with baseline using transrectal ultrasound: full analysis set (FAS) and per-protocol analysis set (PP)(observed case).

Changes from Baseline in Serum Testosterone and Prostate specific Antigen

The median levels of serum testosterone showed no differences between degarelix- and goserelin-treated patients during the trial Figure 5. The median level of testosterone for degarelix-treated patients at weeks 4, 8 and 12 was 0.05 ng/ml and the corresponding figures for goserelin were 0.17, 0.05 and 0.05 ng/ml, respectively.

Overall, there were seven of 180 and five patients of 64 on degarelix and goserelin, respectively, with a serum testosterone level >0.5 ng/ml on at least one occasion. The estimated cumulative probabilities of

testosterone <0.5 ng/ ml between days 28 and 84 were 96% for the degarelix treatment group and 92% for the goserelin treatment group.

The median percentage changes in PSA were also comparable; for degarelix the decreases from baseline at weeks 4, 8 and 12 were -71.6, -84.8 and -89.2%, respectively, whereas for goserelin they were -72.2, -93.1 and -93.0% Figure 5.

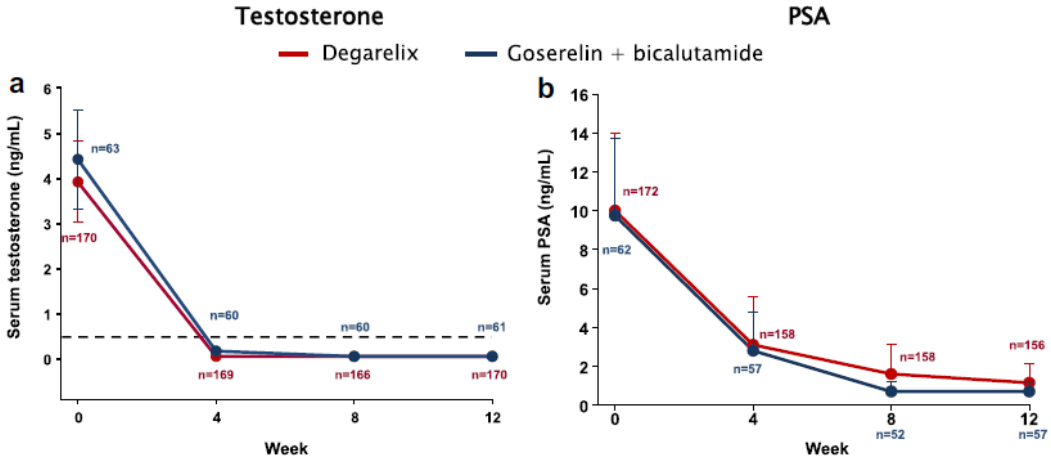


Figure 5 Median (± interquartile range) absolute values (ng/ml) for serum (a) testosterone and (b) PSA during the 12 weeks treatment period.

Changes from Baseline in International Prostate Symptom Score

About 50% of patients had no to mild lower urinary tract symptoms (LUTS), about 40% had moderate and 10% had severe LUTS at baseline. In patients with moderate LUTS at baseline, the mean IPSS (±standard error of the mean) decreased clinically meaningfully (-2.99 ± 0.68, n = 72) in degarelix-treated patients by week 12, whereas it remained virtually unchanged in goserelin-treated patients (-0.48 ±1.29, n = 23, P = 0.06).

In patients with severe LUTS at baseline, the mean IPSS changes from baseline to week 12 were numerically larger in degarelix-treated patients (-6.84 ±1.31, n = 19) compared with goserelin-treated patients (-3.50 ± 3.18, n = 6), but differences did not reach statistical significance (P = 0.21). Similarly, when focusing on patients with a baseline IPSS ≥13 (a commonly used threshold in clinical trials on LUTS management), degarelix elicited more pronounced LUTS relief compared with goserelin (-6.04 ± 0.79, n = 53 versus -3.41 ±1.23, n = 17; P = 0.06). In the total population, 37% of patients in the degarelix group and 27% in the goserelin group experienced clinically meaningful IPSS decreases of at least three points (P = 0.06).

The mean change (± standard error of the mean) from baseline in IPSS was larger in the degarelix group compared with the goserelin group at weeks 8 (-1.53 ± 0.41, n = 178 versus 0.016 ± 0.68, n = 63) and 12 (-1.71 ±0.42, n = 178 versus 0.11±0.65, n=63). At week12, the adjusted (for baseline IPSS) difference between degarelix and goserelin was statistically significant (-1.42 [-2.81; -0.035], P = 0.044) Figure 6.

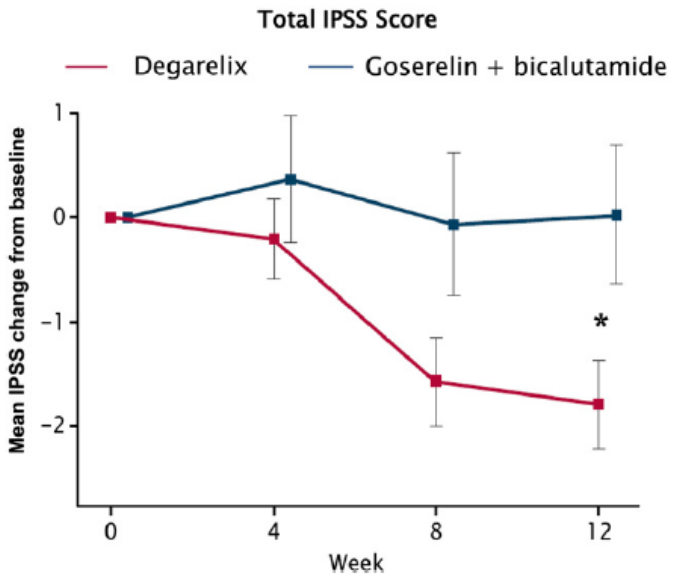


Figure 6 Mean (± standard error of the eman) changes in International Prostate Symptom Score (IPSS) from baseline to degarelix or goserelin plus bicalutamide in prostate cancer patients during the 12 week treatment period. "Statistically significant difference between the group (P<0.05).

Change from Baseline in Quality of Life due to Urinary Symptoms

The relative increases in the reporting of 'delighted' or 'pleased' from baseline to week 12 were greater in the degarelix-treated patients compared with goserelin-treated patients (31% versus -3%) and the relative decreases in the reporting of 'unhappy'/'terrible' from baseline to week 12 were also greater in the degarelix-treated patients compared with goserelin-treated patients (-37% versus 14%). However, the numerical differences did not reach statistical significance.

Study EORTC-1414: Trial Comparing Irradiation Plus Long Term Adjuvant Androgen Deprivation With LHRH Antagonist Versus LHRH Agonist Plus Flare Protection in Patients With Very High Risk Localized or Locally Advanced Prostate Cancer (PEGASUS)-EORTC-1414 A Joint Study of the EORTC ROG and GUCG.

The applicant provides the description of this ongoing clinical trial assessing degarelix in the adjuvant setting (issued from clinicaltrial.gov website)

Methods

Study participants
Inclusion Criteria:

- Histologically confirmed diagnosis of prostate adenocarcinoma
- PSA ≥ 10 ng/ml and two of the following 4 criteria:
    - PSA ⩾ 20 ng/ml,
    - Gleason sum ⩾ 8,
    - cN1 (regional LN with a short axis length >10mm by CT scan or MRI) or pathologically confirmed lymph nodes (pN1),
    - cT3-T4 (by MRI or core biopsy) (i.e. If PSA≥ 20 ng/ml then only one of the other 3 risk factors is needed)
- M0 by standard imaging work-up

- Testosterone ⩾ 200 ng/dl
- Adequate renal function: calculated creatinine clearance ≥ 50 mL/min (Appendix D) Magnesium and potassium within normal limits of the institution or corrected to within normal limits prior to the first dose of treatment.
- Patients with prolonged QT-intervals due to prescribed Class IA (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic medication must be carefully evaluated for LHRHLHRH-agonist or LHRHLHRH antagonist use, because these drugs may prolong the QT-interval.
- WHO Performance status 0-1
- Age ⩾ 18 and ⩽ 80 years
- Participants who have partners of childbearing potential must use adequate birth control measures, as defined by the investigator, during the study treatment period and for at least 3 months after last dose of study treatment. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly
- Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.

