Assessment of Two Formulations of Triptorelin in Chinese Patients with Endometriosis: A Phase 3, Randomized Controlled Trial

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SUPPLEMENTARY FIGURES, TABLES AND MATERIALS

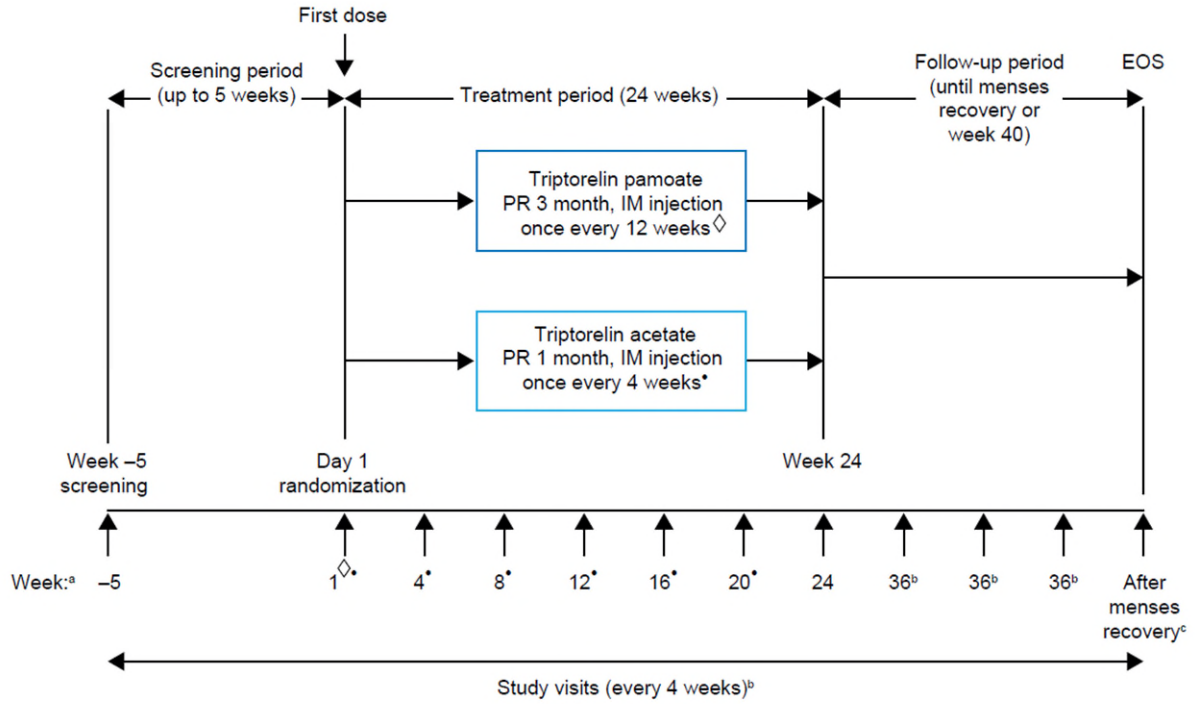

Fig. S1 Study design.

EOS end of study, *IM* intramuscular, *PD* pharmacodynamic, *PK* pharmacokinetic, *PR* prolonged release

[a] Additional visits for patients in the PK/PD subgroups not indicated. A full PK analysis was performed for 14 patients in each treatment group, with additional PD blood samples collected at weeks 1, 2, 3, and 32, and PK samples at day 1 and weeks 4, 8, 12, and 24

[b] Study visits occurred every four weeks for 24 weeks, with the exception of patients participating in the PK and PD evaluations

[c] After 24 weeks of treatment, patients were followed-up once every 4 weeks via telephone, and the first visit after menses recovery or week 40 (whichever is earlier) was considered to be the EOS visit

