A Phase III randomized controlled trial of oral dydrogesterone versus intravaginal progesterone gel for luteal phase support in in vitro fertilization (Lotus II): results from the Chinese mainland subpopulation

Dong-Zi Yang, Georg Griesinger, Wei Wang, Fei Gong, Xiaoyan Liang, Hanwang Zhang, Yingpu Sun, Elke Kahler, Claire Pexman-Fieth, Jan I. Olofsson, Herman Tournaire and Zi-Jiang Chen

Introduction

Infertility rates in China have increased considerably over the last 30 years, with a recent epidemiological study estimating that 15.5% of women of reproductive age experience infertility problems [1]. This increase has been attributed to a shift in various social and environmental conditions that have taken place in China [1–3]. In line with the rise in infertility, demand for in vitro fertilization/assisted reproductive technology (IVF/ART) has increased steadily, with the number of IVF cycles now estimated to be greater than 700,000 annually in China [3]. To cope with this increasing demand, the number of IVF centers has increased each year since 1995 [3], and the number of ART organizations is now thought to exceed 430 [4].

Ovarian stimulation, using exogenous gonadotropins, is undertaken prior to assisted fertilization to induce the development of multiple dominant follicles and to obtain mature oocytes [5,6]. During this process, gonadotrophin-releasing hormone analogs are given concurrently with gonadotrophins to prevent premature ovulation or luteinization [5,6]. However, due to inhibition of pituitary luteinizing hormone secretion, ovarian stimulation often negatively affects the luteal phase, and may result in impaired endometrial receptivity and reduced pregnancy rates [6]. Luteal phase support using progestogens is therefore recommended to increase the likelihood of embryo implantation and improve pregnancy rates [7,8].

Progesterone used for luteal phase support (derived from several species of Dioscorea, widely known as the yam plant [9]) can be formulated for intramuscular, oral, subcutaneous, or vaginal administration [10–13]. No progesterone formulation has, as yet, been shown to be superior in terms of efficacy [8,14,15], while tolerability and safety profiles vary according to the route of administration [10]. For example, although easier for the patient to use, orally administered micronized progesterone is rapidly metabolized by the liver and is associated with drowsiness, flushing, and nausea [10]. On the other hand, intramuscular progesterone administration can result in pain, inflammation, and sterile abscess formation [10,16]. Delivery of micronized progesterone via the vaginal route is most commonly used by

KEYWORDS

Chinese mainland; dydrogesterone; luteal phase support; micronized vaginal progesterone gel; IVF; randomized clinical trial

CONTACT Claire Pexman-Fieth claire.pexman-fieth@abbott.com

© 2019 Abbott. Published by Informa UK Limited, trading as Taylor & Francis Group

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
An alternative treatment option to micronized vaginal progesterone (MVP) is oral dydrogesterone [17], which has the benefit of being a more selective progesterone agonist than progesterone, along with having higher oral bioavailability [15,18]. Several small studies and two meta-analyses have indicated that oral dydrogesterone is at least as efficacious as MVP (given either as vaginal capsules or as an 8% gel) for luteal phase support in women undergoing IVF treatment [8,19–24]. In addition, two recently conducted multinational, Phase III, randomized, controlled studies (Lotus I and Lotus II) compared the efficacy and safety of oral dydrogesterone versus those of MVP capsules or gel for luteal phase support in women undergoing fresh-cycle IVF [25,26]. Both studies achieved their primary objective, demonstrating non-inferiority of oral dydrogesterone to MVP capsules and gel in terms of pregnancy rates at 12 weeks of gestation; furthermore, safety and tolerability profiles were comparable between the oral dydrogesterone and MVP treatment groups [25,26].

As an extension to Lotus I, a prespecified subgroup analysis was conducted on the large Russian subpopulation from the study, which represented approximately 20% of the overall population [27]. In the Russian subpopulation, oral dydrogesterone had a similar efficacy to that of MVP capsules for the primary endpoint of fetal heartbeats at 12 weeks of gestation [27], which was consistent with findings from the overall population of Lotus I [25].

Similarly, in this study, a prespecified subgroup analysis was conducted on the large Chinese mainland subpopulation from Lotus II, which represented 23.1% of the overall study population. The aims of this subgroup analysis were to compare the efficacy and safety of oral dydrogesterone to those of 8% MVP gel for luteal phase support in IVF in the Chinese mainland subpopulation, and to compare these results with those of the overall Lotus II population.