Exclusion Criteria:

- Previous use of androgen deprivation therapy (ADT), antiandrogens. 5-alpha reductase inhibitors are allowed if interrupted for more than 6 months prior to entering the study
- History of severe untreated asthma, anaphylactic reactions or severe urticaria and/or angioedema.
- Hypersensitivity towards the investigational drug
- The following biological parameters: AST, ALT, total bilirubin, prothrombin time, serum albumin above upper level of normal range No severe hepatic impairment (Child Pugh C)
- History of gastro-intestinal disorders (medical disorder or extensive surgery) that may interfere with the absorption of the protocol treatment.
- History of pituitary or adrenal dysfunction
- Uncontrolled diabetes mellitus
- History of ulcerative colitis, Crohn's Disease, ataxia, telangiectasia, systemic lupus erythematous, or Fanconi anemia.
- Clinically significant heart disease as evidence myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) class III or IV heart disease or cardiac ejection fraction measurement of < 50 % at baseline
- Coronary revascularization (PCI or multivessel CABG), carotid artery or iliofemoral artery revascularization (percutaneous or surgical procedure) within the last 30 days prior to entering the trial
- Certain risk factors for abnormal heart rhythms/QT prolongation: torsade de pointes ventricular arrhythmias (e.g, heart failure, hypokalemia, or a family history of a long QT syndrome), a QT or corrected QT (QTc) interval >450 ms at baseline, or intake of medications that prolong the QT/QTc interval
- Uncontrolled hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 95 mmHg); patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment.
- Prior history of malignancies other than prostate adenocarcinoma (except patients with basal cell, squamous cell carcinoma of the skin), or the patient has been free of malignancy for a period of 3 years prior to first dose of study drug(s). Prior history of bladder cancer excludes the patient.
- Prior radical prostatectomy (TURP or suprapubic adenomectomy for benign prostatic hyperplasia is allowed)
- Prior brachytherapy or other radiotherapy that would result in an overlap of radiotherapy fields

- Any contraindication to external beam radiotherapy
- Patients with significantly altered mental status prohibiting the understanding of the study or with psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule or any condition which, in the opinion of the investigator, would preclude participation in this trial

Treatments

Registered LHRH antagonist, degarelix, will be given at the dose of 240 mg given as two subcutaneous injections of 120 mg at a concentration of 40 mg/mL on day 1, followed by 80 mg given as one subcutaneous injection at a concentration of 20 mg/mL every 28 days (±2 days).
External beam radiotherapy (EBRT) to a total dose of 78-80 Gy, delivered as one daily fraction, five days a week, started between d1 and months 6 of the androgen deprivation therapy as per institution policy. The irradiation was the same as in the reference therapy arm.
The minimum duration of androgen deprivation with LHRH agonist or antagonist therapy was 18 months.

Objectives

The primary objective of the trial is to assess if LHRH antagonists in combination with external beam radiation therapy improve progression free survival (progression that can be biological, clinical, or death) compared to LHRH agonists in combination with external beam radiation therapy.
Secondary objectives include:'
-documentation of effect of LHRH antagonists on clinically significant cardiovascular events in the subgroup of patients at high risk of such events at baseline;
-documentation of side effects and quality of life, I-PSS and urinary tract infections;
-assessment of relative treatment effect on secondary efficacy endpoints (clinical progression, time to next line of systemic therapy, time on therapy, overall and cancer specific survival) and on PSA at 6 months after end of RT.

Outcomes/endpoints

Primary Outcome Measures:

1. Progression free survival [Time Frame: through study completion, an average of 1 year]

   The primary endpoint is progression-free survival defined as the time in days from randomization to death, clinical or biochemical progression, whichever comes first.

   Where

   - PSA progression based on Phoenix definition, i.e. a rise by 2 ng/mL or more above the nadir PSA confirmed by a second value measured minimum 3 months later
   - Clinical progression is defined as onset of obstructive symptoms requiring local treatment and demonstrated to be caused by cancer progression or evidence of metastases detected by clinical symptoms and confirmed by imaging
   - Start of another line of systemic therapy in absence of progression
   - Death due to any cause

Secondary Outcome Measures :

1. Clinical progression-free survival [Time Frame: through study completion, an average of 1 year]
2. Time to next systemic anticancer therapy (including secondary hormonal manipulation) [Time Frame: through study completion, an average of 1 year]
3. ♦ Proportion of patients switching from LHRH antagonists to LHRH agonists [Time Frame: through study completion, an average of 1 year]
4. ♦ Overall survival [Time Frame: through study completion, an average of 1 year]
5. Incidence of clinical cardiovascular events [Time Frame: through study completion, an average of 1 year]

   ♦ the incidence of clinical cardiovascular events - CCE (i.e. arterial embolic or thrombotic events, hemorrhagic or ischemic cerebrovascular conditions, myocardial infarction, and other ischemic heart disease) in patients who had cardiovascular events before entering the trial and in those without such events.

6. ♦ Incidence of urinary tract infection [Time Frame: through study completion, an average of 1 year]

Sample size

The number of participants is 885

Randomisation

Not specified

Blinding (masking)

Not applicable as this is an open label study

Statistical methods

The estimated primary completion date is June 2024

Summary of main studies

Study EORTC-1414 is an ongoing study for which the results are not available and Study 00006 is relevant only in confirming the CS21 study's results, therefore only Study CS30 is summarized below.

Table 5 Summary of Efficacy for Trial CS30

Title: Neoadjuvant androgen deprivation therapy for prostate volume reduction, lower urinary tract symptom relief and quality of life improvement in men with intermediate -to high-risk prostate cancer: A randomized non-inferiority trial of degarelix versus goserelin plus bicalutamide			
Study identifier	CS30		
Design	randomized, parallel-arm, active controlled, open-label trial Eligible patients were randomised in a 3:1 ratio to receive treatment with degarelix or goserelin Patients were scheduled to undergo radical radiotherapy treatment and in whom neoadjuvant ADT was indicated		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks not applicable not applicable
Hypothesis	Non-inferiority		
Treatments groups	Degarelix		Degarelix 240/80 mg at D0, D28 and D56, 181 patients randomized
	Control		Goserelin on D3, D31 and D59 + bicalutamide daily from D0 to D17, 65 patients randomized
Endpoints and definitions	Primary endpoint	TVP	Mean percentage change in total prostate volume
	Secondary endpoint	IPSS	reduction in IPSS from baseline at 4, 8, and 12 weeks
	Secondary endpoint	testosterone	change in serum testosterone concentration at 4, 8, and 12 weeks as compared to baseline
	Secondary endpoint	PSA	, change in serum PSA concentration at 4, 8, and 12 weeks as compared to baseline
	Secondary endpoint	oestradiol	change in serum oestradiol concentration at 4, 8, and 12 weeks as compared to baseline
	Secondary endpoint	QoL	quality of life evaluation at 4, 8, and 12 weeks compared to baseline
Database lock	21 October 2011		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	FAS and Per protocol 12 weeks		
Descriptive statistics and estimate variability	Treatment group	degarelix	control
	Number of subject	FAS : 180 PP: 164	FAS : 64 PP: 57
	Mean change TVP (%)	FAS: 36.0 PP:36.2	FAS: 35.3 PP:35.4

	± standard deviation	FAS: 14.5 PP:14.5	FAS: 16.7 PP:16.9
	IPSS mean change	-1.71	-0.11
	± standard error of the mean	0.42	0.65
	Median level of testosterone (ng/ml)	0.05	0.05
	Median change in PSA from baseline (%)	-89.2%	-93.0
Effect estimate per comparison	Primary endpoint	Comparison groups	degarelix vs gosereline+bicalutamide
		TVP changes	FAS -0.3% PP: -0.27%
		95% CI	FAS -4.74,4.14 PP: -5.05, 4.52
		P-value	FAS: 0.8942 PP: 0.9123
	Secondary endpoint	Comparison groups	degarelix vs gosereline+bicalutamide
		IPSS mean change (FAS)	-1.42
		95% CI	-2.81:0.035
		P-value	0.0445
Notes			
Analysis description			

Supportive studies

Three studies assessing LHRH agonist in the neoadjuvant setting, 4 studies assessing LHRH agonist in the adjuvant setting and further two studies *(*McLeod D et al. 2001 and Trachtenberg J, et al. 2002) assessing a LHRH antagonist (abarelix) compared to a LHRH agonist were presented in support of the claimed indications.

Studies assessing LHRH agonists in the Neoadjuvant setting

Neoadjuvant setting indication claim is supported by the clinical trial CS30 described in section 2.4.2. and on three clinical trials: RTOG 86-10, TROG 96.01 and RTOG 94-08 which are described below.

RTOG 86-10: Phase III radiation therapy oncology group (RTOG) Trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. Pilepich M.; *et. al.* Int. J. Radiation Oncology Biol. Phys 2001; 50: 1243-1252

RTOG 86-10 (Pilepich et al.) was a phase III randomized study to assess 16 weeks treatment with goserelin+ flutamide starting 2 months before radiotherapy versus radiotherapy alone in patients with clinical stage T2-T4 i.e. patients with localized disease. The primary end point of the study was locoregional control; secondary end points were disease-free survival (freedom from progression) and survival.After a median follow-up of 6.7 years, the short-term ADT plus radiotherapy combination was associated with improved local control, reduced incidence of distant metastases, improved disease-free survival, and reduced cause-specific mortality. The 10-year results showed that the addition of ADT induced a significant improvement in the 10-year disease-specific mortality (23% versus 36%; p=0.01), disease free survival (11% versus 3%; p<0.0001), and biochemical failure (65% versus 80%; p<0.0001).

TROG 96.01: Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial*;* Denham J*, et.al*.; The Lancet oncology 2011; 12: 451-459

This is a phase III randomized controlled trial to determine whether 3 months or 6 months of androgen deprivation given before and during radiotherapy improves outcomes for patients with locally advanced prostate cancer. Throughout this study 818 men with locally advanced prostate cancer were randomly assigned to no androgen deprivation 3 months' androgen deprivation with 3,6 mg Goserelin or 6 months' androgen deprivation, with the same regimen.

