CLINICAL SUMMARY

Title	A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in *in vitro* fertilization
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Objective

To determine if oral dydrogesterone (Duphaston®) 30 mg daily (10 mg three times daily [TID]) is non-inferior to micronized vaginal progesterone (MVP) 600 mg daily (200 mg TID) (Utrogestan®) for luteal support in in vitro fertilization (IVF), as assessed by the presence of fetal heartbeats determined by transvaginal ultrasound at 12 weeks of gestation?

Study Design

- Lotus I was an international Phase III randomized controlled trial.
- It was performed across 38 sites in Austria, Belgium, Germany, Finland, Israel, Russia and Spain.
- Subjects were premenopausal with a documented history of infertility who were planning to undergo IVF.
- A centralized electronic system was used for randomization, and the study investigators, sponsor's study team, and subjects remained blinded throughout the study.
- It was a double-blind, double dummy design which meant patients were randomized to receive either oral dydrogesterone 10mg with placebo intravaginal capsules three times daily (TID) [Group 1] or micronized vaginal progesterone 200mg capsules with oral placebo tablets TID [Group 2].

Results

- In the full analysis set (FAS), 497 and 477 subjects in the oral dydrogesterone and MVP groups, respectively, had an embryo transfer.
- Non-inferiority of oral dydrogesterone was demonstrated, with pregnancy rates at 12 weeks of gestation of 37.6% and 33.1% in the oral dydrogesterone and MVP treatment groups, respectively (FAS, difference 4.7%; 95% CI: −1.2-10.6%).
- Live birth rates of 34.6% (172 mothers with 213 newborns) and 29.8% (142 mothers with 158 newborns) were obtained in the dydrogesterone and MVP groups, respectively (difference 4.9%; 95% CI: −0.8–10.7%).
- Oral dydrogesterone was well tolerated and had a similar safety profile to MVP.

Conclusions

- Lotus I was a robust study which provides appropriate evidence that dydrogesterone is as effective as the current standard of care in women undergoing IVF.
- Taking into account the safety data collected in this study, dydrogesterone displayed a favorable benefit/risk profile.
- The results of this study, in addition to those of previous studies indicating that oral administration is preferred over intravaginal application, have the potential to induce a paradigm shift for the treatment of the estimated 1.5 million women worldwide undergoing IVF each year who could benefit from this oral form of luteal phase support.