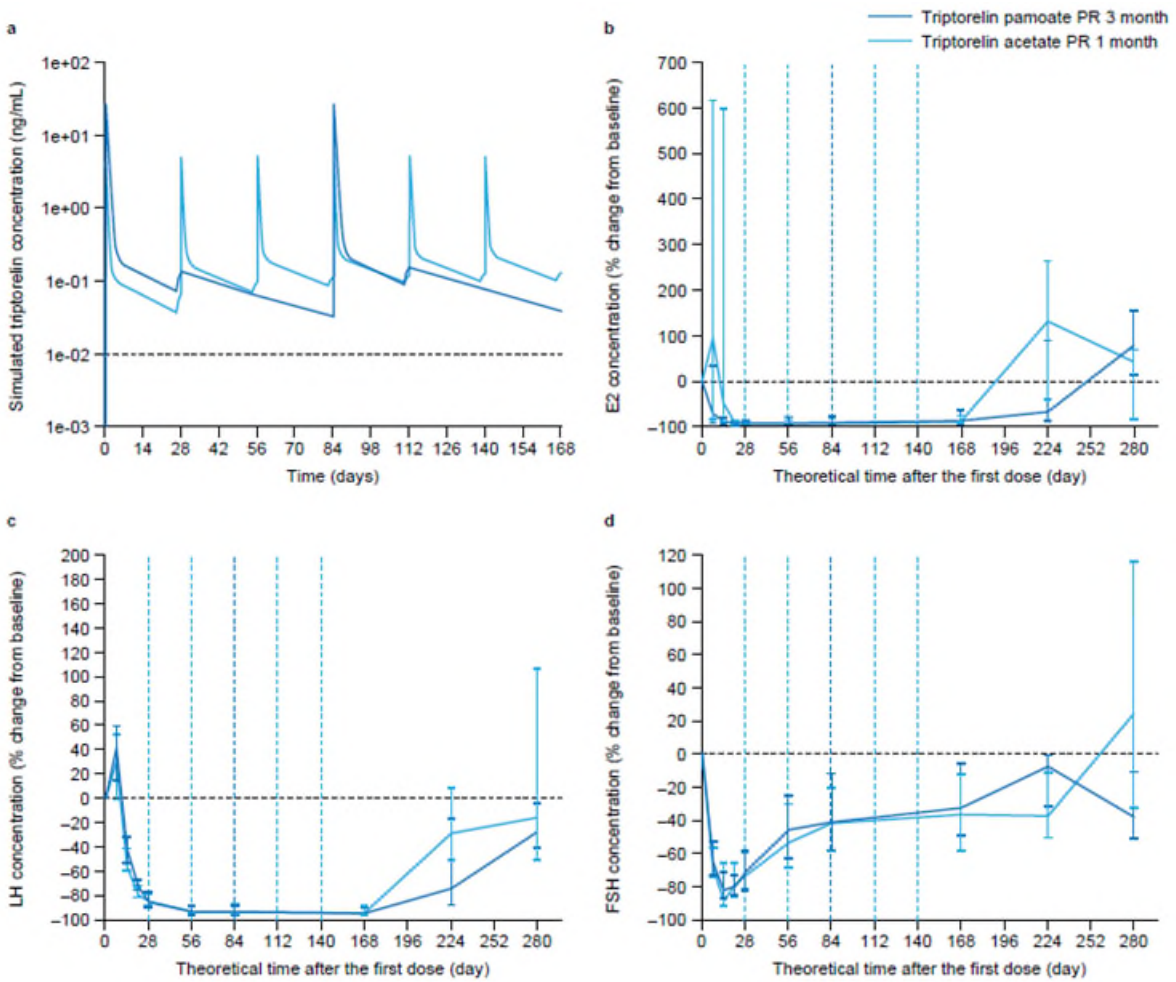

Fig. S2 Triptorelin, E2, FSH, and LH concentration-time profiles.
(**a**) PK model-simulated triptorelin PK profiles after IM administration of triptorelin pamoate PR 3-month formulation and triptorelin acetate PR 1-month formulation. (**b**) Median E2 concentrations (% from baseline) versus time after injection of triptorelin pamoate PR 3-month formulation and triptorelin acetate PR 1-month formulation in all patients. (**c**) Median LH concentrations (% from baseline) versus time after injection of triptorelin pamoate PR 3-month formulation and triptorelin acetate PR 1-month formulation in all patients. (**d**) Median FSH concentrations (% from baseline) versus time after injection of triptorelin pamoate PR 3-month formulation and triptorelin acetate PR 1-month formulation in all patients. Dashed vertical lines in panels **b**–**d** represent time of injection. *E2* estradiol, *FSH* follicle stimulating hormone, *IM* intramuscular, *LH* luteinizing hormone, *PD* pharmacodynamic, *PK* pharmacokinetic, *PR* prolonged release