Materials and methods

The methods and findings from the overall Lotus II study have previously been reported [26]. In brief, Lotus II was a randomized, open-label, parallel-group, Phase III, non-inferiority study conducted at 37 sites in 10 countries/regions (Australia, Belgium, China [mainland], Germany, Hong Kong, India, Russia, Singapore, Thailand, and Ukraine). Six of the sites from which data were collected were located in mainland China, where the study was conducted from August 17, 2015 until April 27, 2017. Key inclusion criteria for Lotus II were women >18 to ≤42 years of age with a documented history of infertility who were planning to undergo IVF with or without intracytoplasmic sperm injection (ICSI); body mass index (BMI) ≥18 to ≤30 kg/m²; early follicular phase (Days 2–4); follicle-stimulating hormone (FSH) ≤15 IU/L and estradiol within normal clinical limits at screening; luteinizing hormone, prolactin, testosterone, and thyroid-stimulating hormone (TSH) within normal clinical limits or not considered clinically significant within 6 months prior to or at screening; normal transvaginal ultrasound at screening (or within 14 days prior to screening). Patients were excluded from the study if they had evidence of head, ear, eye, nose, throat, cardiovascular, respiratory, urogenital, gastrointestinal/hepatic, hematologic/immunologic, dermatologic/connective tissue, musculoskeletal, metabolic/nutritional, endocrine, or neurologic/psychiatric disorders; recent major surgery (within 3 months); current or recent substance abuse, including that of alcohol and tobacco; history of chemotherapy; known allergic reaction to progesterone products; more than three unsuccessful IVF attempts; and history of recurrent pregnancy loss. Additional progesterone products were not permitted during the study.

On the day of oocyte retrieval (Day 1), subjects were randomized to receive either oral dydrogesterone 10 mg tablets three times daily or 8% MVP gel 90 mg once daily, and were stratified according to country and age group (<35 and ≥35 years of age). Embryo transfer was performed on Day 3–6 after oocyte retrieval, according to the clinic-specific IVF protocol; the transfer of up to two embryos was permitted. Luteal phase support continued until 12 weeks of gestation (Week 10 of treatment), and the follow-up period was 30 days after birth for mothers and newborns.

The primary objective of Lotus II was to demonstrate non-inferiority of oral dydrogesterone 30 mg daily to 8% MVP gel 90 mg daily, as assessed by the presence of a fetal heartbeat at 12 weeks of gestation by transvaginal ultrasound. Key secondary objectives were to compare live birth rates; safety and tolerability by documentation of maternal and fetal/neonatal treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs); and the incidence of health problems in the newborn.

This prespecified subgroup analysis included an evaluation of subject disposition and demographics, treatment exposure, efficacy, and safety of the Chinese mainland subpopulation of Lotus II. The same statistical techniques described for generating the primary and secondary outcome data in the overall Lotus II population were applied to the Chinese mainland subpopulation, with the exception that the efficacy analyses in the overall population were adjusted for country [26], which was not applicable for a single-country subpopulation. Lotus II was powered to investigate non-inferiority in the overall population and not in separate subgroups; therefore, no formal statistical comparisons were performed on the data from the Chinese mainland subpopulation.

Results

Study population

Overall, 1225 subjects were screened for inclusion in the Lotus II study, and 1034 subjects were randomized to receive either oral dydrogesterone (n = 520) or MVP gel (n = 514) (Figure 1) [26]. In the Chinese mainland subpopulation, 309 subjects were screened for inclusion and 239 were randomized to receive either oral dydrogesterone (n = 119) or MVP gel (n = 120).

Due to stratified randomization, demographics and baseline characteristics were similar between the oral dydrogesterone and MVP gel groups in the overall population and the Chinese mainland subpopulation (Table 1). The mean ± standard deviation (SD) age of subjects was higher in the overall population, compared with the Chinese mainland subpopulation (31.7 ± 4.5 years versus 29.9 ± 3.9 years, respectively), as was the mean ± SD BMI (23.1 ± 3 kg/m² versus 22.2 ± 2.3 kg/m², respectively). The proportion of subjects who had undergone prior treatment was lower in the overall population than in the Chinese mainland subpopulation (13.4% versus 27.5%, respectively).
**Efficacy**

The Lotus II study met its primary objective, with oral dydrogesterone achieving non-inferiority to MVP gel for pregnancy rates at 12 weeks of gestation (Figure 2) [26]. In the per-protocol sample (PPS), pregnancy rates were 36.7% (180/490) and 34.7% (167/481) (adjusted difference, 2%; 95% confidence interval [CI]: −4 to 8), respectively [26] (data not shown). In the full analysis sample (FAS), pregnancy rates were 38.7% (191/494) and 35% (171/489) in the oral dydrogesterone and MVP gel groups, respectively (adjusted difference, 3.7%; 95% CI: -2.3 to 9.7; Figure 2). Live birth rates were comparable in the oral
dydrogesterone and MVP gel groups in the FAS (34.4% [170/494] and 32.5% [159/489], respectively; adjusted difference, 1.9%; 95% CI: −6.8 to 18.9). Overall, higher pregnancy and live birth rates were observed in the Chinese mainland subpopulation, compared with the overall population from Lotus II.

Several differences in the course and outcomes of pregnancy were observed between the overall Lotus II population and the Chinese mainland subpopulation (Table 2). In the overall population, a greater proportion of subjects in the oral dydrogesterone and MVP gel groups (65.4% and 62.2%, respectively) underwent embryo transfer after ICSI, compared with the Chinese mainland subpopulation (35.1% and 25.9%, respectively). Embryo transfer was carried out at the cleavage stage (defined as <5 days after oocyte retrieval) in 65% and 58.5% of subjects in the oral dydrogesterone and MVP gel groups, respectively; however, the proportion of cleavage-stage embryo transfers was higher in the Chinese mainland subpopulation.

