Original Article

Current Urology

OPEN

Patients and physician satisfaction of Degarelix in androgen deprivation therapy for advanced hormone-dependent prostate cancer in the Netherlands

Hossain Roshani[a,*], Erik P.M. Roos[b], Henk W. Elzevier[c], Cees van de Beek[d], Peter van Winkel[e], Rob C.M. Pelger[c]

[a]Department of Urology, Haga Ziekenhuis, The Hague, The Netherlands; [b]Department of Urology, Antonius Ziekenhuis, Sneek, The Netherlands; [c]Department of Urology, Leiden University Medical Center, Leiden, The Netherlands; [d]Department of Urology, Maastricht University Medical Center, Maastricht, The Netherlands; [e]Medical Affairs, Ferring B.V. Hoofddorp, The Netherlands

Abstract

Background: To explore the effectiveness and safety of the gonadotropin-releasing hormone antagonist, Degarelix, for the treatment of advanced hormone-dependent prostate cancer (PCa) in a real-world setting.

Methods: In this noninterventional study, patients with advanced hormone-dependent PCa were included. Primary endpoints were progression-free survival (PFS) failure defined as either prostate-specific antigen failure, additional therapy related to PCa, or death. Secondary endpoints included patient and physician satisfaction scores, urinary symptoms, and adverse events (AEs).

Results: Of 274 patients with PCa, 271 received at least 1 dose of Degarelix. At a median follow-up of 12.2 (interquartile range 6.2–22.0) months, 148 patients (60.2%) had PFS failure. Thirty-five patients (13%) withdrew from the study due to AEs, 23 patients (8.4%) died, and 36 patients (13%) completed 3 years' follow-up. Urinary symptoms significantly decreased over time. In the safety population, 87.8% of patients reported AEs, with injection-site reactions commonly reported. The majority of physicians and patients considered the therapy satisfactory and well tolerated.

Conclusions: In this observational study, Degarelix treatment was well accepted by men with advanced hormone-dependent PCa. Compared with phase III studies, a higher proportion of patients had PFS failure, possibly due to the inclusion of men with more advanced disease in the current study, and more men reported AEs.

Keywords: Androgen antagonists; Clinical trials; Degarelix; Prostate-specific antigen; Prostatic neoplasms

1. Introduction

Prostate cancer (PCa) is the most common malignancy in men in Europe and the USA, comprising about a quarter of new cancer cases.[1] Androgen ablation by gonadotropin-releasing hormone (GnRH) agonists has been the mainstay of treatment for locally advanced and metastatic PCa for over 20 years. Degarelix, a third-generation GnRH antagonist, is widely approved for the treatment of advanced PCa. A phase III trial with Degarelix showed a comparable safety profile to that of the GnRH agonist, leuprolide, although injection-site reactions were more frequent.[2] The mechanism of action of Degarelix is different from GnRH agonists, as Degarelix reversibly binds to and blocks GnRH receptors on cells in the pituitary gland. However, the targeted end results of chronic hypogonadism, and its associated metabolic consequences, are expected to be comparable. In addition to the more rapid suppression of testosterone and prostate-specific antigen (PSA) compared with GnRH agonists, sub-analyses have shown encouraging results regarding time to PSA progression or death,[3] superior control of serum alkaline phosphatase,[4] and the potential for fewer musculoskeletal, urinary tract, and cardiovascular events.[5,6] The long-term effects of Degarelix, however, have not been thoroughly studied. The primary aim of the current study was to investigate the effectiveness and safety profile of long-term Degarelix therapy in daily practice in The Netherlands.

2. Patients and methods

This was a multicenter, long-term, prospective, observational, noninterventional study conducted in The Netherlands, performed in accordance with ethical principles that originate from the Declaration of Helsinki. As an observational study, ethics committee approval was not required although the Central Committee on Research Involving Human Subjects was consulted.

The planned enrollment was 250 patients treated with Degarelix. The treatment decision was made prior to study inclusion. Enrollment criteria included a confirmed diagnosis of advanced hormone-dependent PCa intended for treatment with Degarelix. Patients provided written informed consent prior to

* Corresponding Author: Dr Hossain Roshani, Haga Teaching Hospital, Els Borst-Eilersplein 275, 2545 AA, The Hague, The Netherlands. E-mail address: H.Roshani@hagaziekenhuis.nl (H. Roshani).