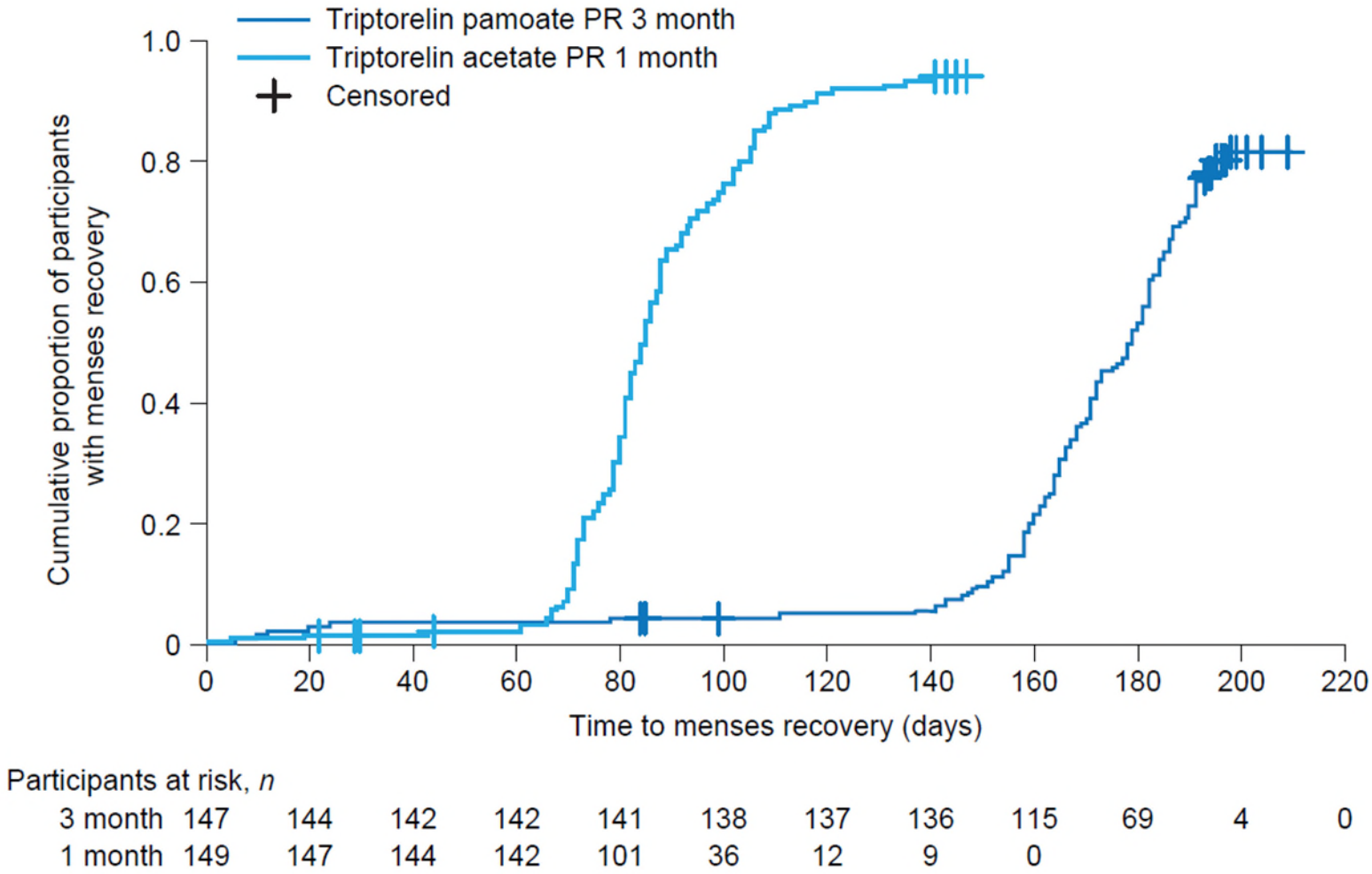

Fig. S3 Kaplan–Meier curve of time in days to menses recovery (FAS).

Time to menses recovery was defined as days between date of last dose of study drug and date of first day the patient observed menstrual bleeding of the next menstrual period. Patients completed/discontinued study without menstrual bleeding was censored at visit dates of EOS/early withdrawal. Patients who did not stop menses during the treatment duration (baseline to week 24) were excluded in this analysis. "Stop menses" was considered as at least one answer "No" for the question "Is the menses recovered since last visit" in eCRF page. "Status of Menses" at least two consecutive stop between baseline (first dose) and week 24. *eCRF* electronic case report form, *EOS* end of study, *FAS* full analysis set, *PR* prolonged release

Table S1 Ethics committees that provided ethical approval at each included each study site

Ethics Committee
• Ethics committee of drug clinical trials of Peking union medical college hospital , Chinese academy of medical sciences No.41 Damucang Hutong, Xicheng District, Beijing, China 100032
• The EC committee of the first affiliated hospital of Dalian medical university No. 222 Zhongshan Road, Dalian City, Liaoning Province, China 116011
• Ethics committee of Beijing maternity hospital affiliated to capital medical university No. 251, Yaojiayuan Road, Chaoyang District, Beijing, China 100026
• Committee of Peking University First Hospital No 8, Xishiku Road, Xicheng district, Beijing, China 100034
• Drug clinical trial of Beijing Friendship Hospital, Capital Medical University No. 95, Yongan Road, Xicheng District, Beijing, China 100050
• Clinical trials ethics committee of The Second Hospital of Hebei Medical University No.215 Heping West Road, Shijiazhuang City, Hebei Province, China 050000
• Sun Yat-sen Memorial Hospital Institutional Review Boards, Sun Yat-sen University No. 107 Yanjiang West Road, Guangzhou, China 10120
• Medical Ethics Committee of the Peking University People's Hospital No. 11, Xizhimen South Road, Xicheng District Beijing, China 100044
• Ethics committee of Tianjin medical university general hospital No. 154, Anshan Road, Heping District, Tianjin, China 300052
• The EC committed of Shanghai Tongji Hospital No. 389 Xincun Road, Putuo District, Shanghai City, China 200065
• The EC committee of The People's Hospital of Guangxi Zhuang Autonomous Region No. 6, Taoyuan Road, Nanning City,Guangxi Province
• Medical Ethics Committee of the General Hospital of People's Liberation Army (301 Hospital) No. 28, Fuxing Road Haidian District Beijing, China 100853
• EC Committee of Obstetrics & Gynecology Hospital of Fudan University, No. 419 Fangxie Road, Huangpu District, Shanghai, China
• Hainan General Hospital Institutional Review Boards No. 19, Xiuhua Road, Xiuying District, Haikou, China 570311
• EC Committee of Sir Run Run Shaw Hospital - Zhejiang University School of Medicine, No. 3 East Qingchun Road, Hangzhou, Zhejiang, China
• Ethics committee of the second hospital of Tianjin medical university No. 23, Pingjiang Road, Hexi District, Tianjin, China 300211
• The First Affiliated Hospital of Guangzhou Medical University Institutional Review Boards No. 151 Yanjiang West Road Guangzhou, Guangdong, China 510120
• EC Committee of Northern Jiangsu People's Hospital, No. 98, West Nantong Road, Jiangsu, China
• IEC for Clinical Research of Zhongda Hospital, affiliated to Southeast University No.87 Dingjiaqiao, Gulou district, Nanjing, Jiangsu Province, China 210009
• EC Committee of General Hospital of Ningxia Medical University, No. 804 South Shengli Street, Yinchuan, Ningxia Province, China
• Medical EC of The Third Affiliated Hospital of Sun Yat-sen University No. 600 Tianhe road, Tianhe district, Guangzhou, Guangdong Province, China 510630
• EC of Women's Hospital School of Medicine Zhejiang University, No. 1 Xueshi Road, Hangzhou, Zhejiang Province, China 310006
• EC of Nanjing Maternity and Child Health Hospital, No. 123, Tianfeixiang, Mochou Road, Nanjing, Jiangsu Province, China 210004.
• Medical science research Ethics Committee of Peking University Third Hospital No. 49, Huayuan North Road, Haidian district, Beijing, China 100191

