

Official Protocol Title:	A Phase III, Multi-Center, Open Label, Single-Group Trial to Investigate the Efficacy and Safety of MK-8962 (corifollitropin alfa) in Combination with human Chorionic Gonadotropin (hCG) for Initiation or Restoration of Puberty as Assessed by Increased Testicular Volume in Adolescent Males 14 to <18 Years Old with Hypogonadotropic Hypogonadism (Phase III; Protocol No. MK-8962-043-06)
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.2	Dose Titration for hCG	A note was added to allow for human Chorionic Gonadotropin (hCG) dose titration outside of the suggested range of 500 IU to 5000 IU following consultation with the Sponsor.	The previous protocol version indicates that the dose of hCG may be titrated between 500 IU and 5000 IU twice weekly. However, it does not clearly indicate that in some cases, the investigator may need to adjust the hCG dose outside of the suggested range of 500 IU to 5000 IU twice weekly, based on total testosterone (Total T) and estradiol (E2) levels and/or clinical assessments, following consultation with the Sponsor. Therefore, this specific wording was added to the protocol to allow for hCG dose titration in the instances outlined above.
2.2	Trial Diagram		
5.2	Trial Treatment(s)		
5.2.2	Timing of Dose Administration	A footnote was added to Figure 1 , Table 2 , and Table 3 to allow for hCG dose titration outside of the suggested range of 500 IU to 5000 IU following consultation with the Sponsor.	
8.1	Statistical Analysis Plan Summary	The hCG dose range was removed from the Treatment Assignment.	

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
NA	Title Page	The Sponsor's name and address have been updated.	The Sponsor's legal name and address have been updated.
5.1.3	Subject Exclusion Criteria	An exclusion criterion has been added for subjects with renal insufficiency as determined by the investigator.	To harmonize the exclusion criteria with the Elonva Summary of Product Characteristics (SmPC) and Company Core Data Sheet (CCDS) and to align with the country specific amendment for Denmark (P043-05).
7.1.3.2	Panel of Endocrine Parameters	Follicle stimulating hormone (FSH) and luteinizing hormone (LH) testing performed as part of the optional gonadotrophin releasing hormone (GnRH) agonist stimulation test or GnRH intravenous (IV) infusion test should be performed at the local laboratory.	To clarify that the LH and FSH assays that are part of the GnRH agonist stimulation test or GnRH IV infusion test should be performed locally, as these are optional procedures to be performed under the discretion of the Principal Investigator.
7.1.4.4	Calibration of Equipment	The specification of "critical" equipment and the list of equipment requiring calibration have been removed.	Textual revisions were applied to clarify investigator responsibility for calibration and maintenance of study/trial equipment.
All	All	Clerical and formatting changes.	Consistency throughout the document.

1.0 TRIAL SUMMARY

Abbreviated Title	MK-8962 (corifollitropin alfa) in adolescent males 14 to <18 years old with hypogonadotropic hypogonadism (HH)
Trial Phase	Phase III
Clinical Indication	Treatment of adolescent males 14 to <18 years old with HH
Trial Type	Interventional
Type of control	Uncontrolled
Route of administration	Subcutaneous (SC) injection
Trial Blinding	Unblinded Open-label
Treatment Groups	MK-8962 100 µg (for subjects with body weight ≤60 kg) or 150 µg (for subjects with body weight >60 kg) once every two weeks for 12 weeks, followed by 52 weeks of combined treatment with MK-8962 once every two weeks and human Chorionic Gonadotropin (hCG) twice a week
Number of trial subjects	Approximately 15 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 2.5 years from the time the first subject signs the informed consent/assent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately 73 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 6 weeks, each subject will be treated for 12 weeks with MK-8962 alone (i.e., priming phase). After completion of the Priming Phase, the subject will start on combined treatment with both MK-8962 and hCG for 52 weeks. At the end of the combined treatment phase or at premature discontinuation, a post-treatment follow-up visit will be scheduled at least 21 days after the last MK-8962 injection (and at least 7 days after the last hCG injection). After the post-treatment follow-up visit, subjects who prematurely discontinue study medication but do not withdraw consent will continue to be followed up until they have reached Week 64 after initial treatment allocation. Subjects discontinued from the treatment due to the presence of neutralizing anti-drug antibodies (ADAs) may continue to be followed until the ADA result becomes negative or until clinically stable for up to 12 months after treatment discontinuation.

A list of abbreviations used in this document can be found in Section 12.8.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multi-center, open-label, single-group trial of MK-8962 (corifollitropin alfa) in adolescent males 14 to <18 years old with hypogonadotropic hypogonadism (HH).

The primary efficacy endpoint for this trial is the change from baseline in testicular volume after 64 weeks of treatment with MK-8962 (given alone once every two weeks for 12 weeks, then in combination with twice-weekly doses of human Chorionic Gonadotropin (hCG) for 52 weeks). The primary safety endpoint is the presence of anti-drug antibodies (ADA) against MK-8962. Subjects with neutralizing anti-MK-8962 antibodies in the ADA assay will discontinue treatment and will be followed with repeat ADA testing, until the ADA result becomes negative or until the subject is clinically stable for up to 12 months after treatment discontinuation, whichever comes first. Each subject will be followed for safety monitoring until the last protocol-specified visit or contact.

This study will be approximately 73 weeks in duration. After signing the informed consent/assent at Visit 1 (V1), the subject will undergo a screening period of up to 6 weeks. Eligible subjects will be allocated to a 12-week MK-8962 priming phase at Visit 2 (V2)/Day 1 (Week 0). The first 3 doses of MK-8962 will be self-administered by the subject (or administered by an appropriately trained person designated by the subject's legal guardian (e.g., caregiver, parent/legal guardian) and witnessed by qualified personnel at the trial site at V2/Day 1, Visit 7 (V7)/Week 2 (Day 15), and Visit 8 (V8)/Week 4 (Day 29). A pharmacokinetic (PK) sample will be collected from each subject prior to the first injection of MK-8962 at V2/Day 1. During the first two weeks of the priming phase, frequent PK sampling will be performed from Visit 2 (V2/Day 1) through Visit 6 (V6/Day 11) to collect PK samples post first dose of MK-8962. Additional PK samples will be collected at other visits throughout the trial as specified in the PK flow chart (see Section 7.1.3.3.1). A telephone contact (TC) will be conducted at Week 8 to monitor AEs, concomitant medication, and study medication compliance.

At Visit 9 (V9)/Week 12 (Day 85), the subject will enter a 52-week MK-8962 and hCG combined treatment phase. The first dose of hCG will be self-administered (or administered by an appropriately trained person designated by the subject's legal guardian) at the trial site as a witnessed dose at V9. During the combined treatment phase, the subject will have site visits every 8 to 12 weeks from V9 until treatment completion at Visit 15 (V15)/Week 64. Telephone contacts will be conducted every 4 weeks between site visits to monitor AEs, concomitant medication, and study medication compliance. The last dose of MK-8962 is scheduled to be home-administered by the subject (or an appropriately trained person designated by the subject's legal guardian) on Week 62. The subject (or the designated person) will continue to home-administer the twice-weekly hCG and the last dose will be administered in Week 64. A post-treatment follow-up visit is to be scheduled at least 21 days (but no more than 45 days) after the last dose of MK-8962, and at least 7 days after the last dose of hCG (whether the subject completed the trial or discontinued from the study treatment prematurely). (See [Figure 1](#))

The subject and his legal guardian (or someone designated by the subject's legal guardian such as a caregiver or parent) will receive instructions on MK-8962 and hCG home-injection prior to the initiation of treatment. After the first three doses of MK-8962 and the first dose of hCG, the subsequent medication will be dispensed by the investigational site to the subject for home-administration unsupervised by the investigator. A paper diary will be used to record the time and amount of MK-8962 and hCG administration.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

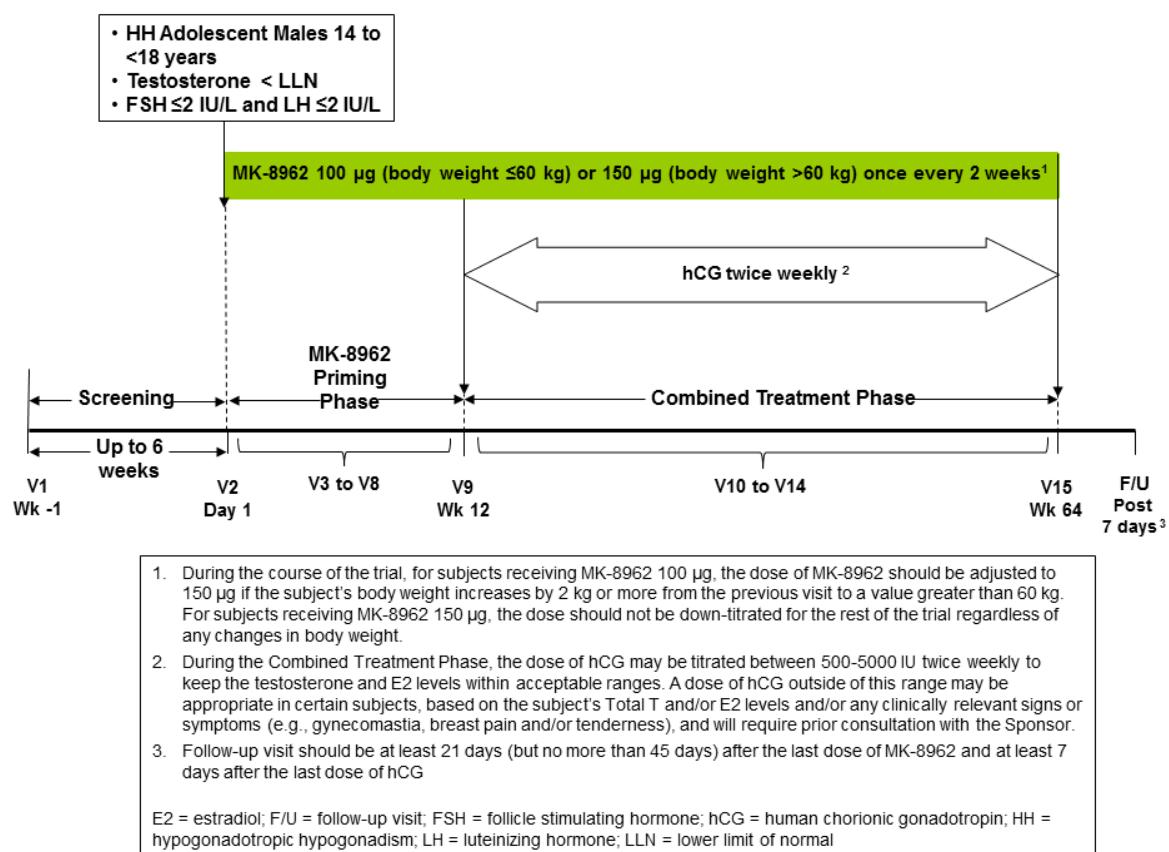


Figure 1 Trial Design Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In adolescent males 14 to <18 years old with HH:

- 1) **Objective:** To estimate the change from baseline in testicular volume (measured as the sum of volumes of left and right testes by ultrasound) after 64 weeks of treatment with MK-8962 (in combination with hCG for the last 52 weeks).
- 2) **Objective:** To evaluate the safety and tolerability of MK-8962 over 64 weeks of treatment, including evaluation of development of antibodies to MK-8962.

3.2 Secondary Objective(s) & Hypothesis(es)

In adolescent males 14 to <18 years old with HH, to evaluate the following parameters over 64 weeks of treatment with MK-8962 (in combination with hCG for the last 52 weeks):

- 1) **Objective:** the change from baseline in inhibin B concentrations.
- 2) **Objective:** growth velocity (height).
- 3) **Objective:** the change from baseline in Tanner Stage of pubertal development.
- 4) **Objective:** the change from baseline in levels of endocrine parameters (i.e., luteinizing hormone [LH], calculated free testosterone [T], total testosterone [Total T], estradiol [E2], sex hormone-binding globulin [SHBG], and anti-Müllerian hormone [AMH]).
- 5) **Objective:** testicular sonographic pattern reflecting pubertal development.
- 6) **Objective:** the PK of MK-8962 (based on serum MK-8962 concentrations).

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-8962.

4.1.1 Pharmaceutical and Therapeutic Background

The testes, or testicles, are the primary organs of the male reproductive system. The testes are immature until the time of puberty, at which time they begin to produce adult levels of T as well as spermatozoa. The first physical sign of puberty in males is testicular enlargement (gonadarche) that is induced by the pulsatile release of hypothalamus-derived gonadotropin releasing hormone (GnRH). Development of male secondary sexual characteristics, including spermatogenesis, male hair growth patterns, and development of adult male T levels then follows. While the average age of puberty varies by race, the onset of puberty generally occurs between the ages of 10 and 13 and is considered to be delayed when there is a lack of pubertal development, specifically gonadarche, by the age of 15.

Successful puberty requires an intact hypothalamic-pituitary-testicular axis. Initially, GnRH stimulation results in an increase in follicle stimulating hormone (FSH) levels that acts at the testes to induce proliferation of the Sertoli cells and an increase in gonadal size. The subsequent exposure to LH halts further proliferation through terminal differentiation of the Sertoli cells, increases T levels and induces further development of secondary sexual characteristics [1]. This sequential exposure is thought to be necessary for normal testicular development and subsequent fertility.

HH is a disease of inadequate production of pituitary derived FSH and LH. HH can be the result of failed gonadotropin secretion by the pituitary or absent or inadequate GnRH secretion by the hypothalamus. The clinical manifestations of HH depend on the stage of development at which the deficiency occurred (pre or post-pubertal). When the deficiency occurs prior to puberty (pre-pubertal), the pubertal transition is delayed or absent. The condition can be congenital or acquired, and can occur in isolation (idiopathic HH [IHH]), in association with anosmia/hyposmia (Kallmann syndrome), or as part of a multiple pituitary hormone deficiency syndrome. IHH is the rarest form, with an incidence of between 1:10,000 and 1:86,000, whereas acquired HH is more common because there are multiple etiologies that lead to the disease [2]. The primary goal in the treatment of male HH is to increase testosterone levels, leading to the development of secondary sexual characteristics. Another important goal is to stimulate spermatogenesis, at an appropriate time, supporting fertility. Historically, boys with HH were not treated with FSH in adolescence as FSH leads to spermatogenesis, which is not the goal of treatment at this age [3; 4]. Instead, these boys were given exogenous testosterone in sufficient quantity to induce the development of male secondary sexual characteristics and then to maintain normal male T levels. However, boys that are not exposed to FSH during the critical pubertal window required for Sertoli cell proliferation may miss this critical state of testicular development. Exposure to LH (or T) causes terminal differentiation of the Sertoli cells, limiting the ability of FSH to induce Sertoli cell proliferation in future exposures. As a result, the testes do not fully develop, and this could have an impact on future fertility [1; 5]. This has been confirmed in studies of adult men who had achieved normal male T levels only using testosterone supplementation in adolescence but then fail to achieve normal range sperm counts, inhibin B levels and adult testicular size when exposed to GnRH therapy later in life [5]. Thus, modern treatment protocols for adolescent males with HH use a 3-staged approach, first using FSH-only for a short time, followed by the combination of FSH and hCG, which occupies the LH receptor and has a longer half-life than an LH [3; 4], until full testicular volume is achieved. In the 3rd stage of treatment, gonadotropin therapy is stopped and testosterone supplementation is used to maintain secondary male characteristics until such time when fertility is desired. This approach allows for both the induction of puberty as well as maturation of the testicular tissue in males with early onset HH so that spermatogenesis and future fertility are not compromised.