Current Urology, (2021) 15, 204–208

Received December 4, 2019; Accepted March 11, 2020.

http://dx.doi.org/10.1097/CU9.0000000000000029

inclusion and could withdraw at any time. Exclusion criteria included any contraindication for the prescription of Degarelix, patients who had previously participated in the study and stopped for any reason, and patients already receiving Degarelix. Prior hormone therapy was not contraindicated.

Baseline data were collected at a routine outpatient visit prior to Degarelix treatment. Follow-up data were collected at routine visits at months 1 and 3, and then every 3 months (±4 weeks) until study discontinuation or for a maximum of 3 years. All visits were intended as part of routine clinical care and no additional procedures or physical examinations were required as part of the study.

2.1. Investigational medicinal product

Degarelix is a GnRH antagonist approved for the treatment of adult male patients with advanced hormone-dependent PCa. The starting dose of 240 mg is administered as 2 subcutaneous injections of 120 mg with a subsequent monthly maintenance dose of 80 mg by subcutaneous injection.

2.2. Endpoints

The primary endpoint was progression-free survival (PFS) failure rate. The protocol definition of PFS failure was either PSA failure, additional therapy related to PCa, or death, (whichever occurred first). PSA failure was defined as an increase in serum PSA of 50%, and at least 5 ng/mL, compared with the lowest PSA value after treatment initiation, measured on 2 consecutive occasions at least 2 weeks apart. Additional therapy related to PCa included radiation, antiandrogens, second-line treatment, and investigator-reported disease progression. Secondary endpoints included adverse events (AEs), patient and physician satisfaction scores, and the International Prostate Symptom Score (IPSS).[7]

2.3. Patient and physician satisfaction scores

At 6 and 12 months, the patients' perceptions of the dosing interval of Degarelix and the frequency of seeing a nurse and urologist were recorded. At the final visit, the overall perception of the therapy according to both the physician and the patient were recorded.

2.4. Clinical laboratory variables

The following parameters were recorded at all visits if available: PSA, testosterone, alkaline phosphatase levels, fasting plasma glucose, and hepatic enzymes (alanine transaminase and aspartate transaminase).

2.5. Safety and adverse events

AEs were recorded and summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) coding system, version 18.0. During the first 6 months of therapy (starting dose and the first 5 monthly maintenance doses), the occurrence of the individual safety report (ISR) was recorded.

2.6. Analysis populations

The following analysis populations were defined: intention to treat (ITT; all enrolled patients), safety (all patients having received at least 1 dose of Degarelix), Per Protocol (PP; all patients having received at least 1 dose of Degarelix according to the approved prescribing information, with data from at least 1 follow-up visit and with no severe protocol violations), and efficacy (all patients in the PP population who were not scheduled on short-term [eg, neoadjuvant] therapy and for whom primary endpoint data were available).

2.7. Statistical analyses

Continuous variables are summarized as mean ± standard deviation or median and interquartile range (IQR). Discrete variables are summarized as frequencies and percentages. The Kaplan–Meier method was used to estimate survival curves of time to PFS failure. The PFS failure rate was calculated as the number of failures per 100 years at risk. Statistical analyses were performed in SPSS version 24.[8] Event rates with 95% mid-P exact confidence intervals and p values for the comparisons of event rates were calculated using OpenEpi.[9] Change from the baseline in IPSS was tested two-sided using a nonparametric test (Wilcoxon rank sum test). A p value of <0.05 was considered significant.

3. Results

Overall, 274 patients were included in the ITT population, of whom 36 (13.1%) completed the 3-year study period. Reasons for study withdrawal were PFS failure (n = 153), treatment discontinuation (n = 67), withdrawal of consent (n = 8), protocol violation (n = 6), and patient no longer treated at participating center or site ending participation in study (n = 4). Patient demographics and baseline characteristics are shown in Table 1. PCa was newly diagnosed in 172 patients (62.8%) and preexisted in 101 patients (36.9%). The median follow-up was 12.4 months (IQR 6.2–22.0 months).

