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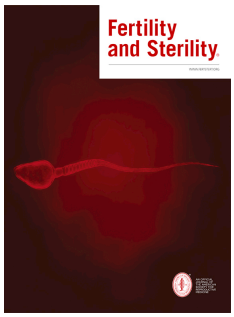


Endocrine profile of the kisspeptin receptor agonist MVT-602 in healthy premenopausal women with and without ovarian stimulation: Results from two randomized, placebo-controlled clinical trials

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**Original Article:**

# Endocrine profile of the kisspeptin receptor agonist MVT-602 in healthy premenopausal women with and without ovarian stimulation: Results from two randomized, placebo-controlled clinical trials

**Short title:**

MVT-602 in healthy women after minimal ovarian stimulation

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**Abstract**

Kisspeptin is an essential regulator of hypothalamic gonadotropin-releasing hormone release and is required for physiological ovulation. Native kisspeptin-54 (KP54) can induce oocyte maturation during *in vitro* fertilization treatment, including in women at high risk of ovarian hyperstimulation syndrome. MVT-602 is a potent kisspeptin receptor agonist with prospective utility to treat anovulatory disorders by triggering oocyte maturation and ovulation during medically assisted reproduction (MAR). Currently, the endocrine profile of MVT-602 during ovarian stimulation is unreported.

**Objective:**

To determine the endocrine profile of MVT-602 in the follicular phase of healthy premenopausal women (Phase-1 trial), and after minimal ovarian stimulation to more closely reflect the endocrine milieu encountered during MAR (Phase-2a trial).

**Design:**

Two randomized, placebo-controlled, parallel group, dose-finding trials.

**Setting:**

Clinical trials unit, Netherlands.

**Participants:**

Healthy women aged 18-35 years, either without (Phase-1; n=24), or with ovarian stimulation (Phase-2a; n=75).

**Interventions:**

Phase-1: Single subcutaneous dose of MVT-602 (0.3, 1.0, or 3.0 µg) or placebo, (n=6 per dose).

Phase-2a: Single subcutaneous dose of MVT-602 (0.1, 0.3, 1.0, or 3.0 µg; n=16-17 per dose), triptorelin 0.2 mg (n=5; active comparator), or placebo (n=5).

**Main Objectives and Outcome Measures:**

Phase-1: Safety/tolerability; pharmacokinetics; pharmacodynamics (LH and other reproductive hormones).

Phase-2a: Safety/tolerability; pharmacokinetics; pharmacodynamics (LH and other reproductive hormones); time to ovulation assessed by transvaginal ultrasound.

**Results:**

In both trials, MVT-602 was safe and well-tolerated across the entire dose-range. It was rapidly absorbed and eliminated, with a mean elimination half-life of 1.3-2.2 hours.

In the Phase-2a trial, LH concentrations increased dose-dependently; mean maximum change from baseline of 82.4 IU/L at 24.8 hours was observed after administration of 3µg MVT-602 and remained above 15 IU/L for 33 hours. Time to ovulation following drug administration was 3.3-3.9 days (MVT-602), 3.4 days (triptorelin), and 5.5 days (placebo). Ovulation occurred within 5 days of administration in 100% (3 µg), 88% (1µg), 82% (0.3µg), and 75% (0.1µg), of women after MVT-602, 100% after triptorelin, and 60% after placebo.

**Conclusions:**

MVT-602 induces LH concentrations of similar amplitude and duration as the physiological mid-cycle LH surge with potential utility for induction of oocyte maturation and ovulation during MAR.

**Trial Registrations**:

EUDRA-CT: 2017-003812-38, 2018-001379-20

## Introduction

Infertility (i.e., the inability to achieve conception within 1 year of regular unprotected intercourse) affects up to 1 in 6 couples (1). Assisted reproductive technologies (ART) such as *in vitro* fertilization (IVF) treatment can help such couples to conceive. Most IVF cycles employ the use of human chorionic gonadotropin (hCG), which binds to the LH receptor on the ovary to induce oocyte maturation, such that oocytes attain competence for fertilization (2). HCG has a supraphysiological action lasting 7-10 days, in contrast to the physiological LH surge which lasts approximately 48 hours during the physiological menstrual cycle. Hence, when hCG is used in IVF treatment to induce oocyte maturation there is an increased risk of the potentially life-threatening complication of ovarian hyperstimulation syndrome (OHSS) (3,4). OHSS is characterized by increased vascular permeability leading to third-spacing of fluid from the intravascular compartment, and ovarian enlargement (3,4).

Gonadotropin releasing hormone receptor agonists (GnRHa) are currently the only available alternative for induction of oocyte maturation. They have a shorter duration of action than hCG with the maximal rise in luteinizing hormone (LH) concentration occurring at 4-6 hours following administration (3). However, the use of GnRHa can exacerbate the luteal phase defect observed in IVF cycles hampering pregnancy rates, due to an insufficient duration to maintain survival of corpora lutea (2). In addition, the amplitude of LH-rise after GnRHa treatment is supraphysiological being 2- to 5-fold that observed during the physiological midcycle LH surge (3,5).

Kisspeptins are a family of hypothalamic neuropeptides encoded by the *KISS1* gene located on chromosome 1q32 (6). They act via the kisspeptin receptor (encoded by *KISS1R*) on hypothalamic gonadotropin releasing hormone (GnRH) neurons to stimulate the release of endogenous GnRH and in turn activate the downstream hypothalamic-pituitary-gonadal (HPG) axis (6). In a rodent model, kisspeptin signaling in the hypothalamus was shown to be essential for the occurrence of the mid-cycle LH surge and ovulation (7). Thus, kisspeptin is part of the physiological mechanism instigating ovulation, and consequently kisspeptin-based therapies could be used to restore ovulation in patients with anovulatory disorders or during medically assisted reproduction (MAR) (8).

Administration of native kisspeptin-54 (KP54) in the pre-ovulatory phase induces a rise in serum LH to an amplitude consistent with that found during the mid-cycle ovulatory LH surge, and commensurate with kisspeptin's potential use as a trigger of oocyte maturation during IVF treatment (9).

