2 SYNOPSIS

SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND/ DRUG NAME:	**MK-8761 (**Ganirelix Acetate Injection, Orgalutran®**)**	
INDICATION:	The prevention of premature luteinising hormone (LH) surges in women undergoing controlled ovarian stimulation (COS [a]) for assisted reproduction techniques (ART)	
PROTOCOL TITLE:	Post-marketing Observational Study to Characterize the Safety and Effectiveness Profile of Orgalutran® in Chinese Women Undergoing Controlled Ovarian Hyperstimulation for Assisted Reproduction Techniques	
STUDY IDENTIFIERS:	Protocol Number:	PN050-00
	Clinical Phase:	IV
ETHICS:	This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.	
STUDY CENTERS:	This study was conducted at 16 ART centers in China.	
DESIGN:	This was a single arm, multi-center, observational study to assess the safety and effectiveness of Orgalutran in Chinese women undergoing controlled ovarian hyperstimulation (COH) during ART, in the setting of routine clinical practice. Patients who received at least one dose of Orgalutran as per approved indications were included in this assessment. For patients who became pregnant, data were collected up to the final outcome of the pregnancy. For patients who did not become pregnant, data were collected until the last visit at the ART clinic or until two weeks after embryo transfer (ET) (i.e., the time of the pregnancy test), whichever was last.	
	Duration of Study:	27.5 months

[a] COS (controlled ovarian stimulation) is interchangeable with COH (controlled ovarian hyperstimulation) used throughout the remainder of the study report.. COS is used here to designate the terminology of the approved INDICATION for the product.; whereas the protocol used COH throughout.

Objectives	**Safety:** To describe the safety profile of Orgalutran among Chinese women undergoing COH for ART in a routine clinical practice setting in China. **Effectiveness and Clinical Outcomes:** To describe effectiveness of Orgalutran among Chinese women undergoing COH for ART in a routine clinical practice setting in China.	
Hypotheses	Not applicable.	
Study Groups	Single arm: Chinese women undergone COH for ART who received Orgalutran according to the local label. 1,025 Subjects enrolled *(actual)*	
Main Outcomes and Definitions	**Safety Outcomes** (treatment period; pre & post treatment period)	At least one adverse event (AE)
		A drug-related AE
		A serious AE (SAE)
		Discontinuation of treatment due to an AE
	Effectiveness Outcomes	Serum concentrations of LH at baseline (prior to FSH administration), prior to Orgalutran administration, and on the day of (or the day prior to) hCG administration
		Days and total dose of FSH administered
		Number and size distribution of follicles
		Number of oocytes retrieved
		Number of embryos on the day of ET

		Proportion of women with a positive pregnancy test/vital/ongoing pregnancy: - *Positive pregnancy test*: Pregnancy proven by a pregnancy test (increase in serum β-hCG approximately14 days after ET) before ultrasound (US) evidence of a gestational sac. - *Vital pregnancy*: Presence of at least one fetus with heart activity as assessed at least 35 days after ET by US. Subjects with an ongoing pregnancy or a live-birth were counted as having a vital pregnancy - *Ongoing pregnancy*: Presence of at least one fetus with heart activity at least 70 days (≥ 10 weeks) after embryo transfer as assessed by US. Subjects with a live-birth were counted as having an ongoing pregnancy.
		Proportion of women with a live-born baby
	New Born Baby Information	Birth weight
		Gestational age at delivery
		Mode of delivery
		Type of gestation (singleton or multiple)
		Occurrence of congenital malformations
STUDY STATUS:	28-Apr-2015 (first subject first visit) to 06-Jun-2017 (last subject last visit)	
DATABASE LOCK:	07-Aug-2017	
RESULTS AND ANALYSIS:	In this study, 1,025 subjects were enrolled. The subject disposition is presented in Table 1 below. All analyses for safety and effectiveness were performed according to the protocol and statistical analysis plan (SAP).	

Table 1
Disposition of Subjects
(ASaT)

	Orgalutran	
	n	(%)
Subjects in population	1,025	(100)
Status for the Study		
Completed	906	(88.4)
Discontinued	119	(11.6)
Adverse Event	2	(0.2)
Lack Of Effectiveness	12	(1.2)
Lost To Follow-Up	6	(0.6)
Physician Decision to Discontinue	95	(9.3)
Withdrawal By Subject	4	(0.4)

Source: [P050MK8761: analysis-adsl]