During the second stage of this 3-stage approach to testicular maturation, injectable recombinant human FSH (recFSH) is used to promote Sertoli cell function and hCG is used to induce Leydig cell function and increase T production [3; 4]. hCG is preferred over T because hCG can stimulate a small amount of additional testicular growth if the testes are still of a sub-optimal volume. [3; 4] Previous studies have shown that this 3-stage therapy protocol has successfully induced puberty as indicated by an increase in testicular size and a

rise in circulating inhibin B levels, findings suggesting proliferation of immature Sertoli cells. Inhibin B has been shown to be a useful surrogate for monitoring spermatogenic activity in boys treated with hCG when semen analysis is not feasible [3; 4], and will be used to monitor testicular development in this study.

MK-8962 (Elonva®, corifollitropin alfa) is a recombinant gonadotropin consisting of the α -subunit of human FSH and a hybrid subunit composed of the sequence of the β -subunit of human FSH and the carboxy-terminal peptide (CTP) part of the β -subunit of the hCG. It has the same pharmacodynamic (PD) profile as FSH, but different PK properties. MK-8962 has an approximately 2-fold longer elimination half-life and an almost 4-fold extended time interval to peak serum levels as compared to that of recombinant human FSH (follitropin beta) [6]. Both MK-8962 and recFSH work via the same FSH receptor in the ovary or testes, therefore either can be used for gonadal stimulation. Three Phase III randomized, controlled clinical trials comparing MK-8962 to recFSH in women undergoing ovulation induction in an Assisted Reproductive Technology (ART) cycle confirmed either non-inferiority (Trials 38819 [7] and P06029 [8]) or equivalence (Trial 107012 [9]) in the clinical outcomes of pregnancy rates or number of oocytes retrieved. In P031[10], a clinical trial in 18 adult males with HH, MK-8962 use resulted in a more than doubling of the mean testicular volume along with induction of spermatogenesis in 77% of adult males who remained azoospermic after treatment with hCG. These findings are consistent with the findings of Trial 37618 [11] where recFSH use resulted in a doubling of mean testicular volume and induction of spermatogenesis in 43% of adult men who remained azoospermic after hCG administration. Although the percentage of men who achieved spermatogenesis was higher in trial P031, the small size of both studies (N= 18 in P031 and N=30 in Trial 37618) limits quantitative comparisons; the stimulation of spermatogenesis in a substantial portion of treated subjects suggests both agents had clinically relevant FSH activity. While there are no comparative trials between MK-8962 and recFSH in HH males, the fact that both drugs work at the same FSH receptor site, have both been successful in stimulating spermatogenesis in men and both have non-inferior/equivalent clinical outcomes in women, it is a reasonable assumption that MK-8962 use in HH males would have a similar response as that seen with the use of recFSH. And since treatment of infertility in HH males usually requires up to 24 months of treatment with frequent injections of FSH, the need for fewer injections with MK-8962 may result in fewer medication errors and improved compliance, a specific benefit for the adolescent population.

MK-8962 is currently approved for Controlled Ovarian Stimulation (COS) in women participating in ART programs in 81 countries worldwide, including all 27 member states of the European Union (EU), Norway, Iceland, Liechtenstein, and 51 countries outside of Europe. As noted above, the efficacy and safety of both 100 and 150 μ g of MK-8962 in comparison to daily doses of 150-300 IU of recFSH has been established in women. In addition, two studies have been conducted in HH men:

- One Phase 1, open label, repeated dose trial with 15 μ g MK-8962 (Trial 38801 [12]) has been conducted in 13 adult HH men to study the first human exposure to corifollitropin alfa. Subjects received four subcutaneous injections of 15 μ g MK-8962 with an interval of ~4 weeks. In these men, a single dose of 15 μ g -8962 was able to induce a rise in serum inhibin B concentrations [12]. Analysis of

pharmacokinetic data from this trial and later Phase I - III trials in women suggest that drug clearance is 40% lower in men as compared to women.

- The safety and efficacy of MK-8962 for the treatment of HH in adult men has been evaluated in a Phase III, multi-center, open-label, single-group trial of MK-8962 in combination with hCG in 18 adult HH men 18-50 years of age (Trial P031 [10]). The dose and interval selection for this trial was based on modeling and simulation (M&S) using PK data from MK-8962 Phase I - III trials as well as recFSH Trial 37618. The M&S showed 150 µg MK-8962 once every two weeks are expected to achieve trough serum FSH-IR Levels comparable to that of ≥ 4 IU/L seen after treatment with recFSH in Trial 37618. Trial P031 was conducted to establish the benefit/risk ratio of MK-8962 in adult HH men before the start of the pediatric trial in HH adolescent boys. As noted above, this study showed that 150 µg MK-8962 administered once every two weeks in combination with twice weekly hCG injections resulted in an increase of testicular volume and induced spermatogenesis. There were no safety concerns with respect to adverse events and immunogenicity. Since the metabolic clearance of MK-8962 in adolescent males over 14 years of age is expected to be similar to that of adult males, the PK data from P031 has been used to predict the exposure in adolescents and to determine final dose selection in the current trial.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

The current trial will evaluate MK-8962 in HH adolescent boys between 14 and < 18 years of age. This trial is a multi-center, open-label, single-group trial to study the treatment of MK-8962 in combination with hCG to induce and/or restore puberty and induce and/or restore spermatogenesis in adolescent males with HH.

The major difference in the treatment schedule between this trial and the previous adult male trial is the use of MK-8962 alone for the first 12 weeks of the trial. This 12 week “priming” period allows for FSH exposure to induce Sertoli cell proliferation to occur before exposure to hCG, which is not applicable to the adult male population who have previously been virilized. The priming period is followed by 52 weeks of combined MK-8962 and hCG stimulation to evaluate the safety and efficacy of longer term use.

Adolescent males aged 14 to < 18 years with an established diagnosis of HH (either congenital or acquired with onset prior to puberty) will be evaluated for eligibility to participate in this trial.

Adolescent males who lack signs of pubertal development (e.g., development of secondary sexual characteristics, testicular enlargement, etc.) by the age of 14 years, and have inappropriately low testosterone and gonadotropin levels (LH and FSH), are considered to have HH. According to International Council on Harmonisation (ICH)/ Committee for Medicinal Products for Human Use (CHMP) E11 guideline, the range of 12 to 16-18 years (depending on region) is defined as “adolescents”. However, for the purpose of this study, the selected age group would be a subgroup of the ICH category: only males from 14 to < 18 year category who are diagnosed with HH will be studied. The lower limit of 14 has been

chosen because the diagnosis of HH in males < 14 years of age is difficult to establish, and more importantly, this condition generally does not require any treatment to induce puberty below 14 years of age.

4.2.2 Rationale for Dose Selection/Regimen/Modification

Population pharmacokinetics (PopPK) analyses were performed on the pooled data from the studies P031 [10] and 38801 [12], which used the protein-free (pf) formulation and non-protein (non-pf) free formulation of MK-8962, respectively. The pharmacokinetics of MK-8962 was well described by a one-compartment model with first-order absorption. A relative bioavailability fraction was estimated to account for differences in formulation (the current pf formulation and the non-pf formulation) used in the two studies. FSH-immunoreactivity (FSH-IR) data were integrated into the analysis by estimating a scaling factor between FSH-IR and MK-8962 concentrations. Body weight was found to be an important covariate for both clearance and volume of distribution (CL and V).

Based on derivations from the PopPK model, treatment with 150 µg MK-8962 every two weeks in Trial P031 [10] resulted in a mean trough serum FSH-IR level of 4.86 IU/L. These results were comparable to the trough serum FSH-IR levels of ≥ 4 IU/L seen after treatment with recFSH in Trial 37618 [11], where 225 IU twice weekly or 150 IU three times weekly was found to double the mean testicular volume and induced spermatogenesis in 43% of azoospermic adult males with HH. As noted in Section 4.1.1, the treatment with MK-8962 is expected to be similar to treatment with recFSH, therefore the results of these two trials were considered in selecting a trough FSH-IR level of ≥ 4 IU/L as the main criteria for dose selection in this adolescent trial.

Simulations using the PopPK model demonstrate that trough serum FSH-IR levels are expected to remain above 4 IU/L when adolescent males are treated once every two weeks with either 100 µg (for a body weight of ≤ 60 kg) or 150 µg (for a body weight of > 60 to 100 kg) of MK-8962. When treating adolescent males weighing > 100 kg, 150 µg MK-8962 every two weeks would result in a trough serum FSH-IR level slightly below 4 IU/L in the majority of subjects.

4.2.2.1 Rationale for Single Arm Design

HH is a rare disease affecting between 1-10:100,000 of all (male and female) live births [6]. Due to the small number of subjects with this disease, recruitment of a sufficient number of subjects for both a treatment and comparator arm would be challenging, likely limiting the size of the MK-8962 group and hence experience. Based upon prior information on MK-8962, as well as information on the natural history of HH in adolescent males, trial objectives can be met in a single-arm, non-controlled study. Rationale supporting the use of a single arm study for the use of MK-8962 in adolescent boys with HH is provided below.

Rationale for not including a placebo arm

HH is associated with extremely low levels of the pituitary hormones (FSH and LH) required for pubertal development, leaving the subject in an infantile developmental state. The psychosocial impact of this condition is significant, leading to depression, anxiety, sexual dysfunction and a lower quality of life, all of which improve significantly with treatment

[13]. The possible negative psychosocial impact in untreated subjects raises ethical considerations that preclude the use of a placebo in this trial.

Since it is possible that some patients diagnosed with HH could have constitutional delay of puberty—and therefore spontaneously progress through puberty—the lack of a placebo group could impact conclusions regarding proportion of patients responding to active treatment (i.e., overestimating treatment response). However, given the small size of a placebo group that could be recruited into this study, robust comparisons to placebo would be limited. Moreover, since no placebo group is planned, the study's enrollment criteria have been carefully crafted to avoid the inclusion of subjects with a constitutional delay of puberty that are misdiagnosed with HH.

The diagnosis of HH will be confirmed using physical findings as well as strict endocrine parameters (Section 5.1.2). The strict enforcement of these enrollment criteria will minimize the possibility of a misdiagnosis and ensure that spontaneous progression to puberty is an uncommon event in this trial. LH levels will be monitored during the study to identify any subjects with spontaneous recovery of endogenous pituitary function.

It is also recognized that spontaneous improvement in HH resulting in improvement in the primary outcomes parameters is a possibility. However, in a review of 308 patients with confirmed HH that specifically looked for evidence of spontaneous reversal of HH, only 39 males and 5 female patients had any physiologic evidence of spontaneous improvement of endocrine functions [14]. When stricter criteria for spontaneous progression based on recovery of serum testosterone, menstrual cyclicity, and/or fertility were applied, the numbers dropped to 29 men and 4 women (~10%), and the earliest age at which this recovery was evident in males was 19.1 years (mean age - 28.3 years) [14]. Additionally, spontaneous reversal of function has not been reported in any treatment naïve subject [14]. Given these findings, it would be unlikely that changes seen in these subjects over the course of the current study would be the result of spontaneous reversal of the disease. As noted, LH levels will be monitored during the study to identify any subjects with spontaneous recovery of endogenous pituitary function. Subjects with LH levels >3 IU/L during the trial will be excluded from the analysis.

Based on the possible negative impact of withholding treatment, the use of strict inclusion criteria, and the low possibility of spontaneous improvement of HH, the use of a placebo in this trial is not planned.

Rationale for not including a comparator arm

The pharmacodynamic profile of MK-8962 had been shown to be similar to that of FSH, and has been well-documented in trials with women undergoing COS [7], [8], [9] and in Trial P031 [10] of adult males with HH. In addition, the use of FSH preparations to induce testicular maturation and pubertal development in the adolescent HH male population is well-documented in the literature [1, 15, 16]. Therefore, it is anticipated that MK-8962 use should result in changes in testicular development that are similar to what is seen with recFSH.

Given the small population available to enter the trial, the robustness of any comparison to recFSH would be very limited. In addition, the strong evidence for appropriate FSH activity of MK-8962, and the prior literature studies looking at response to FSH in this population, support that the single arm study being implemented here should be interpretable.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy endpoint is the change from baseline (Day 1) to Week 64 in log-transformed testicular volume (measured as the sum of volumes of left and right testes by ultrasound).

The initiation of spermatogenesis is dependent on both an increase in testicular volume and an increase in intra-gonadal testosterone levels [17], both of which occur in puberty when the hypothalamic-pituitary-gonadal axis becomes active. Although an increase in testicular size, in response to FSH and to a lesser degree LH stimulation, is required for spermatogenesis, there are little data linking an increase in testicular volume with spermatogenesis in HH adolescent boys. However, data do show an association between testicular volume and future success with fertility-inducing treatments in adult men. Specifically, several studies have found that a small testicular volume (<4 mL) at the initiation of fertility-inducing treatment is a negative predictor of success [15, 18]. Further, there are reports of a longer time to response with smaller testicular volume [19], [20] and better outcomes with hCG mono-therapy in adult men with larger initial testicular volume increases [15], and higher sperm count associated with higher initial testicular volume [21]. From these data it can be inferred that an increase in testicular size in adolescence would result in a greater chance of spermatogenesis later in life. Therefore, the induction of pubertal changes, with the aim of increasing testicular volume and protecting future fertility, is becoming the standard of care for HH adolescent boys.

While semen analysis would be a standard approach to assess changes in spermatogenesis, semen analysis would be difficult to implement in this adolescent population. There are several other endpoints that provide additional support for testicular development and spermatogenesis, as described below.

- Serum inhibin B concentration has been shown to be a useful surrogate biomarker for spermatogenesis [1] and will be monitored over the treatment period.
- Testicular echogenicity. Patients with HH or Kallmann syndrome have a hypoechogenic pattern of the testicular parenchyma, which becomes more normoechogenic with testicular maturation following gonadotropin treatment [22], suggesting that this endpoint may be useful to demonstrate maturation. The ultrasound pattern of the testicular parenchyma will be monitored for this change in this study to determine treatment effect. To date there is no generally accepted standard grading system for testicular echogenicity. To ensure standardization across the study sites, the ultrasound images will be read by a Sponsor-validated central imaging vendor. The assessments will be made according to a categorization system developed by the central imaging vendor and approved by the Sponsor, as described in the Independent Review Charter for imaging.
- Growth velocity (height measurement) and Tanner Stage of Development are well recognized markers for pubertal progress. These will be monitored in all subjects during this study. Details for the growth velocity and Tanner Stage assessment can be found in Section 7.1.2.

- Endocrine parameters to be measured in this study include calculated free T, Total T, E2, SHBG, and AMH. These hormones will serve as markers for the progress of puberty as a result from the study treatment.
- In addition, serum hCG levels will be measured to monitor treatment compliance. During the course of the trial, endogenous LH is expected to remain low in patients with HH. A subject with delayed puberty might experience pituitary maturation with MK-8962 and hCG treatment, which would result in an increase of the LH level. Therefore LH will also be measured during the trial to confirm the initial HH diagnosis.

4.2.3.2 Safety Endpoints

The pre-specified safety endpoint is the confirmed presence of anti-MK-8962 antibodies, which may have an impact on drug response. Previous studies in both men and women have not identified a safety concern with anti-MK-8962 antibodies. A total of 2511 women were tested for the development of anti-corifollitropin alfa antibodies in 3075 cycles. All 2511 women were tested after a single injection of MK-8962, 372 were tested after two injections of MK-8962, and 192 were tested after three injections of MK-8962. Of all these women, 4 developed non-neutralizing antibodies to MK-8962 which showed cross-reactivity with human FSH (hFSH), including one woman who was tested positive only after the second exposure to MK-8962. However, these antibodies did not interfere with the response to pituitary stimulation or with the normal physiologic responses of the Hypothalamic-Pituitary-Ovarian axis. Therefore, these antibodies were judged to be not clinically relevant. Of the 18 adult men who were exposed to MK-8962 for long term treatment of HH, one subject had a positive antibody test that was later deemed to be a false positive.