The following results have been published in the literature:

"802 men were eligible for analysis (270 in the radiotherapy alone group, 265 in the 3-month neoadjuvant androgen deprivation therapy (NADT) group, and 267 in the 6-month NADT group) after a median follow-up of 10·6 years (IQR 6·9–11·6). Compared with radiotherapy alone, 3 months of NADT decreased the cumulative incidence of PSA progression (adjusted hazard ratio 0·72, 95% CI 0·57–0·90; p=0·003) and local progression (0·49, 0·33–0·73; p=0·0005), and improved event-free survival (0·63, 0·52–0·77; p<0·0001). 6 months of NADT further reduced PSA progression (0·57, 0·46–0·72; p<0·0001) and local progression (0·45, 0·30–0·66; p=0·0001), and led to a greater improvement in event-free survival (0·51, 0·42–0·61, p<0·0001), compared with radiotherapy alone. 3-month NADT had no effect on distant progression (0·89, 0·60–1·31; p=0·550), prostate cancer-specific mortality (0·86, 0·60–1·23; p=0·398), or all-cause mortality (0·84, 0·65–1·08; p=0·180), compared with radiotherapy alone. By contrast, 6-month NADT decreased distant progression (0·49, 0·31–0·76; p=0·001), prostate cancer-specific mortality (0·49, 0·32–0·74; p=0·0008), and all-cause mortality (0·63, 0·48–0·83; p=0·0008), compared with radiotherapy alone. Treatment-related morbidity was not increased with NADT within the first 5 years after randomisation."

RTOG 94-08: Radiotherapy and short-term androgen deprivation for localized prostate *cancer.* Jones C, *et.al.* N Engl. J Med 2011; 365: 107-118

This is a phase III, randomized study in localized prostate cancer patients with low TNM staging. From 1994 through 2001, 1979 eligible patients with stage T1b, T1c, T2a, or T2b prostate adenocarcinoma and a prostate-specific antigen (PSA) level of 20 ng per milliliter or less were randomized to radiotherapy

alone (992 patients) or radiotherapy with 4 months of total androgen suppression starting 2 months before radiotherapy (radiotherapy plus short-term ADT, 987 patients).

The following results have been published in the literature:

"The median follow-up period was 9.1 years. The 10-year rate of overall survival was 62% among patients receiving radiotherapy plus short-term ADT (the combined-therapy group), as compared with 57% among patients receiving radiotherapy alone (hazard ratio for death with radiotherapy alone, 1.17; P=0.03). The addition of short-term ADT was associated with a decrease in the 10-year disease-specific mortality from 8% to 4% (hazard ratio for radiotherapy alone, 1.87; P=0.001). Biochemical failure, distant metastases, and the rate of positive findings on repeat prostate biopsy at 2 years were significantly improved with radiotherapy plus short-term ADT. Acute and late radiation-induced toxic effects were similar in the two groups. The incidence of grade 3 or higher hormone-related toxic effects was less than 5%. Reanalysis according to risk showed reductions in overall and disease-specific mortality primarily among intermediate-risk patients, with no significant reductions among low-risk patients."

Among patients with stage T1b, T1c, T2a, or T2b prostate adenocarcinoma and a PSA level of 20 ng per milliliter or less, the authors conclude that the use of short-term ADT for 4 months before and during radiotherapy was associated with significantly decreased disease-specific mortality and increased overall survival. According to post hoc risk analysis, the benefit was mainly seen in intermediate-risk, but not low-risk, men.

Studies assessing LHRH agonists in the Adjuvant setting

Adjuvant setting indication claim is supported by the following 4 clinical trials with LHRH agonists.

EORTC 22961: Duration of androgen suppression in the treatment of prostate cancer; Bolla M, et.al. 2009; 360: 2516-2527

In this randomized phase III study, patients with locally advanced prostate cancer (including a smaller sub-group of high-risk localised patients) who had received external-beam radiotherapy plus 6 months of androgen suppression (LHRH agonist +bicalutamide) were randomized into two groups:

- one to receive no further treatment (short-term suppression) and
- one to receive 2.5 years of further treatment with a LHRH agonist alone (long-term suppression).

The following results have been published in the literature:
A total of 1113 men were registered, of whom 970 were randomly assigned, 483 to short-term suppression and 487 to long-term suppression. After a median follow-up of 6.4 years, 132 patients in the short-term group and 98 in the long-term group had died; the number of deaths due to prostate cancer was 47 in the short-term group and 29 in the long-term group. The 5-year overall mortality for short term and long-term suppression was 19.0% and 15.2%, respectively; the observed hazard ratio was 1.42 (upper 95.71% confidence limit, 1.79; P = 0.65 for no inferiority). Adverse events in both groups included fatigue, diminished sexual function, and hot flushes.

RTOG 92-02: *A phase 3 trial of the duration of elective androgen deprivation in locally advanced prostate cancer: Ten year follow up radiation therapy oncology group protocol 92-02:.* Horwitz E*, et. al.* Journal of clinical oncology 2008; 26: 2497-2504

In this phase III trial, patients with T2c-T4 prostate cancer received 4 months goserelin and flutamide before and during RT and then were randomized to no further ADT (short-term ADT [STAD] + RT) or 24 months of goserelin (long-term ADT [LTAD] + RT).
The following results were published in the literature:
« At 10 years, the LTAD + RT group showed significant improvement over the STAD + RT group for all end points except overall survival: disease-free survival (13.2% *v* 22.5%; *P* < .0001), disease-specific survival (83.9% *v* 88.7%; *P* = .0042), local progression (22.2% *v* 12.3%; *P* < .0001), distant metastasis (22.8% *v* 14.8%; *P* < .0001), biochemical failure (68.1% *v* 51.9%; *P* < .0001), and overall survival (51.6% *v* 53.9%, *P* = .36). One subgroup analyzed consisted of all cancers with a Gleason score of 8 to 10 cancers. An overall survival difference was observed (31.9% *v* 45.1%; *P* = .0061), as well as in all other end points herein »

EORTC 22863 External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomized study. Bolla M , et.al Lancet oncology 2010; 11: 1066-73

This is a randomized phase III trial assessing the benefit of addition of long-term androgen suppression with a LHRH agonist (goserelin) + 1 month cyproterone acetate to external irradiation in patients with prostate cancer with high metastatic risk (10-year follow-up). Patients were randomly assigned (1:1) to receive radiotherapy alone or radiotherapy plus immediate androgen suppression.
The primary endpoint was clinical disease-free survival. The secondary endpoints were overall survival, distant metastasis-free survival, cause-specific mortality, and locoregional control.
The following results were published in the literature:
« Between May 22, 1987, and Oct 31, 1995, 415 patients were randomly assigned to treatment groups and were included in the analysis (208 radiotherapy alone, 207 combined treatment). Median follow-up was 9·1 years (IQR 5·1–12·6). 10-year clinical disease-free survival was 22·7% (95% CI 16·3–29·7) in the radiotherapy-alone group and 47·7% (39·0–56·0) in the combined treatment group (hazard ratio [HR] 0·42, 95% CI 0·33–0·55, p<0·0001).
10-year overall survival was 39·8% (95% CI 31·9–47·5) in patients receiving radiotherapy alone and 58·1% (49·2–66·0) in those allocated combined treatment (HR 0·60, 95% CI 0·45–0·80, p=0·0004), and 10-year prostate-cancer mortality was 30·4% (95% CI 23·2–37·5) and 10·3% (5·1–15·4), respectively (HR 0·38, 95% CI 0·24–0·60, p<0·0001). No significant difference in cardiovascular mortality was noted between treatment groups both in patients who had cardiovascular problems at study entry (eight of 53 patients in the combined treatment group had a cardiovascular related cause of death *vs* 11 of 63 in the radiotherapy group; p=0·60) and in those who did not (14 of 154 *vs* six of 145; p=0·25). Two fractures were reported in patients allocated combined treatment. »

RTOG 85-31 Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma-long-term results of phase III RTOG 85-31 Pilepich M, et.al. Int. J. Radiation Oncology Biol. Phys 2005; 61: 1285-1290

This study was designed to evaluate the effectiveness of adjuvant androgen suppression, using goserelin, in unfavorable prognosis carcinoma of the prostate treated with definitive radiotherapy (RT). Eligible patients were randomized to either RT or adjuvant Goserelin (Arm I) or RT alone followed by observation and application of Goserelin at relapse (Arm II).The primary endpoint was Absolute Survival.
The secondary endpoints were Local Failure, formation of Distant Metastasis and Prostate Cancer Death (also referred to as Disease Specific Mortality).
The following results have been published in the literature:
Between 1987 and 1992, when the study was closed, 977 patients were entered: 488 to Arm I and 489 to Arm II. As of July 2003, the median follow-up for all patients was 7.6 years and for living patients was

11 years. At 10 years, the absolute survival rate was significantly greater for the adjuvant arm than for the control arm: 49% vs. 39%, respectively (p = 0.002). The 10-year local failure rate for the adjuvant arm was 23% vs. 38% for the control arm (p <0.0001). The corresponding 10-year rates for the incidence of distant metastases and disease-specific mortality was 24% vs. 39% (p <0.001) and 16% vs. 22% (p = 0.0052), respectively, both in favor of the adjuvant arm.

