Six-month gonadotropin releasing hormone (GnRH) agonist depots provide efficacy, safety, convenience, and comfort

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Abstract: Two different 6-month GnRH agonist depot formulations approved for palliative treatment of advanced and metastatic prostate cancer in the United States – leuprolide acetate 45 mg and triptorelin pamoate 22.5 mg – provide patients with efficacy and safety comparable to those of existing 1-, 3-, and 4-month GnRH agonist depots. However, the 6-month formulations can increase patient convenience, comfort, and compliance by reducing the number of physician visits and injections required. At the conclusion of their pivotal trials, the 6-month formulations demonstrated efficacy rates in achieving chemical castration (serum testosterone ≤ 50 ng/dL) that ranged between 93% and 99%. As with existing GnRH agonist depot formulations, hot flashes represented the most common adverse event reported in trials of 6-month leuprolide acetate or triptorelin. As such, these products may prove useful not only for their labeled indication, but also as adjuncts to other treatments such as radical prostatectomy, radiotherapy, and chemotherapy. We recommend further research, including head-to-head trials between the 6-month GnRH depots, to refine our understanding of these products.

Keywords: prostate cancer, leuprorelin, leuprolide, triptorelin, 6-month depot, testosterone

Evolution of anti-androgenic therapies
In the United States and Europe, prostate cancer represents the most commonly occurring nonskin cancer in men, among whom it causes more deaths than any cancer other than lung cancer.¹ For men with advanced prostate cancer, testosterone suppression – most often achieved by the administration of a gonadotropin hormone-releasing hormone (GnRH) analog – remains the standard palliative treatment.² In fact, approximately 90% of prostate cancer tumors respond to initial androgen deprivation, thereby improving patients’ quality of life and longevity.³

However, early GnRH agonists required patients to perform daily subcutaneous or intramuscular injections,⁴ which could cause pain, injection site reactions, and compliance challenges. Over the past decade, advances in drug delivery systems have given rise to 1-, 3-, 4-, 6-, and 12-month delivery systems for GnRH agonists.² Along with facilitating physician use, these longer-term formulations have greatly improved patient compliance with therapy.⁵

The recent approval of triptorelin pamoate 22.5 mg (Trelstar®, Watson Pharmaceuticals, Inc, Corona, CA) gives US physicians and patients a second 6-month depot formulation to consider, along with leuprolide acetate (LA) 45 mg (Eligard®, Sanofi-aventis, Paris, France), approved in 2004. Based on large-scale Phase III trials, these products appear to offer safety and efficacy equivalent to those of shorter-term depot formulations.²,⁶ However, 6-month depots allow patients who travel, or who have
other difficulties being evaluated and treated every 3 months, to double the treatment interval.

The concept of androgen deprivation originated in studies published in 1941 in which Huggins and Hodges first noted the relationship between orchietomy and prostate cancer. Specifically, they showed how androgen blockade caused dramatic and significant clinical remissions of metastatic prostate cancer.7

Today, oncologists utilize androgen suppression as monotherapy for selective patients with localized prostate cancer, and in conjunction with radiotherapy for patients with locally advanced disease or intermediate to high-risk localized disease.8 Suppressing circulating testosterone levels is also the most widely used palliative treatment for patients with metastatic disease.9

Researchers first isolated and described gonadotropin releasing hormone (GnRH) in 1971, leading to the discovery of the first clinically used synthetic GnRH analog, leuprolide acetate (also called leuprorelin), in 1973.10,11 Leuprolide acetate’s chemical structure differs from that of GnRH in that it substitutes D-leucine for glycine.12 This difference gives leuprorelin enhanced binding affinity for the anterior pituitary receptor and increased resistance to degradation by peptidases, resulting in a longer half-life than naturally occurring GnRH and 80 times more potency.13

The anterior pituitary gland secretes the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in response to stimulation by GnRH.14,15 In males, FSH supports spermatogenesis, while LH stimulates testosterone production in the testes. Prostate cancer cell growth depends on the presence of testosterone.14 As such, GnRH agonist therapy causes an initial, transient increase in testosterone levels, but long-term use of such drugs suppresses testosterone production.14,16,17