Table S2 Demographic characteristics and gynecological history at baseline (all randomized patients)

	Triptorelin pamoate PR 3-month (*n* = 150)	Triptorelin acetate PR 1-month (*n* = 150)	Overall randomized patients (*N* = 300)
Patient demographics			
Age, years[a]			
Median (range)	33.0 (18–45)	32.0 (21–44)	33.0 (18–45)
Mean (SD)	32.4 (6.1)	32.6 (6.2)	32.5 (6.1)
Race, *n* (%)			
Asian	150 (100)	150 (100)	300 (100)
BMI, kg/m^2[b]			
Median (range)	21.24 (15.8–32.9)	20.91 (15.4–36.9)	21.08 (15.4–36.9)
Mean (SD)	21.84 (3.55)	21.44 (3.45)	21.64 (3.50)
Gynecological history			
Time since endometriosis diagnosis, months[c]			
Median (range)	0.40 (0.0–113.4)	0.50 (0.0–102.9)	0.40 (0.0–113.4)
Mean (SD)	6.05 (18.05)	5.69 (17.28)	5.87 (17.64)
Method of diagnosis, n (%)			
Laparoscopy	130 (86.7)	124 (82.7)	254 (84.7)
Laparotomy	20 (13.3)	25 (16.7)	45 (15.0)
Laparoscopy, laparotomy	0	1 (0.7)	1 (0.3)
Had endometriosis surgery before? *n* (%)			
Yes	150 (100)	150 (100)	300 (100)
Time since endometriosis surgery, months[d]			
Median (range)	0.40 (0.1–113.4)	0.50 (0.1–102.9)	0.50 (0.1–113.4)
Mean (SD)	5.75 (17.55)	5.73 (17.28)	5.74 (17.39)
Age at menarche, year			
Median (range)	13.0 (10–19)	13.0 (10–16)	13.0 (10–19)
Mean (SD)	13.4 (1.5)	13.4 (1.1)	13.4 (1.3)
Number of pregnancies, *n* (%)			
0	51 (34.0)	64 (42.7)	115 (38.3)
1+	99 (66.0)	86 (57.3)	185 (61.7)
Number of births, *n* (%)			
0	65 (43.3)	76 (50.7)	141 (47.0)
1+	85 (56.7)	74 (49.3)	159 (53.0)
Number of days for shortest cycle, days			
Median (range)	28.0 (21–35)	28.0 (21 –35)	28.0 (21– 35)
Mean (SD)	27.9 (2.3)	27.7 (2.6)	27.8 (2.5)
Number of days for longest cycle, days			
Median (range)	30.0 (23–35)	30.0 (23–35)	30.0 (23–35)
Mean (SD)	29.8 (2.4)	29.4 (2.3)	29.6 (2.3)

BMI body mass index, *eCRF* electronic case report form, *PR* prolonged release, *SD* standard deviation

Note: denominators for percentages were based on the number of patients in the randomized population (which included all patients randomly allocated) in each treatment group for the relevant variable

[a] Age was reported from eCRF

[b] BMI was calculated as weight (kg)/height (m)^2

[c] Time since endometriosis diagnosis was calculated as (informed consent date minus date of endometriosis diagnosis + 1)/30.4375

[d] Time since endometriosis surgery was calculated as (informed consent date minus date of endometriosis surgery + 1)/30.4375

Table S3 Significant medical and surgical history at baseline (all randomized patients)

Primary system organ class Preferred term	**Triptorelin pamoate PR 3 month (*n* = 150)**	**Triptorelin acetate PR 1 month (*n* = 150)**	**Overall randomized patients (*N* = 300)**
	Patients, *n* (%)		
Total patients with any medical or surgical history	141 (94.0)	142 (94.7)	283 (94.3)
Blood and lymphatic system disorders	**28 (18.7)**	**36 (24.0)**	**64 (21.3)**
Anemia	27 (18.0)	32 (21.3)	59 (19.7)
Immune system disorders	**8 (5.3)**	**3 (2.0)**	**11 (3.7)**
Drug hypersensitivity	8 (5.3)	1 (0.7)	9 (3.0)
Infections and infestations	**58 (38.7)**	**41 (27.3)**	**99 (33.0)**
Pelvic inflammatory disease	29 (19.3)	16 (10.7)	45 (15.0)
Vaginal infection	9 (6.0)	7 (4.7)	16 (5.3)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	**34 (22.7)**	**39 (26.0)**	**73 (24.3)**
Uterine leiomyoma	30 (20.0)	33 (22.0)	63 (21.0)
Pregnancy, puerperium, and perinatal conditions	**14 (9.3)**	**7 (4.7)**	**21 (7.0)**
Abortion	9 (6.0)	3 (2.0)	12 (4.0)
Reproductive system and breast disorders	**71 (47.3)**	**78 (52.0)**	**149 (49.7)**
Adenomyosis	15 (10.0)	17 (11.3)	32 (10.7)
Dysmenorrhea	16 (10.7)	15 (10.0)	31 (10.3)
Ovarian cyst	8 (5.3)	6 (4.0)	14 (4.7)
Pelvic adhesions	16 (10.7)	19 (12.7)	35 (11.7)
Uterine polyp	9 (6.0)	11 (7.3)	20 (6.7)
Surgical and medical procedures	**103 (68.7)**	**109 (72.7)**	**212 (70.7)**
Abortion induced	17 (11.3)	13 (8.7)	30 (10.0)
Adhesiolysis	48 (32.0)	38 (25.3)	86 (28.7)
Cesarean section	28 (18.7)	34 (22.7)	62 (20.7)
Intestinal adhesion lysis	3 (2.0)	8 (5.3)	11 (3.7)
Myomectomy	16 (10.7)	12 (8.0)	28 (9.3)
Ovarian cystectomy	45 (30.0)	43 (28.7)	88 (29.3)
Salpingectomy	10 (6.7)	5 (3.3)	15 (5.0)
Uterine polypectomy	4 (2.7)	8 (5.3)	12 (4.0)