Table 1. Subject demographics and baseline characteristics (FAS).

|                                | Overall population | Chinese mainland subpopulation |
|--------------------------------|--------------------|--------------------------------|
|                                | Oral DYD (N = 494) | MVP gel (N = 489)               | All (N = 983) | Oral DYD (N = 114) | MVP gel (N = 108) | All (N = 222) |
| Mean age, years (SD)           | 31.8 (4.4)         | 31.6 (4.6)                     | 31.7 (4.5)    | 29.9 (3.9)         | 29.8 (4)          | 29.9 (3.9)    |
| Age category, n (%)            |                    |                                |              |                    |                    |              |
| <35 years of age               | 348 (70.4)         | 344 (70.3)                     | 692 (70.4)    | 98 (86)            | 92 (85.2)         | 190 (85.6)   |
| ≥35 years of age               | 146 (29.6)         | 145 (29.7)                     | 291 (29.6)    | 16 (14)            | 16 (14.8)         | 32 (14.4)    |
| Race or ethnicity, n (%)       |                    |                                |              |                    |                    |              |
| Asian                          | 250 (50.6)         | 237 (48.5)                     | 487 (49.5)    | 114 (100)          | 108 (100)         | 222 (100)    |
| Black                          | 1 (0.2)            | 0 (0)                          | 1 (0.1)       | 0 (0)              | 0 (0)             | 0 (0)        |
| White                          | 237 (48)           | 247 (50.5)                     | 484 (49.2)    | 0 (0)              | 0 (0)             | 0 (0)        |
| Other                          | 6 (1.2)            | 5 (1)                          | 11 (1.1)      | 0 (0)              | 0 (0)             | 0 (0)        |
| Mean BMI, kg/m² (SD)           | 23.1 (3.1)         | 23.1 (3)                       | 23.1 (3)      | 22 (2.2)           | 22.3 (2.5)        | 22.2 (2.3)   |
| Prior treatment, n (%)         | 71 (14.4)          | 61 (12.5)                      | 132 (13.4)    | 30 (26.3)          | 31 (28.7)         | 61 (27.5)    |

BMI: body mass index; DYD: dydrogesterone; FAS: full analysis sample; IVF: in vitro fertilization; MVP: micronized vaginal progesterone; SD: standard deviation.

aData for the overall population were previously reported in [26].

Georg Griesinger et al. Oral dydrogesterone versus intravaginal micronized progesterone gel for luteal phase support in IVF: a randomized clinical trial, Human Reproduction (2018) 33 (12): 2212–2221, doi: 10.1093/humrep/deg306. Reproduced and adapted by permission of Oxford University Press on behalf of the European Society of Human Reproduction and Embryology. © The Author(s) 2018. All rights reserved. This table is not included under the Creative Commons license of this publication. For permissions, please email journals.permissions@oup.com. OUP and the ESC are not responsible or in any way liable for the accuracy of the adaptation. Taylor & Francis Online is solely responsible for the adaptation in this publication/reprint.

bPrior treatment included assisted fertilization, IVF, ovulation induction, and artificial insemination by partner or donor.

Figure 2. Pregnancy and live birth rates posttreatment (FAS). Pregnancy rates at 12 weeks of gestation, and live birth rates for the overall Lotus II population and the Chinese mainland subpopulation. A non-inferiority margin of 10% was used for the overall population, whereby the test drug is non-inferior if the lower bound of the 95% CI excludes a difference greater than −10%. Data for the overall population were previously reported in [26]. aAt 12 weeks of gestation. CI: confidence interval; DYD: dydrogesterone; FAS: full analysis sample; MVP: micronized vaginal progesterone.
Chinese mainland subpopulation (91.2% and 90.7%, respectively). Double embryo transfer was performed frequently in the oral dydrogesterone and MVP gel groups in the overall population (66% and 66.3%, respectively); however, the frequency was greater in the Chinese mainland subpopulation (76.3% and 78.7%, respectively). Notably, the proportion of multiple births was lower in the oral dydrogesterone and MVP gel groups in the overall population (20.6% and 17.6%, respectively), compared with the Chinese mainland subpopulation (37.7% and 27.5%, respectively).

**Safety**

In the overall population, the incidence of maternal TEAEs of oral dydrogesterone and MVP gel were similar; this trend was also largely evident in the Chinese mainland subpopulation, although reporting rates were generally higher (50.9% and 65.5%, respectively; Table 3). The incidence of TEAEs in the oral dydrogesterone and MVP gel groups was 53.1% and 48.6%, respectively, in the overall population, and 73.1% and 58%, respectively, in the Chinese mainland subpopulation. In the overall population, the incidence of TESAEs was similar between the oral dydrogesterone and MVP gel groups (13.7% and 13.1%, respectively); this was also observed in the Chinese mainland subpopulation, although the incidence was markedly higher (23.5% and 26.1%, respectively). The incidence of TEAEs leading to study termination was similar in the oral dydrogesterone and MVP gel groups, both in the overall population (12.4% and 11.1%, respectively) and in the Chinese mainland subpopulation (10.9% and 14.3%, respectively).