Triptorelin was first synthesized in the early 1970s.18,19 Compared with naturally occurring GnRH, triptorelin substitutes D-tryptophan for glycine at position 6, which provides biological potency superior to the native decapeptide while increasing resistance to proteolytic enzymes.14 Radioligand binding and inositol phosphate production assays have shown that triptorelin is 131 times more potent than the natural GnRH.15 Additionally, triptorelin appears to degrade more slowly than natural GnRH.20 Like leuprorelin, use of triptorelin initially stimulates the pituitary gland, causing a temporary increase in testosterone production. Continuous administration of triptorelin downregulates the pituitary GnRH receptors, however, thereby inhibiting secretion of gonadotropins.20

All GnRH agonists possess a short elimination half-life.20 Specifically, in a pharmacokinetic (PK) study in which investigators gave healthy men intravenous 0.5 mg triptorelin acetate, the drug had a geometric mean terminal elimination half-life of 2.8 hours.21 In a similar PK study in which participants received a 1 mg nondepot injection of leuprolide acetate either intravenously or subcutaneously, mean elimination half-life was 2.9 hours and 3.6 hours, respectively.22

For patients receiving the 6-month triptorelin pamoate formulation, those with renal or hepatic impairment, require no dosage adjustments.21 However, no studies to date have evaluated the pharmacokinetics of leuprolide acetate in patient populations with compromised kidney or liver function.8

GnRH agonists’ short elimination half-life initially meant that patients had to inject such medications daily. However, incorporating triptorelin into a biocompatible, biodegradable copolymer (poly-D,L-lactide-co-glycolide) as microgranules has enabled the creation of 1-, 3-, and 6-month depot formulations of the drug.6 Similar advances have facilitated development of long-term leuprolide acetate depot formulations.23,24 The first such product, a monthly 7.5 mg leuprolide acetate depot formulation, earned US Food and Drug Administration (FDA) approval for treatment of advanced prostate cancer in 1989.25 Three- and 4-month formulations earned approval in 2002 and 2003, respectively, for the same indication. In 2004, the FDA approved a 6-month 45 mg depot leuprolide acetate formulation.

Additionally, a 12-month leuprolide acetate implant earned FDA approval for locally advanced or metastatic prostate cancer in 2000 but was discontinued by its manufacturer in 2007.26,27 Some reviewers postulate that this implant failed commercially because it required a minor surgical procedure and rigorous follow-up with patients.8

Comparing and contrasting 6-month formulations

Pivotal trials of 6-month triptorelin pamoate and leuprolide acetate formulations approved in the United States share many design similarities, although subtle differences exist as well. Both trials were 1-year, multicenter, open-label investigations in which investigators evaluated the safety and efficacy of two injections spaced 6 months apart and found high efficacy rates and low rates of serious adverse events (SAEs). Table 1 describes the study design of the two trials.
Leuprolide acetate

The leuprolide acetate trial that led to US approval sought as its primary endpoint a decrease in total serum testosterone to ≤50 ng/dL on at least two consecutive measurements taken 1 week apart. For this study, researchers enrolled 111 patients with a histological or cytological diagnosis of prostate cancer greater than stage T1, a World Health Organization (WHO) performance score of 0–2, and a life expectancy ≥1 year. Mean patient age was 78.2 ± 7.5 years, with nearly half of patients between 70 and 79. Approximately 40% of patients had T2 or M+, 17% had T3, and 4% had stage T1. Investigators administered subcutaneously 45 mg LA at baseline and on day 168 to all patients. Investigators tested patients’ blood samples for testosterone, LH, prostate-specific antigen (PSA), and total acid phosphatase at initial screening, at baseline, and at regular intervals throughout the study. They also took additional blood samples from 27 patients for PK analysis of serum LA.

Of the original 111 patients, 103 patients completed the study, of which 73 had no missing data points. All patients received the first study injection, and 106 received the second. Within 8 hours of the first injection, mean LH increased from 6.9 ± 0.3 mIU/mL to 37.9 ± 2.4 mIU/mL. By day 7, however, mean LH had decreased below baseline. It continued to drop through the first 19 weeks of treatment, to a level of 0.1 ± 0.01 mIU/mL at day 133. Mean LH remained at this level until the second injection occurred, on day 168. On day 169, mean LH rose to 0.2 ± 0.02 mIU/mL, holding relatively constant through the duration of the study. At month 12, mean LH measured 0.2 ± 0.14 mIU/mL.