A single dose of native KP54 has been shown to trigger an LH rise sufficient to induce oocyte maturation (10) whilst avoiding OHSS even in women at high *a priori* risk of OHSS such as those with polycystic ovary syndrome (PCOS) (11). Furthermore, a second dose of KP54 at 10 hours following the first dose, extends the duration of LH elevation and further improves the reliability of induction of oocyte maturation, but importantly also without resulting in OHSS (12). Additionally, kisspeptin may reduce the release of vascular endothelial growth factor (VEGF) through a direct action via ovarian kisspeptin receptors, thereby further mitigating the risk of OHSS (13). Overall, a longer acting kisspeptin receptor agonist may represent a valuable novel agent for the induction of oocyte maturation and ovulation during ART.

Recently, the kisspeptin receptor agonist MVT-602 (previously called TAK-448) was developed through modification of kisspeptin-10 (KP10) to produce a nonapeptide with increased potency, stability, and water solubility (14). After single-dose administration of MVT-602, LH concentrations peaked at 6-12 hours in healthy men (15), and at 24 hours in healthy women (16), returning to baseline within 48-72 hours. This indicates that MVT-602 induces a longer duration of LH elevation as compared to KP54, which triggers peak LH concentrations at 4-6 hours in healthy men (16) and women (16) that return to baseline within 18 hours (16)(17). In addition, MVT-602 induced more potent signaling of kisspeptin receptor mediated accumulation of inositol monophosphate and a longer duration of GnRH neuron firing than KP54 (16).

Kisspeptin-based therapies are also proposed to have putative utility in the treatment of hypoactive sexual desire disorder (HSDD) in both men (18) and women (19), osteoporosis (20), and metabolic dysfunction-associated steatotic liver disease (MASLD) (21). With respect to the treatment of infertility, kisspeptins have the potential to restore hormonal secretion in functional hypogonadal disorders associated with anovulation (6), such as hyperprolactinemia (22,23), PCOS (24), and functional hypothalamic amenorrhea (FHA) (25). The endocrine profile of MVT-602 has recently been

investigated in patients with PCOS and FHA in the absence of ovarian stimulation (16). However, the response to kisspeptin is known to be influenced by the hormonal milieu at the time of administration (9). In the context of ovarian stimulation, estradiol concentrations exceed the threshold beyond which feedback on the HPG axis transitions from negative to positive (16). Thus, the same dose of KP54 induced an LH rise of ~5 fold greater amplitude in the context of ovarian stimulation (10) than in the unstimulated follicular phase (9).

Consequently, we have investigated the endocrine profile of MVT-602 in healthy premenopausal women not seeking fertility by conducting two randomized, double-blind, placebo-controlled trials both without (Phase-1 study), and with (Phase-2a study) application of a minimal stimulation protocol (MSP) mimicking the hormonal milieu encountered during MAR. Here, we present the results from these trials that inform the selection of appropriate doses for future clinical trials investigating the potential of MVT-602 to induce oocyte maturation and ovulation in women with anovulatory disorders.

## Material and methods

Both clinical trials were conducted at QPS Netherlands BV (Groningen, The Netherlands) (Phase-1: Nov 2017 - Mar 2018) and (Phase-2a: May 2018 - Jan 2019) in compliance with the principles outlined in the Declaration of Helsinki, ICH guideline for Good Clinical Practice (GCP) and current regulations in the Netherlands (Wet medisch-wetenschappelijk onderzoek met mensen, Nederland; WMO). They were approved by the local ethics committee (ethical approval numbers: NL63413.056,17; NL65711.056.18) and registered on EudraCT (registration numbers: EudraCT 2017-003812-38, first patient recruitment 07/11/2017, no weblink to registration available as phase-1 trials are not publicly available on EudraCT site; EudraCT 2018-001379-20, first recruitment 25/05/2018, EudraCT registration date 07/05/2018 https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-001379-20/NL). All participants signed an informed consent form prior to any study assessment.

*Study design of Phase-1 trial*

This was a randomized, single-blind, placebo-controlled, parallel-group, dose-ranging Phase-1 study to assess the safety and tolerability, as well as the pharmacokinetic (PK) and pharmacodynamic (PD) properties of MVT-602 in healthy premenopausal women during the follicular phase (**Supplemental Figure 1A**). Participants were randomized to receive a single, subcutaneous dose of MVT-602 (0.3, 1, or 3 μg) or matching placebo. Study drug was administered on study day 1 which occurred during the first six days of the participant's menstrual cycle (i.e., early follicular phase). Safety parameters, PK, and PD were assessed up to 72 hours after drug administration. Thereafter, participants were discharged from the clinical trial unit and returned for a follow-up visit at 7-10 days, and for a pregnancy test at 30-45 days, after drug administration.

*Study design of Phase-2a trial*

This was a randomized, double-blind, placebo- and active comparator-controlled, parallel-group, dose-ranging Phase-2a study to primarily assess the PD as well as the safety, tolerability, and PK of MVT-602 in healthy premenopausal women undergoing an MSP (**Supplemental Figure 1B**). As active

comparator, the GnRH receptor agonist triptorelin (0.2mg) was selected representing a well-characterized and widely used trigger of oocyte maturation.

During the screening phase, participants were synchronized to the start of their next menstrual cycle using combined hormonal contraception (CHC), e.g., Microgynon 30® or generic equivalent containing levonorgestrel (150 μg) and ethinylestradiol (30 μg). In the subsequent run-in phase, each participant's natural follicular development was assessed every other day using transvaginal ultrasound (TVUS). Once the dominant follicle was ≥ 10 mm in diameter, participants were admitted to the clinical trial unit, and TVUS was performed daily. Once a participant's dominant follicle was ≥ 13 mm in diameter, an initial dose of 50 IU follitropin alfa (i.e., recombinant FSH) was commenced followed by once-daily doses of 100 IU, with an optional further increase to 150 IU if the lead follicle growth was < 1mm per day. The GnRH receptor antagonist ganirelix was administered once-daily at a dose of 0.25 mg from the day after follitropin alfa was started to prevent premature ovulation. Follitropin alfa and ganirelix were both subcutaneously administered each morning prior to TVUS scans. Once the dominant follicle was ≥ 17 mm in diameter, daily administration of follitropin alfa and ganirelix was terminated and participants were randomized to receive one of 6 treatments in a 3:1:1 ratio for MVT-602 (0.1 μg, 0.3 μg, 1 μg, 3 μg) : placebo : triptorelin. The randomization aimed to achieve similar numbers in each MVT-602 dosing arm, and three-fold greater numbers in the each MVT-602 dosing arm (n=16-17 per dose) than in the active (triptorelin; n=5) and non-active (placebo; n=5) comparator arms. The randomization was list-based with a block size of 14. Within each block, the first 4 were assigned to any of the 4 MVT-602 doses, and the next 12 to any of the 4 MVT-602 doses, triptorelin, or placebo in a 2:1:1 ratio. Study drug administration was done in a double-blind manner by subcutaneous injection below the umbilicus in the evening at approximately 12 hours after administration of the last dose of follitropin alfa and ganirelix.

