Six-month leuprorelin acetate depot formulations in advanced prostate cancer: a clinical evaluation

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Damian Gruca
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Abstract: For nearly three decades, gonadotropin-releasing hormone (GnRH) agonists, particularly leuprorelin acetate (LA), have served as an important part of the treatment armamentarium for prostate cancer. The introduction of LA depot formulations provided a significant improvement in the acceptance of this therapy; however, their indicated treatment duration of 1 to 4 months was still not long enough to satisfy all medical needs. For this reason some manufacturers developed new injectable formulations that provide testosterone suppression for 6 months. This review article assesses key publications in order to compare these long-acting, commercially available, LA depot formulations and their clinical performance. The literature search identified 14 publications; by excluding reviews, duplications, and non-English articles, only three original papers describing clinical trial remained for review: two focused on microsphere-based LA formulations with either a 30 mg or 45 mg dose and one focused on a gel-based leuprorelin acetate with a 45 mg dose. All products were tested in individual clinical trials and have demonstrated their efficacy and safety.

Keywords: androgen deprivation therapy, GnRH agonist, leuprorelin acetate, prostate cancer, leuprolide acetate

Gonadotropin-releasing hormone (GnRH) agonists, including leuprorelin acetate (LA), have served as an important part of the treatment armamentarium for hormone-sensitive prostate cancer for nearly three decades. Initially this form of androgen deprivation therapy (ADT) was cumbersome, painful for patients, and challenging for physicians as they involved daily injections at the practitioner’s office, severely curtailing patients’ quality of life and increasing adverse effects, such as injection site pain and reaction.

However, the introduction of long-acting LA depot formulations has provided a significant improvement in the acceptance of this therapy, although the initial 1 to 4 month therapies did not have a sufficient duration to satisfy all medical needs. For this reason some manufacturers developed new injectable formulations that provide testosterone suppression for 6 months. These formulations were individually tested in clinical trials to evaluate their benefit–risk profiles as the basis of regulatory approvals.

Therapeutic background
Prostate cancer (PCa) is a solid tumor with a high responsiveness to systemic hormonal therapy. It was described as early as 1840 by Hunter, who noted that physiologic prostatic epithelium demonstrated signs of atrophy after physical castration. A century later in 1941, Huggins showed that a level of testosterone and prostate-specific
antigen (PSA) must be maintained in order for prostate cancer cells to grow and that a suppression of these levels induces a reduction in tumor size. Thus, the treatment of PCa was originally surgical castration or the use of estrogen therapy, and ADT in this form was introduced into the strategy of prostate cancer treatment. In 1971, research performed by Schally et al led to the presentation of a new form of ADT – luteinizing hormone-releasing hormone (LHRH) or GnRH agonists. GnRH agonists were less cardiotoxic than estrogens and offered an easy, more patient-friendly, and reversible method of ADT that proved to be oncologically equivalent to surgical castration.

Initially, the use of GnRH agonists took the form of daily intramuscular or subcutaneous injections. This required daily visits to the oncologist or urologist and greatly increased the chance of adverse effects, such as injection site reactions and injection site pain, but also made patient compliance with therapy more difficult. Over the last 20 years, extended release formulations of 1, 3, 4, and 6 months have been developed, significantly increasing patient acceptance to therapy and easing treatment burdens for physicians.

Since their introduction, the GnRH agonists have been used either as monotherapy or in combination with antiandrogens, especially for the prevention of flare-ups shortly after the start of treatment. Table 1 contains European Urology Association guidelines for the use of ADT in various PCa disease situations.

### Mechanism of action

Although the mechanism of action of LA is well understood, certain aspects of its pharmacology should be noted. The competitive occupation of LH receptors by LA in the anterior pituitary gland leads to their reactive downregulation, which results in the cessation of sex steroid production in the gonads after an initial flare effect. This can be considered an all-or-nothing principal, which does not allow for dose-dependent testosterone (or estrogen) response. The result is the achievement of castration-equivalent sex steroid levels. The reason testosterone levels in men do not reach zero lies in the adrenal pathway of cholesterol metabolism, which is not affected by the action of LA on the hypothalamic–pituitary–gonadal axis or bilateral orchietomy.