In both the overall population and the Chinese mainland subpopulation, no clinically relevant treatment differences were identified for any of the common TEAEs (Table 3). The incidence of healthy newborns; gender proportions; and newborn height, weight, head circumference, and appearance, pulse, grimace, activity, respiration (APGAR) scores, were similar between the two treatment groups in both the overall population and the Chinese mainland subpopulation (data not shown). The proportion of fetuses/newborns with TEAEs was similar in the overall population (15.8% and 15.4%, for oral dydrogesterone and MVP gel, respectively) and in the Chinese mainland subpopulation (17.2% and 22.5% for oral dydrogesterone and MVP gel, respectively) (data not shown).

In the overall population, the incidence of congenital, familial, and genetic disorders in the fetal/neonatal population was similar between the oral dydrogesterone and MVP gel groups (6.3% and 5%, respectively; Table 4). In the Chinese mainland subpopulation, the incidence of these disorders was lower in the oral dydrogesterone group, compared with the MVP gel group, although this difference was not considered clinically relevant (4.6% [4/87] and 12.7% [9/71], respectively).

**Discussion**

Lotus II met its primary objective, with oral dydrogesterone achieving non-inferiority to MVP gel for luteal phase support in IVF, as determined by the presence of fetal heartbeats at 12 weeks of gestation [26]. In line with the overall population from Lotus II, pregnancy rates at 12 weeks of gestation were similar between the two treatment groups in the Chinese mainland subpopulation. Live birth rates were also similar between the oral dydrogesterone and MVP gel groups in the overall population and the Chinese mainland subpopulation.

Given the differences in patient demographics and infertility treatment procedures between the Chinese mainland and other countries, subpopulation analyses could provide valuable information on clinical outcomes that may be influenced by patient population and clinical practices. Consequently, it may be of importance to undertake such analyses to understand how these factors may affect treatment response; furthermore, it may help to modify prescribing practices. A number of differences were identified between the Chinese mainland subpopulation and the other patient populations in terms of patient characteristics, treatment procedures, and clinical outcomes.
The Author(s) 2018. All rights reserved. This table is not included under the Creative Commons license of this publication.

Table 3. Maternal TEAEs (safety sample).

|                        | Overall population | Chinese mainland subpopulation |
|------------------------|-------------------|-------------------------------|
|                        | Oral DYD (N = 518) | MVP gel (N = 512) | All (N = 1030) | Oral DYD (N = 119) | MVP gel (N = 119) | All (N = 238) |
| Maternal TEAEs, no (%) |                    |                 |               |                     |                   |               |
| All TEAEs              | 275 (53.1)        | 249 (48.6)      | 524 (50.9)   | 87 (73.1)           | 69 (58)           | 156 (65.5)    |
| At least one TESAE     | 71 (13.7)         | 67 (13.1)       | 138 (13.4)   | 28 (23.5)           | 31 (26.1)         | 59 (24.8)     |
| At least one severe TEAE | 38 (7.3)      | 35 (6.8)        | 73 (7.1)     | 8 (6.7)             | 16 (13.4)         | 24 (10.1)     |
| At least one TEAE leading to study termination | 64 (12.4) | 57 (11.1) | 121 (11.7) | 13 (10.9) | 17 (14.3) | 30 (12.6) |
| Maternal death         | 0 (0)             | 0 (0)           | 0 (0)        | 0 (0)               | 0 (0)             | 0 (0)         |
| Reproductive system and breast disorders | 89 (17.2) | 82 (16) | 171 (16.6) | 42 (35.3) | 34 (28.6) | 76 (31.9) |
| Vaginal hemorrhage     | 51 (9.8)          | 37 (7.2)        | 88 (8.5)     | 26 (21.8)           | 13 (10.9)         | 39 (16.4)     |
| Ovarian hyperstimulation syndrome | 21 (4.1) | 21 (4.1) | 42 (4.1) | 9 (7.6) | 15 (12.6) | 24 (10.1) |
| Vulvovaginal signs and symptoms | 11 (2.1) | 9 (1.8) | 20 (1.9) | 8 (6.7) | 3 (2.5) | 11 (4.6) |
| Vaginal discharge      | 11 (2.1)          | 3 (0.6)         | 14 (1.4)     | 8 (6.7)             | 2 (1.7)           | 10 (4.2)      |
| Vulvovaginal discomfort | 0 (0)            | 4 (0.8)         | 4 (0.9)      | 0 (0)               | 0 (0)             | 0 (0)         |
| Vulvovaginal pruritus  | 1 (0.2)           | 2 (0.4)         | 3 (0.3)      | 1 (0.8)             | 1 (0.8)           | 2 (0.8)       |
| Gastrointestinal disorders | 69 (13.3) | 67 (13.1) | 136 (13.2) | 20 (16.8) | 14 (11.8) | 34 (14.3) |
| Liver function analyses | 7 (1.4)         | 8 (1.6)         | 15 (1.5)     | 4 (3.4)             | 5 (4.2)           | 9 (3.8)       |
| ALT increased          | 2 (0.4)           | 4 (0.8)         | 6 (0.6)      | 1 (0.8)             | 3 (2.5)           | 4 (1.7)       |
| AST increased          | 2 (0.4)           | 3 (0.6)         | 5 (0.5)      | 1 (0.8)             | 3 (2.5)           | 4 (1.7)       |
| Transaminases abnormal | 1 (0.2)           | 0 (0)           | 1 (0.1)      | 1 (0.8)             | 0 (0)             | 1 (0.4)       |
| Hepatic enzyme increase | 2 (0.4)         | 2 (0.4)         | 4 (0.4)      | 1 (0.8)             | 1 (0.8)           | 2 (0.8)       |
| GGT increased          | 0 (0)             | 2 (0.4)         | 2 (0.2)      | 0 (0)               | 1 (0.8)           | 1 (0.4)       |
| Blood bilirubin decrease | 1 (0.2)        | 0 (0)           | 1 (0.1)      | 1 (0.8)             | 0 (0)             | 1 (0.4)       |
| Blood bilirubin increased | 1 (0.2)        | 0 (0)           | 1 (0.1)      | 0 (0)               | 0 (0)             | 0 (0)         |
| Nervous system disorders | 19 (3.7)      | 19 (3.7)        | 38 (3.7)     | 2 (1.7)             | 1 (0.8)           | 3 (1.3)       |
| Vascular disorders     | 12 (2.3)          | 9 (1.8)         | 21 (2)       | 1 (0.8)             | 0 (0)             | 1 (0.4)       |
| Peripheral embolism and thrombosis | 1 (0.2) | 1 (0.2) | 2 (0.2) | 1 (0.8) | 0 (0) | 1 (0.4) |