Assessments of safety, PK, and PD were repeatedly done up to 48 hours after study drug administration and thereafter once-daily prior to daily TVUS scans for determination of ovulation until participants were discharged. Participants received low-fat meals (breakfast, lunch, and dinner) for the first 48 hours of the Study Treatment Period until collection of the last blood sample for MVT-602 concentrations in

order to avoid the potential impact of lipemic plasma on bioanalytical assay sensitivity. Discharge from the clinic occurred when any one of the following pre-specified criteria was met: (i) 48 hours after a documented ovulation (i.e., follicular rupture on TVUS), (ii) estradiol concentration < 100 pmol/L, (iii) progesterone concentration > 10 nmol/L, or (iv) initiation of menses. Participants returned for two follow-up visits 5 and 13 days after discharge, respectively.

*Study objectives & endpoints*

In the Phase-1 trial, the primary objective was the safety and tolerability of MVT-602 based on adverse event, vital signs, laboratory, and electrocardiography data. Secondary pharmacokinetic (PK) and pharmacodynamic (PD) objectives were assessed based on plasma concentrations of MVT-602 and serum concentrations of luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, and progesterone, respectively. PD endpoints included maximal change in LH, FSH, estradiol, progesterone, and area under the LH concentration-time curve during the first 48 hours following administration.

In the Phase-2a trial, the primary PD study endpoint was the maximum change of serum LH concentrations from the pre-trigger value. Secondary PD endpoints included (i) changes from baseline in serum concentrations of other reproductive hormones (FSH, E2, and P), (ii) area under the LH concentration-time curve, and (iii) time to ovulation as determined by TVUS. PK as well as safety and tolerability were secondary objectives.

In both studies, PK parameters included area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$), area under the concentration-time curve from time zero to last quantifiable time point ($AUC_{0-t}$), maximum plasma concentration ($C_{max}$), time to maximum plasma concentration ($t_{max}$), terminal elimination half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution during the terminal phase (Vz/F).

*Study drugs*

Follitropin alfa (450 IU/0.75 mL; Merck Serono, Switzerland), ganirelix (0.25 mg; Organon for Merck Sharp and Dohme, Switzerland), and triptorelin (0.5 mg/mL; Ferring, Denmark) were purchased as pre-

filled syringes. MVT-602 (0.1 mg/mL) was manufactured according to GMP standards as solution in 2 mL vials (Takeda Pharmaceutical Company, Japan). A solution of glucose 5% for injection (Braun, Germany) was used as placebo.

*Inclusion criteria*

In both trials, healthy premenopausal women aged 18-35 years with BMI 18-30 $kg/m^2$ were enrolled based on a medical screening evaluation including medical history, physical and gynecological examinations, clinical laboratory, vital sign, and ECG data. In addition, participants were required to have regular menstrual cycle lengths of 21 to 35 days and to use non-hormonal contraception methods from screening until at least 90 days after study drug administration (except for intake of CHCs for cycle synchronization during the screening phase of the Phase-2a trial).

In the Phase-1 trial, additional inclusion criteria included use of non-hormonal contraception methods from screening until at least 90 days after study drug administration. In the Phase-2a trial, additional inclusion criteria included (i) a normal Papanicolaou test (i.e., pap smear) result and (ii) intact ovaries without clinically significant abnormalities.

*Exclusion criteria*

In both trials, main exclusion criteria included: (i) clinically significant diseases or other medical problems, (ii) concomitant use of investigational or other drugs prior dosing, (iii) positive pregnancy test, (iv) excessive alcohol or nicotine consumption, (v) history of infertility, ovarian hyperstimulation syndrome, or treatment of infertility within 3 months prior to screening.

In the Phase-2a trial, any contraindication for the use of CHC was also exclusionary. Additional criteria applied for the transition to the run-in phase (i.e., serum concentration of LH ≥12 IU/L or progesterone ≥5 nmol/L) and to the treatment-phase (i.e., dominant follicle diameter <13 mm on Day 15 of the run-in phase or <17 mm within 8 days after first follitropin alfa administration; serum LH concentration ≥10 IU/L at 12 hours after first ganirelix administration).

*Bioanalytics and PK/PD data analysis*

MVT-602 was quantified in plasma by a validated HPLC-MS/MS assay with a lower limit of quantification of 0.5 pg/mL (PPD Laboratories, Richmond, VA, US). Precision and accuracy were evaluated by quantification of quality control pools at three concentrations spanning the calibration range. Both were acceptable as determined by a percent coefficient of variation (CV%) below 15% and a mean percent difference from the theoretical concentration below 10% in both trials. LH, FSH, estradiol, and progesterone were quantified by commercially available Enzyme-linked Immunosorbent Assays (ELISA) at the clinical trial unit.

Plasma concentrations of MVT-602 were analyzed by non-compartmental methods using Phoenix WinNonlin version 6.3 (Pharsight Corporation, St. Louis, MO). Dose-proportionality of exposure parameters was assessed based on the point estimate β and its 95% confidence interval (CI) using a power model (26).

*Sample size estimation and statistical data analysis*

In the Phase-1 trial, no formal sample size estimation was conducted. However, the randomization ratio of 6:2 on active/placebo at each dose level is commonly applied in early-stage dose escalation safety studies.

In the Phase-2a trial, the sample size was estimated based on Multiple Comparison Procedure-Modelling (MCP-Mod) method for planning purposes. The sample size calculation was based on a maximum change in LH concentration ranging from 3 to 10 IU/L with a within-group standard deviation of about 7 IU/L, then 15 participants per MVT-602 treatment group would provide a reasonable power to detect a non-flat dose-response relationship. No formal dose-response analysis was planned *a priori*, however, reliable hormonal profiles have been determined in previous similar studies using similar / smaller sized groups (16).

## Results

*Disposition data*

In the Phase-1 trial, 24 participants were enrolled and equally randomized to receive a single, subcutaneous dose of MVT-602 (0.3, 1, or 3 μg) or matching placebo (n=6 per group). Each participant completed the trial per protocol.