Study published by McLeod D, Zinner N, Tomera K, Gleason D, Fortheringham N, Campion M et.al. A phase 3, multicenter, open-label, randomized study of abarelix versus leuprolide acetate in men with prostate cancer. Urology 2001; 58: 756-6 is summarized below.

Methods

Study participants

Men were eligible for study enrollment if they were at least 18 years of age and were candidates for neoadjuvant hormonal therapy; had metastatic disease (Stage D1 or D2); had increasing PSA levels after radical prostatectomy, radiation therapy, or other local therapy; were scheduled for an initial course of intermittent therapy; had a life expectancy of greater than 6 months; had adequate renal, hepatic, and cardiac function; and had a serum testosterone level between 220 ng/dL and two times the upper limit of normal

Men were excluded if they required immediate treatment for severe bone pain from metastases, spinal cord compression, bilateral hydronephrosis, symptoms of bladder neck outlet obstruction, or azotemia from metastatic prostate cancer.
Men were also excluded if they had a history of, or concurrent, secondary cancer; had a recent history of clinically significant drug hypersensitivity to LHRH agonists or LHRH antagonists; had an unstable concurrent medical condition; had received prior hormonal therapy for prostate cancer, except for neoadjuvant hormonal therapy; were taking or planning to take herbal therapy to treat their prostate cancer; were receiving or had received corticosteroids (including inhalants) within 90 days; or were receiving or had received finasteride or other 5-alpha-reductase inhibitors within 30 days before enrollment.

Treatments

Patients were randomly assigned to receive abarelix injectable suspension 100 mg or leuprolide acetate 7.5 mg. Physician-supervised intramuscular injections were administered on days 1, 29, 57, 85, 113, and 141. Men in the abarelix group received an additional injection of the study drug on day 15. As clinically indicated, patients could continue treatment with the study drug for up to 1 year.

Objectives

The objective of the study was to evaluate the levels of testosterone and other hormones in men with prostate cancer treated with abarelix versus leuprolide acetate

Outcomes/endpoints

Three prospectively defined primary efficacy endpoints were evaluated. A testosterone surge was defined as a serum testosterone measurement that exceeded the baseline level by 10% or greater on any two of days 2, 4, or 8. The rapidity of the reduction in the testosterone values was based on the achievement of castration (castration was defined as a testosterone measurement of 50 ng/dL or less) on day 8. The achievement and maintenance of medical castration from days 29 through 85 was determined by the achievement of medical castration on day 29 with no two consecutive non castrate testosterone values 2 weeks apart between days 29 and 85, inclusive.

The secondary efficacy endpoints included the rate of medical castration on days 2, 4, and 15. Endocrine and biochemical efficacy were also evaluated by the measurement of DHT, LH, FSH, and the rate of change in the PSA level with time.

Sample size

Sample size was composed of 269 men of which 180 received abarelix and 89 received leuprolide acetate.

Randomisation

Patients were randomized (2:1) to treatment according to four strata defined by the screening testosterone values (220 to 500 ng/dL and greater than 500 ng/dL) and body weight (less than 200 lb and 200 lb or more).

Blinding (masking)

Not applicable, this was an open-label trial.

Statistical methods

The proportions of men experiencing a testosterone surge and the proportions of men with medical castration on day 8 were compared between the treatment groups using Fisher's exact test. The equivalence in the proportion of patients who achieved and maintained castration was evaluated using a 95% confidence interval on the difference in the proportions between the two treatment groups. The endocrine and PSA levels were compared between the treatment groups using the Wilcoxon rank sum test

Results

Participant flow

Two hundred sixty-nine men received abarelix (n = 180) or leuprolide acetate (n =89). Ninety-eight percent of the abarelix group and 95% of the leuprolide acetate group completed treatment through day 85.

Baseline data

Table 6. Baseline demographics and disease characteristics

	Treatment Group	
	Abarelix (n = 180)	Leuprolide Acetate (n = 89)
Race/ethnicity* (%)		
White	159 (88)	73 (82)
African American	10 (6)	8 (9)
Hispanic	6 (3)	6 (7)
Asian	5 (3)	2 (2)
Age (yr)		
Median	73	74
Range	49–88	49–89
Weight (lb)		
Median	190	184
Range	132–365	130–300
Testosterone (ng/mL)†		
Median	350	338
Range	162–818	112–834
Disease stage*		
T1, T2 (local)	76 (42)	44 (49)
T3, T4 (regional)	32 (18)	13 (15)
D0–D2 (advanced)	72 (40)	32 (36)
Gleason grade*		
2–4	16 (9)	5 (6)
5–6	68 (38)	32 (36)
7	52 (29)	29 (33)
8–10	37 (21)	19 (21)
Unknown	7 (4)	4 (4)
ECOG performance status*		
0 (normal activity)	170 (94)	86 (97)
1 (symptomatic but ambulatory)	9 (5)	3 (3)
2 (ambulatory >50% of the time)	0	0
Unknown	1 (1)	0
Baseline PSA (ng/mL)*		
0 to <4	30 (17)	15 (17)
4 to 10	60 (33)	32 (36)
>10 to 20	37 (21)	20 (22)
>20	47 (26)	21 (24)
Unknown	6 (4)	1 (1)
Reason for treatment*		
D1/D2 stage	15 (8)	7 (8)
Rising PSA	67 (37)	29 (33)
Neoadjuvant therapy	67 (37)	32 (36)
Intermittent therapy	31 (17)	21 (24)
None of the above	1 (1)	0

Key: ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen.
Numbers in parentheses are percentages.
** Percentages are based on the number of patients in each treatment group.*
† All screening testosterone values ≥220 ng/dL.

Outcomes and estimation

No man who received abarelix experienced a testosterone surge compared with 82% of the men who received leuprolide acetate (P <0.001). The median increase from the baseline testosterone levels on days 2, 4, and 8 in the leuprolide acetate group was 45%, 54%, and 15%, respectively (interquartile range 23% to 68%, 30% to 101%, and -12% to 36%, respectively). After day 29, a comparable percentage of men achieved and maintained castration.

Forty-three (24%) of 176 men in the abarelix group had achieved medical castration on day 2 of the study (1 day after the initial injection), 99 (57%) of 173 on day 4, and 129 (72%) of 180 on day 8 (Table II). None of the leuprolide acetate treated patients had achieved medical castration by day 2, 4, or 8 (P <0.001). On day 15, 134 (75%) of 179 abarelix patients had achieved medical castration compared with 9 (10%) of 88 leuprolide acetate- treated patients (P<0.001). When a post hoc analysis was done defining castration as a testosterone level of 20 ng/dL or less, the results were similar (**Table 7**). Medical castration was achieved and maintained by 91.7% of the abarelix-treated patients and 95.5% of the leuprolide acetate-treated patients (95% confidence interval, -9.7% to 2.1%).

In men who had achieved castration on day 29, castration was maintained by 98.8% of the abarelix group (95% confidence interval, -2.5% to 4.7%) and 97.7% of the leuprolide acetate group

Table 7 Median testosterone values and rapidity of median castration

	Abarelix (n = 180)				Leuprolide Acetate (n = 89)					
Study Day	n	Median T (ng/dL)	T ≤20 ng/dL (n)	T ≤50 ng/dL (n)	n	Median T (ng/dL)	T ≤20 ng/dL (n)	T ≤50 ng/dL (n)	*P* Value*	*P* Value†
Baseline	180	350	—	—	89	338	—	—	—	—
2	178	59	5 (3)	43 (24)	87	529	0	0	NS	<0.001
4	173	37	31 (18)	99 (57)	84	578	0	0	<0.001	<0.001
8	180	29	60 (33)	129 (72)	89	406	0	0	<0.001	<0.001
15	179	20	92 (51)	134 (75)	88	94	0	9 (10)	<0.001	<0.001
29	179	11	136 (76)	167 (93)	88	15	58 (66)	86 (98)	NS	NS

KEY: T = testosterone; NS = not significant.
Percentage of men castrated is based on number of men evaluated in the treatment group that day (n). To be considered castrated on day 2, he must have also been castrated on days 4 and 8; to be considered castrated on day 4, he must have also been castrated on day 8. Lower limit of sensitivity of the assay was 8 ng/dL; values below the detected limit are reported as 8 ng/dL.
** Fisher's exact test, comparison of abarelix and leuprolide acetate castration rates for T ≤20 ng/dL.*
† Fisher's exact test, comparison of abarelix and leuprolide acetate castration rates for T ≤50 ng/dL.

The median (dihydrotestosterone) DHT values followed a similar pattern to that of testosterone during the course of the study (***Table 8***) . The median DHT value in the abarelix group decreased from the baseline median as early as day 2; the median DHT in the leuprolide acetate group was increased over the baseline value through day 8.
In the abarelix group, the median LH decreased to the lower limit of detection by day 2 and remained there through day 85 (***Table 8***). The median LH level in the leuprolide acetate group increased to 4.3 times the baseline value on day 2, remained at or above baseline through day 8, and decreased to the lower limit of detection (1 IU/L) from days 29 through 85.
In the abarelix group, the median FSH level decreased to below the baseline value as early as day 2 and continued to decrease through day 57 to the lower limit of detection (***Table 8***). It increased slightly on day 85, but was still below the level achieved by the leuprolide acetate group. The median FSH level in the leuprolide acetate group increased to 2.3 times the baseline value on day 2, and, although it decreased through day 15, the median FSH value in the leuprolide acetate group appeared to gradually increase through day 85. Patients in the abarelix group attained a statistically significant lower FSH level on all days from day 2 to 85, except for day 15.