Subjects in this study will be monitored by the Sponsor on an ongoing basis for the development of ADA against MK-8962. Subjects with confirmed presence of such ADA will be discontinued from the treatment because of the unknown implication of such ADAs. ADA antibodies that cross-react (depletion confirmed) with FSH have been noted in women without any significant clinical implications. However, the ability to predict the outcome of an ADA exposure in boys who are naïve to FSH and whom have never been exposed to normal levels of endogenous FSH based on exposures in women with normal to elevated endogenous FSH levels remains uncertain. Yet the implications of a boy developing antibodies that would block the action of FSH and might prevent further pubertal development are somewhat more serious than the development of these same antibodies in a woman who had completed puberty and had desired ovulation induction for the treatment of infertility. For this reason, in order to mitigate any possible negative outcome from the development of such ADAs, a subject testing positive for neutralizing anti-MK-8962 antibody will be discontinued from the treatment. These subjects will be followed with repeat ADA antibody testing. This will continue until the ADA result becomes negative or until the subject is clinically stable (e.g., in the absence of hCG use, no clinically meaningful change in testicular volume or testosterone levels for 3 months; if hCG continues to be used, an appropriate response to hCG with stable testosterone levels) for up to 12 months after treatment discontinuation, whichever comes first. (Refer to Section 7.1.5.3 for details on follow-up procedures for these subjects).

Other safety endpoints in this trial are laboratory assessments, vital sign measurements (blood pressure [BP], heart rate [HR], and body weight), and adverse experiences which are monitored routinely.

4.2.3.3 Pharmacokinetic Endpoints

The PK of MK-8962 will be based on serum MK-8962 concentrations determined by a validated immunoassay. Serum FSH concentration will also be measured to support the PK analysis.

MK-8962 is indicated for the treatment of female infertility with a dose regimen based on age and weight:

- 100 µg for subjects with body weight \leq 60 kg and age \leq 36 years
- 150 µg for subjects with body weight $>$ 60 kg regardless of age, or body weight \geq 50 kg and age $>$ 36 years)

Single dose pharmacokinetics of MK-8962 has been studied in pituitary-suppressed female volunteers and in normogonadotropic female patients undergoing COS with MK-8962 using a GnRH antagonist protocol to prevent premature LH surges. A clinically-relevant relationship between drug-exposure and body weight was demonstrated. Prospective clinical studies demonstrated that in subjects \leq 36 years old, exposure to MK-8962 was similar between women who weigh \leq 60 kg and who received 100 µg of MK-8962 and women who weight $>$ 60 kg and who received 150 µg of MK-8962.

Distribution, metabolism and elimination of MK-8962 are very similar to other gonadotropins, such as FSH, hCG and LH. Elimination of MK-8962 predominantly occurs via the kidneys and may be impaired in patients with renal insufficiency. Hepatic metabolism contributes to a minor extent to the elimination of MK-8962. Prior studies confirmed that PK profiles appear similar between males and females. When corrected for body weight, CL in males would be estimated to be about 30% lower compared to females, in line with the original assumption of a 40% difference. MK-8962 has the same mechanism of action as recFSH and interacts only with the FSH receptor on the Sertoli cell. The clearance of MK-8962 in adolescent males aged 14 years or older is expected to be similar to that in adults.

A female population PK model was modified with data from the HH adult male trial (P031) and used to predict serum MK-8962 concentration in HH adolescent males. Dose recommendation for adolescents was selected through simulations based on the modified population PK model.

It is anticipated, based on matured kidney elimination and metabolic drug clearance systems, that PK data of adolescent males aged 14 years or older will be similar to PK data of adult males. To further support the expectation that PK data will be similar, PK sampling will be performed in the current study in adolescent males to confirm predicted exposure levels.

4.2.3.4 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include genetic analyses (DNA),

gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment/vaccination during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male subjects with HH aged 14 to <18 years will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Have a legal representative who understands the study procedures, alternative treatments available and risks involved with the study, and voluntarily agrees to the subject's participation by giving written informed consent, and the subject has an age-appropriate understanding of the same to give informed written assent if applicable (i.e., in accordance with local requirements). Subjects with an illiterate legal representative may be included if, in the opinion of the investigator, the legal representative fully understands the risks of the subject's participation and provides consent. In addition, the legal representative may also consent to (and in accordance with local requirements, the subject may assent to) have the subject participate in Future Biomedical Research by signing a separate consent. **Note:** otherwise eligible patients will be able to participate in the main study even if they opt to not participate in FBR.
2. Be male.

3. Be 14 to <18 years of age at the time when consent/assent is signed, with treatment to begin prior to the subject's 18th birthday.

4. Have been diagnosed with hypogonadotropic hypogonadism (either isolated or associated with panhypopituitarism), either congenital or acquired with onset prior to puberty.

Note: Subjects with drug-induced hypogonadotropic hypogonadism (e.g., misuse of anabolic steroids, chronic use of glucocorticoids or narcotic analgesics, etc.) are excluded.

5. Have bilateral pre-gonadarche testes as defined by testicular volume <4.0 mL for each testicle, as determined by ultrasound and assessed by the investigator (if qualified) or local radiologist with appropriate training and expertise in reading testicular ultrasound.

Note: subjects with a volume of <4.0 mL in one testicle and a volume of 4-8 mL in the other testicle are considered to be pre-gonadarche and may participate, if there is no history or evidence of a primary testicular disorder (see Exclusion Criteria 1 and 2).

6. Have circulating levels of Total T less than the lower limit of normal (LLN) of 8.3 nmol/L as specified by the central lab for a young healthy adult male.

7. Have FSH \leq 2 IU/L and LH \leq 2 IU/L.

8. Have inhibin-B levels \leq 35 pg/mL. [23]

Note: if the subject has inhibin-B levels $>$ 35 pg/mL, but meets all of the other inclusion/exclusion criteria, either a GnRH agonist (GnRHa) stimulation test or GnRH IV infusion test may be performed. The subject may be enrolled if either of the following is met:

- GnRH agonist (GnRHa) stimulation test: LH level of $<$ 3 IU/L at all of the following timepoints: 0, 60, 120, and 180 minutes after subcutaneous administration of a GnRH agonist, e.g., 500 micrograms of leuprolide acetate. [24]
- GnRH IV infusion test: LH peak $<$ 5.8 IU/L and FSH peak $<$ 4.6 IU/L at all of the following timepoints: 0, 15, 30, 45, 60 and 120 minutes during intravenous infusion of GnRH 100 micrograms over 120 minutes.[19]

9. Be in good general physical and mental health, in the opinion of the investigator/sponsor, as assessed by physical examination and routine clinical laboratory tests.

10. Have a parent/guardian able and willing to support the subject's participation by supporting adherence to study drug dosing and visit schedules.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has a history of bilateral cryptorchidism (maldescended testes) or unilateral cryptorchidism treated after the age of 2 years.

2. Has a history or presence of clinically significant testicular problems (e.g., epididymitis, orchitis, testicular torsion, varicocele Grade III, testicular atrophy, occlusive azoospermia, etc.) that in the opinion of the investigator would impair the subjects response to treatment or has had known damage or injury to the vas deferens.
3. Has had any previous treatment with GnRH, gonadotropins (e.g., hCG, FSH) or androgens (e.g., testosterone, etc.). **Note:** Use of GnRH and gonadotropins for diagnostic testing purposes only is allowed. Subjects with use of hCG and androgen therapy prior to the age of 2 years old can be included in the trial. Subjects with transient use of androgens (i.e., for less than 2 weeks) that was stopped at least 6 months prior to signing informed consent can also be included in the trial.
4. Has an untreated or inadequately treated pituitary or hypothalamic tumor.
5. Has uncontrolled endocrinopathies, including thyroid, adrenal, and pituitary disorders not on stable replacement therapies (i.e., subject has not been on stable doses for at least 3 months).

Note: The subject with a free T4 level outside of the normal laboratory range at the time of screening will be excluded, but may be rescreened once he has been on a stable dose of replacement therapies for at least 3 months.

6. Has a history of active pituitary hypersecretion as evidenced by hyperprolactinemia or Cushing's disease, or acromegaly, or any other active pituitary hypersecretion syndrome.
Note: Subjects who have been treated and are clinically stable, with no evidence of hypersecretion for at least 12 months prior to screening, may participate.
7. Has had hypophysectomy within a period of 12 months prior to the start of screening.
8. Has history of oncologic chemotherapy treatment.
9. Has had brain radiotherapy within 12 months of the start of treatment for a primary tumor, or any history of brain radiotherapy for metastatic disease.
10. Has diabetes mellitus.
11. Has a history of Human Immunodeficiency Virus (HIV).
12. Has renal insufficiency as determined by the investigator based on serum creatinine, blood urea nitrogen, and estimated glomerular filtration rate.
13. Has clinically significant liver disease, including active viral hepatitis or cirrhosis. Subjects with a prior history of liver disease which is now inactive or successfully treated may be enrolled if all liver function values (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin) performed within the past year have been normal and are within the normal range (per central lab) at V1. Liver function testing may be repeated once prior to allocation of treatment at the discretion of the investigator if results are inconsistent with the subject's clinical status or recent laboratory results.

14. Has had a recent history (i.e., within 1 year prior to signing the informed consent) of recreational (e.g., for non-medical purposes) or illicit drug use, including marijuana; or routinely consumes >2 alcoholic drinks per day or >14 alcoholic drinks per week, or engages in binge drinking.

Note: (1) Alcohol abuse is defined as routinely consumes >2 alcoholic drinks per day. One alcoholic drink is defined as 5 oz (150 mL) of wine, or 12 oz (350 mL) of beer, or 1.5 oz (50 mL) of 80-proof liquor.

Note: (2) Binge drinking is defined as a pattern of 5 or more alcoholic drinks (male), or 4 or more alcoholic drinks (female) in about 2 hours.

15. Has received any treatment listed in [Table 1](#) more recently than the indicated wash-out period prior to Screening.

Table 1 Prohibited Medications, Supplements, and Other Substances for Entry Into the Trial

Prohibited Medications, Supplements, and Other Substances	Wash-out Period Prior to Screening
Sex hormone preparations other than the trial medication	no prior use allowed (see Exclusion Criterion #3 for exceptions)
Drugs that are known to impair testicular function, such as ¹ : <ul style="list-style-type: none">gonadotoxic chemotherapy agents such as alkylating agents, e.g., cyclophosphamidesulfasalazinecimetidinenitrofurantoinneuroleptics such as valproic acidillicit drugs such as marijuana, phencyclidine (PCP), lysergic acid diethylamide (LSD) and other hallucinogens, cocaine, amphetamines, rohypnol, and 3,4-methylenedioxy-methamphetamine (“Ecstasy”)opiatesnarcoticsbenzodiazepineschloral hydrateparaldehydeketamine	1 month

Prohibited Medications, Supplements, and Other Substances	Wash-out Period Prior to Screening
Agents known to affect sex hormones through induction of liver enzymes and affecting the bioavailability of steroids, such as ¹ : <ul style="list-style-type: none"> • anti-epileptics (e.g., phenytoin, barbiturates, primidone, carbamazepine, oxcarbazepine, topiramate, and felbamate) • bosentan • rifampicin • anti-HIV drugs (e.g., ritonavir, nelfinavir, nevirapine, efavirenz) • griseofulvin • anti-psychotics such as risperidone and amisulpride • herbal remedies containing hypericum perforatum (e.g., St John's wort) 	1 month

¹ In addition to the drugs listed in this table, if there are concerns on any other concomitant medications, the investigator should contact the Sponsor Clinical Director for advice prior to enrolling the subject.

16. Has an allergy/sensitivity to gonadotropins or its/their excipients.
17. Has any clinically significant condition or situation that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial.
18. Has used an investigational drug and/or participated in any other clinical trial within the past 8 weeks (prior to V2), or will participate in any other clinical trials (excluding surveys) during the course of this trial.
19. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in [Table 2](#).

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use
MK-8962	Body weight ≤ 60 kg: 100 μ g Body weight >60 kg: 150 μ g	Once every two weeks	SC	Day 1 (Week 0) through Week 64. The last dose will be administered on the last day of Week 62 (Day 435).	Experimental
hCG ^a	500-5000 IU	Twice a week	SC	The first dose will be administered on the last day of Week 12 (Day 85), and treatment will be continued from Week 13 through Week 64.	Standard of care

^a Note: A dose of hCG outside of this range may be appropriate in certain subjects, based on the subject's Total T and/or E2 levels and/or any clinically relevant signs or symptoms (e.g., gynecomastia, breast pain, and/or tenderness), and will require prior consultation with the Sponsor.

The subject and his legal guardian (or someone designated by the subject's legal guardian such as a caregiver or parent) will receive instructions on MK-8962 and hCG home- injection prior to the initiation of treatment. The first 3 doses of MK-8962 will be self-administered or administered by the legal guardian (or a legal guardian-designated person who has been appropriately trained) at the trial site as witnessed doses at Visit 2 (Day 1/Week 0), Visit 7/Week 2 (Day 15), and Visit 8/Week 4 (Day 29). Note: The first dose of MK-8962 is to be administered after completion of all Visit 2/Day 1 trial procedures (except for the collection of PK sample #02 which is to be performed 6-24 hours after the first MK-8962 injection).

The first dose of hCG will be self-administered or administered by the legal guardian (or a legal guardian-designated person who has been appropriately trained) at the trial site as witnessed dose at Visit 9/Week 12 (Day 85).

The site should record in the source document when the instructions have been provided to the subject and his legal guardian (or someone designated by the subject's legal guardian such as a caregiver or parent) for home administration of MK-8962 and hCG.

The subsequent medication will be dispensed to the subject, for home-administration unsupervised by the investigator. A paper diary will be used to record the time and amount of hCG and MK-8962 administration. The site will collect the diary dispensed at the previous visit, and dispense a new diary to the subject at visits specified in the Trial Flow Chart (Section 6.0). The information as recorded on the diary by the subject serves as the source for data entry on the dosing/medication electronic Case Report Form (eCRF).

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection for MK-8962 and Dose Modification for hCG

5.2.1.1 Dose Selection (Preparation)

The rationale for dose selection of MK-8962 to be used in this trial is provided in Section 4.0 – Background & Rationale. Subjects with body weight ≤ 60 kg will be given MK-8962 100 μg and subjects with body weight > 60 kg will be given MK-8962 150 μg .

During the course of the trial, for subjects receiving MK-8962 100 μg , the dose of MK-8962 should be adjusted to 150 μg if the subject's body weight increases by 2 kg or more from the previous visit to a value greater than 60 kg. For subjects receiving MK-8962 150 μg , the dose should not be down-titrated for the rest of the trial regardless of any changes in body weight.

5.2.1.2 Dose Titration for hCG

The dose of hCG can be adjusted between 500 IU and 5,000 IU (inclusive) in order to keep the Total T and E2 levels within the normal ranges as defined in the paragraph below. As specified in the flow chart (Section 6.0), blood samples collected at Visit 9/Week 12 and each of the subsequent visits will be evaluated for the Total T and E2 levels. Based on the results of these tests, the investigator or qualified designee should log into the Interactive Voice/Web Response System (IVRS/IWRS) between pre-specified visits to request additional medication if hCG up-titration is needed. Note: A dose of hCG outside of this

range may be appropriate in certain subjects, based on the subject's Total T and/or E2 levels and/or any clinically relevant signs or symptoms (e.g., gynecomastia, breast pain, and/or tenderness), and will require prior consultation with the Sponsor.