In the Phase-2a trial, 75 participants were enrolled and randomized to receive MVT-602 at a single, subcutaneous dose of 0.1 μg (n=16), 0.3 μg (n=17), 1.0 μg (n=16), or 3.0 μg (n=16), matching placebo (n=5), or triptorelin 0.2mg (n=5). Two of these participants were prematurely discontinued for non-safety related reasons (i.e., failure to meet the discharge criteria due to persistent follicle; non-compliance with dietary restrictions). These had both been randomized to 1.0 μg MVT-602. All other study participants completed the trial per protocol.

*Demographic data*

In both trials, demographic data was balanced across treatment groups (**Supplemental Table 1**). The study populations comprised of 24 and 75 healthy premenopausal women in the Phase-1 and Phase-2a trial, respectively. In the Phase-1 trial, the study population had a mean age (SD) of 26.3 (3.1) years, height of 168.0 (7.2) cm, body weight of 67.5 (8.6) kg, and BMI of 23.8 (2.2) kg/m$^2$. There were 19 Caucasian/White, 3 Black/African American, and 2 participants of other ethnicities. Drug administration occurred on Day 2 to 4 of the participants' menstrual cycle except for one participant each with administration on Day 5 and 6, respectively.

In the Phase-2a trial, the study population had a mean age (SD) of 25.8 (4.4) years, height of 169.0 (6.1) cm, body weight of 65.7 (8.7) kg, and BMI of 23.0 (2.7) kg/m$^2$. There were 63 Caucasian/White, 10 Black/African American, 1 Asian, and 1 subject of other ethnicity.

*PK data*

The PK properties of MVT-602 were consistent across both clinical trials indicated by low inter-individual variability and similar geometric mean values of PK parameters at equivalent doses (**Table 1**). The $t_{max}$ ranged from 0.25 to 0.5 hours. MVT-602 was eliminated with a mean $t_{1/2}$ ranging from 1.3

to 2.2 hours and its mean CL/F was independent of dose, ranging from 18.7 to 22.0 L/hour. Mean Vz/F ranged from approximately 37.8 to 64.4 L (**Table 1**). Exposure was essentially dose-proportional indicated by a point estimate β for $AUC_{0-\infty}$ (95% CI) of 1.03 (0.92-1.14) and 0.98 (0.93-1.04) in the Phase-1 and Phase-2a trial, respectively. There was no correlation between exposure parameters (i.e., $C_{max}$ and $AUC_{0-\infty}$) and bodyweight (data not shown). Overall, exposure and other PK parameters were similar in both the Phase 1 and Phase 2a clinical trials.

*Safety and tolerability data*

The overall incidence of Treatment Emergent Adverse Events (TEAEs) after administration of MVT-602 was similar to placebo and without indication of dose-dependency (**Supplemental Table 2**). Headache was the most common TEAE in both trials followed by dizziness and abdominal symptoms such as distension, discomfort, or pain. There were no SAEs reported and all TEAEs resolved without need for treatment. Most TEAS were Grade 1 (i.e., mild) except for one participant in the Phase-1 trial with a Grade 2 (i.e., moderate) TEAE of orthostatic presyncope and four participants in the Phase-2a trial with Grade 2 TEAEs of orthostatic hypotension (0.1 µg MVT-602), lower abdominal pain (0.2 mg triptorelin), increased hepatic enzymes alone (0.3 µg MVT-602), or in combination with influenza-like illness (1.0 µg MVT-602). There were no clinically significant post-dose abnormalities of vital sign or ECG data except for the two participants with TEAEs of orthostatic dysregulation (i.e., presyncope, hypotension).

In the Phase-1 trial, no clinically significant abnormalities of laboratory data were determined. However, there were two participants in the Phase-2a trial with elevated serum concentrations of hepatic enzymes after administration of 0.3 and 1.0 µg MVT-602, respectively. Maximum elevations of ALT and AST were approximately 3 to 4-fold above the upper limit of the reference range, while bilirubin elevations were <2-fold above the upper limit of the reference range). These elevations resolved without need for treatment, did not qualify as Hy's law cases, and occurred approximately 2 to 4 weeks after administration of MVT-602, i.e., several days after its complete elimination. One of these two participants had also been diagnosed with influenza-like illness, which may have contributed to the increased concentrations of hepatic enzymes.

*Effect of MVT-602 on LH concentrations*

In both trials, peak LH concentrations (i.e., $E_{max}$) increased compared to placebo at each dose of MVT-602 (**Table 2**). At equivalent doses, peak LH concentrations were approximately 2- to 6-fold higher in the Phase-2a with MSP than in the Phase-1 trial without MSP (**Table 2**).

The LH concentration-time course was overall comparable in both trials with peak elevations between 8 and 24 hours and return to baseline within 48 to 72 hours after administration of MVT-602 (**Figure 1A/B**). In the Phase-2a trial, LH concentrations reached a maximum of 82.4 IU/L at 24.8 hours after 3.0 µg of MVT-602 (**Table 2**). In the Phase-2a trial, triptorelin showed greater peak LH concentrations (184 IU/L) than MVT-602 and a more rapid time to peak LH concentrations (i.e., $TE_{max0\text{-}48h}$ 6.8 hours) (**Table 2 and Figure 1B**).

In the Phase-1 trial, there was no dose-response relationship determined as indicated by determination of the largest peak LH elevations at the intermediate dose of 1.0 µg (**Table 2**). However, in the Phase-2a trial, peak LH concentrations and the area-under-the LH concentration/time curve were lowest at the minimum dose of 0.1 µg (54.8 IU/L), and highest at the highest dose tested of 3.0 µg MVT-602 (82.4 IU/L), respectively (**Table 2**). In addition, the onset time (i.e., time to LH concentration > 15 IU/L) was shortest (10.3 hours) and the duration of LH concentrations > 15 IU/L was longest (33 hours) at the highest tested dose of 3.0 µg MVT-602 (**Table 2**).

*Effect of MVT-602 on FSH concentrations*

In the phase 2 study, at each dose of MVT-602, peak FSH concentrations were higher than placebo without clear dose-response (**Table 2**). Overall, the concentration/time profiles were comparable in both trials with peak concentrations occurring within 24 hours after dosing followed by a return to baseline within the following 24 hours (**Figure 1A/B**). In the Phase-2a trial, peak elevations of FSH were greater and the onset time shorter after administration of triptorelin compared to each dose of MVT-602 (**Table 2 and Figure 1B**).

