PREFERRED ORAL TESTOSTERONE UNDECANOATE THERAPY TO ACHIEVE TESTOSTERONE REPLACEMENT TREATMENT

Background of the Invention

For testosterone replacement therapy (TRT) in hypogonadal men, the FDA has imposed regulatory guidelines on testosterone (T) formulations to balance the benefits and safety risks associated with abnormally high T concentrations (see, e.g., page 13 of *Testosterone Replacement Therapy Advisory Committee Briefing Document*, September 17, 2014). These regulatory guidelines include an average T blood serum concentrations (Cavg) in the normal range of 300 to 1000 ng/dL in 75% of subjects, maximum T blood serum concentrations (Cmax) less than 1500 ng/dL in 85% of subjects, not more than 5% between 1800 and 2500 ng/dL, and none above 2500 ng/dL. These guidelines are the standards used to achieve FDA approval to which all pharmaceutical companies attempting to bring testosterone replacement therapies to the market focus their research. To better manage the benefits and safety risks, it is important that formulations and dosing strategies be designed to achieve favorable pharmacokinetic (PK) performance of testosterone or a testosterone prodrug, such as testosterone undecanoate (TU). Accordingly, new formulations, dosage regimens, and titration schemes are needed to meet these standards and improve therapeutic efficacy.

Summary

The present disclosure features new testosterone undecanoate dosing strategies that include performing plasma or serum measurements of testosterone and titrating the daily dosage up or down, if necessary, in order to achieve favorable PK parameters.

In an aspect, there is provided the use of testosterone undecanoate (TU) in the manufacture of a medicament for the treatment of testosterone deficiency in a subject in need thereof, comprising:

a) a treatment regimen comprising 400 mg of the testosterone undecanoate (TU) to be orally administered to the subject daily with a meal, wherein the TU is to be administered in a pharmaceutical composition comprising TU, a non-sterol solubilizing agent effective for solubilization of the TU, and a phytosterol or phytosterol ester;

b) a first steady state serum concentration of testosterone to be established;

c) a first steady state Serum Value of testosterone in the subject that is measured from about 3 hours to about 6 hours after administration of the pharmaceutical composition to be provided following step (b); and

d) a first titration of the testosterone undecanoate to be performed, wherein:

i) if the first Serum Value of testosterone is less than about 400/F + b ng/dL, then the subject is to be orally administered about 600 mg TU daily to establish a second steady state Serum Value of testosterone that is higher than the first steady state Serum Value of testosterone;

ii) if the first Serum Value of testosterone is from about 400/F + b ng/dL to about 900/F + b ng/dL, then the subject is continued to be orally administered about 400 mg TU daily to maintain the first steady state Serum Value of testosterone; or

iii) if the first Serum Value of testosterone is greater than about 900/F + b ng/dL, then the subject is to be orally administered about 200 mg TU daily to establish a second steady state Serum Value of testosterone that is lower than the first steady state Serum Value of testosterone.

In another aspect, there is provided the use of testosterone undecanoate (TU) in the manufacture of a medicament for the treatment of testosterone deficiency in a subject in need thereof, comprising:

a) a treatment regimen comprising 400 mg of the testosterone undecanoate (TU) to be orally administered to the subject daily with a meal, wherein the TU is to be administered in a pharmaceutical composition comprising TU, a non-sterol solubilizing agent effective for solubilization of the TU, and a phytosterol or phytosterol ester;

b) e a first steady state serum concentration of testosterone to be established;

c) a first steady state Serum Value of testosterone in the subject that is measured from about 3 hours to about 6 hours after administration of the pharmaceutical composition to be provided following step (b); and

d) a first titration of the testosterone undecanoate to be performed, wherein:

i) if the first Serum Value of testosterone is less than about 460 ng/dL, then the subject to be orally administered about 600 mg TU daily to establish a second steady state Serum Value of testosterone that is higher than the first steady state Serum Value of testosterone;

ii) if the first Serum Value of testosterone is from about 460 ng/dL to about 971 ng/dL, then the subject is continued to be orally administered about 400 mg TU daily to maintain the first steady state Serum Value of testosterone; or

iii) if the first Serum Value of testosterone is greater than about 971 ng/dL, then the subject is to be orally administered about 200 mg TU daily to establish a second steady state Serum Value of testosterone that is lower than the first steady state Serum Value of testosterone;

wherein the subject:

is on anti-hypertensive therapy and exhibits an average change in systolic blood pressure of no more than 3.4 mmHg, an average change in diastolic blood pressure of no more than 1.8 mmHg, and/or an average change in heart rate of no more than 1.3 beats per minute; and/or

has diabetes mellitus and exhibits an average change in systolic blood pressure of no more than 3.0 mmHg, an average change in diastolic blood pressure of no more than 1.7 mmHg, and/or an average change in heart rate of no more than 1.9 beats per minute.