The normal range for Total T for this study is defined as the mean \pm 2 standard deviation (SD) for a young, healthy male population, and the exact limits are assay-specific. The reference range used by the Sponsor-designated central lab is 240.00 – 950.00 ng/dL (or 8.3 – 33.0 nmol/L). During hCG treatment, serum E2 levels should also be evaluated to avoid clinically relevant elevations of E2 levels (should be monitored towards maintaining <40% above the upper limit of normal in men [the ULN from the Sponsor-designated central laboratory is 40.00 pg/mL]).

5.2.2 Timing of Dose Administration

MK-8962

Throughout the 64-week treatment period, a single dose of MK-8962 100 μ g (body weight \leq 60 kg) or 150 μ g (body weight $>$ 60 kg) is to be administered subcutaneously in the abdominal wall once every two weeks in the morning on the same day of the week throughout the trial. The fixed day of the week is chosen by the subject depending on individual preference. For the convenience of visit scheduling, a weekday injection is preferred, as most protocol-specified site visits fall on the same day of a scheduled MK-8962 administration. The time and dose of MK-8962 administration should be recorded in a paper diary.

Note: The subject should adhere to the same MK-8962 injection schedule (e.g., on every other Monday, etc.) throughout the trial, whenever possible. In the event that the subject misses a dose on a scheduled dosing day (e.g., a holiday, etc.), the make-up dose should be administered as soon as possible, and can only be administered within one week immediately following the missed dose. Otherwise, the missed dose should be skipped and the subject should continue on with the next regularly scheduled injection.

hCG

Starting from the last day of Week 12 (Day 85), hCG is to be injected twice a week in the morning, on fixed days of the week throughout the trial. The scheduling of hCG injection should be coordinated with the MK-8962 injection, as illustrated in [Table 3](#) below. After addition of the solvent to the freeze-dried substance, the reconstituted hCG solution should be administered by subcutaneous injection. The time and dose of hCG administration should be recorded in a paper diary. Note that [Table 3](#) is meant for illustration only, and the subject, in consultation with the investigator, may utilize any schedule that meets dosing interval requirements for hCG and MK-8962.

Note: The subject should adhere to the same twice-weekly injection schedule throughout the trial. In the event that the subject misses a scheduled hCG dose, the make-up dose should be administered as soon as possible, up to the day before the next scheduled injection day. This instruction for the handling of a missing hCG dose should be followed whether or not the subject also misses the MK-8962 dose at the same time.

Table 3 MK-8962 and hCG Dosing Schedule

Examples of Dosing Schedule Scenario	MK-8962 100 µg or 150 µg	hCG ^a
A	Every other Monday	Every Monday and Thursday
B	Every other Tuesday	Every Tuesday and Friday
C	Every other Wednesday	Every Wednesday and Saturday
D	Every other Thursday	Every Thursday and Monday
E	Every other Friday	Every Friday and Tuesday

^a The dose of hCG may be titrated between 500 IU and 5000 IU twice weekly to keep the Total T and E2 levels within acceptable ranges. A dose of hCG outside of this range may be appropriate in certain subjects, based on the subject's Total T and/or E2 levels and/or any clinically relevant signs or symptoms (e.g., gynecomastia, breast pain, and/or tenderness), and will require prior consultation with the Sponsor.

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

Dispensing of medication and assignment of screening and randomization numbers will be performed via the IVRS/IWRS. After signing informed consent, the investigator or qualified designee should enter the subject in the IVRS/IWRS and the system will assign a screening number. After evaluation of all screening data, indicating that the subject complies with all selection criteria, the subject can be assigned a randomization number to enter the MK-8962 priming phase. (Assignment of the randomization number should be done immediately prior to the initiation of MK-8962 treatment [i.e., on Day 1]).

Note: Even though the trial has an open-label, non-randomized design, a randomization number will be assigned per the Sponsor's standard procedure indicating the subject receives the trial medication. Therefore, in this protocol, the term randomization is equivalent to the term allocation.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

Subjects do not need to adhere to any diet restrictions during the course of the trial. However, subjects should be counseled to refrain from excess intake of alcoholic beverages (>2 per day or binge drinking) and use of illicit substances during course of trial.

5.8 Subject Withdrawal/Discontinuation Criteria

A subject's consent may be withdrawn by the subject or the subject's legally acceptable representative (as appropriate) at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

Discontinuation from treatment is “permanent”. Once a subject is discontinued, he/she shall not be allowed to restart treatment.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent/assent.

A subject must be discontinued from treatment (but may continue to be monitored in the trial) for any of the following reasons:

- The subject develops an immediate or delayed study drug-related hypersensitivity reaction.
- The subject has neutralizing ADA against MK-8962.
- The subject, in the opinion of the investigator, persistently fails to comply with dosing, evaluation or other requirements of the trial.
- Any medical condition or personal circumstance which, in the opinion of the investigator, exposes the patient to risk by continuing with the study medication or does not allow the patient to adhere to the requirements of the protocol.
- The subject develops any condition for which corifollitropin alfa, or hCG is contraindicated in accordance with the local drug label of the country where the subject is participating.
- The subject has a serious drug-related adverse event

If a subject discontinues study medication (i.e., MK-8962 and hCG obtained through the study), he should complete all Discontinuation Visit procedures as described in Section 6.0. Please refer to Section 7.1.5.3 on how to manage patients who discontinue study medication but who do not withdraw consent.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent/assent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

Trial Period:	MK-8962 Priming Phase															Combined Treatment Phase (MK-8962 / hCG) ^a																
	1	2	3	4	5	6	7	8		9	10		11		12		13		14		15		D/C ^b	Follow-up ^c								
Visit Number	1	2	3	4	5	6	7	8		9	10		11		12		13		14		15											
Visit/Contact Title:	Screening	Treatment Allocation								T C			TC		TC		TC		TC		TC			D/C ^b	Follow-up ^c							
Scheduled Week ^d :	-1	0	1	1	1	2	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64 ^e									
Scheduled Study Day:	-7 to -1	1 ^f	3	5	8	11	15	29	57	85	113	141	169	197	225	253	281	309	337	365	393	421	449		+7 ^c							
Scheduling Window (Days):	-42 to -1								+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 7	+/- 7	+/- 7	+/- 7	+/- 7	+24			
Administrative Procedures																																
Informed Consent and Assent ^g	X																															
Informed Consent and Assent for Future Biomedical Research ^h	X																															
Assignment of Screening Number ⁱ	X																															
Inclusion/Exclusion Criteria	X	X																														
Subject Identification Card	X																															
Medical History /Hypogonadotropic Hypogonadism History	X																															
Prior/Concomitant Medication Review ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Assignment of Randomization Number		X																														
Diary Instructions		X								X																						
Dispense/collect Paper Diary		X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					

Trial Period:		MK-8962 Priming Phase									Combined Treatment Phase (MK-8962 / hCG) ^a														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	D/C ^b	Follow-up ^c							
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15										
Visit/Contact Title:	Screening	Treatment Allocation							TC		TC	TC	TC	TC	TC		D/C ^b	Follow-up ^c							
Scheduled Week ^d :	-1	0	1	1	1	2	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64 ^e		
Scheduled Study Day:	-7 to -1	1 ^f	3	5	8	11	15	29	57	85	113	141	169	197	225	253	281	309	337	365	393	421	449		
Scheduling Window (Days):	-42 to -1								+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 7	+/- 7	+24	
Review Diary to monitor compliance with Trial Medication									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Trial Medication																									
Dispense MK-8962 ^k		X				X	X		X	X		X		X		X		X		X		X			
Treatment with MK-8962			Once every two weeks (first dose on Day 1/Week 0 and last dose on Day 435 /Week 62)																						
Dispense hCG ^l									X	X		X		X		X		X		X		X			
Treatment with hCG											Twice weekly (e.g., every Monday and Thursday, or every Tuesday and Friday) ^m														
Clinical Procedures/Assessments																									
Full Physical Examination	X																						X	X	
Focused Physical Examination ⁿ		X								X							X								
Vital Signs (HR, BP measured twice)	X	X							X							X							X	X	
Weight (measured twice)	X	X					X	X		X	X		X		X			X		X		X	X		
Height for Growth Velocity (measured 3 times)	X	X							X						X								X	X	
Testicular ultrasound ^o	X	(X) ^t							X						X							X	X ^p	(X) ^p	
Tanner Staging ^q	X	X							X						X							X	X		
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Trial Period:		MK-8962 Priming Phase									Combined Treatment Phase (MK-8962 / hCG) ^a														
		1	2	3	4	5	6	7	8	9	10		11		12		13		14		15	D/C ^b	Follow-up ^c		
Visit Number																									
Visit/Contact Title:	Screening	Treatment Allocation								TC		TC		TC		TC		TC		TC		D/C ^b			
Scheduled Week ^d :	-1	0	1	1	1	2	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64 ^e		
Scheduled Study Day:	-7 to -1	1 ^f	3	5	8	11	15	29	57	85	113	141	169	197	225	253	281	309	337	365	393	421	449		+7 ^c
Scheduling Window (Days):	-42 to -1								+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 3	+/- 7	+/- 7	+/- 7	+/- 7	+24
Laboratory Procedures/Assessments																									
Serum for free T4	X																								
Hematology	X	X								X							X						X	X	
Chemistry Panel	X	X							X							X							X	X	
Serum for endocrine parameters ^r : FSH, LH, hCG, inhibin-B, AMH, Calc. Free T, and SHBG	X	X								X							X						X	X ^p	(X) ^p
Serum for endocrine parameters ^r : Total T and E2	X	X								X	X		X			X			X		X		X	X ^p	(X) ^p
Pharmacokinetic (PK) sampling for MK-8962 concentration ^s		see Section 7.1.3.3.1 Flow Chart for Pharmacokinetic Assessments																							
Sampling for Anti-MK-8962 antibodies ^r		X							X	X			X			X			X			X	X	X	

AMH = anti-Müllerian hormone; E2 = estradiol; FSH = follicle stimulating hormone; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; LH = luteinizing hormone; SHBG = sex hormone-binding globulin; TC = telephone call; T = testosterone

^a The Combined Treatment Phase starts at the end of Week 12.

^b The Discontinuation (D/C) Visit is to be performed only if the subject does not complete the 64 week treatment. The D/C visit should be performed as soon as possible once the subject has prematurely stopped the study medication.

- c The post-treatment follow-up visit is to be scheduled at least 21 days (but no more than 45 days) after the last dose of MK-8962, and at least 7 days after the last dose of hCG (whether subject completed the trial or discontinued from the trial prematurely). Follow-up blood samples will be collected for assessment of anti-MK-8962 antibodies and PK for MK-8962 concentration. AEs and concomitant medication will also be assessed. For subjects wishing to continue on post-trial gonadotropin treatment, such treatment should not be started until after blood sample collection at this visit. For subjects who prematurely discontinue study medication, after the post-treatment follow-up visit, subjects who do not withdraw consent should: (1) return to the clinic for key visits (V9/Week 12, V12/Week 36 and/or V15/Week 64 as applicable) to have the following procedures performed: focus physical examination, vital signs, weight and height, Tanner staging, testicular ultrasound, laboratory assessment of endocrine parameters, and safety parameters (chemistry panel and hematology), and collection of concomitant medications and adverse events. Subjects discontinued from the treatment due to the presence of neutralizing ADAs will also have serum samples collected for ADA testing. Subjects who are unable or unwilling to return to the clinic at key visits will be contacted by phone to obtain adverse events and concomitant medications. (2) be contacted by phone in a timeframe similar to their original study visit schedule at visits that are not key visits, i.e., at V10, V11, V13, V14, up until the subject has reached Week 64 after V2, to assess for serious adverse events and concomitant medications. (3) Subjects discontinued from the treatment due to the presence of neutralizing antibodies may continue to be followed until the ADA result becomes negative or until clinically stable for up to 12 months after treatment discontinuation. Refer to Section 7.1.5.3 for further details.
- d For visits not involving PK sampling, a scheduling window of \pm 7 days is allowed.
- e No further injection of MK-8962 or hCG is administered at the Week 64 visit.
- f Day 1/Week 0 designates the first dose administration of MK-8962. The study medication is to be administered after completion of all Visit 2/Day 1 trial procedures (except for the collection of PK sample #02 which is to be performed 6-24 hours after the first MK-8962 injection). Visit 2 should be scheduled approximately 7 days after sample collection at Visit 1, when the central lab results are available to evaluate the Day 1 inclusion criteria.
- g Consent form must be signed prior to any study specific procedures; informed consent will be obtained from parent/legal guardian and assent (if applicable) will be obtained from subject.
- h Leftover main study serum from endocrine parameters, anti-MK-8962 antibodies, and PK for MK-8962 concentration will be stored at the end of the study for future biomedical research (FBR) if the subject consents to FBR. Eligible subjects will be able to participate in the main study even if they opt to not participate in FBR.
- i After obtaining the informed consent from the parent/legal guardian and the assent from the subject, the subject should be entered in the Interactive Voice/Web Response System (IVRS/IWRS) to obtain a screening number.
- j Any medication used from 30 days prior to screening through the end of the trial should be recorded.
- k Subject and his legal guardian (or someone designated by the subject's legal guardian such as a caregiver or parent) will be instructed at Visit 2 on home-administration of MK-8962 injections. The first 3 doses of MK-8962 will be administered by the subject at the site on Day 1, Week 2 and Week 4 as witnessed doses. Later injections can be self-administered by the subject or administered by the subject's legal guardian (or the designated person who has been appropriately trained) at home.
- l Subject and his legal guardian (or someone designated by the subject's legal guardian such as a caregiver or parent) will be instructed at Visit 9 on home-administration of hCG injections. The first dose of hCG will be administered by the subject at the site as a witnessed dose, and later injections can be self-administered by the subject or administered by the subject's legal guardian (or the designated person who has been appropriately trained) at home.
- m Treatment with hCG in combination with MK-8962 will start only if the subject has completed the 12-week MK-8962 priming phase.
- n The focused exam will include only heart, lungs, abdomen, extremities, and genitourinary exam.
- o At Visit 1/Screening, testicular ultrasound images will be read locally by the investigator (if qualified) or a local radiologist with appropriate training and expertise in reading testicular ultrasound. This local reader will calculate testicular volume to evaluate Inclusion Criterion #5, and evaluate the ultrasound for any presence of local pathology that would exclude the subject from participating (see Section 5.1.3 Subject Exclusion Criteria). In addition, all testicular ultrasound images will be sent to a central imaging vendor, and will be read in a masked manner after the subject completes participation in the study to assess study endpoints (i.e., testicular volume and sonographic pattern).
- p If testicular ultrasound or endocrine parameters is not able to be completed at study completion (V15) or on the day of D/C, the site should make an effort to schedule a visit within 4 weeks from the last dose of MK-8962 to perform these procedures. This visit can be combined with the post-treatment follow-up visit if it is scheduled at 21-28 days after the last dose of MK-8962. Testicular ultrasound does not need to be performed at D/C if this visit is \leq 6 weeks from the last scheduled testicular ultrasound measurement.

- ^q The investigator will use clinical assessment to assign the Tanner Stage for pubic hair and Tanner Stage for genital growth (e.g., penile length and scrotum development) separately, and perform a testicular ultrasound to measure testicular parameters as according to the procedures outlined in the Site Imaging Manual provided to the investigator site. The Tanner Stage for testicular volume will not be assessed clinically by the investigator and will be completed by the central imaging vendor according to the method described in the Independent Review Charter for imaging.
- ^r These blood sample collections should be performed prior to the injection(s) of MK-8962 or hCG, if there is any injection(s) scheduled for that day. Leftover main study serum will be stored at the end of the study for future biomedical research if the subject consents to future biomedical research.
- ^s A total of 13 PK samples are collected at various time points at Days 1 (2 time points), 3, 5, 8, 11, 29, 85, 169, 253, 337 and 449, as well as the follow-up visit. For details, see **Section 7.1.3.3.1 Flow Chart for Pharmacokinetic Assessments**. Leftover main study serum will be stored at the end of the study for future biomedical research if the subject consents to future biomedical research.
- ^t Testicular ultrasound is only to be performed at Visit 2 if the window is greater than 6 weeks between Visit 1 and Visit 2.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent and/or assent (if applicable) be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent/Assent

The investigator or qualified designee must obtain documented consent/assent (if applicable) from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent/Assent

Consent/assent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent/assent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent/assent form should be given to the subject before participation in the trial.