Table 8. Median dihydrotestosterone, luteinizing hormone, and follicle-stimulating hormone

TABLE III. *Median dihydrotestosterone, luteinizing hormone, and follicle-stimulating hormone*

	DHT* (pg/mL)		LH† (IU/L)		FSH‡ (IU/L)	
Study Day	Abarelix Depot	Leuprolide Acetate	Abarelix Depot	Leuprolide Acetate	Abarelix Depot	Leuprolide Acetate
Baseline	337.0	393.0	6.0	7.0	8.0	9.0
2	93.5	471.0	1.0	30.0	5.0	21.0
4	64.0	510.0	1.8	14.0	3.0	10.0
8	50.0	404.5	1.0	7.0	3.0	4.0
15	37.0	102.0	1.0	2.0	2.0	2.5
29	25.0	29.5	1.0	1.0	1.0	3.0

KEY: DHT = dihydrotestosterone; LH = luteinizing hormone; FSH = follicle-stimulating hormone.
** Lower limit of detection of the assay was 25 pg/mL; values below the detection limit reported as 25 pg/mL.*
† Lower limit of detection of the assay was 1 IU/L; values below the detection limit reported as 1 IU/L.
‡ Lower limit of detection of the assay was 1 IU/L; values below the detection limit reported as 1 IU/L.

The percentage of change in the PSA concentrations was significantly greater in the abarelix group than in the leuprolide acetate group (P<0.001) on days 15 (P<0.001) and 29 (P =0.001) and appeared to be comparable in the two treatment groups after day 29 (***Figure 7***).

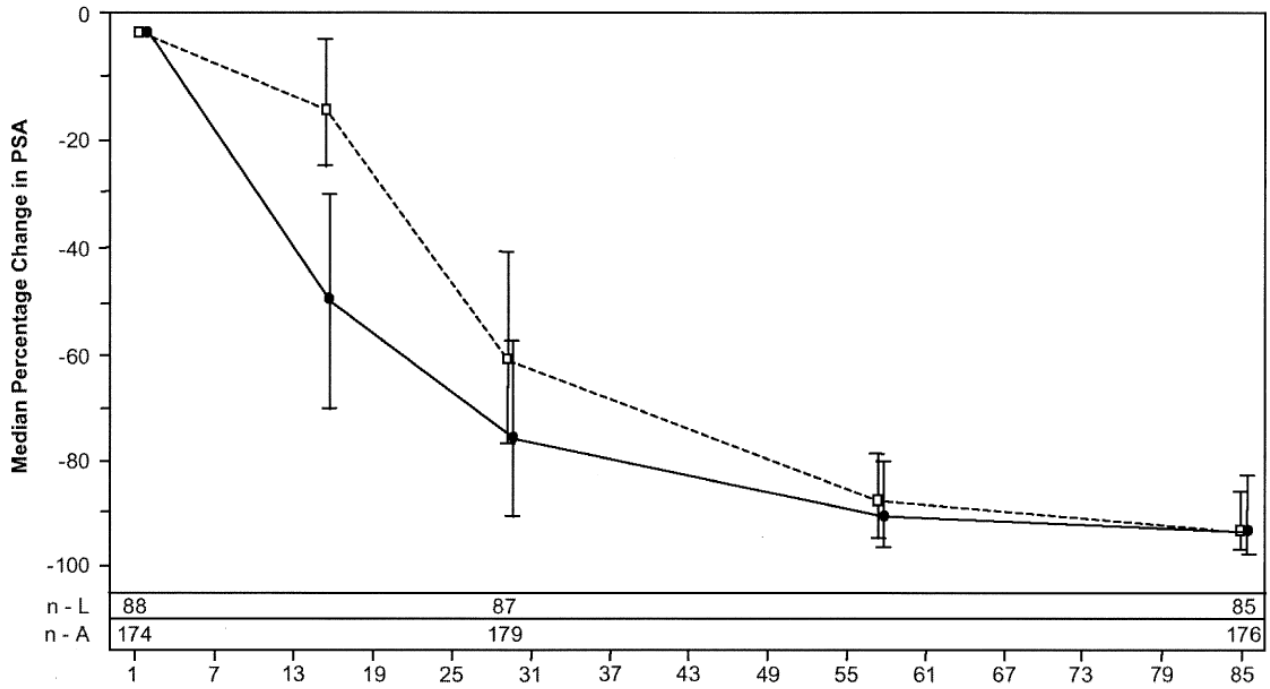


Figure 7. Median percentage of change in levels of PSA through day 85 by treatment group. Bars represent the interquartile range. On day 15, P<0.001 and on day 29, P=0.001. solid line, abarelix (A), leuprolide acetate (L).

Study published by Trachtenberg J, Gittelman M, Steidle C, Brazell W, Friedel W, Pessis D et.al A phase 3, multicentre, open label, randomized study of abarelix versus leuprolide plus daily antiandrogen in men with prostate cancer. Journal of Urology 2002; 167: 1670-1674

Only the abstract was available .

Purpose: *We compared the endocrinological and biochemical efficacy of abarelix depot, agonadotropin-releasing hormone antagonist, with that of a widely used combination of luteinizing hormone releasing hormone agonist and a nonsteroidal antiandrogen.*

Materials and methods: *A total of 255 patients were randomized to receive open label 100 mg.abarelix depot or 7.5 mg. leuprolide acetate intramuscularly injection on days 1, 29, 57, 85, 113 and141 for 24 weeks. Patients in the abarelix group received an additional injection on day 15 and those in the leuprolide acetate group received 50 mg. bicalutamide daily. Patients could continue treatment with study drug for an additional 28 weeks. The efficacy end points were the comparative rates of avoidance of testosterone surge (greater than 10% increase) within 7 days of the first injection and the rapidity of achieving reduction of serum testosterone to castrate levels (50 ng./dl. or less) on day8. Patients were monitored for adverse events and laboratory abnormalities.*

Results: *Abarelix was more effective in avoidance of testosterone surge (p <0.001) and the rapidity of reduction of testosterone to castrate levels on day 8 (p <0.001) than combination therapy. No significant*

difference was seen between the groups in the initial rate of decline of serum prostate specific antigen or the ability to achieve and maintain castrate levels of testosterone. No unusual or unexpected adverse events were reported.

Conclusions: *Abarelix as monotherapy achieves medical castration significantly more rapidly than combination therapy and avoids the testosterone surge characteristic of agonist therapy. Both treatments were equally effective in reducing serum prostate specific antigen, and achieving and maintaining castrate levels of testosterone.*

Analysis performed across trials (pooled analyses and meta-analysis)

2 meta-analysis and 2 reviews were cited in support of the application

Meta-analysis

Bria E, Cuppone F, Giannarelli D, Miella M, Ruggeri EM, Sperduti I, *et. al*. Does hormone treatment added to radiotherapy improve outcome of locally advanced prostate cancer? Meta-analysis of randomized clinical trials. Cancer 2009; 15: 3446-56

This meta-analysis was conducted "to quantify the magnitude of benefit of the addition of hormone treatment (HT) to exclusive radiotherapy for locally advanced prostate cancer". It included 7 clinical trials (4387 patients) with prior and concurrent radiotherapy and concluded that "Hormone suppression plus radiotherapy significantly decreases recurrence and mortality of patients with localized prostate cancer, without affecting toxicity".

Schmidt-Hansen M, Hoskin P, Kirkbride P, Hasler E, Bromham N. Hormone and radiotherapy versus hormone or radiotherapy alone for non-metastatic prostate cancer: a systematic review with meta-analyses. Clinical oncology 2014; e21-e46

This meta-analysis was conducted to compare the outcomes of patients who have received external beam radiotherapy and hormone therapy, alone or in combination, as first-line treatment for prostate cancer, and to examine whether certain patient risk groups benefit from any of the treatment strategies. It include 14 trials and concluded that "the published data support the use of combined treatment with androgen deprivation and radiotherapy for intermediate- and high-risk localised and locally advanced prostate cancer".

Reviews

Shevach J, Chaudhuri P, Morgans A. Adjuvant therapy in high-risk prostate cancer. Clinical advances in hematology and oncology 2019; 17: 45-53

This review summarizes the evidence for and against systemic adjuvant therapy in high-risk prostate cancer and describes ongoing investigations of strategies for risk stratification for optimal targeting of adjuvant treatment.