PR prolonged release

Note: one patient with more than one history in the same SOC/PT was counted once for the SOC/PT

Table S4 LS mean and LS mean change from baseline in serum E2, LH, and FSH concentrations at weeks 4, 8, and 12 (FAS)

		Triptorelin pamoate PR 3 month		Triptorelin acetate PR 1 month		Rate difference (PR 3 month minus PR 1 month)
		Value	Change from baseline	Value	Change from baseline	Change from baseline
E2 (pmol/L)						
Week 4	Patients, *n*	147	147	149	149	
	LS mean (95% CI)	24.473 (19.022, 29.924)	−177.002 (−182.452, −171.551)	19.069 (13.687, 24.450)	−182.405 (−187.787, −177.024)	5.404 (−2.257, 13.064)
Week 8	Patients, *n*	146	146	150	150	
	LS mean (95% CI)	46.066 (28.094, 64.038)	−155.408 (−173.381, −137.436)	22.116 (4.353, 39.878)	−179.359 (−197.121, −161.597)	23.950 (−1.331, 49.232)
Week 12	Patients, *n*	146	146	148	148	
	LS mean (95% CI)	35.601 (26.022, 45.181)	−165.873 (−175.452, −156.294)	26.847 (17.359, 36.334)	−174.628 (−184.115, −165.141)	8.755 (−4.731, 22.240)
LH (IU/L)						
Week 4	Number of patients	147	147	149	149	
	LS mean (95% CI)	0.661 (0.457, 0.865)	−2.764 (−2.968, −2.560)	0.501 (0.298, 0.703)	−2.924 (−3.127, −2.722)	0.160 (−0.128, 0.448)
Week 8	Number of patients	146	146	150	150	
	LS mean (95% CI)	0.442 (0.221, 0.662)	−2.983 (−3.204, −2.763)	0.257 (0.039, 0.476)	−3.168 (−3.386, −2.949)	0.184 (−0.126, 0.495)
Week 12	Number of patients	146	146	148	144	
	LS mean (95% CI)	0.323 (0.258, 0.389)	−3.102 (−3.167, −3.036)	0.252 (0.187, 0.317)	−3.173 (−3.238, −3.108)	0.072 (−0.021, 0.164)
FSH (IU/L)						
Week 4	Patients, *n*	147	147	149	149	
	LS mean (95% CI)	1.759 (1.557, 1.962)	−4.424 (−4.626, −4.221)	1.665 (1.465, 1.864)	−4.519 (−4.718, −4.319)	0.095 (−0.190, 0.379)
Week 8	Number of patients	146	146	150	150	
	LS mean (95% CI)	2.887 (2.682, 3.091)	−3.297 (−3.501, −3.092)	2.726 (2.525, 2.927)	−3.457 (−3.658, −3.256)	0.160 (−0.127, 0.448)
Week 12	Number of patients	146	146	148	148	
	LS mean (95% CI)	3.353 (3.132, 3.575)	−2.830 (−3.051, −2.609)	3.301 (3.083, 3.520)	−2.882 (−3.100, −2.664)	0.052 (−0.259, 0.363)

CI confidence interval, *E2* estradiol, *FAS* full analysis set, *FSH* follicle stimulating hormone, *IMP* investigational medicinal product, *LH* luteinizing hormone, *LS* least-square, *PR* prolonged release

LS means and CIs from a linear model for repeated measurements adjusting for baseline value and its interaction with visit, treatment group and its interaction with visit, and randomized strata and its interaction with treatment group. Baseline was defined as the last available assessment prior to the first dose of IMP

n was number of patients included in linear model

Table S5 TEAEs reported by 5% or more of patients in either treatment arm (safety set)