*Estradiol*

In the Phase-1 trial, estradiol concentrations following administration of MVT-602 were greater compared to placebo in correspondence to the increased gonadotropin concentrations with peak elevations reached approximately 24 hours after dosing. In the phase 2-a trial, estradiol increases were similar after all interventions.

*Progesterone and effects on ovulation in Phase 2-a trial*

The maximum change in progesterone from baseline was 31.2 to 34.5 nmol/L after MVT-602, 34.8 nmol/L after placebo, and 20.0 nmol/L after triptorelin (**Table 2**). Most participants reached progesterone concentrations ≥10 nmol/L, whereas peak progesterone concentration ≥15.9 nmol/L were reached by 75.0-93.8% who received MVT-602, 80% who received triptorelin, and 60% who received placebo (**Table 3**). Only 20% who received triptorelin reached a peak progesterone concentration ≥30 nmol/L as compared to 50.0-68.8 % after MVT-602 and 60.0 % after placebo (**Table 3**).

In those participants who ovulated, the mean time to ovulation (i) was 3.3-4.8 days after MVT-602, 3.4 days after triptorelin, and 5.5 days after placebo (**Table 3**). Ovulation occurred in 100% (3 µg), 88% (1µg), 82% (0.3µg), and 75% (0.1µg), of women within 5 days of receiving MVT-602, as compared to 100% after triptorelin, and 60% after placebo (**Table 3**).

## Discussion

Herein, we report the results of two randomized, placebo-controlled clinical trials that present the endocrine profile of the novel kisspeptin receptor agonist MVT-602, both in the unstimulated follicular phase of healthy women (Phase-1), and after an MSP designed to artificially mimic the endocrine milieu encountered during ovarian stimulation (Phase-2a). The Phase-2a study is the first to determine the endocrine profile of MVT-602 in women who have undergone an MSP, i.e., in a setting relevant to IVF treatment, and demonstrates an LH profile that more closely resembles the physiological mid-cycle LH surge both in terms of amplitude and duration than currently available trigger agents.

In both trials, MVT-602 was safe and well-tolerated across the entire dose range indicated by a similar incidence of TEAEs after administration of MVT-602 and placebo that occurred without indication of dose-dependency. Pharmacokinetic properties of MVT-602 were consistent across both trials. MVT-602 was rapidly taken up into the circulation after subcutaneous administration (i.e., $t_{max}$ 0.25 to 0.5 h) in a dose-proportional manner. Its apparent volume of distribution was only slightly in excess of total body water (i.e., approximately 40 to 60 L) suggesting limited tissue distribution. Elimination kinetics were similar across trials and doses, with a $t_{1/2}$ ranging from 1.3 to 2.2 hours and a mean Cl/F ranging from 18.7 to 22.0 L/hr.

In both trials, PD effects of MVT-602 were determined based on concentration-time profiles of reproductive hormones. During the unstimulated follicular phase in the Phase-1 trial, LH concentrations were highest after the intermediate dose of MVT-602 (1.0 µg). This was in part due to an outlier participant with an LH concentration of 21.1 U/L at baseline and an $E_{max}$ of 96.5 U/L. Additionally, the LH concentration at baseline was also highest at the 1.0 µg, and there was an association between baseline LH concentrations and $E_{max}$ as has previously been reported for native KP54 (3).

The duration of LH elevation was extended after MVT-602 compared to native KP54 despite similar elimination half-lives for both of 1.7-2.0 hours after subcutaneous administration (16). Thus, it is believed that the longer pharmacodynamic action of MVT-602 is due to differential activation of the kisspeptin receptor. MVT-602 is 500-fold more potent than KP54 at the kisspeptin receptor, and

correspondingly ~300-fold lower doses produce a similar amplitude of LH (16). Indeed, MVT-602 induced an at least two-fold longer duration of GnRH neuronal firing when directly applied to murine GnRH neurons *in vitro* in comparison to KP54 (16). It is notable that the amplitudes of the LH rise after MVT-602 and KP54 were similar, but MVT-602 showed a longer duration of effect (16). Indeed, in the present study, MVT-602 induced a rise in LH that was similar to the triphasic physiological midcycle LH surge, which typically has an average amplitude of 56.5 IU/L (range 25-144 IU/L) and lasts for ~48 hours (27).

The response to kisspeptins is amplified when the baseline estradiol concentration is naturally increased during the preovulatory phase of the natural menstrual cycle (9), is artificially increased with estradiol patches (16), or after ovarian stimulation (10). Thus, to determine the LH profile of MVT-602 more accurately in a setting that is more analogous to that found during IVF treatment, we also examined the profile after application of an MSP. We observed that the amplitude of LH rise ($E_{max}$) was increased by 2- to 6-fold after MSP (Phase-2a) in comparison to equivalent doses in the unstimulated follicular phase (Phase-1). However, baseline estradiol concentrations may not have been above the threshold for a switch to positive estradiol feedback in all patients prior to study drug administration. Thus, it is possible that a rise in estradiol after MVT-602 in such participants could have triggered a secondary rise in gonadotropins. Notably, whilst LH concentrations were markedly augmented after the same doses of MVT-602 in the Phase-2a trial compared to the Phase-1 trial (LH $E_{max}$ Phase-1: 14-30 IU/L vs Phase-2a: 70-82 IU/L), FSH responses were more similar (FSH $E_{max}$ Phase-1: 6-9 IU/L vs Phase-2a: 9-16 IU/L). The rise in estradiol after study drug administration could also explain the secondary rise of gonadotropins after triptorelin, which is not usually observed during full ovarian stimulation (28). More usually, in women who have undergone ovarian stimulation with multi-follicular growth, GnRHa's induce a single rise in LH with a peak at 4-6 hours which subsequently falls over 12-24 hours (28). Thus, the duration of LH concentration >15 IU/L after triptorelin could be over-estimated in the current Phase-2a trial.

