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information, including indication of PTB. Pregnancies with oocyte donation, gestational carrier, multiple gestation, and delivery prior to 20 weeks gestation were excluded. Among PCOS and non-PCOS patients, serum AMH values were compared in women who delivered at full term to those who delivered pre-term. Total daily exposure AUCs, C max, and trough levels were calculated for each subject for each administered sequentially with 36- to 48-hr wash-out intervals. Frequent blood sampling occurred for 36 feeding: D - 2 hrs before breakfast and 2 hrs after dinner, E - 1 hr before and 4 hrs after dinner: A - Ovarest 40 mg BID; B - Ovarest 60 mg BID; C - tablet strengths and 2 dosing regimens of Ovarest following an overnight fast in 22 healthy female volunteers in a Clinical Pharmacology Unit. Three regimens were administered under fasting conditions, 4 hrs before breakfast and 4 hrs after dinner: A - Ovarest 40 mg BID; B - Ovarest 60 mg BID; C - Ovarest 120mg QD. Ovarest 60 mg BID was also administered closer to feeding: D - 2 hrs before breakfast and 2 hrs after dinner, E - 1 hr before breakfast and 1 hr after dinner. Frequent blood sampling occurred for 36 hrs after dosing. Total study duration was 10 days with treatments ABCDE administered sequentially with 36- to 48-hr wash-out intervals. RESULTS: 22 subjects were enrolled and dosed, and 21 subjects completed the study; 1 subject discontinued after her fourth treatment. AUCs, C max, and trough levels were calculated for each subject for each treatment period. Total daily exposure (AUC0-24H) following fasting 60 mg BID (Treatment B) was 1.4 times that of fasting 40 mg BID (A), indicating approximate dose proportionality within this range. Total daily exposure following 60 mg BID with 4-hr dose-feeding interval (B) was 1.7 and 2.0 times greater than when administered with a 2-hr (D) and 1-hr interval (E), respectively, reflecting significant time-dependent food effects on PK metrics. Following a maximal dose of 120 mg QD (C), the 24-hr mean C max was 230 ng/mL, occurring at a median T max of 3.0 hrs, and the mean AUC0-24H was 535 ng*hr/mL, both well exceeding corresponding values measured on day 1 in our previous studies with Lupron Depot 3.75 mg im (C max 17.5 ng/mL, AUC 82 ng*hr/mL) or Lupron 1 mg sc (C max 59.4 ng/mL, AUC 163 ng*hr/mL). Frequently reported Treatment Emergent Adverse Events (TEAEs) across all treatment groups were headache (14-27%), dizziness (7-13%) and nausea (0-13%). Study drug was generally well tolerated, with 65 of 76 (85.5%) AEs considered mild, and no severe or serious AEs. Safety issues were observed for clinical lab results or changes in vital signs. CONCLUSIONS: Results confirm oral delivery of leuprolide levels expected to be within established therapeutic ranges. Leuprolide oral tablets in women of daily doses from 80 to 120 mg appear to be safe, well tolerated, and roughly dose proportional. Compared to proprietary Enteris data and published historical data, Ovarest delivered more drug than highly effective injectable leuprolide formulations. IMPACT STATEMENT: PK and safety results support further development of Ovarest as a differentiated alternative to current dosage forms of the GnRH agonist leuprolide eliminating the need for potentially painful injections. SUPPORT: This study was funded in its entirety by Enteris BioPharma Inc.

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PHARMACOKINETIC (PK) STUDY OF ORAL LEU- PROLIDE DELIVERY WITH OVAREST® ACHIEVES DRUG LEVELS EXCEEDING THOSE OF APPROVED INJECTABLE PRODUCTS. Gary A. Shangold, M.D., Arkady Rubin, Ph.D. Thomas Daggis, M.B.A. John Vrettos, Ph.D., Andrejs Rasums, BS, Angelo Consolvo, BS, Nicola Skreet, BS, MS, Sreeja Polpully Varlam, MS, Kalpana Ramakrishnan, Ph.D., Paul Shields, Ph.D 1Enteris BioPharma Inc, Boonton, NJ; 2ARSTAT Inc; 3University of California San Francisco, San Francisco, CA; 4Glow Inc, San Francisco, CA; 5University of California San Francisco, San Francisco, CA

OBJECTIVE: To assess the PK profile of our oral dosage form of leuprolide (Ovarest®) as a bridge to historical data for highly effective injectable leuprolide products. Specific goals: evaluate PK profiles and dose-proportionality of single doses from 40 - 120 mg, evaluate dose-proportionality of daily dosing regimens from 80 - 120 mg/day, compare QD to BID dosing, and further quantify known food effects of Ovarest. MATERIALS AND METHODS: Cross-sectional, nationwide study of reproductive age females users of the menstrual tracker app Glow. All participants were aged 18-55 and lived in the United States. From 3/02/22 to 4/7/22, participants who had at least 6 months of continuous app use prior to and after April 2021 (defined as logging of menstrual cycle data) were invited to participate in a short questionnaire asking about vaccine status, COVID infection status, and symptoms around the time of vaccination and/or infection. This study was approved by the University of California IRB. RESULTS: Out of 218,977 eligible individuals, 11,591 completed the study. 10,922 (representing 269,278 cycles) were included. Some patients were excluded due to not having 6 cycles of data before or after the vaccine or infection and for reporting hormonal birth control use. 75% received two doses of the vaccine (60% Pfizer-BioNTech, 34% Moderna, and 7% J&J), 5% received one dose (63% Pfizer-BioNTech, 37% Moderna, and 1% J&J), and 20% were unvaccinated. There was no change in menstrual cycle length after one or two doses of the vaccine (-0.01 day, 95% CI -0.05 to 0.03 and -0.01 days, 95% CI 0.06 to 0.03, respectively), as was the case in unvaccinated patients (0.05 days, 95% CI -0.02 to 0.12). While participants who reported a COVID infection were noted to have a shorter first cycle after infection (-0.07 days, 95% CI -0.11 to -0.02), this difference was not clinically significant. There were no differences in months 2-6 after infection, or in average cycle length in the 6 months after infection. Of note, whether a patient was symptomatic or asymptomatic with vaccination or infection did not meaningfully impact the menstrual cycle length. Safety issues were observed for clinical lab results or changes in vital signs. CONCLUSIONS: The COVID-19 vaccine and COVID-19 infection do not result in meaningful menstrual cycle changes compared to unvaccinated or uninfected individuals, respectively. IMPACT STATEMENT: This is the largest study to date to describe that the COVID-19 vaccine and COVID-19 infection do not appear to result in menstrual cycle changes and adds to the body of literature supporting the safety of the COVID-19 vaccine.