The initial informed consent/assent form, any subsequent revised written informed consent/assent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent/assent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements. The assent, as applicable, will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent/Accent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent/assent to the subject, answer all of his/her questions, and obtain written informed consent/assent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent/assent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent/assent.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee at screening. Include any medical history related to andrologic history on this form (e.g., hypogonadotropic hypogonadism; prior genital, pelvic or inguinal surgery; infections such as epididymitis or orchitis; presence of varicocele, including grade; etc).

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use (i.e., used within 6 months of starting the trial) by the subject. Additionally, the use of any medications noted in [Table 1](#) should be reviewed to determine that the required washout periods have been met.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.8 Trial Compliance (Medication)

A paper diary will be used to record the time and dosage of MK-8962 and hCG administration. The first paper diary will be dispensed at Visit 2, and the site staff should train subjects on how to complete the paper diary. At subsequent visits specified in the Trial Flow Chart (Section 6.0), the site will collect and review the diary dispensed at the previous visit, and dispense a new diary to the subject. The information as recorded on the diary by the subject serves as the source for data entry by the site on the medication eCRF.

At all protocol-specified visits, the investigator or qualified designee is to record whether treatment has been taken per protocol in the preceding interval. If not, the date(s) and reason for each dosing noncompliance must be recorded.

Interruptions from the protocol specified treatment (in the case when the subject misses more than 2 doses of MK-8962 or more than 2 consecutive doses of hCG) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of the first 3 doses of MK-8962 and the first dose of hCG will be witnessed by the investigator and/or trial staff.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

A full physical examination will be performed at screening and at the end-of trial or discontinuation visit. Focused physical examinations will be performed during the trial, as specified in the Trial Flow Chart (Section 6.0). Focused physical examination will involve an examination for abnormalities of the heart/lungs, abdomen, extremities, and genitourinary exam. Only abnormal findings should be recorded on eCRFs, either as medical history (present at the screening visit) or as an adverse event (new findings during the trial). Refer to Section 7.2 for instructions on adverse event reporting.

These exams should be conducted by a licensed clinician (i.e., physician, physician's assistant, or nurse practitioner).

7.1.2.2 Vital Signs, Height, and Weight

Vital signs (including HR and BP), body weight and height will be obtained at screening and at subsequent visits specified in the Trial Flow Chart (Section 6.0).

BP and *HR* will be measured (to be performed in duplicate) using an electronic blood pressure monitor.

Body weight will be measured (to be performed in duplicate) using a calibrated digital scale.

Height will be measured (to be performed in triplicate) using a wall-mounted calibrated stadiometer. The Sponsor will calculate growth velocity of height based on these measurements.

For details on measuring techniques, refer to Section 12.7.

7.1.2.3 Testicular Ultrasound

A testicular ultrasound scan (USS) should be performed at protocol specified visits (see Section 6.0, Trial Flow Chart) to assess the testicular volume and testicular sonographic pattern. To avoid variability, the site should designate a single staff member who is trained in the technique of testicular ultrasound to perform the exam whenever possible. The same ultrasound equipment should be used throughout the trial.

At Visit 1/Screening, testicular ultrasound images will be read locally by the investigator (if qualified) or a local radiologist with appropriate training and expertise in reading testicular ultrasound. This local reader will calculate testicular volume to evaluate Inclusion Criterion #5, and evaluate the ultrasound for any presence of local pathology that would exclude the subject from participating (see Section 5.1.3 Subject Exclusion Criteria). Testicular volume is calculated using the formula for prolate ellipsoid, i.e., $[\pi/6] \times (\text{longitudinal}) \times (\text{antero-posterior}) \times (\text{transverse})$ diameters. The screening ultrasound assessment made by the site should be recorded on the source document. Additionally, the testicular ultrasound of each testis will be evaluated by the investigator or a local radiologist with appropriate training and expertise in reading testicular ultrasound for any pathological findings throughout the trial. These findings will be recorded on the source document, and reported in the eCRF as a pre-existing condition in the medical history (if noted at screening), or as an adverse event (if new findings during the trial). Refer to Section 7.2 for instructions on adverse event reporting.

All testicular ultrasound images will be sent to a Sponsor-validated central imaging vendor to be read in a masked manner after the subject completes participation in the study to assess study endpoints (i.e., testicular volume and sonographic pattern). The central imaging vendor will assess adequacy of all submitted ultrasound scans; if a scan is deemed inadequate, the site will be contacted and a repeat scan requested. The ultrasound images will be read by the central imaging vendor according to the description in the Independent Review Charter for imaging to calculate the total testicular volume (i.e., the sum of left and right testes). The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual. The evaluation of the echogenicity will also be made by the vendor according to criteria described in the Independent Review Charter for imaging.

7.1.2.4 Tanner Staging of Pubertal Development

At protocol specified visits (see Section 6.0, Trial Flow Chart), Tanner Staging will be assessed by genital development and pubic hair distribution as noted in Section 12.6. The investigator will use clinical assessment to assign the Tanner Stage for pubic hair and Tanner Stage for genital growth (e.g., penile length and scrotum development) separately. The investigator will perform testicular ultrasound to measure testicular parameters as according to the procedures outlined in Site Imaging Manual provided to the investigator site. However, the Tanner Stage for testicular volume will not be assessed clinically by the investigator and will be completed by the central imaging vendor according to the method described in the Independent Review Charter for imaging. Each score will be considered independently and there will not be a composite score.

7.1.2.5 Adverse Events Monitoring

Adverse events will be monitored throughout the trial. Refer to Section 7.2 for details.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood to be drawn over the course of the trial (from pre-trial to post-trial visits), including approximate blood volumes drawn by visit and by sample type per subject can be found in Section 12.4.

7.1.3.1 Laboratory Safety Evaluations (Hematology and Chemistry)

Laboratory tests for hematology and chemistry to be performed by a central laboratory are specified in [Table 4](#). Blood samples for safety laboratory tests should be taken pre-dose, i.e., prior to administration of MK-8962 or hCG on the day of the visit, whenever possible.

See the Trial Flow Chart (Section 6.0) for the sampling times. For handling, storage and shipment of these samples please refer to the Central Laboratory Manual.

Table 4 Laboratory Tests

Hematology	Chemistry	Other
Hematocrit	Albumin	Free T4
Hemoglobin	Alkaline phosphatase	
Platelet count	Alanine aminotransferase (ALT)	
WBC (total and differential)	Aspartate aminotransferase (AST)	
	Bicarbonate	
	Calcium	
	Chloride	
	Creatinine (for determination of eGFR)	
	Glucose (non-fasting)	
	Phosphorus	
	Potassium	
	Sodium	
	Total Bilirubin	
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal	
	Total protein	
	Blood Urea Nitrogen	

eGFR: estimated glomerular filtration rate

7.1.3.2 Panel of Endocrine Parameters

The following hormones will be assessed by the Sponsor designated central laboratory: FSH, LH, hCG, inhibin-B, AMH, Total T, calculated free T, E2 and SHBG. All blood sample collection for endocrine parameters should be performed prior to injection(s) of MK-8962 or hCG on the day of visit, if there is any injection(s) scheduled for that day.

See the Trial Flow Chart (Section 6.0) for the sampling times. For handling, storage and shipment of these samples please refer to the Central Laboratory Manual.

Note: The LH and FSH assays that are part of the optional GnRHa stimulation test or GnRH IV infusion test as described in Inclusion Criterion 8 (Section 5.1.2) should be performed by the local laboratory; refer to local laboratory instructions as appropriate.

7.1.3.3 Pharmacokinetic Evaluations

A total of 13 serum samples for assessment of MK-8962 concentration will be collected at specified time points indicated in Section 7.1.3.3.1, Flow Chart of Pharmacokinetic Assessments. For handling, storage and shipment of these samples please refer to the Central Laboratory Manual. Concentrations of MK-8962 in serum will be determined using a validated assay.

7.1.3.3.1 Flow Chart of Blood Sample Collection for Pharmacokinetic Assessments of MK-8962^a

Scheduled Week	Scheduled Study Day	Visit Number	Time [range]	Sample Number
0	1	V2	15 minutes prior to first MK-8962 injection	01
0	1	V2	6-24 h after first dose ^b	02
1	3	V3	32-52 h after first dose and -at least 12 hours after sample 02^b	03
1	5	V4	+96 ±24 [72-120] h after first dose ^b	04
1	8	V5	+168 ±24 [144-192] h after first dose ^b	05
2	11	V6	+240 ±24 [216-264] h after first dose ^b	06
4	29	V8	Predose to 3 rd MK-8962 injection ^c	07
12	85	V9	Predose to 7 th MK-8962 injection and prior to 1 st hCG injection ^c	08
24	169	V11	Predose to 13 th MK-8962 injection and prior to hCG injection ^c	09
36	253	V12	Predose to 19 th MK-8962 injection and prior to hCG injection ^c	10
48	337	V13	Predose to 25 th MK-8962 injection and prior to hCG injection ^c	11
64	449	V15	--	12
--	--	<i>Discontinuation (if Subject did not complete V15)</i>	--	12
Post 7 days	--	Follow-up	--	13

^a Blood serum samples for MK-8962 will be processed according to the central laboratory procedures outlined in their manual for handling biological samples. The timing of each sampling is to be recorded on the eCRF.
^b Samples 02 through 06 may be obtained at any time-point within the specified time frame. The timing of each sampling is to be recorded on the eCRF.
^c A visit window of ±3 days is allowed.

7.1.3.4 Anti-MK-8962 Antibodies

Serum samples will be collected for the assessment of anti-MK-8962 antibodies. Baseline samples MUST be taken prior to the first dose of MK-8962. See the Trial Flow Chart (**Section 6.0**) for the sampling times. All blood sampling for antibodies should be performed prior to injection(s) of MK-8962 or hCG on the day of visit, if there is any injection(s) scheduled for that day.

For handling, storage and shipment of these samples please refer to the Central Laboratory Manual.

7.1.3.5 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- Leftover main study serum from endocrine parameters, anti-MK-8962 antibodies, and PK for MK-8962 concentration stored for future research

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the Discontinuation Visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Refer to Section 7.1.5.3 on how to manage patients who discontinue study medication but who do not withdraw consent.

7.1.4.1.1 Withdrawal From Future Biomedical Research

A Subject's consent for Future Biomedical Research may be withdrawn by the subject or the subject's legally acceptable representative (as appropriate). Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. A subject's consent may be withdrawn. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Domiciling

No domiciling is required. At Visit 2/Day 1, the first and second PK serum samples will be collected at two time points: one at about 15 minutes before the first dose of MK-8962, another at 6-24 hours after the first dose of MK-8962. Subjects will report to the site in the morning for the pre-dose blood sample collection. Subject is not required to remain at the site to wait for the collection of the second PK sample, as long as he returns within the window of 6-24 hours after first MK-8962 injection to have the second PK sample collected.

7.1.4.4 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical trial that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

At V1 (approximately 7 days prior to treatment allocation), potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening safety labs may be repeated once per protocol if results are inconsistent with the subject's clinical status or any other recent laboratory evaluations. The period between V1 and treatment allocation (V2) is up to 6 weeks. This time limit may be increased under special circumstances after the site obtains the agreement from the Sponsor.

Subjects may only be rescreened once.

7.1.5.2 Treatment Period

The Study Days when the visits should be scheduled are prespecified in Section 6.0 (Trial Flow Chart). Subjects should adhere to the visit schedule described in the Flow Chart as much as possible.

The allowed windows for the sampling time of each of the 13 PK samples are designated in Section 7.1.3.3 (Flow Chart of Pharmacokinetic Assessment). The first PK sample should be collected approximately 15 minutes before the first witnessed dose of MK-8962, and samples #02 to #06 are to be collected within the window after first MK-8962 dose, as specified in the PK Flow Chart. For subsequent PK assessment visits V8 to V13 (corresponding to the collection of PK samples #07 to #11, respectively), a scheduling window of up to 3 days is allowed.

For V8 (corresponding to the collection of PK sample #07), if a subject is to adjust the visit by up to 3 days (e.g., returns to the clinic 3 days earlier or 3 days later than the prespecified Scheduled Study Day in the Trial Flow Chart), the site should ensure that blood samples

(including PK samples) are collected prior to the witnessed injection of MK-8962 at that visit.

For PK assessment visits V9 through V13, if the subject returns to the clinic up to 3 days earlier or up to 3 days later than the prespecified Scheduled Study Day in the Trial Flow Chart, he should keep his regularly scheduled injection of MK-8962 and not change it to correspond to the PK visit. For example, if the subject is to delay V9 (prespecified for Day 85 in the Trial Flow Chart) by three days to Day 88, the site should remind the subject to administer the home-injection of his 7th MK-8962 dose as originally scheduled (i.e., on Day 85 according to the Trial Flow Chart), and return to the clinic on Day 88 for collection of PK sample #08. The actual timing of each injection and each PK sample collection should be accurately documented, whether or not any variation to the protocol-specified schedule occurs.

Subjects should adhere to their hCG injection schedules independent of the visit deviations or altered MK-8962 dosing schedules discussed above. PK sample #12 is to be collected at study completion (V15) or discontinuation (D/C), and the last PK sample (#13) is to be collected at the post-treatment follow-up visit.

For visits where no PK samples are collected (V7, V10, and V14), a 7-day visit adjustment window is allowed. If a non-PK visit is adjusted to a non-prespecified Study Day, the subject should not change his regular injection schedules of MK-8962. When an adjustment in the schedule is required for a specific visit, this should not impact subsequent visits and the schedule for subsequent Study Days should remain as specified in the Trial Flow Chart. This is to ensure adherence to the 64 week treatment period for this study.

There may be cases where visits need to be scheduled outside the allowed visit window. These should be rare incidences. In these cases, the subjects should be scheduled as soon as possible to the required time point, taking into consideration a subject's supply of the trial medication.

Phone visits are required visits and should be conducted within the protocol-specified time frame (see Section 6.0).

Any visits scheduled outside the specified visit window for that particular visit is not considered a major protocol deviation and the Sponsor does not need to be contacted for approval.

7.1.5.3 Post-Treatment

- Post-treatment Follow-up Visits for Subjects Who Complete the Study or Who Discontinue Treatment but Do Not Withdraw Consent***

The last dose of MK-8962 is scheduled to be self-administered or administered by the subject's legal guardian (or someone designated by the legal guardian who has been appropriately trained) on Week 62. The subject will continue twice-weekly hCG injections with the last two doses administered in Week 64. A post-treatment follow-up visit is to be scheduled at least 21 days (but no more than 45 days) after the last dose of MK-8962, and at least 7 days after the last dose of hCG, whether the subject completed the trial or discontinued from the trial treatment prematurely. Follow-up blood samples will be

collected for assessment of anti-MK-8962 antibodies and endocrine parameters. AEs and concomitant medication will also be assessed. For subjects wishing to continue on post-trial gonadotropin treatment, such treatment should not be started until after blood sample collection at this visit.