N = number of subjects in safety sample. 
N = number of subjects with TEAEs.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; DYD: dydrogesterone; GGT: gamma-glutamyltransferase; MVP: micronized vaginal progesterone; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse event.

Table 4. Fetal/neonatal population TEAEs.

|                        | Overall population | Chinese mainland subpopulation |
|------------------------|-------------------|-------------------------------|
|                        | Oral DYD (N = 221) | MVP gel (N = 201) | All (N = 422) | Oral DYD (N = 87) | MVP gel (N = 71) | All (N = 158) |
| Congenital, familial, and genetic disorders, no (%) | 14 (6.3) | 10 (5) | 24 (5.7) | 4 (4.6) | 9 (12.7) | 13 (8.2) |
| Atrial septal defect   | 5 (2.3)           | 7 (3.5)         | 12 (2.8)     | 2 (2.3)             | 6 (8.5)           | 8 (5.1)       |
| Heart disease congenital | 2 (0.9)       | 4 (2)           | 6 (1.4)      | 2 (2.3)             | 4 (5.6)           | 6 (3.8)       |
| Patent ductus arteriosus | 1 (0.5)       | 4 (2)           | 5 (1.2)      | 0 (0)               | 4 (5.6)           | 4 (2.5)       |
| Congenital aortic anomaly | 0 (0)         | 1 (0.5)         | 1 (0.2)      | 0 (0)               | 1 (1.4)           | 1 (0.6)       |
|Accessory auricle       | 1 (0.5)          | 0 (0)           | 1 (0.2)      | 0 (0)               | 0 (0)             | 0 (0)         |
| Amniotic band syndrome | 1 (0.5)          | 0 (0)           | 1 (0.2)      | 0 (0)               | 0 (0)             | 0 (0)         |
| Congenital central nervous system anomaly | 1 (0.5) | 0 (0) | 1 (0.2) | 1 (1.1) | 0 (0) | 1 (0.6) |
| Congenital cystic kidney disease | 1 (0.5) | 0 (0) | 1 (0.2) | 0 (0) | 0 (0) | 0 (0) |
| Congenital hand malformation | 1 (0.5) | 0 (0) | 1 (0.2) | 1 (1.1) | 0 (0) | 1 (0.6) |
| Cystic lymphangioma     | 1 (0.5)          | 0 (0)           | 1 (0.2)      | 1 (1.1)             | 0 (0)             | 1 (0.6)       |
| Intestinal malrotation  | 1 (0.5)          | 0 (0)           | 1 (0.2)      | 0 (0)               | 0 (0)             | 0 (0)         |
| Kinematic imbalance due to occipital strain | 1 (0.5) | 0 (0) | 1 (0.2) | 0 (0) | 0 (0) | 0 (0) |
| Renal dysplasia         | 1 (0.5)          | 0 (0)           | 1 (0.2)      | 0 (0)               | 0 (0)             | 0 (0)         |
| Turner's syndrome       | 1 (0.5)          | 0 (0)           | 1 (0.2)      | 0 (0)               | 0 (0)             | 0 (0)         |

N = overall number of fetuses/newborns. 
n = number of fetuses/newborns with anomalies.
DYD: dydrogesterone; MVP: micronized vaginal progesterone; TEAE: treatment-emergent adverse event.