3.1. Progression-free survival failure

In the efficacy population (n = 246), 148 patients (60.2%) experienced PFS failure. The median time until PFS failure was 14.8 months (Fig. 1). The PFS failure rate was higher in patients who had a previous therapy for PCa (74.7 failures per 100 years) than newly diagnosed patients (41.3 failures per 100 years) ($p = 0.003$) (Table 2). Patients with a Gleason score > 7 had a higher failure rate than those with a Gleason score < 7 ($p = 0.01$). There was no clear relationship between nadir testosterone in the first 6 months of therapy and PFS failure.

3.2. Patient satisfaction scores

Monthly Degarelix administration was considered a satisfactory frequency by 82% (173/211) of patients at 6 months and 83.6% (117/140) at 12 months. Administration frequency was perceived as too often by 17.5% (37/211) of patients at 6 months and 16.4% (23/140) at 12 months. After 1 year of treatment, seeing the urologist approximately every 3 months was thought "just right" by 90.0% (126/140) of patients and "too little" by 5.7% (8/140). Routine monthly nurse visits for Degarelix administration were perceived as "too often" by 5.1% (10/196) and 9.6% (13/136), and "just right" by 93.4% (183/196) and 90.4% (123/136) of patients at 6 months and 12 months, respectively. Regular contact with a doctor or nurse was considered reassuring by 71.9% (151/210) and 66.9% (93/139) of patients at 6 and 12 months, respectively. According to the majority of patients (69.6%, 165/237), treatment tolerability was either "good" or "very good" whereas 8.4% (20/237) of patients rated tolerability as "poor." Most patients reported being "satisfied" or "very satisfied" with the therapy (68.7%, 162/236), 23.3% (55/236) were "moderately satisfied," and 6.4% (15/236) of patients were "not satisfied." No differences in patient satisfaction were observed between hormone treatment-naïve patients (82%) or those with a history of previous hormone treatment (84%), including 3-month depot GnRH agonists.

Table 1

Patient demographics and baseline characteristics (ITT population).

Parameter	Number of patients assessed	ITT population (n = 274)
Age, yr	273	
Median (IQR)		72.0 (66.0–78.0)
Range		47.0–92.0
Body mass index (kg/m^2)	253	
Median (IQR)		25.8 (24.1–28.2)
Range		15.8–41.4
PSA (ng/mL)	273	
<10		33 (12.1)
10–20		37 (13.6)
20–50		63 (23.1)
>50		140 (51.3)
Testosterone (ng/mL)	107	
<0.1		6 (5.6)
0.1–0.2		8 (7.5)
0.2–0.5		6 (5.6)
>0.5		87 (81.3)
Gleason score, n (%)	274	
6		27 (9.9)
7		90 (32.8)
8–10		139 (20.7)
Unknown		18 (6.6)
Tumor characteristics, n (%)	274	
T1		15 (5.5)
T2		37 (13.5)
T3		143 (52.2)
T4		78 (28.5)
Unknown		1 (0.4)
Regional lymph node status, n (%)	274	
N0		69 (25.2)
N1		49 (17.9)
N2		22 (8)
N3		3 (1.1)
Nx[a]		128 (46.7)
Unknown		3 (1.1)
Distant metastases	274	
M0		87 (31.8)
M1		151 (55.1)
Mx[a]		32 (11.7)
Unknown		4 (1.5)
Previous therapy[b]	274	90 (32.8)
Hormonal therapy		73 (26.6)
Maximum androgen blockade		20 (7.3)
Anti-androgen monotherapy		25 (9.1)
GnRH agonists		28 (10.2)
Nonhormonal therapy		47 (17.2)
Radical prostatectomy		16 (5.8)
Radiotherapy		36 (13.1)
Other		5 (1.8)
Unknown		1 (0.4)

IQR = interquartile range; ITT = intention to treat; PSA = prostate-specific antigen; GnRH = gonadotropin-releasing hormone.

[a] Not known.

[b] More than 1 response possible; therefore, sum of subgroups may exceed group total.

3.3. Physician satisfaction scores

The tolerability of the therapy was reported as "good" or "very good" by the treating physician for 75.5% (194/257) of patients whereas for 8.2% (21/257) of patients, tolerability was deemed "poor." Physicians reported that in 63% (160/254) of patients they were "satisfied" or "very satisfied" with the therapy and in 9.5% (24/254) of cases they were not satisfied. The therapy was deemed as either "effective" or "very effective" by physicians in 67.3% (173/257) of patients and as "ineffective" in 3.9% (10/257).