Baseline testosterone averaged 351.4 ± 28.6, 352.8 ± 8.0, 367.5 ± 26.0, and 385.1 ± 24.0 ng/dL for patients with T1, T2, C, or M+ disease stage, respectively. Mirroring the initial LH increase, mean testosterone rose to 588.6 ± 23.9 ng/dL by day 2. By day 28, 108 of the 111 patients (97%) had reached castrate testosterone levels commonly defined as testosterone <50 ng/dL. However, some authors advise using plasma testosterone levels that approximate the level achieved through surgical castration, 20 ng/mL. At day 28, 92 patients had testosterone levels <20 ng/dL. Using testosterone <50 ng/dL as the definition of castration, patients took an average of 21.2 days to reach testosterone suppression. No patients reported clinically relevant flare reactions to the initial testosterone increase.

Baseline PSA measured ≥4 ng/mL in 83/110 patients (75.5%) and averaged 39.8 ± 21.5 ng/mL. Throughout the study, mean PSA declined, to the point that at month 12, only 4/103 patients then participating had increased PSA. Patients reported no changes in bone pain, urinary symptoms, and urinary pain at any point during the study.

Triptorelin

Investigators for the US pivotal trial of a 6-month triptorelin pamoate depot enrolled 120 patients with histologically proven prostate cancer stage T3 to 4NxMx, TxN1Mx, or TxNxM1 (where T = tumor, N = node, and M = metastasis) or rising serum PSA after failed local therapy. Patients were also required to have serum testosterone ≥5 nmol/L (144 ng/dL) and life expectancy >18 months. Researchers calculated the sample size required to demonstrate achievement and maintenance of castrate testosterone levels in 95% of patients with a 2-sided 95% confidence lower limit of 88.7%.

All patients underwent intramuscular triptorelin injections on day 1 and at week 24. Investigators drew blood samples for testosterone assessments at baseline, then monthly thereafter. To assess serum PSA, investigators drew samples on day 1 and at months 3, 6, 9, and 12. For safety assessments, investigators took blood samples at baseline, month 6, and month 12.

Ultimately, 115 patients completed the study. Mean patient age was 71.1 ± 8.5 years. More than 60% of patients were Caucasian. More than half (51.6%) of patients had T3N0Mx or T3NxMx cancer. The latter category accounted for 45.8% of the total patient population. Conversely, a total of 22.5% had either T4NxM1 (5.0%) or T4NxMx (17.5%).
Baseline serum PSA averaged 19.1 µg/L and testosterone levels averaged 17.8 nmol/L.

Study investigators also reported concomitant baseline diagnoses occurring in at least 10% of patients. In this regard, 61.7% of the study population had hypertension; 14.2% had hypercholesterolemia; and 10.0% had diabetes mellitus.

Regarding efficacy, 97.5% (95% confidence interval [CI]: 92.9%–99.5%) of the intent-to-treat population (120 patients) achieved castrate serum testosterone levels (≤50 ng/dL) by day 29. Additionally, 93.0% (95% CI: 86.8%–97.0%) or 107 of the 115 who completed the study maintained castration from months 2 through 12. Also at month 12, 98.3% (113/115) patients had castrate serum testosterone levels. In keeping with these results, median relative decreases in serum PSA from baseline were 97% and 96% at months 6 and 12, respectively.

**Discussion**

Both of these US trials investigated the efficacy and safety of 6-month GnRH agonist trials in more than 100 patients with mean ages between 71.1 (triptorelin trial) and 73.6 years (US leuprolide acetate trial) with life expectancy of ≥1 year. Inclusion criteria differed between the two studies. For example, the triptorelin trial included patients with PSA relapses after failed local therapies. Specifically, 28.3% in the triptorelin trial had PSA relapse after either radical prostatectomy or radiotherapy. In contrast, the US leuprolide acetate trial included no PSA failures after local therapy.

As for main inclusion criteria, the US leuprolide acetate trial required patients to have a histological or cytological diagnosis of prostate cancer greater than stage 1 and a WHO performance score of 0 to 2. However, the triptorelin trial included patients with locally advanced or metastatic prostate cancer but did not specify any WHO status.

**Efficacy**

In assessing the drugs’ clinical performance, both studies reported on the proportion of patients who reached serum testosterone levels ≤50 ng/dL at various time intervals. Although each trial presented its results somewhat differently, a consistent picture emerges, with overall efficacy rates well above 90%. Table 2 summarizes the results of the castration efficacy of the two studies.