Primary system organ class Preferred term	**Triptorelin pamoate PR 3 month (*n* = 149)**	**Triptorelin acetate PR 1 month (*n* = 150)**	**Overall safety population (*N* = 299)**
	Patients, *n* (%) [E]		
Patients with at least one TEAE	132 (88.6) [389]	135 (90.0) [402]	267 (89.3) [791]
Gastrointestinal disorders	**17 (11.4) [19]**	**22 (14.7) [33]**	**39 (13.0) [52]**
Abdominal pain lower	4 (2.7) [4]	13 (8.7) [19]	17 (5.7) [23]
Abdominal pain upper	6 (4.0) [7]	8 (5.3) [10]	14 (4.7) [17]
Diarrhea	8 (5.4) [8]	4 (2.7) [4]	12 (4.0) [12]
General disorders and administration site conditions	**6 (4.0) [6]**	**8 (5.3) [9]**	**14 (4.7) [15]**
Pyrexia	6 (4.0) [6]	8 (5.3) [9]	14 (4.7) [15]
Infections and infestations	**58 (38.9) [74]**	**53 (35.3) [71]**	**111 (37.1) [145]**
Nasopharyngitis	16 (10.7) [19]	24 (16.0) [30]	40 (13.4) [49]
Upper respiratory tract infection	37 (24.8) [46]	27 (18.0) [34]	64 (21.4) [80]
Vaginal infection	8 (5.4) [9]	7 (4.7) [7]	15 (5.0) [16]
Investigations	**9 (6.0) [9]**	**8 (5.3) [8]**	**17 (5.7) [17]**
Protein urine present	9 (6.0) [9]	8 (5.3) [8]	17 (5.7) [17]
Musculoskeletal and connective tissue disorders	**18 (12.1) [33]**	**22 (14.7) [38]**	**40 (13.4) [71]**
Arthralgia	12 (8.1) [19]	13 (8.7) [15]	25 (8.4) [34]
Back pain	9 (6.0) [11]	9 (6.0) [10]	18 (6.0) [21]
Pain in extremity	2 (1.3) [3]	9 (6.0) [13]	11 (3.7) [16]
Nervous system disorders	**15 (10.1) [18]**	**18 (12.0) [22]**	**33 (11.0) [40]**
Dizziness	6 (4.0) [7]	9 (6.0) [11]	15 (5.0) [18]
Headache	10 (6.7) [11]	9 (6.0) [11]	19 (6.4) [22]
Psychiatric disorders	**14 (9.4) [14]**	**8 (5.3) [8]**	**22 (7.4) [22]**
Insomnia	14 (9.4) [14]	8 (5.3) [8]	22 (7.4) [22]
Reproductive system and breast disorders	**74 (49.7) [92]**	**73 (48.7) [88]**	**147 (49.2) [180]**
Menorrhagia	11 (7.4) [13]	6 (4.0) [6]	17 (5.7) [19]
Vaginal hemorrhage	66 (44.3) [79]	68 (45.3) [82]	134 (44.8) [161]
Respiratory, thoracic, and mediastinal disorders	**4 (2.7) [4]**	**8 (5.3) [9]**	**12 (4.0) [13]**
Oropharyngeal pain	4 (2.7) [4]	8 (5.3) [9]	12 (4.0) [13]
Skin and subcutaneous tissue disorders	**29 (19.5) [30]**	**25 (16.7) [25]**	**54 (18.1) [55]**
Hyperhidrosis	10 (6.7) [10]	12 (8.0) [12]	22 (7.4) [22]
Night sweats	19 (12.8) [20]	13 (8.7) [13]	32 (10.7) [33]
Vascular disorders	**86 (57.7) [90]**	**89 (59.3) [91]**	**175 (58.5) [181]**
Hot flash	86 (57.7) [90]	89 (59.3) [91]	175 (58.5) [181]

[E] number of events, *MedDRA* Medical Dictionary for Regulatory Authorities, *PR* prolonged release; *PT* preferred term, *TEAE* treatment-emergent adverse event

Note: if a patient experienced more than one event in a category, the patient was counted only once in that category. MedDRA version 22.1

Table S6 Triptorelin PK parameters based on final population PK model after the first injection of triptorelin pamoate PR 3-month formulation and triptorelin acetate PR 1-month formulations

	C_{max} (ng/mL)		t_{max}[a] (d)		C_{min} (ng/mL)		t_{min}[a] (d)		C_{last}[b] (ng/mL)		t_{last}[a] (d)		AUC_{last}[c] (ng.d/mL)	
Triptorelin formulation	**PR 3-month**	**PR 1-month**	**PR 3-month**	**PR 1-month**	**PR 3-month**	**PR 1-month**	**PR 3-month**	**PR 1-month**	**PR 3-month**	**PR 1-month**	**PR 3-month**	**PR 1-month**	**PR 3-month**	**PR 1-month**
n	149	150	149	150	149	150	149	150	149	150	149	150	149	150
Mean	26.9	5.30	-	-	0.0320	0.0429	-	-	0.0320	0.110	-	-	29.6	4.39
SD	1.68	0.302	-	-	0.00446	0.00842	-	-	0.00446	0.0727	-	-	2.50	0.590
SE	0.137	0.0247	-	-	0.000365	0.000687	-	-	0.000365	0.00594	-	-	0.205	0.0482
Min	23.5	3.88	0.0810	0.0810	0.0125	0.0143	80.8	20.9	0.0125	0.0143	80.8	24.0	22.0	3.07
Median	26.9	5.27	0.0830	0.0830	0.0328	0.0456	84.0	21.0	0.0328	0.102	84.0	28.0	29.8	4.35
Max	32.6	6.86	0.171	0.0860	0.0403	0.0734	91.0	35.0	0.0403	0.430	91.0	35.0	35.5	6.02
CV%	6.23	5.70	-	-	13.9	19.6	-	-	13.9	66.1	-	-	8.42	13.4
Geometric mean	26.9	5.29	-	-	0.0317	0.0419	-	-	0.0317	0.0880	-	-	29.5	4.35
Geometric CV%	6.13	5.71	-	-	16.9	23.6	-	-	16.9	79.4	-	-	8.64	13.6

AUC_{last} area under the curve to the last quantifiable concentration, *AUC_{tau}* area under the curve over a dosing interval, *C_{last}* last measurable concentration over a dosing interval, *C_{max}* maximum concentration over a dosing interval, *C_{min}* minimum concentration over a dosing interval, *C_{trough}* concentration at the end of a dosing interval, *CV* coefficient of variation, *max.* maximum, *min.* minimum, *N* number of patients in population, *PK* pharmacokinetic, *PR* prolonged release, *SD* standard deviation, *SE* standard error, *t_{last}* time to C_{last}, *t_{max}* time to C_{max}, *t_{min}* time to C_{min}