Despite the maintenance of castration levels of androgens in serum, prostate cancer usually progresses and can eventually reach the castration resistant (CRPC) stage. It has been demonstrated that the production of androgens also takes place in prostatic tumor cells, promoting tumor progression. In order to counteract this mechanism for fueling the growth of CRPC cells, new agents have been discovered, such as abiraterone acetate, enzalutamide (formerly known as MDV3100), and orteronel (TAK-700). These new agents target either the androgen receptor within the tumor cell directly, or counteract the androgen production through enzyme inhibition. In the vast majority of patients, the use of GnRH agonists continued as the base therapy while many of these new compounds were tested. Due to the fact that the development of the new 6-month LA formulations and the new CRPC drugs were conducted at approximately the same time, little is known about their concomitant use.

### Formulations

Although the active pharmacological ingredient (API) is the same for all leuprorelin acetate products, there are significant differences in the way their formulation is designed and how these differences affect their individual pharmacological profile.

Over the last few years several different manufacturers have developed a variety of GnRH agonist formulations that have been approved for a 6-month treatment interval based on their ability to suppress testosterone below the castration level of 50 ng/dL in patients with prostate cancer. These products include two formulations of the microsphere-based LA (Lupron®, Lucrin®, Daronda®, Sixantone®, Procrin®, Procrin® [name varies by country]) with either 30 mg or 45 mg doses. The 30 mg dose is mainly used in Europe, Asia, and Latin America, whereas the 45 mg doses were introduced either as microspheres (Lupron®) in the USA only or as a gel-based formulation (Eligard®) in the EU and the USA.

Based on the different delivery technologies, regardless of API, some differences in clinical performance exist between the formulations that need to be discussed. While all iterations of LA have an identical molecular structure, the delivery system of each varies considerably. For many years LA has been delivered by only using a lyophilized, microsphere, drug depot delivery system.

The microsphere-based LA products achieve their drug release in a biphasic manner. In the first phase the product is released within a relatively short time from the surface of the spheres, and this function as the initiation dose and establishes an effective plasma concentration. In the second phase, the microspheres are “digested” over 6 months and release the API as a maintenance dose to achieve the same constant plasma concentrations over time. The chemical compositions of the microspheres differ slightly between

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**Table 1: European Urology Association guidelines for the use of ADT in various PCa disease situations**

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Treatment Options</th>
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<tr>
<td>Localized PCa</td>
<td>Surgery (if possible) or ADT</td>
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<tr>
<td>Locally advanced PCa</td>
<td>ADT with or without radiation therapy</td>
</tr>
<tr>
<td>Metastatic PCa (M1a)</td>
<td>ADT with or without radiopharmaceuticals</td>
</tr>
<tr>
<td>Metastatic PCa (M1b)</td>
<td>ADT with or without abiraterone acetate, enzalutamide, or orteronel</td>
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**Note:** ADT = androgen deprivation therapy
Eligard, on the other hand, is a gel-based formulation delivered by using a biodegradable polymer of D,L-lactide-co-glycolide dissolved in N-methyl-2-pyrolidone. In this delivery system, the polymer is provided separately from the lyophilized drug compound (LA) and must be mixed within 30 minutes or less of injection. It is injected in a liquid form that condenses into a solid subcutaneous depot, which releases the drug over time. Over the treatment period of 6 months, the gel is slowly dissolved and the API is released into the blood.

<table>
<thead>
<tr>
<th>Table 1 Indications for hormonal therapy</th>
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<tr>
<td><strong>Hormonal therapy indications</strong> for castration</td>
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<tr>
<td>General guidelines</td>
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<td>M1 symptomatic</td>
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<td>M1 asymptomatic</td>
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<td>N+</td>
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<tr>
<td>Locally advanced M0</td>
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<tr>
<td>Locally advanced disease treated with radiotherapy</td>
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<tr>
<td>Localized disease treated with radiotherapy</td>
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<tr>
<td>High-risk d’Amico</td>
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<tr>
<td>Intermediate-risk d’Amico</td>
</tr>
<tr>
<td>Locally advanced asymptomatic</td>
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<tr>
<td>unfit for local definitive treatment</td>
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<tr>
<td>Antiangdrenes</td>
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<tr>
<td>Short-term administration</td>
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<td>Nonsteroidal antiandrogen monotherapy</td>
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</table>