In one example, the disclosure features a method of treating testosterone deficiency in a subject in need thereof. The subject to be treated is a male, e.g., a hypogonadal male. The method includes performing a treatment regimen that includes administering to the subject a pharmaceutical composition including testosterone undecanoate (TU), a non-sterol solubilizing agent effective for solubilization of the TU, and a phytosterol or phytosterol ester. About 400 mg TU may be administered, e.g., at the onset of the treatment regimen. The method may include establishing a first steady state serum concentration of testosterone. The method may include providing a first Serum Value of testosterone in the subject following administration of the TU. Additionally, the method may further include performing a first titration of the testosterone undecanoate, e.g., if necessary. If the first Serum Value of testosterone is less than about 400/F or 400/F + b ng/dL (e.g., a serum concentration of less

than about 449 ng/dL or less than about 460 ng/dL or a plasma concentration of less than about 400 ng/dL), then the daily dosage may be increased, e.g., to about 600 mg TU. F corresponds to a predetermined empirical factor that relates the plasma and serum concentrations and is described in more detail below. This may establish a second steady state Serum Value of testosterone that is higher than the first steady state Serum Value of testosterone. If the first Serum Value of testosterone is from about 400/F ng/dL to about 900/F ng/dL or from about 400/F + b ng/dL to about 900/F + b ng/dL (e.g., a serum concentration of from about 449 ng/dL to about 1011 ng/dL or from about 460 ng/dL to about 971 ng/dL or a plasma concentration of from about 400 ng/dL to about 900 ng/dL), then the daily dosage may be maintained. This may maintain the first steady state Serum Value of testosterone. If the first Serum Value of testosterone is greater than

about 900/F ng/dL or 900/F +b ng/dL (e.g., a serum concentration of greater than about 1011 ng/dL or greater than about 971 ng/dL or a plasma concentration of greater than about 900 ng/dL), then the daily dosage may be decreased, e.g., to about 200 mg TU. This may establish a second steady state Serum Value of testosterone that is lower than the first steady state Serum Value of testosterone.

In another example, the disclosure features a method of treating testosterone deficiency in a subject in need thereof. The subject to be treated may be a male, e.g., a hypogonadal male. The method includes performing a treatment regimen that includes administering to the subject a pharmaceutical composition including testosterone undecanoate (TU), a non-sterol solubilizing agent effective for solubilization of the TU, and a phytosterol or phytosterol ester. About 400 mg TU may be administered, e.g., at the onset of the treatment regimen. The method may include establishing a first steady state serum concentration of testosterone. The method may include providing a first Serum Value of testosterone in the subject following administration of the TU. Additionally, the method may further include performing a first titration of the testosterone undecanoate, e.g., if necessary. If the first Serum Value of testosterone is less than about 460 ng/dL, then the daily dosage may be increased, e.g., to about 600 mg TU. This may establish a second steady state Serum Value of testosterone that is higher than the first steady state Serum Value of testosterone. If the first Serum Value of testosterone is from about 460 ng/dL to about 971 ng/dL, then the daily dosage may be maintained. This may maintain the first steady state Serum Value of testosterone. If the first Serum Value of testosterone is greater than about 971 ng/dL, then the daily dosage may be decreased, e.g., to about 200 mg TU. This may establish a second steady state Serum Value of testosterone that is lower than the first steady state Serum Value of testosterone. The subject may be, for example, on anti-hypertensive therapy and exhibit an average change in systolic blood pressure of no more than 3.4 mmHg, an average change in diastolic blood pressure of no more than 1.8 mmHg, and/or an average change in heart rate of no more than 1.3 beats per minute. The subject may have diabetes mellitus and exhibit an average change in systolic blood pressure of no more than 3.0 mmHg, an average change in diastolic blood pressure of no more than 1.7 mmHg, and/or an average change in heart rate of no more than 1.9 beats per minute.

The Serum Value of testosterone may be measured from about 3 hours to about 6 hours (e.g., 3 hours, 4 hours, 5 hours, or 6 hours, e.g., from about 3 hours to about 5 hours) after administration. The Serum Value of testosterone may be measured from about 3 hours to about 5 hours after administration. The pharmaceutical composition may be administered with a meal. The pharmaceutical composition may be administered in two or more doses (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) doses. The pharmaceutical composition may be administered in two doses per day (e.g., twice daily administration). The pharmaceutical composition may be administered in three doses per day. A first dose may be administered in the morning, and a second dose may be administered in the evening. The first dose may include about 200 mg TU, and the second dose may include about 200 mg TU.

In some examples, following the first titration: the daily dosage may be increased to about 600 mg TU, and the first dose includes about 300 mg TU, and the second dose includes about 300 mg TU; the daily dosage may be maintained at about 400 mg TU, and the first dose includes about 200 mg TU, and the second dose includes about 200 mg TU; or the daily dosage may be decreased to about 200 mg TU, and the first dose includes about 100 mg TU, and the second dose includes about 100 mg TU.