Notably, GnRHa's induced a greater initial rise in serum progesterone immediately post-triggering for every oocyte collected than either hCG or KP54 (3). In the present Phase-2a study, the amplitude of

luteal phase progesterone rise (i.e., $\Delta E_{max}$) after MVT-602 (31.2-34.5 nmol/L) was more similar to that of the spontaneous ovulatory progesterone rises observed after placebo (34.8 nmol/L) than after triptorelin (20.0 nmol/L). In addition, whereas 47-63% of those who received MVT-602 had a progesterone rise of at least 30 nmol/L, this was the case in 40% after placebo, and only 20% after triptorelin. There have been several recent reports suggesting that insufficient progesterone concentrations on the day of transfer, typically less than this threshold of ~30 nmol/L (8.8-10.6 ng/ml) (29–31), could be associated with impaired implantation, usually in the context of frozen embryo transfer. Although a threshold of 30 nmol/L (10 ng/mL) has commonly been used in the past to confirm ovulation in guidelines, a lower threshold of >5 ng/ml (15.9 nmol/L) has a specificity of 98.4% (95% CI 96.0-99.5%), with a sensitivity of 89.6% (95% CI 85.2-92.9%) for the confirmation of ovulation (32). In addition to their predominant role at hypothalamic GnRH neurons, kisspeptin receptors are also present in the ovary, where they could theoretically play a role in augmenting oocyte maturation at lower LH concentrations (2,3,33–35), and could be able to act directly at corpora lutea to enhance luteal progesterone production (36). Furthermore, kisspeptin receptors are also present in the endometrium where they could have a role in regulating physiological implantation (37–40). Thus, it would be of interest to ascertain whether any differences in luteal progesterone dynamics are observed in future studies in full IVF cycles and whether these factors impact on clinical outcomes after fresh embryo transfer.

Limitations of this study include that full ovarian stimulation was not performed in order to avoid the need for retrieval of multiple oocytes in women not seeking fertility treatment. Moreover, the present trials were deemed necessary to establish the safety and likely efficacy to mature oocytes based on the endocrine profile before progression to a full IVF cycle assessing clinical outcomes.

In summary, MVT-602 can induce a prolonged duration of gonadotropin secretion and based on the endocrine response induced in women with anovulatory disorders such as FHA (16), has potential utility to treat reproductive disorders. The data presented here suggests that MVT-602 can induce an LH-rise in the context of minimal ovarian stimulation that has a profile that more closely mimics that of the endogenous LH surge, both in terms of amplitude and duration, than currently available triggers of

445 oocyte maturation. Further clinical trials are now indicated to assess whether this translates into
446 improved clinical outcomes during IVF treatment in a direct comparison to currently used agents.

## Author contributions

All authors contributed to drafting and revising the article and provided final approval of the version to be published. Here are the most important contributions of each author: AA and MU wrote the manuscript, analyzed and interpreted the data; CVP was the principal investigator of both clinical studies and acquired the data; AA, ME, LB, JCAF, EM, and WSD designed the study; RW and TYL analyzed the data; TYL was responsible for biochemical analyses. WSD takes the final responsibility for this article.

## Conflict of interest statement

AA and WSD have undertaken consultancy work for Myovant Sciences Ltd.