Specifically, after 1 month of treatment, 99% (108/109) of patients participating in the US leuprolide acetate trial achieved castration levels as well as 97% of the trial’s 111-patient intent-to-treat population. Similarly, 97.5% of patients in the triptorelin study’s intent-to-treat population (120 patients) achieved chemical castration at 1 month.

At month 12, 99% (102/103) of patients in the US leuprolide acetate trial had castrate testosterone levels as did 98.3% (113/115) of patients in the triptorelin trial. Mean time to castration in these trials was 21.2 days and 18.8 days (the latter calculated in a subset of 15 patients), respectively. Generally, daily and extended-release leuprolide acetate injections induce serum castrate testosterone in 3 to 4 weeks.

The leuprolide acetate trial also reported how many of their subjects reached serum testosterone levels ≤20 ng/dL. In the US leuprolide acetate trial, this figure was 88%. These data were not available for the triptorelin study.

Taken together, the efficacy rates for these two studies compare favorably to efficacy rates achieved by shorter-term GnRH agonist depot formulations. In particular, end-of-study castration (≤50 ng/dL) rates in published studies of existing 1-, 3-, and 4-month LA formulations were 100%, 100%, and 98%, respectively, in studies ranging from 6 to 8 months. Also, at the conclusion of these shorter-term GnRH analog studies, 94%, 94%, and 90% of patients had achieved testosterone levels ≤20 ng/dL. The castration rates for these studies after 1 month of therapy ranged between 94% and 98%. In a Phase III study of a 1-month, 3.75 mg LA depot formulation, 96.8% of patients sustained testosterone levels ≤50 ng/dL from month 1 through the study’s 6-month duration.

At completion (final day) of the respective studies, the percentage of 1, 3, and 6-month triptorelin treated patients who were at castrate levels ranged between 97%–99%. Table 3 compares the results from the 1, 3, and 6-month depots.

Ultimately, the 6-month depot achieved similar results to the currently approved 1- and 3-month triptorelin formulations both on day 29 and from months 2 through 9. Using

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**Table 2 Comparison of results leuprolide acetate with triptorelin pamoate**

|                  | Leuprolide | Triptorelin |
|------------------|------------|-------------|
| **Castration efficacy** |            |             |
| Day 29**         | 97.0%      | 97.5%       |
| Month 12         | 99.0%      | 98.3%       |
| **Castration time** |            |             |
|                  | 21.2 days  | 18.8 days   |
| **PSA decreases** |            |             |
| Month 12         | 90.2%      | 96.0%       |
| **Adverse events** |            |             |
| Hot flashes      | 57.6%      | 71.7%       |

**Notes:** Castration ≤50 ng/dL; **Intent to treat population.

Abbreviation: PSA, prostate specific antigen.

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**Table 3 Comparison of results triptorelin depot with other depot formulations**

|                  | Triptorelin depot | Other depot formulations |
|------------------|-------------------|-------------------------|
| **Castration efficacy** |              |                         |
| Day 29**         | 97.0%            | 95.5%                   |
| Month 12         | 99.0%            | 98.3%                   |
| **Castration time** |              |                         |
|                  | 21.2 days        | 18.8 days               |
| **PSA decreases** |              |                         |
| Month 12         | 90.2%            | 96.0%                   |
| **Adverse events** |              |                         |
| Hot flashes      | 57.6%            | 71.7%                   |

**Notes:** Castration ≤50 ng/dL; **Intent to treat population.

Abbreviation: PSA, prostate specific antigen.
Table 3 Comparison of 6-month vs shorter depots leuprolide acetate and triptorelin pamoate

|                | Leuprolide | Triptorelin |
|----------------|------------|-------------|
|                | Day 29     | Study completion |
| 1-month depot  | 94.0%      | 100.0%      |
| 3-month depot  | 98.0%      | 100.0%      |
| 6-month depot  | 99.0%      | 99%         |
| 1-month depot  | 92.7%      | 99%         |
| 3-month depot  | 97.7%      | 97%         |
| 6-month depot  | 97.5%      | 98%         |

During the plateau phase (days 3 to 168), serum leuprolide acetate averaged between 0.2 and 2.0 ng/mL with a 6-month mean value of 0.20 ± 0.14 ng/mL (median: 0.16). A similar pattern emerged after the second injection.