In some examples, a second Serum Value of testosterone may be measured.

In some examples, a second titration may be performed, e.g., following the second Serum Value of testosterone measurement.

The first Serum Value of testosterone may be less than about 400/F ng/dL or 400/F + b ng/dL (e.g., a serum concentration of less than about 449 ng/dL or less than about 460 ng/dL or a plasma concentration of less than about 400 ng/dL) and the daily dosage may be increased to about 600 mg TU. This may establish a third steady state Serum Value of testosterone that is higher than the second steady state Serum Value of testosterone. The first Serum Value of testosterone may be from about 400/F ng/dL to about 900/F ng/dL or from about 400/F + b ng/dL to about 900/F + b ng/dL (e.g., a serum concentration of from about 449 ng/dL to about 1011 ng/dL or from about 460 ng/dL to about 971 ng/dL or a plasma concentration of from about 400 ng/dL to about 900 ng/dL) and the dosage may be maintained. This may maintain the second steady state Serum Value of testosterone. The first Serum Value of testosterone may be greater than about 900/F ng/dL or 900/F +b ng/dL (e.g., a serum concentration of greater than about 1011 ng/dL or greater than about 971 ng/dL or a plasma concentration of greater than about 900 ng/dL) and the dosage may be decreased to about 200 mg TU. This may establish a third steady state Serum Value of testosterone that is lower than the first steady state Serum Value of testosterone.

Following the first titration, about 600 mg TU may be administered daily to the subject. If the second Serum Value of testosterone is less than about 400/F ng/dL or 400/F + b ng/dL (e.g., a serum concentration of less than about 449 ng/dL or less than about 460 ng/dL or a plasma concentration of less than about 400 ng/dL), then the method may include orally administering about 800 mg TU daily to the subject to establish a third steady state Serum Value of testosterone that is higher than the second steady state Serum Value of testosterone. If the second Serum Value of testosterone is from about 400/F ng/dL to about 900/F ng/dL or from about 400/F + b ng/dL to about 900/F + b ng/dL (e.g., a serum concentration of from about 449 ng/dL to about 1011 ng/dL or from about 460 ng/dL to about 971 ng/dL or a plasma concentration of from about 400 ng/dL to about 900 ng/dL), then the method may include continuing to orally administer about 600 mg TU daily to the subject to maintain the second steady state Serum Value of testosterone. If the second Serum Value of testosterone is greater than about 900/F ng/dL or 900/F +b ng/dL (e.g., a serum concentration of greater than about 1011 ng/dL or greater than about 971 ng/dL or a plasma concentration of greater than about 900 ng/dL), then the method may include orally administering about 400 mg TU daily to the subject to establish a third steady state Serum Value of testosterone that is lower than the second steady state Serum Value of testosterone.

Following the first titration, about 400 mg TU may be administered daily to the subject. If the second Serum Value of testosterone is less than about 400/F ng/dL or 400/F + b ng/dL (e.g., a serum concentration of less than about 449 ng/dL or less than about 460 ng/dL or a plasma concentration of less than about 400 ng/dL), then the method may include orally administering about 600 mg TU daily to the subject to establish a third steady state Serum Value of testosterone that is higher than the second steady state Serum Value of testosterone. If the second Serum Value of testosterone is from about 400/F ng/dL to about 900/F ng/dL or from about 400/F + b ng/dL to about 900/F + b ng/dL (e.g., a serum concentration of from about 449 ng/dL to about 1011 ng/dL or from about 460 ng/dL to about 971 ng/dL or a plasma concentration of from about 400 ng/dL to about 900 ng/dL), then the method may include continuing to orally administer about 400 mg TU daily to the subject to maintain the second steady state

Serum Value of testosterone. If the second Serum Value of testosterone is greater than about 900/F ng/dL or 900/F +b ng/dL (e.g., a serum concentration of greater than about 1011 ng/dL or greater than about 971 ng/dL or a plasma concentration of greater than about 900 ng/dL), then the method may include orally administering about 200 mg TU daily to the subject to establish a third steady state Serum Value of testosterone that is lower than the second steady state Serum Value of testosterone.