Payne H and Mason M. Androgen deprivation therapy as adjuvant/neoadjuvant to radiotherapy for high-risk localised and locally advanced prostate cancer: recent developments. BJC. 2011; 105: 1628-1634

This review examines ADT use in combination with radiotherapy to improve outcomes in localised or locally advanced disease and examines some of the latest developments in hormonal therapy for PCa with LHRH antagonists:
*Given the rapid onset of testosterone and PSA suppression with degarelix, there has been interest in the use of LHRH antagonists in combination with radiotherapy. In a study of NHT (*NB: neoadjuvant hormonal therapy) *in 378 men with localised PCa, biochemical response (i.e., PSA reduction) to NHT was a more important predictor of therapeutic benefit than the duration of NHT (Alexander et al, 2010). Consequently, for patients who achieve a rapid fall in PSA after starting NHT, it may be possible to minimise the duration of ADT and its related toxicities. Thus, rapid biochemical control with LHRH antagonists may therefore shorten the duration of NHT. Preclinical data also suggest that tumour volume reduction may be greater with the blocker degarelix than with the agonist leuprolide (Princivalle et al, 2007).*
The authors conclude that "*Biochemical response to neoadjuvant ADT before RT, not duration, appears to be the critical determinant of benefit in the setting of combined therapy. Individually tailored ADT duration based on PRPH-PSA (pre-RT, post-hormone PSA) would maximize therapeutic gain, while minimizing the duration of ADT and its related toxicities*."

2.4.3. Discussion on clinical efficacy

The mechanism of action of testosterone suppression by the LHRH antagonist degarelix has been validated in the initial MAA with appropriate studies. The non-inferiority of degarelix compared with the LHRH agonist leuprorelin to decrease testosterone level was also demonstrated in the initial MAA (CS21, Klotz et al.). Regarding the newly claimed indications, the MAH provided references to 5 studies (Study CS21, Study CS12, Study 00006, Study CS30 and study EORTC-1414) assessing degarelix with one of which ongoing (study (EORTC-1414).
Studies CS21 and study CS12 were assessed in the context of the initial MAA.

Study 00006 (PANDA) published by Sun *et al.* in 2019 was a phase III randomized trial assessing the effect of degarelix versus goserelin±bicalutamide of testosterone decrease in a population with all stage disease over 1 year. The baseline characteristics did not discriminate in intermediate and high risk of localized disease. The results showed non inferiority of degarelix versus goserelin ±bicalutamide on testosterone decrease at castration level. On the secondary endpoints, PFS and the absence of PSA failure was not different between both groups at Day 364. Of note, the PSA-PFS was significantly in favor of degarelix (82.3 vs 71.7 for degarelix and goserelin groups respectively).

Study CS30 published by Mason *et al.* in 2013 was a phase III randomized trial assessing the effect of 3 months neoadjuvant androgen suppression with degarelix or goserelin+bicalutamide in patients in men with intermediate- to high-risk prostate cancer who were scheduled to undergo subsequent radiotherapy. The primary endpoint was tumour volume reduction at week 12. This study was assessed in a previous variation for FIRMAGON (EMEA/H/C/000986/II/0015) and could support the indication in neoadjuvant setting as no difference was observed between degarelix and goserelin + bicalutamide.

Finally study EORTC-1414 assessing the effect of degarelix versus LHRH agonists + antiandrogen in adjuvant setting is ongoing and no data have been provided**.**

Three further studies, evaluated in the context of extension of indications for LHRH agonists, have been provided in support of the neoadjuvant treatment for patients with high-risk localized and localized disease: RTOG 86-10 (Pilepich et al.), TROG: 96.01 (Denham et al.) and RTOG 94-08 (Jones et al.).

RTOG 86-10 (Pilepich et al.) was a phase III randomized study to assess 16 weeks treatment with goserelin+ flutamide starting 2 months before radiotherapy versus radiotherapy alone in patients with clinical stage T2-T4 i.e. patients with localized disease. The primary end point of the study was locoregional control; secondary end points were disease-free survival (freedom from progression) and survival. From this publication it cannot be determined the proportion of patients with high-risk localized disease nevertheless in conjunction with study RTOG 92-02 (below) in which patients with high risk localized prostate cancer represented a large subgroups of the total study population, it is agreed that the study population as a whole benefits from combination treatment.

TROG 96.01 (Denham *et al.*) was phase III randomized trial to compare 3- or 6- neoadjuvant therapy with goserelin + flutamide versus radiotherapy alone in patients with locally advanced prostate cancer according to the title but with intermediate and high risk localized disease in addition according to the inclusion criteria. Primary endpoints were time to local failure and prostate-cancer-specific survival. The secondary endpoints were distant failure, disease-free survival, and freedom from salvage treatment. Analyses were done by intention to treat 6-month neoadjuvant androgen deprivation therapy (NADT) decreased distant progression (0·49, 0·31–0·76; p=0·001), prostate cancer-specific mortality (0·49, 0·32–0·74; p=0·0008), and all-cause mortality (0·63, 0·48–0·83; p=0·0008), compared with radiotherapy alone. In this study only two short term regimes were compared with no ADT, long-term ADT was not included but clinical data from other studies (not shown) demonstrated clinical benefit by addition of long-term ADT (3 years) to RT compared to short-term (6 months).

RTOG 94-08 (Jones *et al.*) was a phase III randomized trial in localized prostate cancer patients to assess the effect of 4 months neoadjuvant therapy with flutamide +goserelin or leuprorelin versus radiotherapy alone. The primary end point was overall survival. Secondary end points included disease-specific mortality, distant metastases, biochemical failure (an increasing level of PSA), and the rate of positive findings on repeat prostate biopsy at 2 years. Although "In all three risk subgroups, short-term ADT was associated with a significant reduction in biochemical failure », the authors discussed that a "reanalysis of the data according to risk subgroups showed that the gains in overall survival and reductions in disease-specific mortality were mainly limited to men in the intermediate-risk subgroup. […] Although the addition of short-term ADT to radiotherapy also appeared to be beneficial in the high-risk patients, the persistent significant increase in 10-year disease-specific mortality provides support for observations from other clinical trials showing that more than 4 months of ADT is required for maximum benefit. According to the described inclusion criteria on staging, patients included had low to intermediate risk prostate cancer which makes this publication not relevant for the claimed indications.

In these 3 studies the primary endpoints were not the volume reduction of the tumor but locoregional control, time to local failure, prostate-cancer-specific survival or overall survival were assessed depending on the trial, thus challenging their relevance in the current neoadjuvant indication. In RTOG 86-10 study, the proportion of patients with high-risk localized disease could not be determined. In study TROG 96.01 no significant reductions in mortality have been noted in either group assigned androgen deprivation. In *Study* 94-08 the gains in overall survival and reductions in disease-specific mortality were mainly limited to men in the intermediate-risk subgroup. The persistent significant increase in 10-year disease-specific mortality provides support for the observations from other clinical trials that more than 4 months of ADT is required for maximum benefit.
However, although it is considered that the primary goal of neoadjuvant therapy is still to cure the patient and not only to reduce the tumor volume, the testosterone and the PSA levels, the relevance of these 3 surrogate endpoints is considered widely accepted to allow a favorable outcome.

Adjuvant setting

No data with studies assessing degarelix in the adjuvant setting were provided, the only information available derives from a currently ongoing clinical trial sponsored by the EORTC cited above (EORTC-1414).

Studies supporting this application in the adjuvant setting are represented by studies conducted with LHRH agonists (EORTC 22961, RTOG 92-02, EORTC 22863, and RTOG 85-31).

EORTC 22961 (Bolla et al.) was a phase III randomized trial comparing radiotherapy plus short-term androgen suppression with radiotherapy plus long-term androgen suppression in the treatment of locally advanced prostate cancer (patients with high risk localized disease were also included). Androgen suppression was achieved by goserelin or triptorelin associated with an antiandrogen therapy (flutamide or bicalutamide for 6 months). OS was statistically significantly increased by long term androgen therapy.

RTOG 92-02 (Horowitz *et al*.) was a phase III randomized trial to assess Disease Free Survival (DFS), OS, local progression (LP), distant metastasis (DM), biochemical failure (BF), and disease-specific survival (DSS) of 4 months goserelin + flutamide before and during radiotherapy. Patient were then radomized to no further ADT or 24 months of goserelin. A statistically improvement in OS for long term ADT was observed in a subgroup of patients with a Gleason score of 8 to 10. After 10 years a benefit in terms of DFS and disease-specific survival, but not in terms of OS, was shown for RT in combination with 28 months ADT, compared to RT in combination with 4 months ADT

EORTC 22863 (Bolla *et al*.) was a phase III trial assessing the benefit of addition of long-term androgen suppression with goserelin + cyproterone acetate for 1 month in patients with prostate cancer with high metastatic risk with a 10-year follow-up. The primary endpoint was clinical disease-free survival. Analysis was by intention to treat. The secondary endpoints were overall survival, distant metastasis-free survival, cause-specific mortality, and locoregional control. The OS and clinical disease-free survival were statistically significant in favor of the combination treatment.

RTOG 85-31 (Pilepich *et al.*) was a phase III randomized trial to assess the effect of goserelin without anti-androgen started the last week of radiotherapy or at relapse in patients with locally advanced prostate cancer after a median follow-up of 7.6 years, confirmed the long-term benefit of adjuvant ADT, with a significantly greater 10-year OS (49% versus 39% in the ADT plus radiotherapy versus radiotherapy only group, p=0.002). The conclusion of this study mainly focusses on high-risk patients as described above, especially the high-risk definition referring to a Gleason Score ≥ 8. To note that this patient sub-population comprises only one third (32%) of patients.