**Abbreviations:** IAD, intermittent androgen deprivation; ADT, androgen-deprivation therapy; CAB, complete androgen blockade; CSS, cancer-specific survival; EPC, Early Prostate Cancer Trialists’ Group; LE, level of evidence; LHRH, luteinizing hormone-releasing hormone; QoL, quality of life; OS, overall survival; PCa, prostate cancer; PFS, progression-free survival; RP, radical prostatectomy; M1, metastatic patient; M0, no metastases; N, nodes; T, tumor; Gy, gray.

the 1-, 3-, 4-, and 6-month formulations and determine the timeframe over which API is released.

Eligard, on the other hand, is a gel-based formulation delivered by using a biodegradable polymer of D,L-lactide-co-glycolide dissolved in N-methyl-2-pyrolidone. In this delivery system, the polymer is provided separately from the lyophilized drug compound (LA) and must be mixed within 30 minutes or less of injection. It is injected in a liquid form that condenses into a solid subcutaneous depot, which releases the drug over time. This transformation is independent of body temperature and can occur in vivo as well as ex vivo. Over the treatment period of 6 months, the gel is slowly dissolved and the API is released into the blood.

The microsphere-based LA was compared directly to the gel-based LA in only one phase I study. This single-center trial was conducted with 1-month depots (7.5 mg)
in 32 healthy male volunteers (mean age 38.3 ± 8.4 years; range 21–52 years). The pharmacokinetic measurements showed an initially higher release of LA from microspheres compared to gel-based product ($C_{\text{max}}$ 27.0 ± 4.9 ng/mL versus 19.0 ± 8.0 ng/mL at $T_{\text{max}}$ 1.0 ± 0.4 hours versus 2.1 ± 0.8 hours). After an initial lower release of LA from the gel-based LA formulation, the total area under the curve was greater from the gel-based formulation than for microspheres (479 ± 132.6 ng·hours/mL versus 248 ± 65.0 ng·hours/mL), which resulted in longer testosterone suppression (49 days versus 35 days).19

Based on the promising data from early development, pivotal trials were conducted to achieve registrations for the 6-month formulations. This review article identifies key publications of now commercially available 6-month depot formulations of LA and evaluates their clinical performance.

Materials and methods


The major subjects for the search were leuprorelin acetate 6-month depots and prostate cancer, combined with the following keywords and phrases: mechanism of action, efficacy, safety, pharmacokinetics (PK), pharmacodynamics (PD), along with patient perspective on quality of life, product preferences, satisfaction, convenience, cost, benefit, and health economics. We excluded from the review non-English articles, reviews and duplications, nonoriginal papers and case reports.

Results

The literature search identified twelve publications for three different products: two microsphere-based leuprorelin acetate formulations of either 30 mg or 45 mg dose depots and a gel-based leuprorelin acetate 45 mg dose depot formulation.120–30 Of the twelve publications identified, only three original papers of the 6-month formulations fulfilled the criteria for comparison in this review (Table 2).

Efficacy and safety

The safety and efficacy of leuprorelin acetate depots have been studied at each formulation level and published by Kienle and Lubben (1-month depot),21 Tunn et al (1- and 3-month depots),32 Jocham (3-month depot),33 Tunn and Wiedey (3- and 6-month depots),1 and Spitz et al (6-month depot)20 for microsphere-based LA formulations. Gel-based LA was tested separately and published by Perez-Marreno et al (1-month depot),34 Chu et al (3-month depot),35 and Crawford et al (6-month depot).28

Microsphere-based 30 mg LA depot

In a study by Tunn and Wiedey1 comparing the LA 3-month (11.25 mg) depot to the LA 6-month (30 mg) depot formulations, efficacy parameters again included the reduction of serum testosterone to castrate levels and the reduction of PSA levels. Tunn and Wiedey1 found that in 178 patients, results were similar between the two groups. Median values of testosterone and rate of response showed no relevant differences. PSA levels decreased 88% and 89% in 3-month and 6-month groups, respectively. In the 3-month treatment group, 77.6% of patients experienced an adverse event (AE) while 79.2% of patients in the 6-month group experienced an AE. Other safety variables were similar, with 3.4% and 4.2% of patients experiencing an AE leading to withdrawal, 12.1% and 15.8% of patients experiencing a serious adverse event (SAE), and two and four deaths occurring in the study in the 3-month and 6-month groups, respectively. Most common AEs included flushing (43.1%, 34.2%, respectively), increased sweating (10.3%, 5.8%), injection site induration (3.4%, 5.8%), and fatigue (1.7%, 1.7%).