Following the first titration, about 200 mg TU may be administered daily to the subject. If the second Serum Value of testosterone is less than about 400/F ng/dL or 400/F + b ng/dL (e.g., a serum concentration of less than about 449 ng/dL or less than about 460 ng/dL or a plasma concentration of less than about 400 ng/dL), then the method may include orally administering about 400 mg TU daily to the subject to establish a third steady state Serum Value of testosterone that is higher than the second steady state Serum Value of testosterone. If the second Serum Value of testosterone is from about 400/F ng/dL to about 900/F ng/dL or from about 400/F + b ng/dL to about 900/F + b ng/dL (e.g., a serum concentration of from about 449 ng/dL to about 1011 ng/dL or from about 460 ng/dL to about 971 ng/dL or a plasma concentration of from about 400 ng/dL to about 900 ng/dL), then the method may include continuing to orally administer about 200 mg TU daily to the subject to maintain the second steady state Serum Value of testosterone. If the second Serum Value of testosterone is greater than about 900/F ng/dL or 900/F +b ng/dL(e.g., a serum concentration of greater than about 1011 ng/dL or greater than about 971 ng/dL or a plasma concentration of greater than about 900 ng/dL), then the method may include orally administering about 100 mg TU daily to the subject to establish a third steady state Serum Value of testosterone that is lower than the second steady state Serum Value of testosterone.

In some examples, following the second titration: the dosage may be increased to about 800 mg TU and the first dose includes about 400 mg TU, and the second dose includes about 400 mg TU. In some examples, the dosage may be decreased to about 100 mg TU and the subject receives a single dose of about 100 mg TU. The single dose of about 100 mg TU may be administered in the morning.

The first Serum Value of testosterone may be measured once steady state has been achieved. For example, the first Serum Value of testosterone may be measured prior to day 21, e.g., on from about day 1 to about day 21 (e.g., day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21, e.g., 14) of a treatment regimen. The first Serum Value of testosterone may be measured on from about day 30 to about day 60 (e.g., day 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60) of a treatment regimen.

The first titration may be performed any time after the first Serum Value of testosterone is measured, e.g., on from about day 1 to about day 35, e.g., on from about day 7 to about day 35, e.g., from about day 21 to about day 35 (e.g., day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35, e.g., 28) of the treatment regimen. The first titration may be performed on from about day 30 to about day 60 (e.g., day 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60) of a treatment regimen.

For example, the first Serum Value of testosterone may be measured on about day 14 of the treatment regimen and/or the first titration may be performed on about day 28 of the treatment regimen.

A second Serum Value of testosterone may be measured. For example, the second Serum Value of testosterone may be measure on from about day 35 to about day 49 (e.g., day 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or 49, e.g., 42) of the treatment regimen.

A second titration may be performed, e.g., following the second Serum Value of testosterone measurement. The second titration may be performed on from about day 49 to about day 63 (e.g., day 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, or 63, e.g., 56) of the treatment regimen. For example, the second Serum Value of testosterone may be measured on about day 42, and the second titration may be formed on about day 56.

In some examples, the first titration may be performed on about day 28 of the treatment regimen, and/or the second titration may be performed on about day 56 of the treatment regimen.

In some examples, the first titration may be performed, e.g., on from about day 21 to about day 35 (e.g., day 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35, e.g., 28) of the treatment regimen. Following the first titration, the second steady state Serum Value of testosterone may be established. Then, a second Serum Value of testosterone may be measured. A second titration may then be performed.

The subject has not previously been administered TU or other testosterone replacement therapies (e.g., a prodrug of TU) for a period of at least seven days (e.g., 2 weeks, 3 weeks, 4 weeks, 2 months, 3 months, 4 months, 5 months, 6 months, 1 year, or more). For example, the period may be sufficient to wash out all exogenous testosterone from the body.

In some examples, the method is performed on a population of human subjects. The population of subjects may include, e.g., at least 10 subjects, at least 50 subjects, at least 100 subjects, at least 200 subjects, at least 500 subjects, or more.

In some examples, the method achieves a Cavg in the serum normal range of about 300 ng/dL to about 1000 ng/dL in at least 75% of the population; achieves a Cmax of less than about 1500 ng/dL in at least 85% of the population; achieves a Cmax of from about 1800 ng/dL to about 2500 ng/dL in no more than 5% of the population; and/or achieves a Cmax of greater than about 2500 ng/dL in no more than 0% of the population.

In some examples, the method reduces an average number of incorrect titrations or the risk of incorrect titrations per subject in the population in order to achieve a steady state testosterone Serum Value of from about 300 ng/dL to about 1000 ng/dL relative to a population receiving a treatment regimen in which an initial dosage is not about 400 mg TU and/or the Serum Value is not measured from about 3 hours to about 6 hours after administration.

In some examples, the method achieves a Cavg in the serum normal range of about 300 ng/dL to about 1000 ng/dL in a greater number of subjects in the population as compared to a treatment regimen in which an initial dosage is not about 400 mg TU and/or the Serum Value is not measured from about 3 hours to about 6 hours after administration; achieves a Cmax of less than about 1500 ng/dL in a greater number of subjects in the population as compared to the treatment regimen in which the initial dosage is not about 400 mg TU and/or the Serum Value is not measured from about 3 hours to about 6 hours after administration; achieves a Cmax of from about 1800 ng/dL to about 2500 ng/dL in a fewer number of subjects in the population as compared to the treatment regimen in which the initial dosage is not about 400 mg TU and/or the Serum Value is not measured from about 3 hours to about 6 hours after

administration; and/or achieves a Cmax of greater than about 2500 ng/dL in a fewer number of subjects in the population as compared to the treatment regimen in which the initial dosage is not about 400 mg TU and/or the Serum Value is not measured from about 3 hours to about 6 hours after administration.