For subjects who discontinue treatment but do not withdraw consent, after the discontinuation visits and post-treatment follow-up visit, they should:

1. Return to the clinic for key visits (V9/Week 12, V12/Week 36 and/or V15/Week 64 as applicable) to have the following procedures performed: focus physical examination, vital signs, weight and height, Tanner staging, testicular ultrasound, laboratory assessment of endocrine parameters, and safety parameters (chemistry panel and hematology), and collection of concomitant medications and adverse events. Subjects who discontinued treatment due to presence of ADA will also have serum samples collected for ADA testing at these visits. Subjects who are unable or unwilling to return to the clinic at key visits will be contacted by phone to obtain adverse events and concomitant medications.
2. Be contacted by phone in a timeframe similar to their original study visit schedule at visits that are not key visits, i.e., at V10, V11, V13, V14, up until the subject has reached the Week 64 visit. The purpose of these telephone contacts will be to assess for serious adverse events that occurred and to collect the subject's concomitant medications. The date of the telephone contact should be recorded and any serious adverse events that have occurred and concomitant medications that were used should be recorded in the eCRF.
3. In addition to the above procedures, if a subject discontinues treatment due to the presence of neutralizing ADA, he may continue to be followed every three months with repeat ADA testing after the Week 64 visit. This will continue until the ADA result becomes negative or until the subject is clinically stable (e.g., in the absence of hCG use, no clinically meaningful change in testicular volume or testosterone levels for 3 months; if hCG continues to be used, an appropriate response to hCG with stable testosterone levels) for up to 12 months after treatment discontinuation, whichever comes first.

Note: Study sites must make all reasonable efforts to counsel the subject to stay in the study even if they discontinued the study medication, and make all reasonable efforts to contact the subject. Subjects must be counseled regarding the importance of complete follow up, even when they are not continuing on study medication. Sites should make at least three attempts to make telephone contact. If telephone contacts are not successful, sites should make at least two attempts to reach the subject via certified letter before considering the subject as lost to follow-up.

If any adverse event requires supplemental procedures, they should be performed as medically necessary and recorded in the Procedures eCRF.

• ***Follow Up of Subjects Who Withdraw Consent Prior to Study Completion***

Subjects who withdraw consent and discontinue from the study will not be contacted for post-trial follow-up.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through the follow-up visit (i.e., at least 21 days following last dose of MK-8962) following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.2.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose for MK-8962 is any dose exceeding the doses as prescribed by the protocol, or if two doses of MK-8962 are given less than 7 days apart. For hCG, investigators/site personnel are to consult the local approved hCG product label for guidance on the definition of overdose.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a non-serious adverse event, unless other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious adverse event, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Immediate Reporting of Adverse Events to the Sponsor

7.2.2.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements.

- Is a cancer;
- Is associated with an overdose.

Refer to [Table 5](#) for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through the follow-up visits following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.2.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through the follow-up visits following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

2. Hypersensitivity reaction: A potential sign or symptom of a hypersensitivity reaction after injection of MK-8962 such as new emergent skin rash, urticaria, hypotension, allergic asthma, chest tightness, broncho-spasm, dyspnea, or wheezing. Minor localized skin rash not suggesting hypersensitivity will not be considered an ECI.

7.2.3 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in [Table 5](#). The investigator's assessment of causality is required for each adverse event. Refer to [Table 5](#) for instructions in evaluating adverse events.

Table 5 Evaluating Adverse Events

Maximum Intensity	Mild	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	† Results in death; or	
	† Is life threatening; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	† Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	† Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	† Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); or	
	Overdose, although not serious per ICH definition, whether accidental or intentional, with or without an accompanying adverse event/serious adverse event, is reportable to the Sponsor within 24 hours to meet certain local requirements.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:		Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
Yes, there is a reasonable possibility of Sponsor's product relationship.		There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
No, there is not a reasonable possibility of Sponsor's product relationship		Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)

7.2.4 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to study finalization, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2 to 8.12.

Study Design Overview	A phase III, multi-center, open label, single-group trial to investigate the efficacy and safety of MK-8962 (corifollitropin alfa) in combination with human Chorionic Gonadotropin (hCG) for initiation or restoration of puberty as assessed by increased testicular volume in adolescent males 14 to <18 years old with hypogonadotropic hypogonadism
Treatment Assignment	Open-label treatment with MK-8962. During 12 weeks of Priming phase, all subjects receive 100 µg (for subjects with body weight ≤ 60 kg) or 150 µg (for subjects with body weight > 60 kg) MK-8962 once every two weeks, followed by 52 weeks of combined treatment with MK-8962 and hCG (titrated to maintain appropriate Total T and E2 levels) twice a week.
Analysis Populations	Efficacy: Full Analysis Set (FAS), Completers Safety: All Subjects as Treated (ASaT) Pharmacokinetics: All-Subjects-Pharmacokinetically-Evaluable (ASPE)
Primary Endpoint(s)	Change from baseline (Day 1) to Week 64 in log-transformed testicular volume (measured as the sum of volumes of left and right testes by ultrasound);
Key Secondary Endpoints	N/A
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The mean change from Day 1 (Baseline) in log-transformed testicular volume will be evaluated by using a mixed model with a fixed effect for baseline and time point and a random effect for subject. The geometric mean increase from Day 1 to Week 64 in testicular volume and its 95% CI will be obtained by exponentiation.

Statistical Methods for Key Safety Analyses	The percentage of subjects with anti-MK-8962 antibodies and its exact 95% CI will be calculated using the exact binomial method of Clopper Pearson.
Interim Analyses	No interim analyses are planned
Multiplicity	No multiplicity adjustment is planned as this is an estimation study
Sample Size and Power	This is an estimation study. Assuming a screen failure rate of approximately 50-60%, approximately 30-40 subjects will be screened to enroll approximately 15. Assuming a discontinuation rate of 30%, it is estimated that 10 subjects will complete. If the discontinuation rate exceeds 30%, enrollment will be re-opened to assure the target number of completers. The total number of enrolled subjects shall not exceed 35.

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This trial is being conducted as a single-group, open-label study, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the allocation schedule(s) for study treatment assignment. Randomization will be implemented in an interactive voice response system (IVRS).

8.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.0. This is an estimation study, no hypothesis will be tested.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below, followed by the descriptions of the derivations of selected endpoints.

8.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint for this trial is the Change from Baseline (Day 1) to Week 64 in log-transformed testicular volume (measured as the sum of volumes of left and right testes by ultrasound).

Secondary Efficacy Endpoint

- Change from baseline in serum inhibin B concentrations at Week 64;
- Growth velocity at Week 36 and Week 64;
- Tanner Stage of pubertal development at Weeks 12, 36 and 64.
- Characterization of MK-8962 pharmacokinetics (based on serum MK-8962 concentrations) through 64 weeks of treatment.

- Characterization of testicular sonographic pattern reflecting pubertal development through 64 weeks of treatment;
- Changes from baseline in endocrine parameters (LH, calculated free testosterone, Total T, E2, SHBG, and AMH at Weeks 12, 36 and 64;

8.4.2 Safety Endpoints

Initial description of safety measures is provided in Section 4.2.3.2.

The pre-specified safety endpoint is the presence of anti-MK-8962 antibodies.

Events of Clinical Interest

Liver function: an elevated AST or ALT lab value that is $\geq 3 \times$ the upper limit of normal (ULN) and an elevated total bilirubin lab value that is $\geq 2 \times$ ULN and, at the same time, an alkaline phosphatase lab value that $< 2 \times$ ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

Hypersensitivity reaction: a potential sign or symptom of a hypersensitivity reaction after injection of MK-8962 such as new emergent skin rash, urticaria, hypotension, allergic asthma, chest tightness, broncho-spasm, dyspnea, or wheezing. Minor localized skin rash not suggesting hypersensitivity will not be considered an ECI.

Other safety endpoints include:

- Change from baseline for laboratory safety parameters and vital signs;
- Clinical review of adverse events;
- Predefined limits of changes (PDLCs) for laboratory values. Details about the safety ranges for each parameter (hematology/biochemistry) will be specified in the sSAP.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized subjects who:

- receive at least one dose of study treatment
- have baseline and at least one post-baseline measurement of testicular volume
- have LH levels ≤ 3 IU/L during anytime of the study
- have received at least 36 weeks¹ of treatment (12 weeks of priming with MK-8962 followed by 24 weeks of combined treatment with MK-8962 and hCG) and have no more than 4 weeks from the last dose of MK-8962 when the last measurement is made

¹ This time point is based on the observations regarding changes in testicular volume in a study of males with HH pre-treated with recFSH for 4 months followed by 24 months of pulsatile GnRH therapy (equivalent of combined treatment with FSH and LH/hCG) [17].

A supportive analysis using the Completers population will be performed for the primary efficacy endpoint only if there are at least 5 completers. The Completers population comprises subjects who remained on the study treatment regimen and completed through Week 64.

Another supportive analysis using the modified Intent-to-Treat population will be performed for the primary efficacy endpoint. The modified ITT population comprises all randomized subjects who have received at least 36 weeks of treatment (12 weeks of priming with MK-8962 followed by 24 weeks of combined treatment with MK-8962 and hCG), and have baseline and at least one post-baseline measurement of testicular volume at ≥ 36 weeks of treatment.

8.5.2 Safety Analysis Populations

The All-Subjects-as-Treated (ASaT) population consists of all randomized subjects who received at least one dose of MK-8962 and will be used for the analysis of safety data in this study.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

All-Subjects-Pharmacokinetically-Evaluable (ASPE) population: Consists of all subjects from the ASaT group, for whom at least one PK parameter can be calculated according to the protocol and who did not have any protocol violation interfering with PK. Subjects included in the ASaT group, but excluded from the ASPE group will be listed including the reason(s) for exclusion.

The final determination on major protocol deviations interfering with PK, and thereby the composition of the ASPE population, will be made prior to the finalization of the database and will be documented in a separate memo.

8.6 Statistical Methods

Statistical testing and inference for safety analyses are described in 8.6.2.

8.6.1 Statistical Methods for Efficacy Analyses

All efficacy analyses will be performed for the FAS.

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the supplemental SAP.

8.6.1.1 Primary Efficacy Analysis

The mean change from Day 1 (Baseline) in log-transformed testicular volume will be analyzed using a mixed model with a fixed effect for baseline and time point and a random effect for subject. For each time point (i.e., Week 1-64), the mean change from Day 1 to that time point and the associated 95% confidence interval (CI) will be calculated. The geometric mean increase in testicular volume and its 95% CI will be obtained by exponentiation.

The mean change from the first day of combined treatment (Week 12) to Week 64 in log-transformed testicular volume will also be analyzed using a mixed model with a fixed effect for time point and a random effect for subject. For each time point, the mean change from Week 12 to that time point and the associated 95% CI will be calculated. The geometric mean increase in testicular volume and its 95% CI will be obtained by exponentiation.

An unstructured covariance matrix will be used to model the correlation among repeated measurements. In the event of model convergence issues, other covariance structures will be considered.

In addition, the change from Day 1 to Week 12 (i.e., during the priming phase alone) in log-transformed testicular volume will be summarized. The associated geometric mean increase and its 95% CI will be obtained by exponentiation.

Sensitivity analyses

A supportive analysis using only subjects who completed Week 64 will be performed for the primary efficacy endpoint only if there are at least 5 such completers. The mean change from Day 1 (Baseline) to Week 64 in log-transformed testicular volume will be analyzed using an Analysis of Covariance (ANCOVA) model including baseline as a covariate. The geometric mean change in testicular volume and its 95% CI will be obtained by exponentiation. The mean change from the first day of combined treatment (Week 12) to Week 64 will also be analyzed for the completers only.

Changes in log-transformed testicular volume will also be analyzed separately for the left and right testes using the same mixed model as for the primary analysis. Last Observation Carried Forward (LOCF) approaches will be used to investigate the robustness of the results for the testicular volume (as the sum of volumes of left and right testes) as well as for the left and right testes separately.

Accounting for Missing Data

Assuming that data are Missing at Random (MAR), the mixed model for the primary efficacy analysis accounts for missing data.

8.6.1.2 Secondary Efficacy Analysis

The change in serum inhibin B concentrations after 64 weeks will be summarized. In addition, changes from Day 1 to Week 12, and from Week 12 to Week 64 will also be summarized. A listing by subject and time point will also be provided for each treatment phase.

The growth velocity (cm/year) will be summarized as follows:

For each subject, the growth velocity over the 36 and 64 week treatment periods will be extracted using the slopes estimated from an overall mixed random intercept and random slope model of height (cm) and time (in years) and age as covariates. Overall growth velocity slope over 36 and 64 weeks will also be presented based on the same model. An unstructured covariance matrix will be used to model the correlation among repeated measurements. In the event of model convergence issues, other covariance structures (i.e. AR or compound symmetry) will be considered.

In addition, growth in cm over 12, 36 and 64 weeks will be listed for each age (14, 15, 16 and 17 years of age at randomization). Annualized growth velocity (cm/year) at 36 and 64 weeks will also be calculated and listed.

For each male subject, Tanner Staging will be recorded for both pubic hair and testicular volume. Tanner Stage of development at Baseline, week 12, week 36 and at the end of the 64 weeks of combined treatment will be summarized by shift table. A listing of Tanner Stage by time point and subject will also be provided.

Descriptions of sonographic testicular patterns will be listed at Baseline and weeks 12, 36 and 64. Any changes over time will be described.

For continuous variables, summary statistics will include the number of observations, mean, standard deviation, median, minimum and maximum. For categorical variables, frequency distributions will be provided.

Serum concentrations of hormones (LH, Total T, E2, SHBG, and AMH) will be summarized by assessment (Week 1-64). Additional summary statistics will include first and third quartile as well as geometric mean together with coefficient of variation. Values below the Lower Limit of Quantification (LLOQ) will be set to $\frac{1}{2}$ times the LLOQ for the calculation of descriptive statistics. The number and percentage of values below the LLOQ will be reported. Additionally, serum hormone concentrations will be summarized by treatment phase.

The summary of the key efficacy analyses is provided in [Table 6](#).

Table 6 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach [†]	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint				
Change from Baseline to Week 64 in log-transformed testicular volume (measured as the sum of volumes of left and right testes by ultrasound);	P	Linear Mixed Model [#]	FAS	Model-based
Change from Baseline to Week 64 in log-transformed testicular volume (measured as the sum of volumes of left and right testes by ultrasound);	S	Linear Mixed Model [#]	FAS	LOCF ^{\$\$}
Change from Baseline to Week 64 in log-transformed testicular volume (measured as the sum of volumes of left and right testes by ultrasound);	S	ANCOVA	Completers	N/A

[†] P=Primary approach; S=Supportive approach.

[#] Linear Mixed Model with terms for treatment.

^{\$\$} LOCF = last-observation-carried-forward method.

8.6.2 Statistical Methods for Safety Analyses

All safety analyses will be conducted for the ASaT.

Due to the small study size and single treatment, the tiered approach will not be followed for this study.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests and vital signs measurements.

For this protocol, the percentage of subjects with confirmed presence of anti-MK-8962 antibodies and its exact 95% CI will be calculated using the exact binomial method of Clopper Pearson. The presence of anti-MK-8962 antibodies will be summarized at each visit as well as overall and by treatment phase.

Adverse events (specific terms as well as system organ class terms) and predefined limits of change in laboratory and vital signs parameters will be summarized by treatment phase.

In addition, the broad AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE will be summarized by treatment phase.

Continuous measures such as changes from baseline in laboratory and vital signs parameters will be summarized: summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment phase in table format.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Demographic and Baseline Characteristics

The comparability of the treatment phases for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. The cumulative percentage of subjects that discontinued treatment prematurely will be calculated by treatment phase and overall using the Kaplan-Meier method and plotted against trial week. Demographic variables (e.g., age [yrs], body weight [kg], body height [cm], body mass index [BMI] [kg/m^2] and race), baseline characteristics [testicular volume (left and right testes, as well as total)], results from serum hormone levels [FSH, LH, hCG, Total T, E2, SHBG, inhibin-B, and AMH], primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

8.6.3.2 Disposition of Subjects

The number of subjects that enter the MK-8962 priming phase, the number of subjects that enter the combined treatment phase (MK-8962 and hCG) and the number of subjects that complete the combined treatment phase will be tabulated. All subjects that discontinue will be listed by main reason for discontinuation.