Analysis Description	**Safety Analysis:** The main safety endpoints are: the proportion of patients with (1) at least one AE; (2) a drug-related AE; (3) an SAE; (4) discontinuation of treatment due to an AE. These safety endpoints were summarized by count, point estimate and corresponding 95% confidence interval if applicable. The incidence of ovarian hyperstimulation syndrome (OHSS) were estimated as following: the numerator was the number of subjects with OHSS that occured in the all subject as treated (ASaT) population, and the denominator was the ASaT population of this study. Additional analyses for OHSS included number and proportion of OHSS by OHSS severity grade (based upon investigator's assessment with use of the criteria per investigators' routine clinical practice. **Effectiveness Analysis:** The effectiveness measurements and subsequent clinical outcomes were summarized. These measurements were: (1) median serum concentrations of LH at baseline (prior to FSH administration), prior to Orgalutran administration, and on the day of (or the day prior to) hCG administration; (2) mean/median days and total dosage of FSH administered; (3) mean/median number of each size category of the follicles; (4) mean/median number of oocytes retrieved; (5) mean number of (vital) embryos obtained on the day of ET and number of embryos used for 1st transfer; (6) proportion of women with a positive pregnancy test/vital/ongoing pregnancy; (7) proportion of each gestation type; and (8) proportion of women with a live-born baby. These measurements were summarized by count (n)/proportion, point estimate (mean/median) with standard deviation/quantiles or range if applicable. All the proportions above were defined in the protocol and SAP. **Newborn Baby Analysis:** Information collected on newborns include: (1) birth weight; (2) gestational age at delivery; (3) mode of delivery; (4) type of gestation (singleton vs. multiple); (5) occurrence of congenital malformations. These measurements were summarized by count (n)/proprotion, point estimate (mean) with standard deviation if applicable.

Analysis Description	**Other Analysis:** Start and stop date for Orgalutran (relative to FSH start and stop date) along with mean/median of the total dose. These measurements were summarized by count (n)/proprotion, point estimate (mean/median) with standard deviation/range if applicable.
Analysis Population and Time Point Description	**Safety:** The safety analyses including OHSS were performed on the ASaT population. The ASaT population includes all subjects who received at least one dose of Orgalutran. Safety results were summarized by treatment period, pre- and post-treatment periods. **Effectiveness:** The effectiveness analyses for LH, total number of days of gonadotropin (e.g. FSH) along with the total dose, number and size of follicles, number of oocytes retrieved, embryos surviving at the day of ET were performed on the population consisting of subjects in ASaT population undergoing one COH cycle using Orgalutran. The outcomes following ET (positive pregnancy test, biochemical pregnancy, miscarriage/fetal loss, vital pregnancy etc.) based upon the first transfer were analyzed on subjects within the ASaT population who reached the ET stage and had at least one embryo transferred. The final clinical outcomes (vital pregnancy, ongoing pregnancy and live birth) allowing for multiple ETs (all ETs during the study period, including those with only one ET) were also summarized in the ASaT population reaching ET stage and per attempted cycle (includes all women in the ASaT population who started the ART cycle and received at least one dose of gonadotropins and Orgalutran). **Newborn Baby:** The analyses on newborn babies (including congenital malformations) were performed on the population of all live-born babies conceived after treatment. **Other Measurements:** Timing of administration of Orgalutran (i.e., start and stop date) relative to start and stop date for FSH, along with the total dose were performed on the ASaT population. The list of definitions is included in the protocol and the SAP.

Results	**Safety:** The overall summary of AEs for treatment period is depicted in Table 2. One or more AEs were reported in 124 (12.1%) subjects. Thirteen subjects (1.3%) experienced AEs (insomnia, pruritus, dermatitis allergic, progesterone increased (i.e, abnormal rise in progesterone deemed clinically significant as judged by the investigator), premature ovulation, intentional overdose, injection site erythema, injection site pain) which were determined to be related to study drug by the primary investigators. A total of 2 subjects did not complete the study due to AEs. One experienced pruritus while another experienced dermatitis after the administration of Orgalutran; these events were judged by the investigator to be related to study drug, and both AEs were of mild intensity and both AEsresolved. As shown in Table 3, twenty-five (2.4%) subjects experienced SAEs including hospitalization for OHSS (21), procedural pain (1), ovarian cyst torsion (1), adverse drug reaction (1), and hydrosalpinx (1). There was no serious drug-related AE or death. In terms of OHSS events, a total of 49 (4.78%) subjects were judged as having developed OHSS by the investigators. Among those, 17 (1.66%) were mild, 19 (1.85%) were moderate, and 13 (1.27%) were severe with the use of criteria per investigators' routine clinical practice (see Table 4).

Table 2
Adverse Event Summary
(Treatment Period)
(ASaT)

	Orgalutran	
	n	(%)
Subjects in population	1,025	
with one or more adverse events	124	(12.1)
with no adverse event	901	(87.9)
with drug-related[†] adverse events	13	(1.3)
with serious adverse events[a]	25	(2.4)
with serious drug-related adverse events	0	(0.0)
who died	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)
discontinued[‡] due to an adverse event	2	(0.2)
discontinued due to a drug-related adverse event	2	(0.2)
discontinued due to a serious adverse event	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.