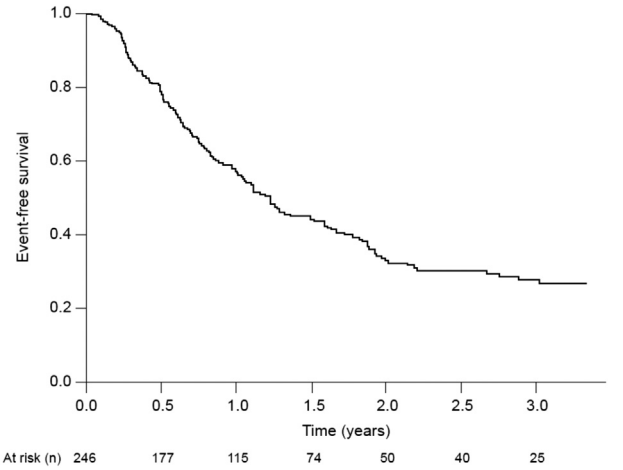

Figure 1. Survival curve of time in years until PSA failure or additional therapy for the treatment of PCa or death (efficacy population). PCa = prostate cancer; PSA = prostate-specific antigen.

3.4. International prostate symptom score

At 1-month follow-up, the IPSS score had significantly decreased compared with the baseline ($p < 0.001$). At the end of treatment, the average IPSS score reduction was 2.4 points (n = 32; $p = 0.029$). Patients with serious lower urinary tract symptoms (LUTS) at the baseline (IPSS 20–35) had the greatest reduction in IPSS throughout the study, with a mean reduction of 7.7 points at the end of study ($p = 0.012$; Table 3).

3.5. Adverse events

Of the safety population, 87.8% (238/271) of patients reported an AE, while the majority of events (91.2%) were nonserious. Forty patients (14.8%) had a serious AE, 5.5% had more than 1 serious AE, and 35 patients (13%) withdrew due to AEs. Overall (ITT population), 23/274 patients (8.4%) died and all deaths were considered unrelated or unlikely to be related to treatment. Twenty deaths were considered due to PCa and 1 each due to lung metastases, colon metastases, and cerebral hematoma. The AEs observed were generally as expected and no new safety signals were reported.

The majority of AEs were injection-site reactions, which were reported by 67.5% (183/271) of patients, while 168 injection-site reactions were not considered serious. injection-site reactions included erythema (7.4%), injection-site pain (4.4%), swelling (3.7%), and injection-site swelling (3.7%). The incidence of injection-site reactions fell over time with 63.9%, 62.4%, and 54.0% of patients reporting injection-site reactions after 1, 3, and 6 months, respectively. The occurrence of an ISR did not affect the likelihood of completing the study, with 86.1% (180/209) of patients reporting an ISR and 88.1% (53/60) of those who did not report an ISR discontinued the study before 3 years. General disorders/administration-site events, and skin and subcutaneous tissue disorders were reported as AEs leading to treatment discontinuation in 35 patients. Therefore, it can be postulated that a maximum of 12.9% of patients (35/271) discontinued due to injection-site reactions.

Table 2

Failure rate (per 100y at risk) by previous PCa therapy, Gleason score, and nadir testosterone (efficacy population).

			PFS failure	
	n	Years at risk	Patients with event, n (%)	Failure rate per 100yr at risk (95% CI)
Total	246	298	148 (60.2)	49.7 (42.2–58.2)
New diagnosis of PCa	150	206	85 (56.7)	41.3 (33.2–50.8)
Already diagnosed	95	91	62 (65.3)	67.9 (52.5–86.5)
Previous therapy for PCa				
Watchful waiting	11	12	3 (27.3)	24.4 (6.2–66.3)
Any previous therapy	84	79	59 (70.2)	74.7 (57.4–95.7)
Nonhormonal	44	46	32 (72.7)	69.0 (48.0–96.2)
Hormonal	69	51	50 (72.5)	97.3 (73.0–127.3)
Maximum androgen blockade	20	10	18 (90.0)	173.8 (106.2–269.4)
Anti-androgen monotherapy	23	19	13 (56.5)	69.9 (38.9–116.5)
GnRH agonists	26	2	19 (73.1)	84.8 (52.6–130.0)
Gleason score				
<7	23	36	8 (34.8)	22.0 (10.2–41.7)
7	79	99	47 (59.5)	47.7 (35.4–62.9)
>7	127	150	79 (62.2)	52.5 (41.9–65.1)
Unknown	17	12	14 (82.4)	112.9 (64.3–184.9)