In some examples, the method decreases the risk of elevated blood pressure, e.g., in the population of human subjects. For example, in some examples, daytime systolic blood pressure, night time systolic blood pressure, and/or 24-hour average systolic blood pressure does not increase by more than about 5 mmHg (e.g., no more than about 4, 3, or 2 mmHg) relative to baseline. In some examples, daytime systolic blood pressure, night time systolic blood pressure, and/or 24-hour average systolic blood pressure does not increase by more than about 3 mmHg relative to baseline. In some examples, daytime systolic blood pressure, night time systolic blood pressure, and/or 24-hour average systolic blood pressure does not increase by more than about 2 mmHg relative to baseline when measured by ambulatory blood pressure monitoring (ABPM). In some examples, the subject is diabetic or hypertensive and the daytime systolic blood pressure, night time systolic blood pressure, and/or 24-hour average systolic blood pressure does not increase by more than about 4 mmHg relative to baseline when measured by ambulatory blood pressure monitoring (ABPM).

In some examples, the population averages has a Cmax/Cavg ratio for 0-24 hours of less than 2.5; a Cmax/Cavg ratio for 0-12 hours of less than 2.2; and/or a Cmax/Cavg ratio for 12-24 hours of less than 2.2.

The pharmaceutical composition may include from about 5% to about 40% (e.g., about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, e.g., about 18.2%) by weight TU. The pharmaceutical composition may include about from about 2% to about 45% (e.g., about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, or 45%, e.g., about 25%) by weight of a phytosterol or phytosterol ester. The phytosterol may include phytosterols, phytosterol esters, or combinations thereof. The pharmaceutical composition may include phytosterol esters. The formulation may include from about 10% to about 90% (e.g., about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%) by weight of a non-sterol solubilizing agent. The non-sterol solubilizing agent may be selected from lipids, surfactants (e.g., hydrophobic and/or hydrophilic surfactants), and mixtures thereof. The pharmaceutical composition may be self-emulsifying or self-microemulsifying.

In some examples, the non-sterol solubilizing agent includes propylene glycol monolaurate.

In some examples, the non-sterol solubilizing agent includes polyoxyl 40 hydrogenated castor oil.

In some examples, the pharmaceutical composition includes from about 10% to about 25% (e.g., about 15%, 20%, or 25%, e.g., about 18.2%) by weight of solubilized testosterone undecanoate; from about 5% to about 40% (e.g., about 10%, 15%, 20%, 25%, 30%, 35%, or 40%, e.g., about 15%) by weight of a hydrophilic surfactant; from about 15% to about 65% (e.g., about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, or 65%, e.g., about 39.9%) by weight of a hydrophobic surfactant; from about 2% to about 45% (e.g., about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, or 45%, e.g., about 25%) by weight of phytosterol esters; and from about 0 to about 15% (e.g., about 1%, 2%, 3%, 4%, 5%, 10%, or 15%, e.g., about 2%) by weight of a solubilizer.

In some examples, oral formulation includes from about 10% to about 40% (e.g., from about 10% to about 30%, e.g., about 25%) by weight of one or more phytosterol esters.

In some examples, the solubilizer includes dl-alpha-tocopherol and/or an ester or acetate thereof.

In some examples, the pharmaceutical composition includes: about 18.2% by weight of solubilized testosterone undecanoate; about 15.0% by weight of polyoxyl 40 hydrogenated castor oil; about 39.9% by weight of propylene glycol monolaurate; about 25.0% by weight of one or more phytosterol esters; and about 2.0% by weight of dl-alpha-tocopherol and/or an ester or acetate thereof.

In some examples of any of the above aspects, the first Serum Value and/or the second Serum Value is measured by measuring testosterone concentration of serum clotted at room temperature for about 30 minutes prior to centrifugation in a tube, measuring testosterone concentration of plasma in a tube supplemented with EDTA and NaF and multiplying the testosterone concentration by the inverse of a predetermined factor F (1/F), or a comparable method thereof. The predetermined factor may be, for example from about 0.70 to about 1.10, e.g., about 0.81 to about 0.94 (e.g., 0.81, 0.82, 0.83, 0.84, 0.85, 0.86, 0.87, 0.88, 0.89, 0.90, 0.91, 0.92, 0.93, or 0.94). For example, the predetermined factor may be 0.70, 0.71, 0.72, 0.73, 0.74, 0.75, 0.76, 0.77, 0.78, 0.79, 0.80, 0.81, 0.82, 0.83, 0.84, 0.85, 0.86, 0.87, 0.88, 0.89, 0.90, 0.91, 0.92, 0.93, 0.94, 0.95, 0.96, 0.97, 0.98, 0.99, 1.00, 1.01, 1.02, 1.03, 1.04, 1.05, 1.06, 1.07, 1.08, 1.09, or 1.10. In one example, the predetermined factor is 0.82. In one example, the predetermined factor is 0.83. In one example, the predetermined factor is 0.88. In one example, the predetermined factor is 0.89. In another example, the predetermined factor is 0.92.