Table 2 Summary of included publications

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Microsphere-based 30 mg</th>
<th>Microsphere-based 45 mg</th>
<th>Gel-based 45 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>Safety and clinical efficacy of a new 6-month depot formulation of leuprorelin acetate in patients with prostate cancer in Europe</td>
<td>Efficacy and Safety of leuprolide acetate 6-month depot for suppression of testosterone in patients with prostate cancer</td>
<td>A 12-month clinical study of LA-2585 (45.0 mg): a new 6-month subcutaneous delivery system for leuprolide acetate for the treatment of prostate cancer</td>
</tr>
<tr>
<td>Author</td>
<td>UW Tunn and K Wiedey1</td>
<td>A Spitz, JM Young, L Larsen, C Mattia-Goldberg, J Donnelly, and K Chwalsiz28</td>
<td>E David Crawford, Oliver Sartor, Franklin Chu, Ramon Perez, Gary Karlin, and J Steve Garrett28</td>
</tr>
<tr>
<td>Journal</td>
<td>Prostate Cancer and Prostatic Diseases</td>
<td>Prostate Cancer and Prostatic Diseases</td>
<td>Journal of Urology</td>
</tr>
</tbody>
</table>
Microsphere-based 45 mg LA depot
Spitz et al\(^2\) also studied safety and efficacy in a microsphere-based LA 45.0 mg 6-month formulation over 12 months. The primary endpoint for this study was the proportion of patients with suppressed serum testosterone, which was achieved in 93.4% of 151 subjects within the first 4 weeks of the study and maintained for 24 weeks with each depot injection. In addition, after week 14 of the study, PSA levels were reduced to below 3 ng/mL and remained there through the end of the study. Hot flush was reported by 58.3% of subjects, injection site pain was reported by 17.9%, and fatigue was reported by 11.9%.

Gel-based 45 mg LA depot
The safety and efficacy of the gel-based LA 45.0 mg 6-month depot formulation was studied by Crawford et al\(^2\) in a 12-month open-label study of 111 subjects. The primary endpoint was the reduction of serum testosterone to castrate level and the reduction of PSA. Of the 111 subjects, 93% completed the study. Testosterone suppression was achieved by 99% of subjects within 28 days (mean 21.2 days). In addition, PSA was reduced from 39.8 ± 21.5 ng/mL to 1.2 ± 0.3 ng/mL after 12 months. Eighty-two subjects reported 211 AEs, only one of which was considered to be severe and not related to the study drug. The most common AEs included hot flush, injection site burning, fatigue, testicular atrophy, and gynecomastia.