Data for the overall population were previously reported in [26].

and the overall population, including patient age, frequency of double embryo transfer, proportion of subjects undergoing ICSI, and the use of cleavage-stage embryos.

Patient age is known to be an important factor influencing pregnancy outcomes, with decreasing success of ART procedures being observed with increasing age [29]. It is therefore important
to note that the mean age of subjects in the Chinese mainland subpopulation was approximately 2 years younger than in the overall population, with 70.4% and 85.6% of subjects in the overall population and Chinese mainland subpopulation, respectively, being under 35 years of age.

Notably, double embryo transfer occurred more frequently in the Chinese mainland subpopulation, compared with the overall population (77.5% versus 66.1%, respectively), which may have influenced the pregnancy and live birth rates [30,31]. It was found that the average number of embryos transferred per woman was 1.78 in the Chinese mainland subpopulation, compared with 1.67 in the overall population (data not shown). In 2015, the Society of Reproductive Medicine in China reported that the average number of embryos transferred per woman (under 35 years of age) was 1.88 (based on 168 reproductive centers) [32]. In 2016, this value was reduced to 1.85 (based on 179 reproductive centers) [33], which is similar to that of the Chinese mainland subpopulation of Lotus II. It should be noted that there has been an increasing worldwide trend of performing single embryo transfers and utilizing frozen-thawed embryos, due to the increased risk of maternal and fetal complications associated with multiple gestations [34].

The proportion of subjects who underwent ICSI was substantially lower in the Chinese mainland subpopulation, compared with the overall population (30.6% and 63.8%, respectively). This is following the guidelines from the Ministry of Health of the People’s Republic of China, which mandates ICSI only in the presence of severe oligospermia, asthenospermia, or teratospermia; irreversible obstructive azoospermia; spermatogenic dysfunction (excluding genetic defects); immune infertility; IVF failure; sperm acrosome abnormalities; or a need to perform pre-implantation embryo genetic testing [35]. In a recently conducted population-based cohort study that compared the impact of IVF and ICSI on treatment outcome, it was found that ICSI resulted in a similar cumulative live birth rate compared with conventional IVF for couples with non-male factor infertility [36]. As a result, it is difficult to predict whether the lower incidence of ICSI in the Chinese mainland subpopulation contributed to the higher pregnancy and live birth rates (versus the overall population).

Interestingly, cleavage-stage embryos were transferred in approximately 90% of subjects in the Chinese mainland subpopulation, compared with approximately 60% of subjects in the overall population. At present, it is difficult to interpret the impact the differences in clinical/laboratory practice for the selection of embryo transfer day may have had on the clinical outcomes reported herein, given that the study was not designed for such a confirmatory comparison between the Chinese mainland centers and the overall study centers.

Several observations from the comparison of the Chinese mainland subpopulation with the overall Lotus II population are consistent with findings from a retrospective study that used data collected from ART institutions in Beijing from 2013 to 2015 [4]. It was reported that, in general, Chinese patients were younger, more embryos were transferred, and multiple pregnancy rates were higher than in other countries [4]. It is also important to note that during 2016, mid-way through the period of data collection for Lotus II, the two-child policy was implemented in China [3]. While initial data on the demographics of women having a second child in China are beginning to emerge [37], it is difficult to assess the impact that this may have had on the study outcomes, if any.

Safety parameters were similar between the two treatment groups, for the mother as well as for the developing fetuses/newborns in both the overall population and the Chinese mainland subpopulation. A higher incidence of TEAEs was reported in the Chinese mainland subpopulation, compared with the overall population. However, a clinically relevant treatment difference was not observed in any of the populations.

While Lotus II was methodologically robust, the authors note that some statistical limitations exist for this prespecified subgroup analysis. For example, Lotus II was not powered to investigate non-inferiority in separate subgroups, but in the overall population. As a result, no formal statistical comparisons were performed on the data from the Chinese mainland subpopulation and non-inferiority could not be directly investigated. The findings from the Chinese mainland subpopulation are in line with those from the overall population in Lotus II, which demonstrated non-inferiority of oral dydrogesterone to MVP gel for pregnancy rates at 12 weeks of gestation [26]. Collectively, the data suggest that oral dydrogesterone may be a viable alternative to MVP gel for luteal phase support in fresh-cycle IVF in China.

Conclusions

In conclusion, this prespecified subgroup analysis of the Chinese mainland subpopulation from the overall Lotus II study population showed that oral dydrogesterone has similar efficacy to MVP gel for luteal phase support in fresh-cycle IVF, despite differences in subject demographics and IVF treatment procedures versus the overall population. Furthermore, there was no clinically relevant difference observed between the safety and tolerability profiles of the two treatment groups in the Chinese mainland subpopulation. Based on the convenience of oral administration and the lower cost of oral dydrogesterone versus MVP capsules (per live birth in China) [38], the use of oral dydrogesterone monotherapy for luteal phase support has the potential to transform IVF luteal phase support regimens for the benefit of women in China.