In some examples of any of the above aspects, the subject is at risk of high blood pressure, heart attack, or stroke.

The subject may be suffering from low testosterone levels due to aging.

The subject may be suffering from low testosterone levels due to a disease which decreases testosterone production.

The subject may have diabetes (e.g., diabetes mellitus), hypertension, a metabolic disorder, or is obese.

In some examples, the subject has been treated or is being treated with an anti-hypertensive medication.

The subject may have osteoporosis, reduced sexual function or libido, muscle strength or muscle stamina, aplastic anemia, AIDS wasting syndrome, obstructive sleep apnea, metabolic disorders, non-alcoholic fatty liver disease (NAFLD), or non-alcoholic steatohepatitis (NASH).

The subject mat be at risk of a testosterone related adverse event (e.g., blood pressure increase).

Definitions

As used herein, the term “about” refers to a value that is +/- 10% of a recited value. For example, a dose of about 400 mg TU refers to a dose that contains from 360 mg to 440 mg of TU. When referring to days, the term about refers to a value of +/- 3 days. For example, an event (e.g., a serum T measurement or a dose titration) that occurs on about day 14 may occur from day 11 to day 17.

As used herein, the term “phytosterol” refers to a class of plant sterol molecules, which are naturally occurring compounds found in plant cell membranes. Phytosterols include both plant sterols

What is claimed is:

CLAIMS

1. Use of testosterone undecanoate (TU) in the manufacture of a medicament for the treatment of testosterone deficiency in a subject in need thereof, comprising:

a) a treatment regimen comprising 400 mg of the testosterone undecanoate (TU) to be orally administered to the subject daily with a meal, wherein the TU is to be administered in a pharmaceutical composition comprising TU, a non-sterol solubilizing agent effective for solubilization of the TU, and a phytosterol or phytosterol ester;

b) a first steady state serum concentration of testosterone to be established;

c) a first steady state Serum Value of testosterone in the subject that is measured from about 3 hours to about 6 hours after administration of the pharmaceutical composition to be provided following step (b); and

d) a first titration of the testosterone undecanoate to be performed, wherein:

i) if the first Serum Value of testosterone is less than about 400/F + b ng/dL, then the subject is to be orally administered about 600 mg TU daily to establish a second steady state Serum Value of testosterone that is higher than the first steady state Serum Value of testosterone;

ii) if the first Serum Value of testosterone is from about 400/F + b ng/dL to about 900/F + b ng/dL, then the subject is continued to be orally administered about 400 mg TU daily to maintain the first steady state Serum Value of testosterone; or

iii) if the first Serum Value of testosterone is greater than about 900/F + b ng/dL, then the subject is to be orally administered about 200 mg TU daily to establish a second steady state Serum Value of testosterone that is lower than the first steady state Serum Value of testosterone.

2. The use of claim 1, wherein step (a) comprises the pharmaceutical composition to be administered twice daily.

3. The use of claim 2, wherein:

a) a first dose is to be administered in the morning and a second dose is to be administered in the evening; and/or

b) the first does comprises about 200 mg TU, and the second dose comprises about 200 mg TU.

4. The use of claim 3, wherein following the first titration,

i) about 600 mg TU is to be administered daily to the subject, and the first dose comprises about 300 mg TU, and the second dose comprises about 300 mg TU;

ii) about 400 mg TU is to be administered daily to the subject, and the first dose comprises about 200 mg TU, and the second dose comprises about 200 mg TU; or

iii) about 200 mg TU is to be administered daily to the subject, and the first dose comprises about 100 mg TU, and the second dose comprises about 100 mg TU.

5. The use of any one of claims 1-4, further comprising:

e) a second steady state serum concentration of testosterone to be established;

f) following step (e), a second steady state Serum Value of testosterone in the subject to be provided; and

g) a second titration of the TU to be performed.