CI = confidence interval; GnRH = gonadotropin-releasing hormone; PCa = prostate cancer; PFS = progression-free survival.

4. Discussion

The primary objective of this noninterventional study was to assess the long-term effectiveness and safety of Degarelix in men with advanced hormone-dependent PCa in a real-world setting. The patients enrolled more accurately reflected the clinical use of Degarelix than in randomized studies and the actual care that patients received was recorded, generating long-term effectiveness and safety data. However, real-world data may suffer from incomplete information and a greater chance of bias and/or confounding.[10]

We would like to emphasize that 68.3% of our patients were suffering from advanced metastatic disease. The majority of them (80.7%) were diagnosed to be T3 or more with higher PSA above 10 ng/mL (88%) and Gleason scores above 8 in >50% of the cases. These factors may be the reason for "low real-world numbers" of median PFS of 12.2 months while 13.1% of patients completed the 3 years of study as described in the results. The majority of withdrawals (153/274) was due to the PFS failure, which again reflects that these patients suffered from advanced disease.

After 1 year of follow-up, we found a greater proportion of patients had PFS failure than in the pivotal randomized phase III study (around 40% compared with 7.7%, respectively).[3] There may be because of 2 main reasons. First, many more patients had advanced disease (TNM stage 3) than in the phase III study (55% and 19%, respectively). The relatively low number of T1 and T2 patients in our study (5.5% and 13.5%, respectively) is possibly because these patients were diagnosed with stage T1/T2 PCa but not included in the current study until their disease progressed. Second, the PSA failure rate may have been higher than previously reported as PSA failure was defined by either the treating physician's opinion or meeting the protocol-defined definition. Treating physicians were twice as likely to report PSA failure than recorded according to the protocol definition. This is, however, in line with clinical practice, that after 2 or 3 consecutive increases in PSA levels a treatment intervention would be considered, irrespective of the percentage PSA increase or absolute PSA values. Also, the patient may request a change in treatment as increasing PSA levels are seen as a major concern.

Injection-site reactions were also reported at a higher rate than in phase III studies,[2,3] particularly for patients receiving maintenance doses. This is likely explained by an awareness among patients and physicians that injection-site reactions can occur and proactive questioning of patients of their experience leading to increased reporting compared with clinical trials where only spontaneous reports were recorded. Interestingly, injection-site reactions did not appear to be associated with patients discontinuing treatment, with similar percentages of those who did and did not report an ISR not completing the study.

Degarelix may provide improved LUTS relief in symptomatic patients compared with a GnRH agonist, especially in patients with a baseline IPSS > 13.[11–13] A similar trend was noted in the current study, with patients with serious LUTS at the baseline (IPSS score 20–35) having decreases in IPSS of more than 6 points at all assessed time points.

Axcrona et al.[11] also found higher relief in IPSS in the Degarelix group in comparison with Goserelin treated patients. They reported that the higher the baseline of IPSS, the greater the

Table 3

IPSS change from the baseline by the baseline LUTS (PP population).

	1 month			3 months			End of study		
Baseline LUTS	n	Mean ± SD	p	n	Mean ± SD	p	n	Mean ± SD	p
Mild	22	−0.3 ± 1.8	0.5	21	1.0 ± 2.7	0.123	11	1.0 ± 2.9	0.232
Moderate	34	−1.7 ± 4.3	0.046	31	−0.7 ± 9.0	0.118	13	6.0 ± 27.3	0.183
Severe	19	−6.1 ± 5.0	<0.001	13	−6.4 ± 10.3	0.071	9	−7.7 ± 5.3	0.012

IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; PP = per protocol; SD = standard deviation.

relief of symptoms when treated. This is also our experience as described in Section 3.4.