These data essentially mirror PK patterns observed in other leuprolide acetate studies, specifically the 7.5 mg 1-month formulation, a 22.5 mg 3-month formulation, and a 30 mg 4-month formulation. These products reached C_max approximately 4.66, 5, and 3.3 hours after injection, respectively, followed by gradual leuprolide acetate declines.32,44,45

Similarly, investigators in the triptorelin trial selected a 15-patient subset in which they assessed triptorelin’s pharmacokinetics by measuring serum testosterone levels at baseline and monthly thereafter, as well as on days 2, 3, 5, 8, 15, and 22. Among all treated patients, mean LH levels rose from 7.9 to 38.3 IU 2 hours after the first injection. In keeping with this initial pituitary LH stimulation, an initial increase in testosterone levels (C_max 25.8 nmol/L) occurred after the first injection in the 15 patients analyzed for pharmacodynamic and pharmacokinetic data. However, a rapid and sustained decrease in testosterone levels followed.

The “acute-on-chronic” or microsurge effect refers to agonistic testosterone stimulation occurring in response to serial injections of GnRH agonist depots.46 In the triptorelin trial, only 2 of 60 patients whom investigators selected to assess this effect showed an acute-on-chronic increase in testosterone greater than 50 ng/dL 48 hours after the second injection.

Moreover, 2 hours after the second triptorelin injection, investigators observed virtually no LH increases from a fully suppressed level to only 0.1 IU/L. Only two patients failed to achieve complete pituitary desensitization; one of them was severely obese. The second experienced an increase of just 1.1 IU/L.

Consistent with triptorelin’s success in maintaining long-term castration, PSA in this study fell by a median of 97% by month 6 and 96% at month 12. Similarly, at month 12 in the

Table 4 Advantages of 6-month depots

| Advantage          | Results                                      |
|--------------------|----------------------------------------------|
| Fewer frequent injections | Reduced anxiety                           |
| Fewer doctor visits    | Decreased emotional burden                 |
|                      | Improved flexibility with scheduling        |
|                      | Improved comfort                            |
|                      | Decreased site reactions                    |
|                      | Decreased cost                              |
|                      | Less missed visits                          |
|                      | Decreased breakthrough (theoretical)        |
survival. In a retrospective study, the clearest evidence of clinical consequences of such leaks ranges between 4% and 12.5%. Perhaps analog therapy. In published reports, the long-term rate of elevations above 50 ng/dL in patients on continuous GnRH analogs is generally mild and stem from testosterone suppression. Among the two trials of 6-month GnRH agonists, the triptorelin trial presented the most detailed testosterone escape data. Specifically, eight patients who completed the study failed to maintain castration at all visits between months 2 and 12. Five of these patients had only an isolated testosterone escape with no increase in serum PSA. Investigators considered three of these five events minimal, with one serum testosterone level measuring 67.15 ng/dL at month 2, and two serum testosterone levels measuring 55.91 ng/dL and 56.77 ng/dL at month 6. The other two isolated escapes occurred at month 4 and measured 96.54 ng/dL and 176.37 ng/dL.

Clear clinical failures occurred in three patients, as reflected by increases in serum PSA levels. In one of these patients (the obese patient previously mentioned), the first triptorelin injection failed to achieve clinical castration, although the second injection succeeded. The other two patients escaped castration from month 9 (serum testosterone 150 ng/dL) and at month 12 (1213 ng/dL), respectively.

Safety

As with existing GnRH analogs, side effects associated with 6-month depot formulations are generally mild and stem from testosterone suppression. Among the two studies, adverse event (AE) reporting rates ranged from 74% in the US leuprolide acetate study (82/111 patients) to 95% in the triptorelin study (115/120 patients). In the latter study, investigators judged 86.7% of these events to be mild. Hot flashes represented the most commonly reported AE in the two studies, occurring at rates ranging from 57.6% (33.3% mild, 24.3% moderate) of patients in the leuprolide acetate study to 71.7% in the triptorelin study. In studies of existing 1-, 3-, and 4-month LA formulations, hot flashes (mostly mild) also ranked as the most common AE, occurring in 56.7%, 59%, and 78.9% of patients, respectively.

Rates of injection site reactions were fairly similar in both studies of 6-month depots, and the vast majority of these reactions were considered mild. The lowest rate of injection site reactions, 6.7%, occurred in the triptorelin trial. Conversely, 15.3% of patients in the leuprolide acetate trial experienced injection-site burning.