6. The use of claim 5, wherein following the first titration, about 600 mg TU is to be administered daily to the subject, and

a) if the second Serum Value of testosterone is less than about 400/F + b ng/dL, then about 800 mg TU is to be orally administered daily to the subject to establish a third steady state Serum Value of testosterone that is higher than the second steady state Serum Value of testosterone;

b) if the second Serum Value of testosterone is from about 400/F + b ng/dL to about 900/F + b ng/dL, then about 600 mg TU is continued to be orally administered daily to the subject to maintain the second steady state Serum Value of testosterone; or

c) if the second Serum Value of testosterone is greater than about 900/F + b ng/dL, then about 400 mg TU is to be orally administered daily to the subject to establish a third steady state Serum Value of testosterone that is lower than the second steady state Serum Value of testosterone.

7. The use of claim 5, wherein following the first titration, about 400 mg TU is to be administered daily to the subject, and

a) if the second Serum Value of testosterone is less than about 400/F + b ng/dL, then about 600 mg TU is to be administered daily to the subject to establish a third steady state Serum Value of testosterone that is higher than the second steady state Serum Value of testosterone;

b) if the second Serum Value of testosterone is from about 400/F + b ng/dL to about 900/F + b ng/dL, then about 400 mg TU is continued to be orally administered daily to the subject to maintain the second steady state Serum Value of testosterone; or

c) if the second Serum Value of testosterone is greater than about 900/F + b ng/dL, about 200 mg TU is to be orally administered daily to the subject to establish a third steady state Serum Value of testosterone that is lower than the second steady state Serum Value of testosterone; or

8. The use of claim 5, wherein following the first titration, about 200 mg TU is to be administered daily to the subject, and

a) if the second Serum Value of testosterone is less than about 400/F + b ng/dL, about 400 mg TU is to be orally administered daily to the subject to establish a third steady state Serum Value of testosterone that is higher than the second steady state Serum Value of testosterone;

b) if the second Serum Value of testosterone is from about 400/F + b ng/dL to about 900/F + b ng/dL, then about 200 mg TU is continued to be orally administered daily to the subject to maintain the second steady state Serum Value of testosterone; or

c) if the second Serum Value of testosterone is greater than about 900/F + b ng/dL, about 100 mg TU to be administered daily to the subject to establish a third steady state Serum Value of testosterone that is lower than the second steady state Serum Value of testosterone.

9. The use of claim 6, wherein following the second titration, about 800 mg TU is to be administered daily to the subject, and the first dose comprises about 400 mg TU, and the second dose comprises about 400 mg TU.

10. The use of claim 8, wherein following the second titration, about 100 mg TU is to be administered daily to the subject, and the subject receives a single dose of about 100 mg TU.

11. The use of any one of claims 1-10, wherein the pharmaceutical composition comprises:

a) from about 10% to about 25% by weight of solubilized testosterone undecanoate;

b) from about 5% to about 40% by weight of a hydrophilic surfactant;

c) from about 15% to about 65% by weight of a hydrophobic surfactant;

d) from about 2% to about 45% by weight of phytosterol esters; and

e) from about 0 to about 15% by weight of a solubilizer.

12. The use of claim 11, wherein the pharmaceutical composition comprises:

a) about 18.2% by weight of solubilized testosterone undecanoate;

b) about 15.0% by weight of polyoxyl 40 hydrogenated castor oil;

c) about 39.9% by weight of propylene glycol monolaurate;

d) about 25.0% by weight of one or more phytosterol esters; and

e) about 2.0% by weight of dl-alpha-tocopherol and/or an ester or acetate thereof.

13. The use of any one of claims 1-12, wherein:

a) the subject is a hypogonadal male;

b) the subject has not previously been administered TU or other testosterone replacement therapy for a period of at least seven days or a period of time sufficient to completely wash exogenous testosterone from the subject; and/or

c) the use is to be performed on a population of human subjects.

14. The use of claim 13, wherein:

a) the population comprises at least 10 subjects, at least 50 subjects, at least 100 subjects, at least 200 subjects, at least 500 subjects, or more;

b) the use achieves a Cavg in the serum normal range of about 300 ng/dL to about 1000 ng/dL in at least 75% of the population;

c) the use achieves a Cmax of less than about 1500 ng/dL in at least 85% of the population;

d) the use achieves a Cmax of from about 1800 ng/dL to about 2500 ng/dL in no more than 5% of the population;

e) the use achieves a Cmax of greater than about 2500 ng/dL in no more than 0% of the population;

f) the use reduces an average number of incorrect titrations or the risk of incorrect titrations per subject in the population in order to achieve a steady state testosterone Serum Value of from about 300 ng/dL to

about 1000 ng/dL relative to a population receiving a treatment regimen in which an initial dosage is not about 400 mg TU and/or the Serum Value is not measured from about 3 hours to about 6 hours after administration

g) the use achieves a Cavg in the serum normal range of about 300 ng/dL to about 1000 ng/dL in a greater number of subjects in the population as compared to a treatment regimen in which an initial dosage is not about 400 mg TU and/or the Serum Value is not measured from about 3 hours to about 6 hours after administration;