Both patients and physicians indicated satisfaction with the treatment. Irrespective of the outcome or AEs, as the majority of patients and physicians considered the tolerability of the therapy to be either "good" or "very good" and a similarly large proportion were satisfied or very satisfied with the treatment. Over 80% of patients also agreed that monthly administration of Degarelix was acceptable. This was possibly related to the reassurance of regular contact with a doctor or nurse, which was also reported by the majority of patients when questioned. These results of both patients and physician satisfaction with the treatment are similar to those as previously reported.[2]

5. Conclusions

Monthly administration of Degarelix is well accepted among men with advanced hormone-dependent PCa in The Netherlands. The PFS failure rate was likely due to the higher proportion of patients with more advanced disease at the baseline compared with other studies and that the treatment could be discontinued according to the judgement of the treating physician. injection-site reactions were common, although the majority were not serious and were not associated with treatment discontinuation. Importantly, this real-world study confirmed that physicians and patients were mostly satisfied with Degarelix treatment and patients were satisfied with regular visits to or from healthcare professionals.

Acknowledgments

Medical writing support, provided by Dr Matthew deSchoolmeester (PhD) of Bioscript, Macclesfield, UK, was funded by Ferring Pharmaceuticals.

Statement of ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As an observational study, ethics committee approval was not required although the Central Committee on Research Involving Human Subjects (CCMO) was consulted. Informed consent was obtained from all individual participants included in the study.

ClinicalTrials.gov Identifier: NCT01215526.

Conflict of interest statement

H Roshani: no conflict of interest.
EPM Roos, HW Elzevier, C van de Beek, and RCM Pelger: received study fees from Ferring.
P van Winkel: full-time employee of Ferring B.V., The Netherlands.

Funding source

This study was sponsored by Ferring B.V., The Netherlands.

Author contributions

None.

References

[1] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013;49(6):1374–1403.
[2] Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: A 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int* 2008;102 (11):1531–1538.
[3] Tombal B, Miller K, Boccon-Gibod L, et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. *Eur Urol* 2010;57 (5):836–842.
[4] Schröder FH, Tombal B, Miller K, et al. Changes in alkaline phosphatase levels in patients with prostate cancer receiving degarelix or leuprolide: results from a 12-month, comparative, phase III study. *BJU Int* 2010;106 (2):182–187.
[5] Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. *Eur Urol* 2014;65(3):565–573.
[6] Klotz L, Miller K, Crawford ED, et al. Disease control outcomes from analysis of pooled individual patient data from five comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone agonists. *Eur Urol* 2014;66(6):1101–1108.
[7] Barry MJ, Fowler FJJr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148(5):1549–1557.
[8] IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, IBM Corp.
[9] Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health. www.openepi.com, version 3.01, updated 06/04/2013.
[10] Mahajan R. Real world data: Additional source for making clinical decisions. *Int J Appl Basic Med Res* 2015;5(2):82.
[11] Axcrona K, Aaltomaa S, da Silva CM, et al. Androgen deprivation therapy for volume reduction, lower urinary tract symptom relief and quality of life improvement in patients with prostate cancer: Degarelix vs goserelin plus bicalutamide. *BJU Int* 2012;110(11):1721–1728.
[12] Cui Y, Zong H, Yan H, Li N, Zhang Y. Degarelix versus goserelin plus bicalutamide therapy for lower urinary tract symptom relief, prostate volume reduction and quality of life improvement in men with prostate cancer: A systematic review and meta-analysis. *Urol Int* 2014;93(2): 152–159.
[13] Mason M, Richaud P, Bosnyak Z, Malmberg A, Neijber A. Degarelix versus goserelin plus bicalutamide in the short-term relief of lower urinary tract symptoms in prostate cancer patients: Results of a pooled analysis. *Low Urin Tract Symptoms* 2017;9(2):82–88.

How to cite this article: Roshani H, Roos EP, Elzevier HW, van de Beek C, van Winkel P, Pelger RC. Patients and physician satisfaction of Degarelix in androgen deprivation therapy for advanced hormone-dependent prostate cancer in the Netherlands. *Curr Urol.* 2021;15 (4):204–208. doi: 10.1097/CU9.0000000000000029.