Source: [P050MK8761: analysis-adsl] [P050MK8761: tabulations-aeplus]
[a] Include AEs reported as other important medical events (OMEs).

Table 3
Listing of Subjects With Serious Adverse Events
(Treatment Period)

Subject ID	Onset Epoch	Rel Day of Onset	Adverse Event	Duration	Intensity	Serious	Related	Action Taken	Outcome
PPD									

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PPD									

Source: [P050MK8761: analysis-adsl] [P050MK8761: tabulations-aeplus; ceplus; explus]

[a] This adverse events is summaried as SAE as it was assessed as other important medical event (OME) due to clinical treatment intervention was provided for risk prevention.

Table 4
Number of Subjects with Ovarian Hyperstimulation Syndrome (OHSS)
(ASaT)

Severity Rating of OHSS	Orgalutran	
	n	(%)
Subjects in population	1025	
Mild	17	(1.66)
Moderate	19	(1.85)
Severe	13	(1.27)
Total	49	(4.78)

Source: [P050MK8761: analysis-adsl]

Results	**Effectiveness:** Among 1,025 subjects enrolled, a total of 1,008 subjects achieved oocyte retrieval. The mean (SD) number of oocytes retrieved was 11.2 (8.0) per subject. The number and percentage of outcomes following the first ET are shown in Table 5. Eight hundred and forty nine (849) subjects underwent fresh ET or had their first ET after a frozen/thaw cycle. The percentage of subjects with a positive serum pregnancy test following their first ET was 53.9%, and 42.2% of subjects reached the stage of a vital pregnancy. Table 6 presents the outcomes per attempted cycle (n=1,025 subjects) and per ET population, allowing for multiple ETs (n=849 subjects having at least one ET). The vital & ongoing pregnancy rates per attempted cycle were 42.1% & 40.3%, respectively, and these rates per ET were 50.9% & 48.6%, respectively. The proportions of women with live birth per attempted cycle and within the ET population were 39.4% and 47.6%, respectively.

Table 5
The Number and Percentage of First Embryo Transfer Outcomes
(ASaT per ET Stage)

	Orgalutran	
	n	(%)
Subjects in population	849	
No Pregnancy	391	(46.1)
Positive Pregnancy Test	458	(53.9)
Biochemical Pregnancy	30	(3.5)
Ectopic Pregnancy	12	(1.4)
Miscarriage/abortion	58	(6.8)
Vital pregnancy	358	(42.2)
The population comprises of subject with fresh embryo transferred, and subject with 1st embryos transferred after frozen.		

Source: [P050MK8761: analysis-adsl]

Table 6
Number and Percentage of Pregnancy Outcomes
Based on Multiple ET
(ASaT per Attempted Cycle and per ET stage)

	N	Vital Pregnancy n (%)	Ongoing Pregnancy n (%)	Live Birth n (%)
Per Attempt	1025	432 (42.1)	413 (40.3)	404 (39.4)
Per ET population	849	432 (50.9)	413 (48.6)	404 (47.6)

Source: [P050MK8761: analysis-adsl]

Results	**Newborn Baby:** Four hundred and four (404; 39.4%) women gave birth to 523 newborn babies including 286 singletons, 117 twins and 1 triplet. The mean (SD) birth weight was 2966.5 (742.5) grams with a mean (SD) gestational age of 36.9 (2.7) weeks. Tables 7 and 8 present the occurrence and types of congenital malformations reported in the babies. Of the 523 babies, seven (1.3%) were reported to have congenital malformations.

Table 7
Occurrence of Congenital Malformations in New Born Babies
(New Born Babies)

	N	n (%)
Congenital Malformations	523	7 (1.3)

Source: [P050MK8761: analysis-adsl]

Table 8
Listing of Congenital Malformations in NewBorn Babies

CONCLUSIONS:	**Safety:** - The safety profile of Orgalutran when used among Chinese women undergoing COH for ART in a routine clinical practice setting is supported by this post-marketing observational study. - The incidence rate of OHSS and the severity of the reported cases is comparable to the reported rates within China and the previously submitted Phase 3 registration trial for Orgalutran. - No unexpected safety findings were observed. **Effectiveness:** - The ET and pregnancy outcomes achieved in this observational study support that the antagonist protocol using Orgalutran is effective. - Pregnancy rates observed in the current study are within expectations and consistent with the clinical pregnancy rate achieved in the Phase 3 registration trial for Orgalutran. - No unexpected findings were observed with respect to the clinical outcomes of Orgalutran use in this study. **Congenital Malformations:** - The current study provides data to support the conclusion that the congenital malformation rate in babies following maternal Orgalutran COH treatment is consistent with all babies (ART and spontaneously conceived) in routine clinical practice.
REPORT DATE:	05-DEC-2017