h) the use achieves a Cmax of less than about 1500 ng/dL in a greater number of subjects in the population as compared to the treatment regimen in which the initial dosage is not about 400 mg TU and/or the Serum Value is not measured from about 3 hours to about 6 hours after administration;

i) the use achieves a Cmax of from about 1800 ng/dL to about 2500 ng/dL in a fewer number of subjects in the population as compared to the treatment regimen in which the initial dosage is not about 400 mg TU and/or the Serum Value is not measured from about 3 hours to about 6 hours after administration;

j) the use achieves a Cmax of greater than about 2500 ng/dL in a fewer number of subjects in the population as compared to the treatment regimen in which the initial dosage is not about 400 mg TU and/or the Serum Value is not measured from about 3 hours to about 6 hours after administration; and/or

k) the use decreases the risk of elevated blood pressure of the population of human subjects.

15. The use of claim 14, wherein:

a) the daytime systolic blood pressure, night time systolic blood pressure, and/or 24-hour average systolic blood pressure does not increase by more than 3 mmHg as compared to the blood pressure before onset of treatment in the population of human subjects

b) the subjects are diabetic or hypertensive and the daytime systolic blood pressure, night time systolic blood pressure, and/or 24-hour average systolic blood pressure does not increase by more than 4 mmHg as compared to the blood pressure before onset of treatment in the population of human subjects.

16. The use of any one of claims 13-15, wherein the population averages has:

a) a Cmax/Cavg ratio for 0-24 hours of less than 2.5;

b) a Cmax/Cavg ratio for 0-12 hours of less than 2.2; and/or

c) a Cmax/Cavg ratio for 12-24 hours of less than 2.2.

17. The use of any one of claims 1-16, wherein the first Serum Value is to be measured by:

(a) testosterone concentration of serum clotted at room temperature for about 30 minutes prior to centrifugation in a tube to be measured;

(b) testosterone concentration of plasma in a tube supplemented with EDTA and NaF and multiplying the testosterone concentration by the inverse of a predetermined factor F (1/F) to be measured; or

(c) a comparable use thereof.

18. The use of any one of claims 1-17, wherein:

a) the subject is at risk of high blood pressure, heart attack, or stroke;

b) the subject is suffering from low testosterone levels due to aging;

c) the subject is suffering from low testosterone levels due to a disease which decreases testosterone production;

d) the subject has diabetes, hypertension, a metabolic disorder, or is obese;

e) the subject has previously been treated with an anti-hypertensive medication;

f) the subject has osteoporosis, reduced sexual function or libido, muscle strength or muscle stamina, aplastic anemia, AIDS wasting syndrome, obstructive sleep apnea, metabolic disorders, non-alcoholic fatty liver disease (NAFLD), or non-alcoholic steatohepatitis (NASH); and/or

g) the subject is at risk of a testosterone related adverse event.

19. The use of claim 18, wherein the diabetes is diabetes mellitus.

20. Use of testosterone undecanoate (TU) in the manufacture of a medicament for the treatment of testosterone deficiency in a subject in need thereof, comprising:

a) a treatment regimen comprising 400 mg of the testosterone undecanoate (TU) to be orally administered to the subject daily with a meal, wherein the TU is to be administered in a pharmaceutical composition comprising TU, a non-sterol solubilizing agent effective for solubilization of the TU, and a phytosterol or phytosterol ester;

b) e a first steady state serum concentration of testosterone to be established;

c) a first steady state Serum Value of testosterone in the subject that is measured from about 3 hours to about 6 hours after administration of the pharmaceutical composition to be provided following step (b); and

d) a first titration of the testosterone undecanoate to be performed, wherein:

i) if the first Serum Value of testosterone is less than about 460 ng/dL, then the subject to be orally administered about 600 mg TU daily to establish a second steady state Serum Value of testosterone that is higher than the first steady state Serum Value of testosterone;

ii) if the first Serum Value of testosterone is from about 460 ng/dL to about 971 ng/dL, then the subject is continued to be orally administered about 400 mg TU daily to maintain the first steady state Serum Value of testosterone; or

iii) if the first Serum Value of testosterone is greater than about 971 ng/dL, then the subject is to be orally administered about 200 mg TU daily to establish a second steady state Serum Value of testosterone that is lower than the first steady state Serum Value of testosterone; wherein the subject:

is on anti-hypertensive therapy and exhibits an average change in systolic blood pressure of no more than 3.4 mmHg, an average change in diastolic blood pressure of no more than 1.8 mmHg, and/or an average change in heart rate of no more than 1.3 beats per minute; and/or

has diabetes mellitus and exhibits an average change in systolic blood pressure of no more than 3.0 mmHg, an average change in diastolic blood pressure of no more than 1.7 mmHg, and/or an average change in heart rate of no more than 1.9 beats per minute.