Ethical approval and consent

Lotus II was performed in accordance with the Declaration of Helsinki and ICH E6 Good Clinical Practice guidelines. Abbott Laboratories GmbH (or an authorized representative) or the investigator (according to national provisions) obtained written approval of the clinical study protocol (including amendments), the written subject informed consent form, informed consent updates, subject recruitment procedures, and any other written information provided to subjects from an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), complying with the local regulatory requirements. Written approval of the study was obtained from the IEC/IRB before study commencement.

Acknowledgements

We would like to thank all the study investigators.

Disclosure statement

Dong-Zi Yang has no conflicts of interest to be declared regarding the publication of this paper. Georg Griesinger has received investigator fees from Abbott during the conduct of the study. Outside of this submitted work, Georg Griesinger has received non-financial
support from MSD, Ferring, Merck Serono, IBSA, Finox, TEVA, Glycosto, and Gedeon-Richter, as well as personal fees from MSD, Ferring, Merck-Serono, IBSA, Finox, TEVA, Glycosto, VitroLife, NMC Healthcare, ReprodWissen, Biosilu, Gedeon-Richter, and ZIVA. Wei Wang, Fei Gong, Xiaoyan Liang, Hanwang Zhang, Yingru Sun, and Zi-Jiang Chen have no conflicts of interest to be declared regarding the publication of this paper. Elke Kahler is an employee of Abbott Laboratories GmbH, Hannover, Germany and owns shares in Abbott. Claire Pexman-Fieth is an employee of Abbott GmbH & Co. KG, Wiesbaden, Germany and owns shares in Abbott. Jan I. Olofsson is an employee of Abbott Products Operations AG, Allschwil, Switzerland. Herman Tournaye’s institute has received grants from Merck, MSD, Goodlife, Cook, Roche, Cooper-Surgical, Besins, Ferring, and Allergan; and Herman Tournaye has received consultancy fees from Gedeon-Richter, Merck, Ferring, Abbott, and ObsEva.

Funding
This study was sponsored by Abbott. Abbott study support: Erik van Leeuwen. Editorial support: Josh Lilly of Alpharmax Healthcare Communications, funded by Abbott Established Pharmaceuticals.