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**Figure 1a**

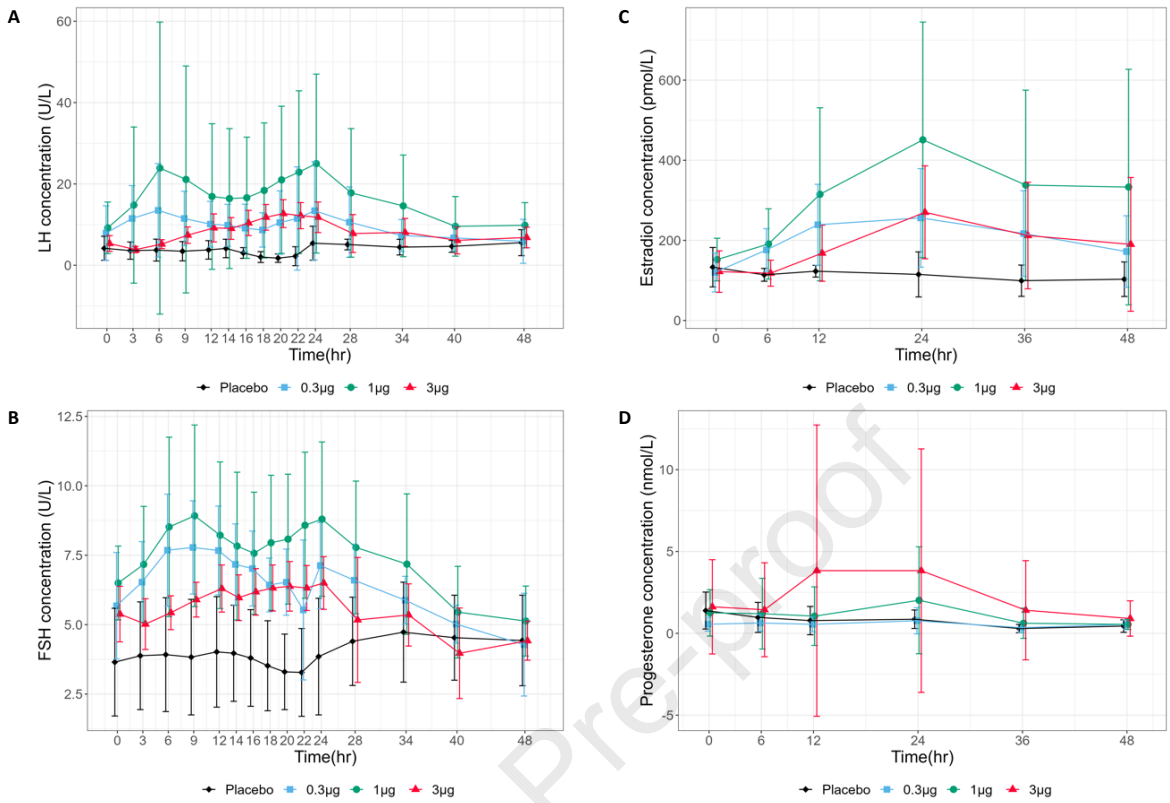


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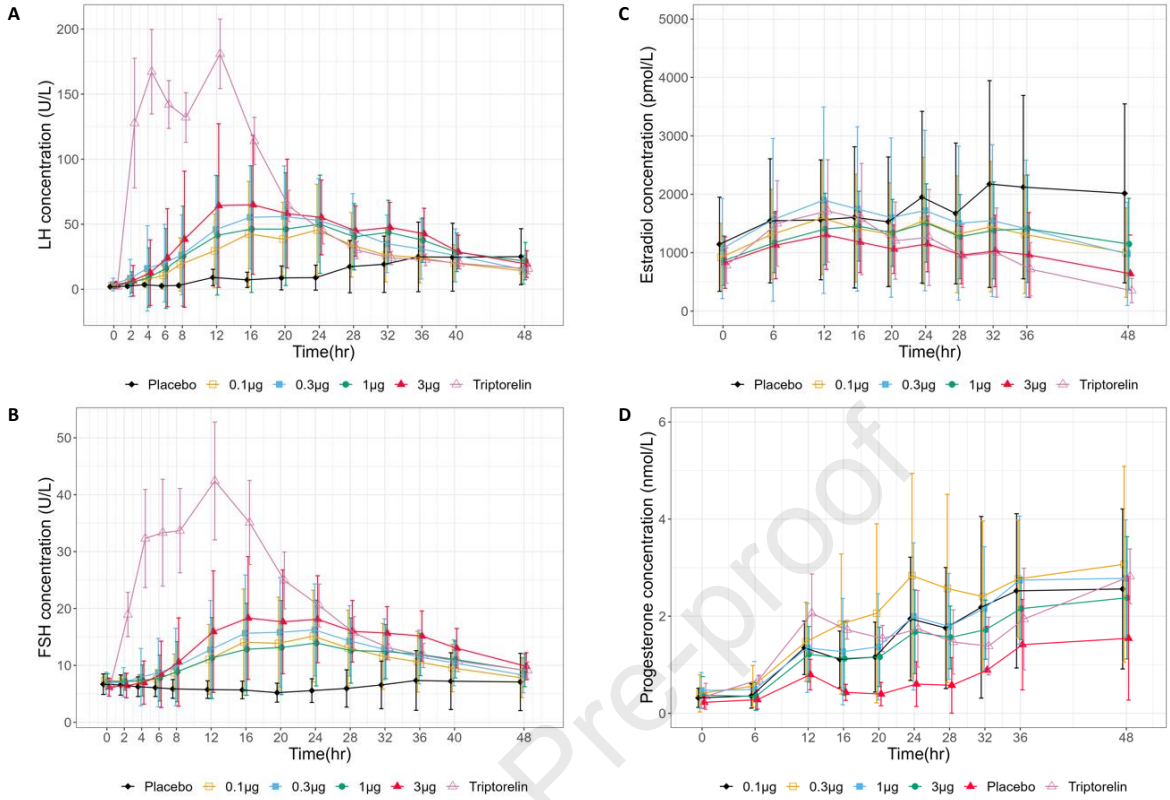
**Figure 1b**