In these studies of 6-month (30 mg and 45 mg) formulations, the results of safety and efficacy endpoints were remarkably similar. Incidence of adverse events was also comparable across these studies. Results of the pivotal studies are summarized in Table 3. These studies used similar efficacy and safety endpoints and parameters, allowing a direct comparison.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Microsphere-based 30 mg</th>
<th>Microsphere-based 45 mg</th>
<th>Gel-based 45 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>Men (age 18–85) with newly diagnosed prostate cancer of any stage or grade requiring hormonal therapy</td>
<td>Male (age 18+) with confirmed prostate cancer NCI Stage 2–4</td>
<td>Male with prostate cancer of Stage &gt; T1</td>
</tr>
<tr>
<td>Sample size</td>
<td>296 patients enrolled in study; 120 were in 30 mg 6-month depot group</td>
<td>151 patients entered</td>
<td>111 patients with prostate cancer enrolled; 103 completed study</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Safety and tolerability of a new 6-month versus 3-month depot</td>
<td>Efficacy measured by suppression of serum T to ≤50 ng/dL from week 4 through week 48</td>
<td>Efficacy measured as decrease in total serum T to ≤50 ng/dL during study</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td>Efficacy comparison measured by suppression of serum T to ≤50 ng/dL, PSA, LH, FSH, and EORTC response</td>
<td>Safety and other efficacy parameters: PSA and LH concentrations</td>
<td>Safety and PSA concentrations</td>
</tr>
<tr>
<td>Efficacy results</td>
<td>EORTC response rate: no progression in 90% of patients. Partial remission was seen in 46.6% of the 3-month group and 58.8 in the 6-month group. Response rate by month 12: 98% in 6-month depot and 100% in 3-month depot patient’s group</td>
<td>T suppressed to &lt;50 ng/dL from week 4 through week 48 in 93.4% of patients. PSA decrease from &gt;4 ng/mL to ≤4 ng/mL by 86% of patients</td>
<td>T-suppression by day 28 to castrate levels in 97% of patients. PSA decrease throughout the 12-month study in 96% of patients</td>
</tr>
<tr>
<td>Safety results</td>
<td>Most common ADRs: Flushing 34.2%, Increased sweating 5.8%, Injection-site induration 5.8%, Fatigue 1.7%</td>
<td>Most common treatment related AEs: Hot flushing 58.3%, Injection site pain 17.9%, Fatigue 11.9%, Constipation 9.9%</td>
<td>Most common treatment-related AEs: Hot flashes 57.6, Injection site, Burning 15.3%, Fatigue 11.7%</td>
</tr>
</tbody>
</table>

Abbreviations: NCI, National Cancer Institute; T1, tumor 1; T, testosterone; PSA, prostate-specific antigen; LH, luteinizing hormone; FSH, follicle-stimulating hormone; EORTC, European Organization for Research and Treatment of Cancer; ADRs, adverse drug reactions.

Discussion
Based on the above described data, the overall efficacy and safety of all three formulations appeared to be similar. However, the amount of data is still limited so it is more important to compare clinical performance with the established 1-, 3-, and 4-month formulations.

Low-dose microsphere depot
The low-dose microsphere formulations have been studied at a variety of levels. Kienle and Lubben\(^3\) assessed the...
long-term use of an LA 3.75 mg monthly depot formulation in patients with PCa for more than 3 years, with the aim of determining if LA could reduce and maintain testosterone to castration levels over a 45-month period. In this study, each monthly injection of LA was followed by an initial burst of LA in the blood, reaching a steady state within 2 days of injection. Testosterone levels were reduced as were dihydrotestosterone, LH, and follicle-stimulating hormone. Adverse events included fatigue (15%), headaches (5%), and local pain at injection site (4.4%).

Tunn et al12 compared the LA 3.75 mg 1-month and the 11.25 mg 3-month depot formulations. In this study 15 patients received the 3.75 mg 1-month depot and a further 27 patients received the 11.25 mg 3-month depot. Both groups showed a reduction of testosterone and dihydrotestosterone to castration levels within 1 month, which was maintained over the 9-month study period. PSA was decreased to 97.8% in the 1-month depot group and 96.6% in the 3-month depot group. Both groups also showed similar disease progression at 6.7% for the 1-month group and 3% in the 3-month group. Adverse events were also similar for both groups with the most common being hot flush and sweating.

Thus, the LA low-dose formulations of 1 month (3.75 mg) and 3 months (11.25 mg) show characteristics that were repeated in the 30 mg 6-month depot formulation. Tunn and Więcky7 found that the LA 6-month depot formulation (30 mg) reduced serum testosterone to castrate levels during the first month of treatment and that these levels were maintained in the same manner as in the 1- and 3-month depot formulations. The response rate in terms of T suppression below castration level at 12 months was 98% for 6-month and 100% for 3-month formulations. The 6-month formulation was also comparable to earlier depots in the reduction of PSA, showing an 89% reduction compared to an 88% reduction in the 3-month 11.25 mg depot. Adverse events were also similar; the most common AEs were flushing, sweating, and injection site induration.

High-dose microsphere depot
High-dose LA microsphere formulations, including the 7.5 mg 1-month depot, the 22.5 mg 3-month depot, and the 45 mg 6-month depot formulations, have been studied by Sharifi et al16-38 and Spitz et al.20

In a recent study, Spitz et al20 found that 93.4% of patients achieved the primary endpoint of suppression of testosterone to castrate levels by the fourth week of the study, maintaining that level through 48 weeks. Flushing and injection site reactions were the most commonly reported AEs.