2.4.4. Conclusions on the clinical efficacy

The efficacy data provided by the MAH support the indication for high-risk localised and locally advanced patient in neoadjuvant setting.

Regarding the adjuvant setting, the evidence of biological activity and indirect comparisons are convincing and demonstrate the ability to achieve chemical castration.

2.5. Clinical safety

The safety profile of FIRMAGON is well described.

The known adverse events of ADT are in relation with androgen deprivation: hot flushes, fatigue, loss of libido, weight increase, decrease in haemoglobin, and prolongation of the QT/QTc interval.

The most important risks associated with ADT are an increased risk of cardiovascular disease, a decreased bone density and new onset of diabetes.

For what concern the increase risk of cardiovascular disease a QT/QTc specific study, Study CS22 (EMA/H/C/986/II/0986/014G) was conducted to evaluate if degarelix had an impact on the QT/QTc prolongation and confirmed that degarelix has no inherent effect on the QT-interval.

Pooled data from the MAH phase 3 trials comparing LHRH agonists to degarelix suggested a lower risk of serious CV event or death from any cause with degarelix (Albersten *et al,* Eur Urol. 2014; 65 (3):565-73)

A safety study in patients with advanced prostate cancer treated with FIRMAGON (FE 200486 CS39 PASS) focused on cardiovascular events after long term treatment with degarelix compared to LHRH agonists. This study showed no significant differences between the groups.

In the same CS39 PASS study, glucose intolerance and type 2 diabetes mellitus were also compared between the groups with no difference observed.

Moreover, the approved RMP for degarelix concluded that known risks associated with degarelix no longer require additional risk minimization measures (RMM).

Regarding the safety profile of ADT with radiotherapy, a review published by Dorff *et al.* refers to a meta-analysis based on 8 randomized controlled trial suggests that the safety profile of ADT is not altered when used in combination with RT.
Moreover, results from a post-hoc analysis of RTOG 85-31 data suggested that there is no increased cardiovascular mortality of adjuvant ADT over salvage ADT (LHRH agonist administered at recurrence). Accordingly, RTOG 92-02 and EORTC 22961 also failed to detect an increase in cardiovascular mortality for the long-term ADT arm over the short-term ADT arm.

Safety information of degarelix or LHRH antagonists in combination with radiotherapy were presented in the Study 00006 and Study CS30.

Study 00006: Efficacy and safety of degarelix in patients with prostate cancer: Results from a phase 3 study in China Sun Y, *et.al*. Asian Journal of Urology 2019

Most of the AEs were mild to moderate in intensity. The incidence of treatment-emergent AEs was higher with degarelix than with goserelin (76.1% and 58.9%, respectively) Table 9. Predominantly general disorders and administration site conditions were reported in 52.1% of the degarelix patients. Most injection site reactions (35.0%) occurred after the first dose of degarelix and 29% following the other dosing intervals Table 9. There were 13 discontinuations due to an AE (four in the degarelix and nine in the goserelin group), however, none of these were assessed as treatment-related and none of the discontinuations were due to injection site reactions.
No marked trends were noted in data stratified by baseline PSA category and previous use of 5-alpha reductase inhibitors. Patients with metastatic disease reported higher incidence of severe AEs in the goserelin group as compared to the degarelix group (14.1% versus 6.7%, respectively).
There were 14 serious AEs (SAEs) reported by 12 patients (8.5%) treated with degarelix and 27 SAEs reported by 18 (12.8%) patients treated with goserelin. The most common SAEs were cardiac disorders, which occurred in five patients (3.5%) in the degarelix group and two patients (1.4%) in the goserelin group. Two patients each in the degarelix and the goserelin group had SAEs assessed as treatment-related (acute kidney injury and lung infection possibly related to degarelix and femur fracture and

haematuria possibly related to goserelin). Two patients (1.4%) receiving degarelix had increased PSA levels that were reported as SAEs, of which one SAE led to withdrawal of the patient from the study. There were no other notable AEs

Table 9. Treatment-emergent adverse events-safety analysis set (5% in either group)

	Degarelix (*N*=142)	Goserelin (*N*=141)
All AEs, *n* (%)	108 (76.1%)	83 (58.9%)
Cardiac disorders	11 (7.7%)	15 (10.6%)
Gastrointestinal disorders	11 (7.7%)	12 (8.5%)
General disorders and administration site conditions	74 (52.1%)	12 (8.5%)
Infections and infestations	27 (19.0%)	20 (14.2%)
Procedural complications investigations	18 (12.7%)	29 (20.6%)
Musculoskeletal and connective tissue disorders	11 (7.7%)	15 (10.6%)
Nervous system disorders	6 (4.2%)	7 (5.0%)
Renal and urinary disorders	9 (6.3%)	11 (7.8%)
Skin and subcutaneous tissue	10 (7.0%)	4 (2.8%)
Vascular disorders	18 (12.7%)	18 (12.8%)
Any injection site reactions (initiation dose)	49 (35.0%)	1 (0.7%)
Any injection site reactions (maintenance dose)	41 (29.0%)	1 (0.7%)

AEs, adverse events.

Study CS30: Neoadjuvant androgen deprivation therapy for prostate volume reduction, lower urinary tract symptom relief and quality of life improvement in men with intermediate -to high-risk prostate cancer: A randomized non-inferiority trial of degarelix versus goserelin plus bicalutamide. Mason M, *et.al*.. Clinical Oncology 2013;25:190-196

Safety Treatment-emergent adverse events were reported by 87 and 83% of patients in the degarelix and goserelin groups, respectively. Treatment-emergent adverse events that were considered possibly/probably related to the drug (i.e. adverse drug reactions) were reported by 78 and 73% of patients in the degarelix and goserelin groups, respectively (Table 10). Most of the treatment-emergent adverse drug reactions were hot flushes (60% degarelix, 63% goserelin).
Other commonly reported reactions were injection site reactions (predominantly pain 33%, erythema 25%, pruritus 7% and swelling 6%), which were reported by degarelix treated patients only, erectile dysfunction (8% degarelix, 9% goserelin), asthenia (7 and 9%), fatigue (6 and 9%) and decreased libido (7 and 6%). Serious adverse events considered as probably/possibly related to treatment by the investigator were reported in two patients in the degarelix group and the events included liver enzyme elevations (four reports from one patient) and urinary retention (one report from one patient).

Table 10 Incidences of adverse drug reactions occurring in ≥5% of any group by MedDRA system organ class and preferred term

MedDRA system organ class/preferred term	Degarelix	Goserelin/ bicalutamide
Safety analysis set	181 (100%)	64 (100%)
Any adverse drug reaction*	142 (78%)	47 (73%)
Gastrointestinal disorders		
Nausea	2 (1%)	3 (5%)
General disorder and administration site conditions		
Injection site pain	60 (33%)	1 (2%)
Injection site erythema	45 (25%)	0 (0%)
Asthenia	13 (7%)	6 (9%)
Injection site pruritus	13 (7%)	0 (0%)
Injection site swelling	11 (6%)	0 (0%)
Fatigue	10 (6%)	6 (9%)
Injection site induration	9 (5%)	0 (0%)
Psychiatric disorders		
Libido decreased	12 (7%)	4 (6%)
Reproductive system and breast disorders		
Erectile dysfunction	14 (8%)	6 (9%)
Vascular disorders		
Hot flush	108 (60%)	40 (63%)

* An adverse event with a causality assessed as possibly or probably related to treatment.

2.5.1. Discussion on clinical safety

No new safety data of degarelix are provided within this variation application. The safety profile of FIRMAGON is well described.

The safety profile of degarelix or LHRH antagonists in combination with radiotherapy is less known. However, safety data from the neoadjuvant study CS30 suggested that the safety profile of degarelix is similar to that of goserelin + bicalutamide with the exception of injection site reaction. This is in line with the safety data from CS21 study assessing degarelix versus leuprorelin.
Regarding the adjuvant indication, the ongoing PEGASUS trial -is considered to be of interest in providing such data.
Relevant data regarding the combination with radiotherapy provided by the MAH applies to LHRH agonists.
While no Clinical Study Report of ongoing studies of degarelix in combination with RT are available yet, preliminary safety data do not indicate new emerging signals.

2.5.2. Conclusions on clinical safety

Safety data provided by the MAH support the indication for high-risk localised and locally advanced patient in neoadjuvant setting. While only preliminary data were provided, the safety profile of degarelix in combination with RT is reassuring and it is endorsed that no new safety data could be presented.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The last PSUSA dates from 2019 which covered the period from February 17, 2016 to February 17, 2019.

The frequency of PSURs is 3 years so the next one is expected in 2022

2.6. Risk management plan

No RMP has been submitted with this application.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 5.1, and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH claims the use in high-risk localized and locally advanced hormone dependent prostate cancer in combination with radiotherapy and as neo-adjuvant treatment prior to radiotherapy in patients with high-risk localized or locally advanced prostate cancer.