Availability of data and material
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References
[1] Zhou Z, Zheng D, Wu H, et al. Epidemiology of infertility in China: a population-based study. BJOG: Int J Obstet Gy. 2018;125:432–441.
[2] Qiao J, Feng HL. Assisted reproductive technology in China: compliance and non-compliance. Transl Pediatr. 2014;3:91–97.
[3] Wei D, Wang I, Qiu Y, et al. Development of in vitro fertilization in China. In: Kovacs G, Brinsden P, DeCherney A, editors. In vitro fertilization: The pioneers’ history. Cambridge: Cambridge University Press; 2018. p. 152–157.
[4] Zhou Z, Chen L, Wu H, et al. Assisted reproductive technology in Beijing. 2013–2015. Reprod Biomed Online. 2018;37:521–532.
[5] Farquhar C, Marjoribanks J, Brown J, et al. Management of ovarian stimulation for IVF: narrative review of evidence provided for World Health Organization guidance. Reprod Biomed Online. 2017;35:3–16.
[6] Macklon NS, Fauser BC. Impact of ovarian hyperstimulation on the luteal phase. J Reprod Fertil Suppl. 2000;55:101–108.
[7] Practice Committee of the American Society for Reproductive Medicine. Progesterone supplementation during the luteal phase and in early pregnancy in the treatment of infertility: an educational bulletin. Fertil Steril. 2008;89:789–792.
[8] van der Linden M, Buckingham K, Farquhar C, et al. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. 2015;7:CD009154.
[9] Jasem Y, Khan M, Taha A, et al. Preparation of steroid hormones with an emphasis on transformations of phytosterols and cholesterol – a review. Mediterr J Med. 2014;3:796–830.
[10] Tavaniotou A, Smitz J, Bourgain C, et al. Comparison between different routes of progesterone administration as luteal phase support in infertility treatments. Hum Reprod Update. 2006;6:139–148.
[11] Vaibhush E, Leong M, Shoham Z. Progesterone support in IVF: is evidence-based medicine translated to clinical practice? A worldwide web-based survey. Reprod Biomed Online. 2012;25:139–145.
[12] Sator M, Radiocini M, Cometti B, et al. Pharmacokinetics and safety profile of a novel progesterone aqueous formulation administered by the s.c. route. Gynecol Endocrinol. 2013;29:205–208.
[13] Doblinger J, Cometti B, Trevisan S, et al. Subcutaneous progesterone is effective and safe for luteal phase support in IVF: an individual patient data meta-analysis of the Phase III trials. PLoS One. 2016;11:e0151388.
[14] Child T, Leonard SA, Evans JS, et al. Systematic review of the clinical efficacy of vaginal progesterone for luteal phase support in assisted reproductive technology cycles. Reprod Biomed Online. 2018;36:630–645.
[15] Griesinger G, Tournaye H, Macklon N, et al. Dydrogesterone: pharmacological profile and mechanism of action as luteal phase support in assisted reproduction. Reprod Biomed Online. 2019;38:249–259.
[16] Beltso AN, Sanchez MD, Doody KJ, et al. Patients’ administration preferences: progesterone vaginal insert (Endometrin®) compared to intramuscular progesterone for luteal phase support. Reprod Health. 2014;11:78.
[17] Griesinger G, Blockeel C, Tournaye H. Oral dydrogesterone for luteal phase support in fresh in vitro fertilization cycles: a new standard? Fertil Steril. 2018;109:756–762.
[18] Rüüner TL, Brožić P, Doucette C, et al. Selectivity and potency of the retroprogesterone dydrogesterone in vitro. Steroids. 2011;76:607–615.
[19] Chakravarty BN, Shirazie HH, Dam P, et al. Oral dydrogesterone versus intravaginal micronised progesterone as luteal phase support in assisted reproductive technology (ART) cycles: results of a randomised study. J Steroid Biochem Mol Biol. 2005;97:416–420.
[20] Patki A, Pawar VC. Modulating fertility outcome in assisted reproductive technologies by the use of dydrogesterone. Gynecol Endocrinol. 2007;23:68.
[21] Ganesh A, Chakravorty N, Mukherjee R, et al. Comparison of oral dydrogesterone with progesterone gel and micronized progesterone for luteal support in 1,373 women undergoing in vitro fertilization: a randomized clinical study. Fertil Steril. 2011;95:1961–1965.
[22] Saharkhiz N, Zamanian M, Salehpour S, et al. A comparative study of dydrogesterone and micronized progesterone for luteal phase support during in vitro fertilization (IVF) cycles. Gynecol Endocrinol. 2016;32:213–217.
[23] Zargar M, Saadati N, Ejtahed MS. Comparison the effectiveness of oral dydrogesterone, vaginal progesterone suppository and progesterone ampule for luteal phase support on pregnancy rate during ART cycles. Int J Pharm Res Allied Sci. 2016;3:229–236.
[24] van der Linden M, Buckingham K, Farquhar C, et al. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. 2011;CD009154.
[25] Tournaye H, Sukhikh GT, Kahler E, et al. 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. Hum Reprod. 2017;32:1019–1027.
[26] Griesinger G, Blockeel C, Sukhikh GT, et al. Oral dydrogesterone versus intravaginal micronized progesterone gel for luteal phase support in in vitro fertilization: a randomized clinical trial. Hum Reprod. 2018;33:2212–2221.
[27] Sukhikh GT, Baranov II, Melnichenko GA, et al. Lotus I: A Phase III randomized controlled trial of oral dydrogesterone versus micronized vaginal progesterone for luteal support in vitro fertilization, with focus on the Russian subpopulation. Akush Ginekol. 2017;75:75–95. Russian.
[28] De Geyter C, Calzar-Jorge C, Kupka MS, et al. ART in Europe, 2014: results generated from European registries by ESHRE: the European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). Hum Reprod. 2018;33:1586–1601.
[29] Toner JP, Coddington CC, Doody K, et al. Society for assisted reproductive technology and assisted reproductive technology in the United States: a 2016 update. Fertil Steril. 2016;106:541–546.
[30] McLennon DJ, Harrild K, Bergh C, et al. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. BMJ. 2010;341:c6945.
[31] Pandian Z, Marjoribanks J, Ozturk O, et al. Number of embryos for transfer following in vitro fertilisation or intra-cytoplasmic sperm injection. Cochrane Database Syst Rev. 2013;5:CD003416.
[32] Ministry of Health of the People’s Republic of China. Reproductive Centre Statistics. National Data Annual Report 2015.
[33] Ministry of Health of the People’s Republic of China. Reproductive Centre Statistics. National Data Annual Report 2016.
[34] Kushnir VA, Barad DH, Albertini DF, et al. Systematic review of worldwide trends in assisted reproductive technology 2004–2013. Reprod Biol Endocrinol. 2017;15:6.
[35] Ministry of Health of the People’s Republic of China. Specifications for Human Assisted Reproductive Technology. Chin J Reprod Health. 2004;15:4–8.
Li Z, Wang AY, Bowman M, et al. ICSI does not increase the cumulative live birth rate in non-male factor infertility. *Hum Reprod*. 2018; 33:1322–1330.

Xu X, Zuo H, Shi Z, et al. Determinants of second pregnancy among pregnant women: a hospital-based cross-sectional survey in China. *BMJ Open*. 2017;7:e014544.

Griesinger G, Tournaye H, Connolly MP, et al. A comparison of live birth rates and cost-effectiveness analysis in luteal support based on a multicenter, double-blind *RCT* of oral dydrogesterone vs. micronized vaginal progesterone. Abstract 2017. 7th Congress of the Asia Pacific Initiative on Reproduction (ASPIRE 2017); 30 Mar–2 Apr 2017; Kuala Lumpur, Malaysia; 2017.