[a] For t_{last}, t_{min} and t_{max} only median, min., and max. were reported

[b] C_{trough} and C_{last} were equivalent and, therefore, only C_{last} was reported

[c] AUC_{tau} and AUC_{last} were equivalent and, therefore, only AUC_{last} was reported

Table S7 Triptorelin PK parameters based on final population PK model after the second injection of triptorelin pamoate PR 3 month

	C_{max} (ng/mL)	t_{max}[a] (d)	C_{min} (ng/mL)	t_{min}[a] (d)	C_{tau}[b] (ng/mL)	C_{last} (ng/mL)	t_{last}[a] (d)	AUC_{tau}[c] (ng.d/mL)	AUC_{last} (ng.d/mL)
n	143	143	143	143	143	143	143	143	143
N_{miss}	6	6	6	6	6	6	6	6	6
Mean	27.7	-	0.0322	-	0.0425	0.0136	-	32.1	34.2
SD	1.64	-	0.00422	-	0.00543	0.00490	-	2.18	2.10
SE	0.137	-	0.000353	-	0.000454	0.000410	-	0.183	0.176
Min.	21.5	0.0810	0.0145	0	0.0162	0.000272	163	23.4	25.3
Median	27.7	0.0830	0.0330	0	0.0437	0.0139	168	32.2	34.4
Max.	37.5	0.174	0.0403	0	0.0583	0.0268	170	45.1	47.1
CV%	5.92	-	13.1	-	12.8	36.1	-	6.79	6.14
Geometric mean	27.7	-	0.0318	-	0.0420	0.0120	-	32.1	34.1
Geometric CV%	5.60	-	15.3	-	15.9	72.5	-	6.55	5.96

AUC_{last} area under the curve to the last concentration, *AUC_{tau}* area under the curve over a dosing interval, *C_{last}* last measurable concentration over a dosing interval, *C_{max}* maximum concentration over a dosing interval, *C_{min}* minimum concentration over a dosing interval, *C_{tau}* observed concentration at the end of a dosing interval immediately before next administration, *CV* coefficient of variation, m*ax.* maximum, *min.* minimum, *N* number of patients in population, *N_{miss}* number of patients missing data, *PK* pharmacokinetic, *PR* prolonged release, *SD* standard deviation, *SE* standard error, *t_{last}* time to C_{last}, *t_{max}* time to C_{max}, *t_{min}* time to C_{min}

[a] For t_{last}, t_{min}, and t_{max} only median, min., and max. were reported

[b] C_{tau} was reported using a tau value of 84 days

[c] AUC_{tau} was computed using a tau value of 84 days

Supplementary materials: Further information on noncompartmental pharmacokinetic analysis

Objectives

To assess the pharmacokinetic (PK) parameters for the triptorelin pamoate prolonged release (PR) 3-month formulation and triptorelin acetate PR 1-month formulations, a noncompartmental PK analysis was performed in a subset of patients (the full PK/pharmacodynamic [PD] subgroup) who underwent a more extensive sampling strategy.

Data

Fourteen patients in each treatment arm were included in the PK/PD subgroup. Additional hormone samples (estradiol [E2], luteinizing hormone [LH], and follicle stimulating hormone [FSH]) were collected for PD assessments at weeks 1, 2, 3, and 32 in the full PK/PD subgroup. For triptorelin pamoate PR 3 month, data after the first and second (last) injection were used (473 triptorelin concentrations with 45 values below the lower limit of quantification [LLOQ]). For triptorelin acetate PR 1 month, data after the first injection and trough concentrations after the first, second, third, and sixth (last) injection were used, representing 222 triptorelin concentrations (with 14 values below the LLOQ for the noncompartmental analysis [NCA], while overall 278 samples were assayed).

Methods

NCA was only performed on PK data collected for the PK/PD subgroup and population PK analysis (modelling) was performed on PK data from all patients. NCA was performed using Statistical Analysis System (SAS)® software (version 9.4). For triptorelin pamoate PR 3 month, the following were assessed: PK parameters after the first injection, PK parameters after the second (last) injection, and comparison of PK parameters after the first and second injection. For triptorelin acetate PR 1 month, the following were assessed: PK parameters after the first injection, and comparison of trough concentrations after the first, second, third, and sixth (last) injection.

Results

No patients were excluded from the PK data set and no triptorelin concentrations were excluded; all available triptorelin concentrations were used for the NCA, including outliers.

Non-zero pre-dose triptorelin concentration (> LLOQ) was observed for one patient in the triptorelin pamoate PR 3-month group (with a concentration of 0.0774 ng/mL, corresponding to less than 5% of the maximum concentration over a dosing interval [C_{max}; 26.4 ng/mL]). C_{max} on the first time point was observed for one patient in the triptorelin pamoate PR 3-month group after the first injection (at time + 0.5h). For almost all patients in both groups, it was not possible to determine the elimination half-life associated with the terminal slope of the semi-logarithmic triptorelin concentration- time curve ($t_{1/2z}$), the main reason being that the adjusted square coefficient of regression was under 0.85.

Triptorelin pamoate PR 3-month group

After the first injection, median time to C_{max} (t_{max}) was 4 hours, with a corresponding median value of C_{max} of 23.9 ng/mL, associated with a moderate interindividual variability (31.2% coefficient of variation [CV]). The median value of concentration at the end of the dosing interval (C_{trough}) was 0.0697 ng/mL with a high interindividual variability (95.2% CV). The median value for the area under the curve over the dosing interval (AUC_{tau}), corresponding to the area under the curve from time 0 to the last quantifiable concentration (ng.d/mL) ($AUC_{0\text{-}last}$), was calculated at 33.4 ng.d/mL, with a low interindividual variability (19.6% CV).