8.6.3.3 Pharmacokinetic Analysis

The PK analysis will be conducted in the ASPE group.

For characterization of MK-8962 PK in adolescents, serum samples will be collected at specific time points throughout the study (see flowchart in Section 6.0).

Serum MK-8962 concentrations will be obtained using a solid phase enzyme-immunoassay specific for MK-8962. Descriptive statistics for the serum concentrations by time-point will be calculated and will comprise number of observations (n), number of missing or substituted observations, arithmetic mean together with standard deviation and coefficient of variation, geometric mean together with coefficient of variation, minimum, median and maximum.

The existing PopPK model in HH men will be updated using the serum MK-8962 concentration data obtained in the current study. A covariate analysis will be performed to identify important relationships between PK parameters (ka MK-8962, CL MK-8962, V MK-8962, f MK-8962, and FSH baseline) and patient characteristics (i.e., gender, body weight, height, BMI, age). The updated model will be used to derive estimates for at least the following PK parameters in adolescent males: AUC_{ss}, C_{max_ss}, C_{min_ss}, Cl and V. Descriptive statistics for the PK parameters will be calculated and will comprise number of observations (n), arithmetic mean, standard deviation and arithmetic coefficient of variation, geometric mean and geometric coefficient of variation, minimum, median and maximum.

In addition, through the PopPK approach, analysis will be performed using the serum MK-8962 concentration data obtained in this study relative to prior studies in adult HH men and in women to identify possible differences in MK-8962 PK between females, HH men and adolescent males. It was identified based on the HH adult men PopPK analysis that MK-8962 clearance was 30% lower in male subjects as compared to female subjects. The updated PopPK model in adolescent males will be used to validate the assumptions also apply to adolescent males. This analysis will be reported separately.

8.7 Interim Analyses

No interim analyses are planned for this study.

8.8 Multiplicity

No multiplicity adjustment is planned as there is a single estimation of one treatment using one endpoint. No hypothesis will be tested. Other efficacy analyses will be considered supportive and/or explanatory.

8.9 Sample Size and Power Calculations

8.9.1 Sample Size and Power for Efficacy Analyses

This is an estimation study.

Assuming a screen failure rate of 50-60%, approximately 30-40 subjects will be screened to enroll approximately 15. Assuming a discontinuation rate of 30%, it is estimated that 10 subjects will complete the study. If the discontinuation rate exceeds 30%, enrollment will be re-opened to assure the target number of completers (i.e., 10). The total number of enrolled subjects shall not exceed 35.

[Table 7](#) summarizes estimates of the geometric mean increase in testicular volume (mL) under various assumptions. These calculations are based on a difference in paired means with 10 completed subjects at an overall one-sided 2.5% alpha-level and are carried out using [SAS v9.3].

In P031 (adult men with HH) the estimated geometric mean increase in testicular volume from Day 1 to Week 52 was 2.30 (95% CI: 2.03-2.62). This corresponds to a difference from baseline and SD (both on log-scale) of 0.84 and 0.47, respectively. These finding are consistent with similar results observed in other studies [1, 17] where at least a doubling of mean testicular volume of adolescent males was observed after recFSH treatment. Based upon these experiences, a 2-fold (or greater) increase in testicular volume is expected. Applying generally similar SD as observed in P031, the study should be able to estimate a larger than 2-fold increase with the lower margin of the 95% CI excluding an increase of less than 1.7-fold. The CI, with 10 completers, suggests reasonable precision to estimate the change in testicular volume.

Table 7 The 95% Confidence Limits for Geometric Mean Increase in Testicular Volume (mL) by Underlying Difference and SD Assumptions (log-scale) for 10 Completers

Underlying Difference from Baseline to Week 64 (log-scale)	Underlying SD (log-scale)	Geometric Mean Increase	95% Confidence Limit†
0.4	0.45	1.49	1.18, 1.89
	0.5		1.15, 1.93
	0.55		1.12, 1.99
0.5	0.45	1.65	1.30, 2.08
	0.5		1.27, 2.14
	0.55		1.24, 2.19
0.6	0.45	1.82	1.44, 2.30
	0.5		1.40, 2.36
	0.55		1.37, 2.43
0.7	0.45	2.01	1.59, 2.54
	0.5		1.55, 2.61
	0.55		1.51, 2.68
0.8	0.45	2.23	1.76, 2.81
	0.5		1.72, 2.89
	0.55		1.67, 2.96

† One-sided 95% CI based on a difference in paired means.

8.10 Subgroup Analyses and Effect of Baseline Factors

The primary endpoint of log-transformed testicular volume may also be summarized by weight group (≤ 60 kg, > 60 kg) if there are a sufficient number of subjects in each category.

8.11 Compliance (Medication Adherence)

Drug accountability data for MK-8962 will be collected during the study. Compliance rates will be summarized (N, mean, median, SD, range [min and max]) by treatment phase and overall. The compliance rate for a subject will be defined as the total number of injections divided by the total number of injections the subject was supposed to have during the treatment period.

8.12 Extent of Exposure

The extent of exposure to study treatment will be evaluated by summary statistics (N, mean, median, standard deviation) and frequencies for the “Number of Days on Therapy” by treatment phase and overall.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in [Table 8](#). This includes both MK-8962 (investigational product of this trial) and hCG (standard of care). For hCG and/or its solvent, if local regulations do not permit use of the centrally sourced supplies OR centrally sourced supplies become unavailable, a local source may be used but requires prior approval from the Sponsor.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 8 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
corifollitropin alfa (MK-8962) 100 µg/0.5 mL	Pre-filled syringe (Sterile Solution for subcutaneous Injection, 0.5 mL)	Provided centrally by the Sponsor.
corifollitropin alfa (MK-8962) 150 µg/0.5 mL	Pre-filled syringe (Sterile Solution for subcutaneous Injection, 0.5 mL)	
human Chorionic Gonadotropin (hCG) 1500 IU	Ampoule or vial (Sterile Dry Powder for subcutaneous injection after reconstitution)	Provided centrally by the Sponsor. If local regulations do not permit use of the centrally sourced supplies OR centrally sourced supplies become unavailable, a local source may be used but requires prior approval from the Sponsor.
human Chorionic Gonadotropin (hCG) 5000 IU	Ampoule or vial (Sterile Dry Powder for subcutaneous injection after reconstitution)	
Sodium Chloride Solution 0.9%, 1 mL	Ampoule or vial (Sterile Solution for Reconstitution of hCG, 1 mL)	

All supplies indicated in [Table 8](#) will be provided per the “Source/Additional Information” column depending on local country operational requirements.

Any commercially available product not included in [Table 8](#) will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open label kits of Pre-filled syringe and ampoules (or vials) to maintain the dosing schedule.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction>Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator

when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to <http://www.clinicaltrials.gov>, www.clinicaltrialregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives

and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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9. Clinical Study Report, Multicenter Study: A phase III, randomized, double-blind, active-controlled, equivalence clinical trial to investigate the efficacy and safety of a single injection of 100 µg Org 36286 (corifollitropin alfa) to induce multifollicular development for controlled ovarian stimulation (COS) using daily recombinant FSH (recFSH) as a reference. (Protocol P05690). (Protocol 107012).
10. Clinical Study Report, Multicenter Study: A phase III, multi-center, open label, uncontrolled trial to investigate the efficacy and safety of MK-8962 (corifollitropin alfa) in combination with human Chorionic Gonadotropin (hCG) in inducing increased testicular volume and spermatogenesis in adult men with hypogonadotropic hypogonadism who remain azoospermic when treated with hCG alone. (Protocol P031) (Protocol SCH 900962, P07937).
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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*

Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

- a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.¹
- b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.²
- c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.²
- d. DNA: Deoxyribonucleic acid.
- e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.5 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of patient consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated

mailbox (clinical.specimen.management@merck.com) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available

through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

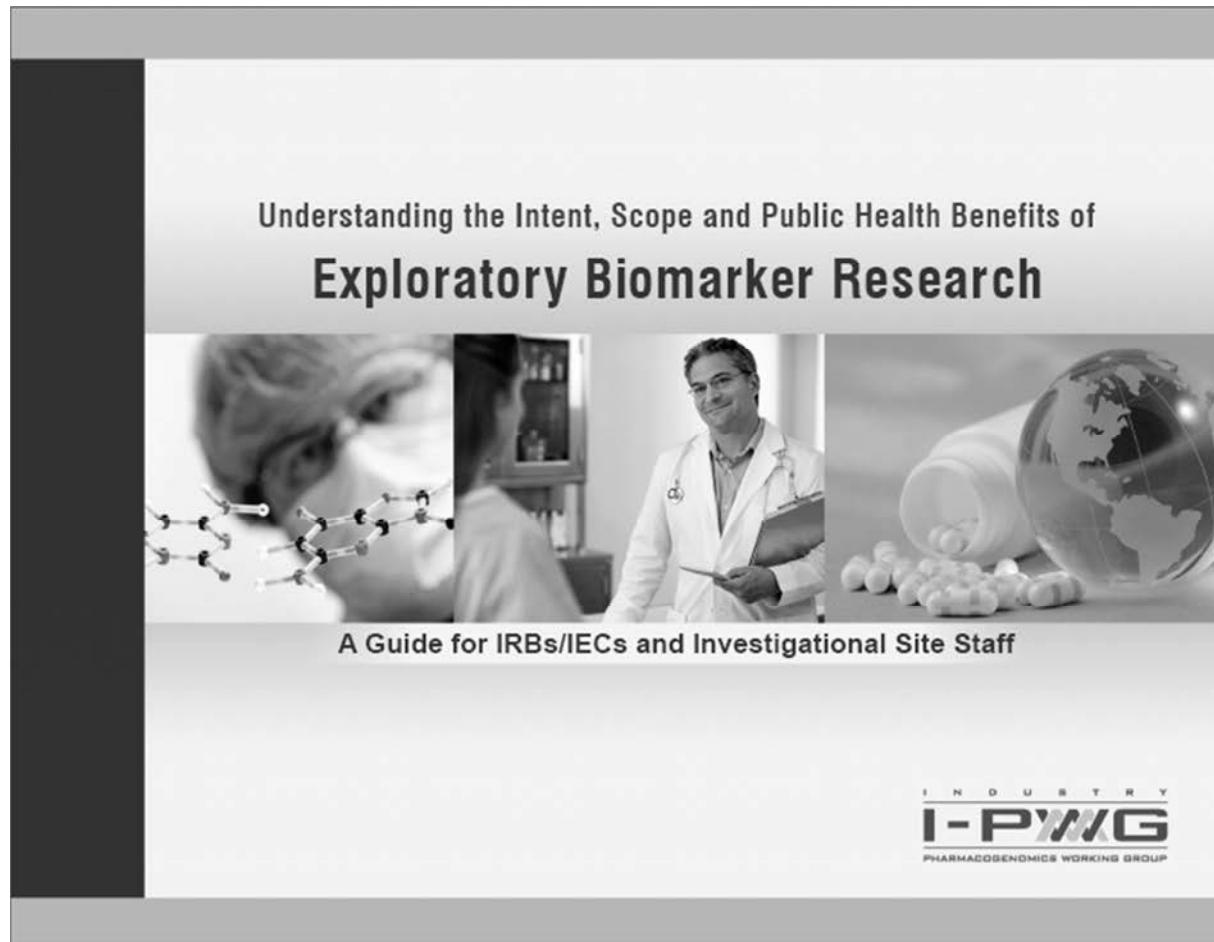
12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: <http://www.cancer.gov/dictionary/?searchTxt=biomarker>
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; <http://www.ich.org/LOB/media/MEDIA3383.pdf>

12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff



This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".¹*

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and pre-clinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure² and ICH Guidance E15³ for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.⁴ The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).⁵ By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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I-PWG
INDUSTRY PHARMACOGENOMICS WORKING GROUP

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.

3. Importance of Biomarkers to Regulatory Authorities

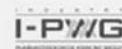
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.^{3, 6-24}

4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.⁷ Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.



5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.²⁵ Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin[®]) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec[®]) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix[®]) or cetuximab (Erbitux[®]) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving dapsone and ethinyl estradiol (Yasmin[®]) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen[®]).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor[®]), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as sur-

rogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearchTM to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.²⁶⁻²⁷

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies



and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.²⁶⁻³¹

Optional vs. Required Subject Participation
Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

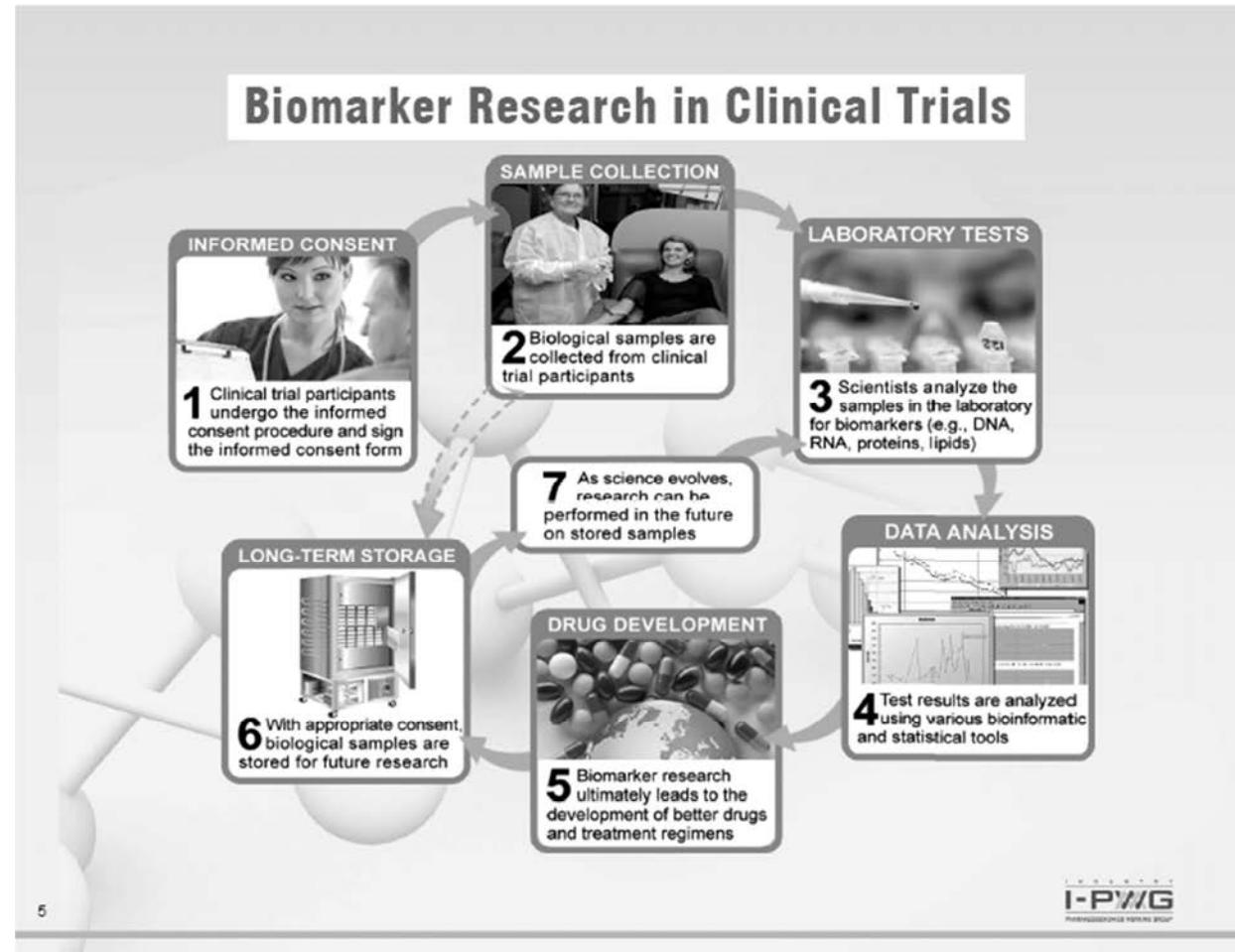
Consent for Future Research Use
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.^{3, 31} Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

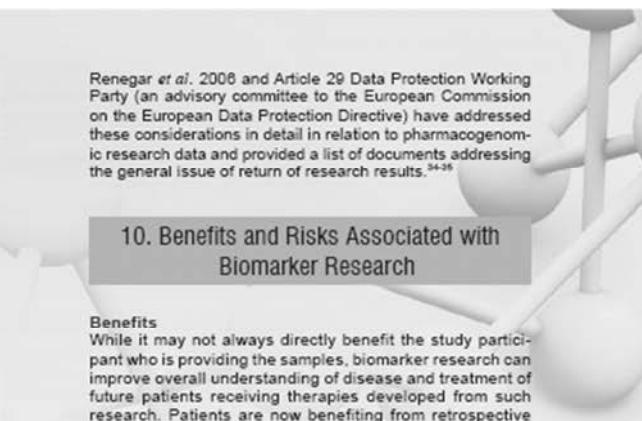
Important elements of informed consent for future use of samples include, but are not limited to:³²

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.³ In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.³³

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.