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**Supplemental Figure 1**

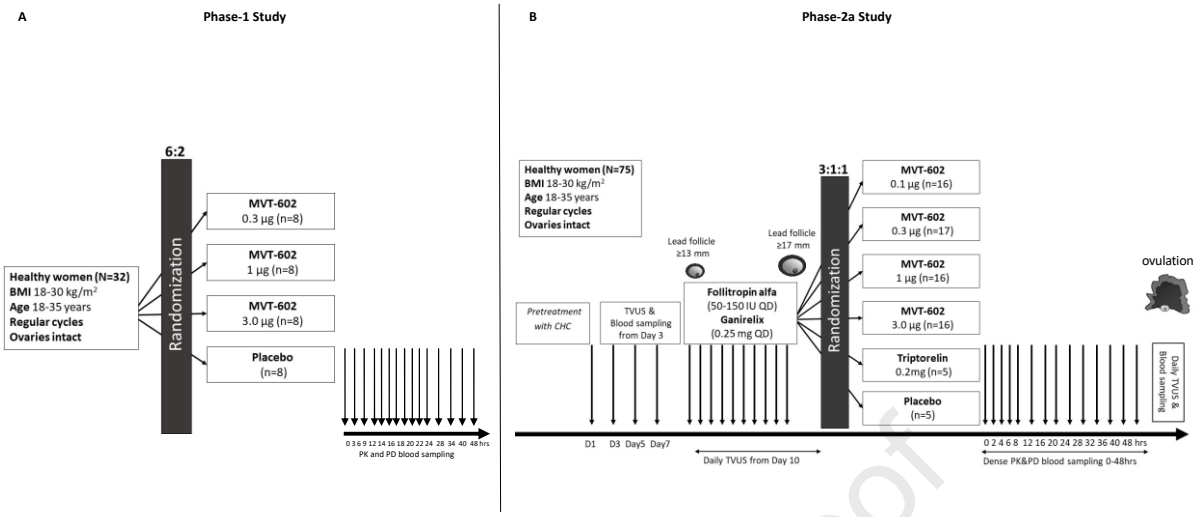


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**Figure Legends**

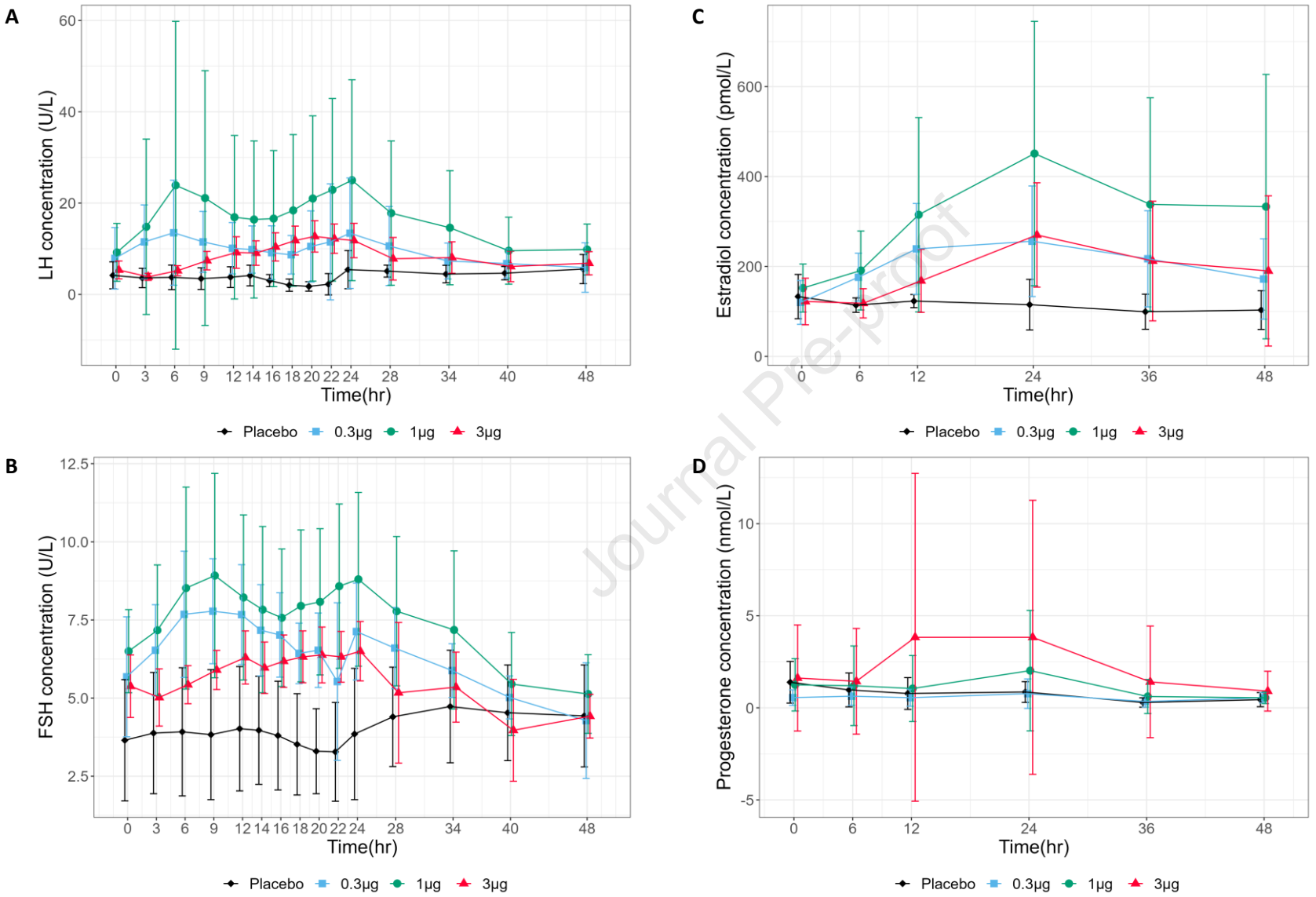
**Figure 1 A/B: Serum concentration/time profiles of LH, FSH, estradiol, and progesterone in the Phase-1 (A) and Phase-2a study (B)**

Mean serum concentrations of LH (IU/L), FSH (IU/L), estradiol (pmol/L), and progesterone (nmol/L) over time are displayed by treatment. Error bars represent the standard deviation.

**Supplemental Figure 1 A/B: Protocol diagram for the Phase-1 and Phase-2a study**

CHC: Combined hormonal contraceptive; TVUS: Transvaginal ultrasound; QD: Once-daily

**Figure 1a**



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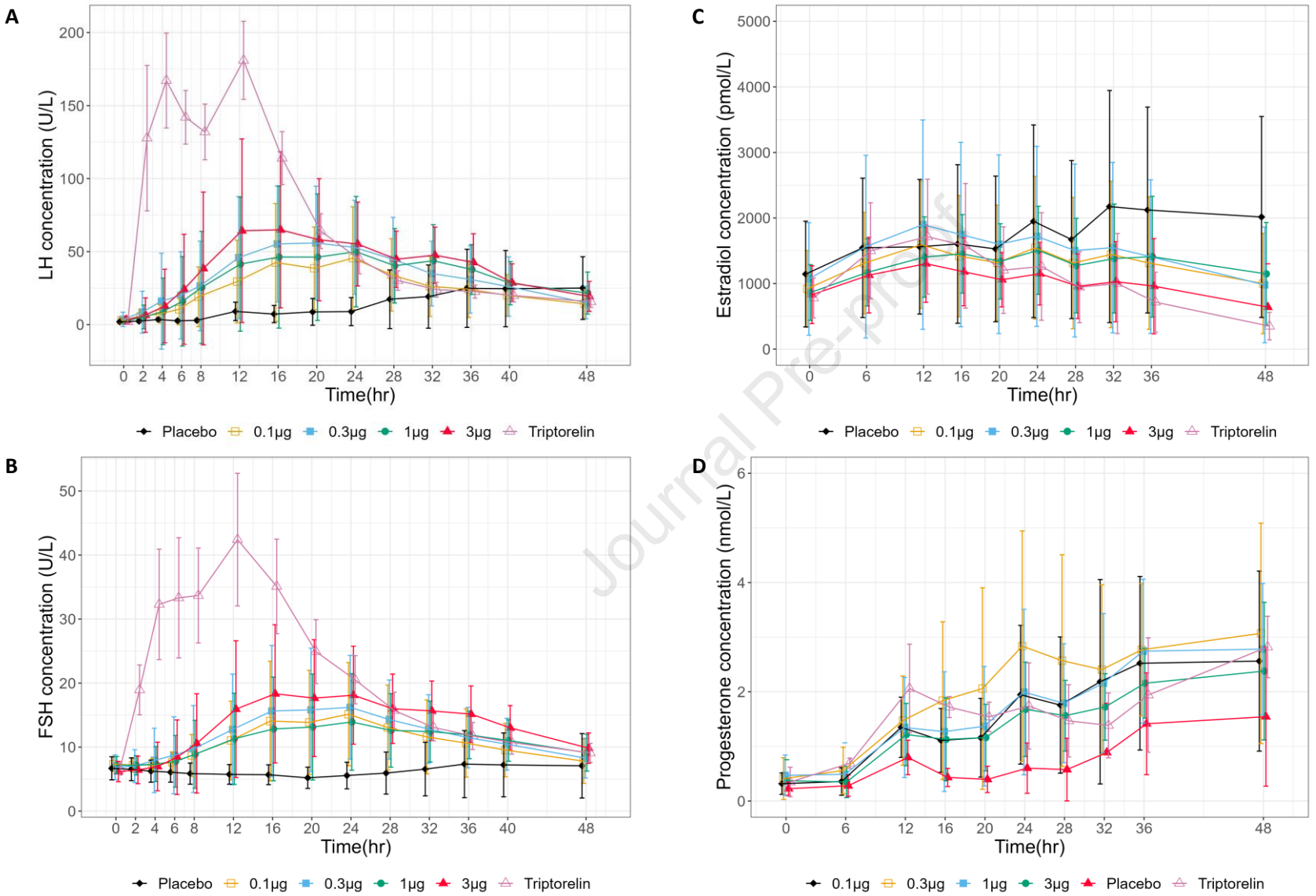

**Supplemental Figure 1**