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ORIGINAL RESEARCH—MEN'S SEXUAL HEALTH

Pharmacokinetic Profile of Subcutaneous Testosterone Enanthate Delivered via a Novel, Prefilled Single-Use Autoinjector: A Phase II Study

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ABSTRACT

Introduction. Hypogonadism is one of the most common male endocrine problems. Although many treatments are currently available, unmet need exists for new testosterone (T) replacement therapies that are simple to administer and use, are safe, and mimic physiologic T levels.
Aim. The study aim was to determine the pharmacokinetics (PK), safety, and tolerability of T enanthate (TE) administered via a novel single-use autoinjector system, which was designed to eject high-viscosity solutions from a prefilled syringe fitted with a five-eighths-inch 27-gauge needle.
Methods. Thirty-nine men with hypogonadism entered this dose-finding, open-label, parallel-group study. Patients were washed out of their topical T regimens and randomized to receive 50 or 100 mg of subcutaneous (SC) TE weekly. The reference group were patients with hypogonadism who were maintained on standard 200-mg intramuscular (IM) TE.
Main Outcome Measure. The primary outcome measure was the PK profile of SC TE, analyzed in reference to T levels used by the Food and Drug Administration to approve T products. Secondary outcome measures were safety and tolerability assessments.
Results. Both doses of SC TE achieved normal average concentrations of serum T within a 168-h dosing interval after injection. Concentration ranges were similar at all time points following 50-mg SC TE injections and following the third injection in the 100-mg arm. Mean steady-state T concentration at week 6 was 422.4 and 895.5 ng/dL for the 50- and 100-mg SC TE arms, respectively. SC TE demonstrated PK dose proportionality. SC TE restored normal serum T with low variation relative to 200-mg IM without clinically significant adverse events.
Conclusions. Administration of TE via this novel injection system restored T levels to normal range in men with hypogonadism. SC TE dosed weekly demonstrated steady, dose-proportional measures of exposure and was well-tolerated. **Kaminetsky J, Jaffe JS, Swerdloff RS. Pharmacokinetic profile of subcutaneous testosterone enanthate delivered via a novel, prefilled single-use autoinjector: A phase II study. Sex Med 2015;3:269–279.**

Key Words. Subcutaneous Injection; Testosterone; Autoinjector; Viscosity; Hypogonadism; Male; Clinical Trial; Phase II

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Introduction

Hypogonadism in men is a deficiency in serum testosterone (T) levels with symptoms secondary and responsive to T replacement [1,2]. Diagnosis may be made in men of any age [3]. Prevalence varies according to different reports, as it is influenced by the nature of the populations used in the study as well as the criteria used to define both the study and reference populations. According to one estimate, up to five million men are afflicted with this disorder in the United States and this number may reach 6.5 million by 2025 [3,4]. Use of T replacement therapy (TRT) has increased in recent years [5]. Available TRTs in the United States include intramuscular injections (IM), transdermal, transbuccal and intranasal applications, and implantable pellets. Selection of treatment modality is often influenced by convenience and cost of therapy [6–8]. TRT benefits patients with hypogonadism by restoring T to physiologic levels, consequently improving mood, increasing bone and muscle mass, reducing adiposity, and improving libido and sexual function [9].

While TRT may benefit many patients, there are important class safety factors to consider. TRT is contraindicated for patients with prostate and male breast cancer [1]. T gels carry a warning due to the potential for secondary exposure to those in close contact with the patient [10]. A large volume, long-acting formulation of T in oil injected IM through a large bore needle carries a boxed warning for pulmonary oil embolism [11]. Uncertainty exists as to whether or not patients may suffer adverse cardiovascular effects. Some outcome studies have indicated that TRT is associated with an increased risk of cardiovascular adverse events (AEs) [12,13]. Meanwhile, other outcome studies find no effect or reductions in cardiovascular events related to TRT [14,15], or rather that decrease in T levels (T deficiency) is associated with increased mortality and risk of cardiovascular disease [16,17].

Drawbacks exist with each of the currently available T delivery mechanisms. For example, IM injections can be painful [18,19]; the discomfort associated with large needle bore and length required for manual IM injection of viscous oil solutions can negatively impact patient compliance [20]. Because office visits are commonly recommended by providers, there is inconvenience to users. In addition, IM injection of T enanthate (TE) in sesame oil (e.g., Delatestryl®) is often administered in 200–400 mg doses every 2–4 weeks leading to peak and trough T levels outside of physiologic range [21,22]. Resulting fluctuations may lead to mood swings and disturbances in energy level [9,23]. Transdermal patches are commonly associated with skin reactions, which can lead to discontinuation of therapy [24]. Gels carry a risk of transference to women and children and are considered messy and may have an unpleasant odor to some users [10]. Nasally administered T and oral TRT in development appear to require multiple daily doses [25,26]. Oral TRT can cause gastrointestinal side effects. Because there are limitations to these delivery systems, patient compliance with treatment is an issue and TRT discontinuation rates are high [27]. Therefore, weekly subcutaneous (SC) administration of TE in oil solution, via a device optimized to inject highly viscous solutions through a five-eighths-inch 27-gauge needle (Supplemental Figure S1), is proposed as a viable alternative to other routes of administration, such as IM delivery systems. The objective of our phase II study was to assess the steady-state pharmacokinetics (PK) of two strengths of TE administered SC via a drug-device combination, as a multiple-dose regimen, to evaluate the possible utility of this modality for chronic replacement therapy.

Aims

This was a multicenter, phase II, three-arm, open-label, multi-dose, parallel-group study of two dosing levels of TE to determine the PK profile of a novel drug-device combination product to administer SC TE in oil once weekly.

Methods

Study Population

Male patients (18–75 years) with a history of physician-diagnosed hypogonadism of any etiology and with serum total T (TT) levels <300 ng/dL recorded on two occasions at least 1 week apart were eligible for this study. Patients were required to be in good general health without significant comorbidities and with a body mass index (BMI) between 18 and 32 kg/m^2. All patients were provided complete information of all AEs related to T and were subsequently required to provide written informed consent to be screened for all study requirements and restrictions. Patients were excluded if they had normal T levels (>300 ng/dL) or if they were deemed to have any