8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

- i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)
- ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable
- iii) whether genetic counseling is recommended (for genetic results)
- iv) the ability to accurately link the result to the individual from whom the sample was collected
- v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux[®]) and panitumumab (Vectibix[®]) which highlights the value of KRAS status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.^{28,33} Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.^{28,32}

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways:
i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

“...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected”

where confidentiality is defined as, *“The prevention of disclosure, to other than authorized individuals, of a sponsor’s proprietary information or of a subject’s identity.”*

This standard dictates that *“the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.”*³¹

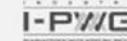
Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant’s health. In addition, exploratory research data should not be included as part of a participant’s medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).³⁶⁻³⁷

12. Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group’s activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-



ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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12.4 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Approximate Blood Volume for Laboratory Safety Evaluations
 (Hematology and Chemistry)

Trial Visit:	Screening Visit 1	Treatment Visit 2	Treatment Visit 9	Treatment Visit 12	Treatment Visit 15/ D/C Visit
Blood Parameter	Approximate Blood Volume (mL)				
Hematology	2.00-3.00	2.00-3.00	2.00-3.00	2.00-3.00	2.00-3.00
Serum Chemistry	0.50	0.50	0.50	0.50	0.50
Serum for Free T4	0.35	N/A	N/A	N/A	N/A
Expected Total (mL)	2.85-3.85	2.85-3.85	2.85-3.85	2.85-3.85	2.85-3.85

Approximate Blood Volume for Panel of Endocrine Parameters

Trial Visit:	Screening Visit 1	Treatment Visit 2	Treatment Visit 9	Treatment Visit 10	Treatment Visit 11	Treatment Visit 12	Treatment Visit 13	Treatment Visit 14	Treatment Visit 15/ D/C Visit/ Post-Treatment
Blood Parameter	Approximate Blood Volume (mL)								
Serum Estradiol	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Serum FSH	0.35	0.35	0.35			0.35			0.35
Serum LH	0.40	0.40	0.40			0.40			0.40
Serum SHBG	0.30	0.30	0.30			0.30			0.30
Serum AMH	0.35	0.35	0.35			0.35			0.35
Serum Inhibin B	0.30	0.30	0.30			0.30			0.30
Serum hCG	0.27	0.27	0.27			0.27			0.27
Calculated Free T	1.00	1.00	1.00			1.00			1.00
Total T	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70
Expected Total (mL)	4.67	4.67	4.67	1.70	1.70	4.67	1.70	1.70	4.67

Approximate Blood Volume for Anti-MK-8962 Antibodies

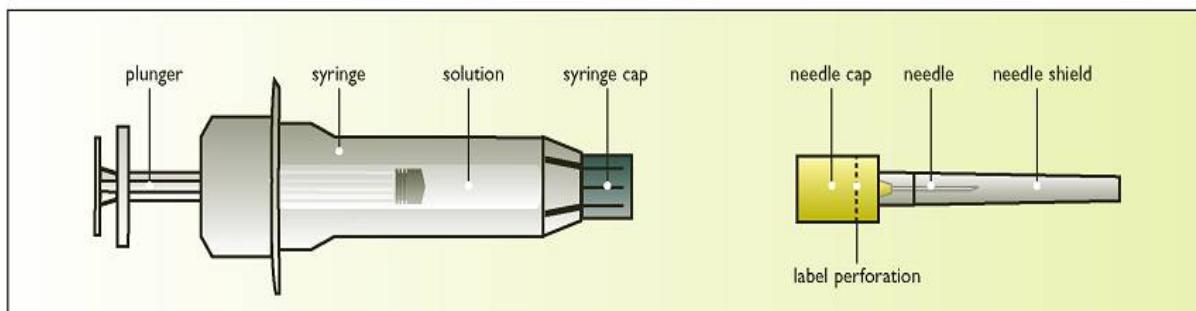
Trial Visit:	Treatment Visit 2	Treatment Visit 8	Treatment Visit 9	Treatment Visit 11	Treatment Visit 12	Treatment Visit 13	Treatment Visit 15/ D/C Visit	Post-Treatment
Blood Parameter	Approximate Blood Volume (mL)							
Sampling for Anti-MK-8962 antibodies	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00

Approximate Blood Volume for Pharmacokinetic Evaluations

Trial Visit:	Treatment Visit 2		Treatment Visit 3	Treatment Visit 4	Treatment Visit 5	Treatment Visit 6	Treatment Visit 8	Treatment Visit 9	Treatment Visit 11	Treatment Visit 12	Treatment Visit 13	Treatment Visit 15/ D/C Visit	Post-Treatment
Sample Number:	01	02	03	04	05	06	07	08	09	10	11	12	13
Blood Parameter	Approximate Blood Volume (mL)												
Pharmacokinetic sampling for MK-8962 concentration	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00

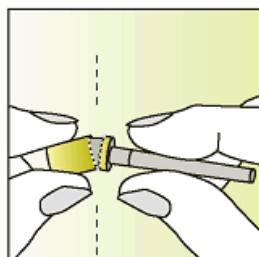
12.5 Instructions on home-administration of MK-8962 (as provided to subjects)

Components of the MK-8962 syringe with needle



Injections should be administered in the morning once every two weeks from Visit 2 (Day 1) onwards subcutaneously into the abdominal wall. Please see the Medication Diary for detailed injection schedule.

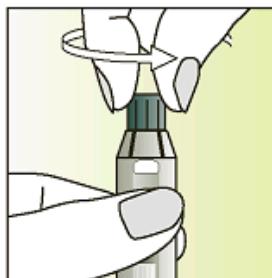
Wash your hands thoroughly and clean the skin area where the needle will enter with a disinfectant.
Preparing the injection



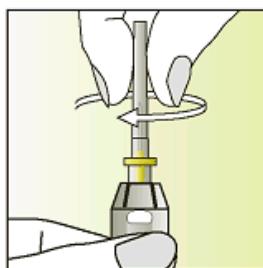
Step 1:
Break the label perforation and pull off the needle-cap.
Leave the needle shield on the needle.
Place the needle shield (containing the needle) on a clean dry surface, while preparing the syringe.



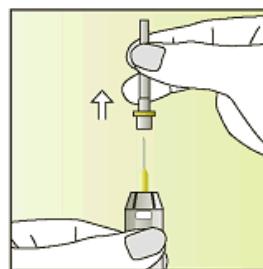
Step 2:
Peel off the label on the syringe.
Hold the syringe with the grey cap pointing upwards.
Tap the syringe gently with your finger to help air bubbles rise to the top.
Check that the liquid in the syringe is clear. Do not use if it is not clear or has particles in it.



Step 3:
Keep the syringe pointing upwards.
Unscrew the syringe cap counter-clockwise.

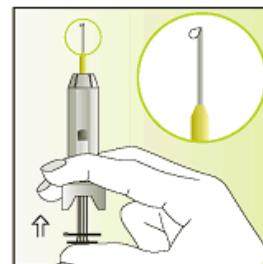


Step 4:
Keep the syringe pointing upwards.
Screw the needle shield from Step 1 (containing the needle) clockwise onto the syringe.

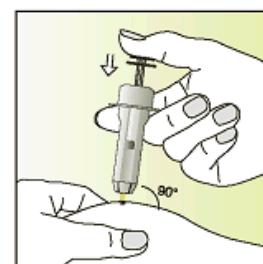


Step 5:
Keep the syringe pointing upwards.
Remove the needle shield by pulling straight up and then discard the shield.
BE CAREFUL with the needle.

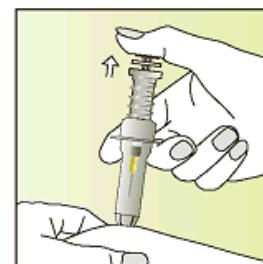
Injecting



Step 6:
Take the syringe between your index and middle finger, keeping the needle pointed upwards. Place your thumb on the plunger.
Carefully push the plunger upwards until a tiny droplet appears at the tip of the needle.



Step 7:
Pinch a fold of the abdomen skin between your thumb and index finger.
Insert the entire needle at a 90 degree angle into the fold of the skin.
CAREFULLY press the plunger until it cannot go any further.
Keep holding down the plunger and COUNT TO FIVE to ensure that all of the solution is injected.



Step 8:
Release your thumb from the plunger.
The needle will withdraw automatically into the syringe where it will be locked permanently.
Properly discard the used syringe into a bio-hazard container.

Note: Please record the date and time of injection on the medication diary

12.6 Tanner Staging (Male)

Pubic hair

- Tanner I -- none (prepubertal state)
- Tanner II -- small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum
- Tanner III -- hair becomes more coarse and curly, and begins to extend laterally
- Tanner IV -- adult-like hair quality, extending across pubis but sparing medial thighs
- Tanner V -- hair extends to medial surface of the thigh

Genitals

- Tanner I -- prepubertal (testicular volume less than 1.5 ml; small penis)
- Tanner II -- testicular volume between 1.6 and 6 ml; skin on scrotum thins, reddens and enlarges; penis length unchanged
- Tanner III -- testicular volume between 6 and 12 ml; scrotum enlarges further; penis begins to lengthen
- Tanner IV -- testicular volume between 12 and 20 ml; scrotum enlarges further and darkens; penis increases in length and circumference
- Tanner V -- testicular volume greater than 20 ml; adult scrotum and penis

12.7 Blood Pressure and Anthropometric Measurements

Blood Pressure

Ensure patient has not had any caffeine or tobacco within 30 minutes. BP should be measured in the sitting position. The patient will remain in the sitting position for at least 5 minutes before any blood pressure readings are recorded. The same arm, preferably the non-dominant arm, should be used for all blood pressure determinations at each visit. Systolic and diastolic BP will be determined by obtaining two measurements, 1 to 2 minutes apart. The consecutive systolic BP readings should be within 5 mm Hg of each other and the consecutive diastolic BP readings should be within 5 mm Hg of each other. The final BP measurement must be recorded.

Weight

Weight will be taken on the same calibrated digital scale throughout the study, after voiding and while wearing only a gown and underwear (no street clothes, no shoes or socks). Subjects should step gently onto the scale, place both feet together in the center of the scale and stand straight with eyes directed ahead. **Subjects should be instructed to stand still and not sway. Measurement will be recorded after the weight has stabilized.**

Weight will be measured after voiding (to the nearest 0.2 kg). Measurements will be collected until 2 consecutive measurements do not differ by more than 0.2 kg from each other. The final weight measurement must be recorded. The same digital scale must be used throughout the study.

The SPONSOR will provide a scale and/or 10-kg certified weight to study sites that do not have them. **The scale must be calibrated according to the manufacturer's instructions at set-up and when it is transferred or moved. Additional calibration should be performed according to the manufacturer's instructions.**

Height

Standing height will be measured without shoes using a stadiometer.

Standing height will be assessed through maximum vertical stature for persons who can stand unassisted. Hair ornaments, barrettes, braids, jewelry, or cornrows should be moved or removed from the top of the head before the measurement is taken.

A fixed stadiometer with vertical backboard, fixed floorboard and movable headboard must be used. Subjects should stand with the heels of their feet against the vertical backboard with feet pointing outward at approximately a 60-degree angle. Body weight should be distributed evenly with both feet flat on the floor. The examiner should check several contact points with the vertical backboard, including heels, buttocks, shoulder blades, and the back of the head. This may be difficult for subjects with certain body shapes. However, the head should be in the Frankfort plane (an imaginary line from the ear canal to just below the lower orbit of the eye should be parallel to the floor). Subject should be looking straight ahead, and be asked to take a deep breath and stand tall. Once the subject is positioned, the headboard will be placed on top of the head, with sufficient pressure to compress the hair. The measurement is

recorded in cm, to the nearest mm. **Measurements will be collected until 3 consecutive measurements do not differ by more than 1.0 cm from each other. The final height measurement must be recorded.** Some patients may have physical conditions that may limit the ability to measure height accurately (e.g., kyphosis). In such cases, height should be measured to the best of the examiner's ability, a note should be made of the condition and measurements should be repeated in the same manner for the rest of study.

The stadiometer must be calibrated upon mounting the stadiometer to the wall, and according to the manufacturer's instructions thereafter.

12.8 List of Abbreviations

Abbreviation/Term	Definition
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
AMH	Anti-Müllerian hormone
ANCOVA	Analysis of covariance
ART	Assisted Reproductive Technology
ASaT	All-Subjects-as-Treated
ASPE	All-Subjects-Pharmacokinetically-Evaluable
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL	Clearance
COS	Controlled Ovarian Stimulation
CTP	Carboxy-terminal peptide
DNA	Deoxyribonucleic acid
E2	Estradiol
ECI	Event of Clinical Interest
eCRF	Electronic Case Report Form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ERC	Ethics Review Committee
FAS	Full Analysis Set
FBR	Future Biomedical Research
FSH	Follicle stimulating hormone
FSH-IR	Follicle stimulating hormone-immunoreactivity
GnRH	Gonadotropin releasing hormone
GnRHa	Gonadotropin releasing hormone agonist
hCG	Human chorionic gonadotropin, choriogonadotropin beta
hFSH	Human follicle stimulating hormone
HH	Hypogonadotropic hypogonadism
HIV	Human Immunodeficiency Virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IHH	Idiopathic hypogonadotropic hypogonadism (HH)
IRB	Institutional Review Board
IU	International unit
IVRS/IWRS	Interactive Voice/Web Response System
LH	Luteinizing hormone
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LSD	Lysergic acid diethylamide
MAR	Missing at Random
non-pf	Non-protein free
PCP	Phencyclidine

Abbreviation/Term	Definition
PD	Pharmacodynamic
PDLC	Predefined limits of changes
pf	Protein free
PK	Pharmacokinetic
PopPK	Population pharmacokinetics (PK)
RCF	relative centrifugal force
recFSH	Recombinant human follicle stimulating hormone (FSH)
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SHBG	Sex hormone-binding globulin
SOC	System Organ Class
sSAP	Supplemental Statistical Analysis Plan (SAP)
T	Testosterone
TC	Telephone contact
Total T	Total testosterone
ULN	Upper limit of normal
USS	Ultrasound scan
V	Volume of distribution
WBC	White blood cell

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	