Locally advanced prostate cancer is defined as prostate cancer that has spread through the prostatic capsule to involve tissues and structures adjacent to the prostate gland, including regional lymph nodes, the urinary bladder and seminal vesicles, but not nodes and organs distant to the pelvis. In contrast, localised prostate cancer describes a condition where the neoplasm is confined within the prostate gland itself and where the prostatic capsule has not been breached by the tumour.

High-risk prostate cancer includes locally advanced prostate cancer (T3–4 N0-X M0) and high-risk localized prostate cancer (T2c N0-X M0) with either a Gleason score >7 and/or a baseline PSA of >20 ng/ml.

3.1.2. Available therapies and unmet medical need

According to European guidelines for high–risk localized disease, possible treatments are radical prostatectomy with extended pelvic lymph node dissection to selected patients with low tumor volume or radiotherapy (external beam radiation therapy-EBRT) in combination with long term ADT.

Regarding locally advanced disease radical prostatectomy with extended pelvic lymph node dissection is recommended only in highly selected patients with cT3b-T4 N0 or any cN1 only as part of multi-modal therapy. EBRT in combination with long term ADT is an option for patients with cN0 disease. Moreover ADT monotherapy may be offered only to patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < 12 months, and either a PSA > 50 ng/mL, a poorly-differentiated tumour or troublesome local disease related symptoms.

Currently only LHRH agonists are authorized in the claimed indications of neoadjuvant/adjuvant for high-risk localized disease and locally advanced disease. No LHRH antagonists are authorized in the claimed indications.

3.1.3. Main clinical studies

To support the indication, the MAH summarised study results described in literature. The main efficacy results are based on a number of randomized studies assessing degarelix versus LHRH agonists on testosterone suppression.

3.2. Favourable effects

Regarding the neoadjuvant setting, only study CS30 (Mason *et al*.) is considered relevant. This study demonstrated non inferiority of degarelix versus goserelin +bicalutamide for the reduction of the prostate volume when administered for 12 weeks as neoadjuvant before radiotherapy with mean (± standard deviation) percentage changes of -36.0 ± 14.5% and -35.3 ± 16.7% for degarelix and goserelin, respectively, for the FAS and -36.2 ±14.5% and -35.4 ±16.9% for degarelix and goserelin, respectively, for the per-protocol analysis set. Data on testosterone and PSA reduction confirm the non-inferiority of degarelix compared to goserelin. The median level of testosterone for degarelix-treated patients at weeks 4, 8 and 12 was 0.05 ng/ml and the corresponding figures for goserelin were 0.17, 0.05 and 0.05 ng/ml, respectively.

Overall, there were seven (of 180) and five patients (of 64) on degarelix and goserelin, respectively, with a serum testosterone level >0.5 ng/ml on at least one occasion. The estimated cumulative probabilities of testosterone <0.5 ng/ ml between days 28 and 84 were 96% for the degarelix treatment group and 92% for the goserelin treatment group.
The median percentage changes in PSA were also comparable; for degarelix the decreases from baseline at weeks 4, 8 and 12 were -71.6, -84.8 and -89.2%, respectively, whereas for goserelin they were -72.2, -93.1 and -93.0%.

3.3. Uncertainties and limitations about favourable effects

The main uncertainty is the lack of efficacy data with degarelix in the adjuvant setting however the mechanism of action and the similar reduction in testosterone and PSA level of degarelix compared to LHRH agonists supports an extrapolation of efficacy in terms of clinical endpoints in the adjuvant setting.

Moreover the provision of results from the ongoing PEGASUS study, requested as soon as available, will further clarify efficacy and safety data of degarelix with RT in the adjuvant setting.

3.4. Unfavourable effects

The safety profile of FIRMAGON is well established:

The known adverse events of ADT in relation with androgen deprivation are: hot flushes, fatigue, loss of libido, weight increase, decrease in haemoglobin, and prolongation of the QT/QTc interval.

The most important risks associated with ADT are increased risk of cardiovascular disease, decreased bone density and new onset of diabetes.

The recently assessed PSUR of degarelix included a PASS which did not provide any information in the claimed indications. No indication of combination with radiotherapy was detailed as off label use.

Safety data of CS30 suggest a similar safety profile between degarelix and LHRH agonists when used in neoadjuvant setting except for System Organ Classes of General disorder and administration site condition. This is in line with study 00006 with 52.1% and 8.5% for degarelix and goserelin respectively and with study CS21 for Preferred Term injection site reaction 40% and <1 % for degarelix and leuprorelin respectively.

3.5. Uncertainties and limitations about unfavourable effects

Specific data with degarelix for long term use as adjuvant therapy in combination with radiotherapy are missing. However, based on experience with LHRH agonists deleterious adverse effects of degarelix when administrated concomitantly to radiotherapy are not expected. A phase III study (EORTC 1414, PEGASUS) assessing degarelix versus goserelin is ongoing and will provide further confirmation.

3.6. Effects Table

Table 11 ***Effects Table for degarelix in neoadjuvant and in combination with radiotherapy in high-risk localized and locally advanced hormone dependant prostate cancer (Mason* et al. *2013)***

Effect	Short description	Unit	Degarelix	Goserelin plus bicalutamide	Uncertainties / Strength of evidence
TPV	Decrease in prostate volume (FAS)	%	-36.0±14.5	-35.3±16.7	
	Decrease in prostate volume PP	%	-36.2±14.5	-35.4±16.9	
Testosterone	Median testosterone serum level week 4	ng/ml	0.5	0.17	
	Median testosterone serum level week 8 and 12	ng/ml	0.5	0.5	
PSA	change serum PSA level from baseline week 4	%	-71.6	-72.2	
	change serum PSA level from baseline week 8	%	-84.8	-93.1	
	change serum PSA level from baseline week 12	%	-89.2	-93.0	

Effect	Short description	Unit	Degarelix	Goserelin plus bicalutamide	Uncertainties / Strength of evidence
hot flush	Incidence of hot flush	%	60	63	
General disorders and administration site conditions	Incidence of general disorders and administration site conditions	%	54	22	This difference is in line with previous studies of degarelix vs a LHRH agonist
erectile dysfunction	Incidence of erectile dysfunction	%	8	9	
Asthenia	Incidence of asthenia	%	7	9	
Fatigue	Incidence of fatigue	%	6	9	
decreased libido	Incidence of deceased libido	%	7	6	

Abbreviations: TVP: total volume prostate, PSA: prostate specific antigen

Notes: Efficacy and safety data in adjuvant setting were not available.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The similar total volume prostate reduction observed with goserelin and degarelix in study CS30 is relevant for neoadjuvant setting. Others results in this study show a similar reduction of testosterone and PSA serum level up to 12 weeks of ADT. This is in accordance with previous observation of non-inferiority of degarelix compared to leuprorelin in achieving decrease in testosterone and PSA level up to 12 months in patients with no curative options, not planned to receive radiotherapy (Study CS21).

Comparison of degarelix to LHRH agonists on testosterone level and PSA can be relevant when considering the adjuvant setting. The antitumoral Mechanism of Action of degarelix and LHRH agonists is indirect and depends on the depth of castration. The effect of degarelix to reduce testosterone to castration level has been established. An extrapolation of efficacy in terms of clinical endpoints based on the mechanism of action in the adjuvant setting for which direct data are not available yet can be acceptable. An ongoing phase III trial will further confirm this aspect.

The safety profile of degarelix is well established and the last PSUSA dated from 2019 didn't show unexpected issues. The safety profile of degarelix in adjuvant to radiotherapy is not documented, however, and adverse interaction with concurrent RT is not expected.

3.7.2. Balance of benefits and risks

Considering the neoadjuvant setting, it is acknowledged that degarelix reduces the volume of the prostate to similar extend to that of goserelin and it is already described in section 5.1 of the SmPC of degarelix. Testosterone levels and PSA levels were also decreased to similar extend between both groups. Both groups showed similar safety profiles except for injection site reactions for which degarelix shows a poorer toxicity profile than goserelin. This difference was however expected.

Considering the adjuvant setting, the mechanism of action and the similar reduction in testosterone and PSA level of degarelix compared to LHRH agonists supports the claimed indication.

Result from the ongoing PEGASUS study are requested as soon as they are available to further clarify efficacy and safety data of degarelix with RT in the adjuvant setting.

3.7.3. Additional considerations on the benefit-risk balance

A phase III study assessing degarelix versus goserelin is ongoing (Phase IIIb Randomized Trial Comparing Irradiation Plus Long Term Adjuvant Androgen Deprivation With GnRH Antagonist Versus GnRH Agonist Plus Flare Protection in Patients With Very High Risk Localized or Locally Advanced Prostate Cancer. A Joint Study of the EORTC ROG and GUCG. PEGASUS. EORTC 1414, EUdraCT 2015-005098-19, EORTC 1414, PEGASUS).

3.8. Conclusions

The overall B/R of Firmagon is positive.

The MAH is recommended to provide the results of the PEGASUS-EORTC1414 to confirm efficacy and safety data of degarelix in combination with radiotherapy.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indications to include:

- Extension of indication to include treatment of high-risk localized and locally advanced hormone dependent prostate cancer in combination with radiotherapy. As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

- Extension of indication to include treatment as neo-adjuvant prior to radiotherapy in patients with high-risk localised or locally advanced hormone dependent prostate cancer. As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.