Gel-based high dose depot
LA is also available in 1-, 3-, and 6-month depots in the gel-based formulation. These formulations have been studied by Perez-Marrenno et al.34 Chu et al.35 and Crawford et al.28

In a 6-month study of the LA 1-month high-dose (7.5 mg) depot formulation, Perez-Marrenno et al.34 found that the mean (standard deviation) serum testosterone level was 6.12 (4.3) ng/dL among the 120 patients and that no patient experienced a breakthrough during treatment. Again, the most common AEs were hot flushes, fatigue, dizziness, and injection site burning sensation.

Similarly, Chu et al.35 studied 117 patients who received a 22.5 mg 3-month depot formulation for 6 months. Serum testosterone was decreased to castrate levels in 98% of patients by day 28 and was maintained throughout the study. PSA was also decreased by 98%. The most commonly reported AEs were hot flashes, fatigue, nausea, and dizziness.

A 6-month, gel-based, LA formulation (45 mg) was studied by Crawford et al.28 In this study, 111 patients received a 45 mg 6-month depot dose of LA over the course of 12 months (two injections). Of these patients, 103 completed the study; 109 patients achieved testosterone suppression by day 28, and PSA declined by 97% from baseline. Mild to moderate hot flashes were the most commonly reported AE.

Microsphere (30 and 45 mg) and gel-based (45 mg) formulations
In the three 6-month LA depot formulations studied,120,28 primary endpoints of serum testosterone suppression to castrate levels, observed decreases of PSA, and incidence of adverse events were similar across the board. Efficacy endpoints for the microsphere-based LA 30 mg depot formulation showed a response rate of 98%, no progression in 90% of patients, remission rate of 58.5%, and 89% decrease in observed PSA levels. In the microsphere-based LA 45 mg 6-month depot formulation, serum testosterone was suppressed to <50 ng/dL from week 4 through week 48 in 93.4% (95% confidence interval [CI] 89.2%, 97.6%) of patients. For the prespecified endpoint, serum T was suppressed to <50 ng/dL from week 4 to 48 in 93.6% of subjects (90% CI 90.2%, 97.0%). The gel-based LA 45 mg depot formulation showed that a 97% reduction of serum testosterone levels was reached within 28 days and maintained until the study end. PSA levels also declined throughout the study for 96% of patients. In all of these studies, the most common AEs were hot flush, injection site reactions, and fatigue.

In studies of patient preferences, the advent of LA formulations ranging from 30 to 45 mg dose depots has
greatly improved the quality of life for many prostate cancer patients. The increased time between injections and office visits has a variety of repercussions. Fewer total injections mean reduced pain and stress for patients and should also be associated with fewer injection-site reactions. It can be hypothesized that key efficacy and safety aspects go hand-in-hand with an improvement of compliance and adherence for the 6-month formulations. In conjunction with a lower frequency of clinic visits due to a reduced need for injections or the treatment of injection-related side effects, it can be assumed that there is a pharmacoeconomic benefit for the 6-month depot even when overall product costs are the same on an annual basis. These aspects could remain strong regardless whether the formulations are used continuously or intermittently. Due to the fact that drug prices differ from country to country, specific cost assessments are needed to support this pharmacoeconomic argument more broadly.

Conclusion
All three 6-month LA formulations fulfilled the efficacy and safety criteria for the registration in countries of submission based on their pivotal trial data. These products are an additional tool in the treatment of prostate cancer. Due to their longer treatment duration, an improvement of compliance and adherence for the 6-month formulations could be considered. In conjunction with a lower frequency of clinic visits due to a reduced need for injections or the treatment of injection-related side effects, it can be assumed that there is a pharmacoeconomic benefit for the 6-month depot even when overall product costs are the same on an annual basis. Based on these arguments, it can be postulated that the 6-month depots could become preferred formulations for both physicians and for patients with stable disease.

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Disclosure
Dr Tunn has no conflict of interest to declare. Drs Grucza and Bacher are employees of AbbVie and own Abbott and/or AbbVie stock. AbbVie is the producer of two products discussed in this article.

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