SAE rates were relatively low in both studies. The triptorelin trial SAE rate was approximately 14% (17 of 120 patients). Only one patient in the US leuprolide acetate trial experienced an SAE, although investigators did not report whether it was related to the study medication.

None of the SAEs in the triptorelin was judged by investigators to be related to study medications. Additionally, investigators in the triptorelin study observed clinically significant treatment-emergent laboratory abnormalities in nine patients. However, only two mild events in the same patient (increased alanine transaminase/ALT and aspartate transaminase/AST) were related to the study drug. These investigators also reported 17 events of hypertension or its worsening, but considered only one to be drug-related. Furthermore, the rate of hypertension events was likely to be high due to 62% baseline hypertension.

Conclusion

For patients with locally advanced or metastatic prostate cancer, hormonal therapy has long been a mainstay of palliative treatment. Additionally, physicians frequently integrate androgen deprivation with radiotherapy in certain intermediate and high risk patients with localized disease. In use for more than two decades, GnRH agonists represent the most frequently chosen hormonal therapy for achieving androgen deprivation in patients with prostate cancer. Depot formulations of GnRH agonists have proven preferable to earlier options including daily injections and bilateral orchiectomy for several reasons. These include the reversibility of chemical castration and, for patients, the ability that injectable GnRH agonists provide to avoid psychological and other comorbidities associated with orchiectomy.

Introduced to the US market in 1989, GnRH agonist depot formulations have evolved to offer treatment intervals of 1, 3, 4, and 6 months, all of which offer similarly acceptable safety and efficacy profiles. Monthly and daily formulations increase the likelihood that patients may delay or miss treatments, which can result in testosterone breakthrough and potentially compromise tumor control and increase symptom progression. Accordingly, 3- and 4-month depot leuprolide acetate formulations represent the most commonly used hormonal treatments for prostate cancer. Longer-term formulations give patients the flexibility to choose an
administration schedule that works for them so that patients miss fewer visits, have fewer doctor’s visits, and have less frequent injections. This in turn allows for flexibility in scheduling a treatment plan and has the potential to decrease emotional burden and anxiety. Thus, longer acting depots have the potential to decrease injection site reaction, decrease cost, improve comfort, increase compliance and theoretically decrease tumor breakthrough.5,32,33,46,47,60–62

Regarding potential indications for 6-month GnRH agonist depots, research has evaluated shorter-duration GnRH agonists as adjuvant and neoadjuvant treatments for patients undergoing radical prostatectomy and radiation therapy.53,63,64 One reviewer predicts that 6-month triptorelin pamoate will prove a valuable adjunct to radiation therapy and chemotherapy because it possesses similar efficacy, but fewer side effects, than adjunctive therapies now commonly available.65

Moreover, two clinical trials have shown that depot products often suppress testosterone for longer than the labeled interval.66,67 Accordingly, researchers have begun investigating the clinical merits of intermittent androgen deprivation therapy (IADT) with GnRH agonists. Such strategies involve periodic evaluation of serum testosterone levels to guide injection intervals, and to detect nonresponders and testosterone breakthroughs.8 Once a patient reaches castrate testosterone levels, the physician suspends GnRH agonist therapy until PSA rises to a set threshold, at which point therapy resumes.39 This approach can help patients avoid morbidity associated with continuous androgen deprivation and may forestall the development of hormone resistance.68,69

The appropriateness of 6-month GnRH agonists has not yet been evaluated in the context of IADT or as adjuvant/ neoadjuvant therapy. Also yet to be evaluated is whether or not 6-month LA depots require dosing adjustments in special patient populations such as patients experiencing kidney or liver failure.8

Additionally, research has not yet established whether a castration target of serum testosterone below 50 ng/dL or below 20 ng/dL provides clinical benefit. In one report, breakthrough increases above 32 ng/dL predicted shorter survival free of androgen-independent prostate cancer progression.29

Finally, a randomized, controlled trial pitting the 6-month GnRH agonist against each other would further illuminate which product works best in which clinical situations. However, it is unlikely that such a trial will be performed. We look forward to learning more in all the above areas as physicians’ and researchers’ experience with 6-month depot products accumulates.

Disclosure
ED Crawford has financial interests and/or other relationships with GlaxoSmithKline, Sanofi-aventis, the National Institutes of Health, the University of Colorado Cancer Center, and Watson Pharmaceuticals. J Phillips has nothing to disclose. Editorial assistance provided by Carden Jennings funded by Watson Pharmaceuticals, Inc.

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