After the last injection, t_{max} was 4 hours with a corresponding median value of C_{max} of 33.9 ng/mL, associated with a moderate interindividual variability (41.0% CV). Median value of C_{trough} was 0.0427 ng/mL with a moderate interindividual variability (52.0% CV). Median value for $AUC_{0\text{-}last}$ (or AUC_{tau}) was calculated at 33.7 ng.d/mL with a low interindividual variability (26.6% CV). There was no accumulation after the second injection of triptorelin pamoate PR 3 month (median accumulation ratio for AUC_{tau} (R_{AUC}) was around 1).

Triptorelin acetate PR 1-month group

After the first injection, t_{max} was 2 hours with a corresponding median value of C_{max} of 5.36 ng/mL, and interindividual variability around C_{max} was low (24.6% CV). The median value of C_{trough}, corresponding to C_{last}, was 0.151 ng/mL, with a high interindividual variability (75.3% CV). The median value for AUC_{tau} was calculated at 4.82 ng.d/mL with a low interindividual variability (28.1% CV).

There was no accumulation after repeat administration of triptorelin acetate PR 1-month formulation and steady-state was reached after the first injection, when looking at median C_{trough} values after the first, second, third, and sixth injection (0.151, 0.123, 0.137, and 0.149 ng/mL, respectively).

Conclusions

Maximum plasma concentration values were reached within a few hours for both triptorelin formulations. Geometric mean C_{max} was 4.5-times higher after injection of the triptorelin pamoate PR 3-month formulation than the triptorelin acetate PR 1-month formulation. Although C_{min} was higher (1.5–fold) for triptorelin acetate PR 1 month than for triptorelin pamoate PR 3 month, overall C_{min} ranges were similar for both formulations.

At the end of the dosing interval (28 days for triptorelin acetate PR 1 month and 84 days for triptorelin pamoate PR 3 month), C_{trough} was higher (1.8-fold) for triptorelin acetate PR 1 month than for triptorelin pamoate PR 3 month. However, ranges of C_{trough} were similar for both formulations.

After administration of triptorelin pamoate PR 3 month, the exposure was similar between the two injections ($R_{AUC} \approx 1$). After administration of triptorelin acetate PR 1 month, the values of the different C_{trough} show that steady-state was reached after the first injection and no accumulation was observed.

Supplementary Materials: Further information on the population pharmacokinetic and pharmacokinetic/pharmacodynamic analysis

Objectives

The objectives were to describe the population pharmacokinetics (pop PK), investigate relationships between triptorelin pharmacokinetic (PK) parameters and several covariates (such as body size, age), and perform an exploratory graphical analysis of the available estradiol (E2), luteinizing hormone (LH), and follicle stimulating hormone (FSH) concentrations.

Data

The final PK data set consisted of 299 patients who received triptorelin pamoate prolonged release (PR) 3 month (*n* = 149 patients) or triptorelin acetate PR 1 month (*n* = 150). The PK model was developed using patients from the PK/PD subgroup (two times 14 patients with rich PK sampling strategy), and then applied to the remaining patients with sparse PK sampling strategy (135 patients and 136 patients, respectively). Overall, 1686 triptorelin concentrations were used to compute individual PK parameters and 649 triptorelin concentrations to build the pop PK model and estimate the pop PK parameters.

For PD biomarkers, among the 1626 observations available, 922 observations were below the lower limit of quantification (LLOQ; 18.355 pmol/L) for E2 (representing 56.7% of the available data), one value was below LLOQ (0.028 IU/L) for LH, and all data were at or above the LLOQ (0.12 IU/L) for FSH.

Methods

The pop PK analyses were performed using the nonlinear mixed effects model (NONMEM) (version 7.3.0) and the first order conditional estimation (FOCE) method with Interaction [1]. R software (version 3.2.3) [2] or Statistical Analysis System (SAS)® software (version 9.4) were used for evaluation goodness-of-fit plots and model evaluation.

Exploratory graphical analysis of triptorelin concentrations and PD biomarkers (E2, LH, and FSH) was performed. NONMEM of the triptorelin concentration was based on a published pop PK model [3], using data from PK/PD subgroup patients with a rich PK sampling strategy (*n* = 14 in each treatment group), and using parameters for disposition and elimination from a previous study after intravenous (IV) administration. This was a multistage approach with the following steps.

1. Development of a pop PK model combining triptorelin data from the PK/PD subgroup of patients using data from the two formulations, starting with data after the first injection.
2. Search of covariates on absorption parameters, based on the selected pop PK model from step 1.
3. Simulations of triptorelin PK profile, at the population level, showing the effect of the covariates influencing triptorelin PK parameters.
4. Use of the final pop PK model defined in step 2, providing individual PK parameters for all randomized patients from the study (*n* = 299).

PK Results

An additional first-order absorption process from Romero et al. was required [3] to be able to describe triptorelin concentrations correctly after administration of the two formulations. Therefore, the PK model was a three-compartment disposition model with fixed parameters from a previous study after intravenous (IV) administration (data on file) and four absorption processes: one zero-order and three first-order processes associated with a lag time.

For the absorption processes, the same PK parameters were used for both PR formulations; only the fraction of the dose for each absorption process and the absolute bioavailability were different between the two PR formulations. Triptorelin clearance was fixed to 159 L/day (based on the previous IV study) and absolute bioavailability was estimated to be 0.439 for triptorelin pamoate PR 3 month and 0.334 for triptorelin acetate PR 1 month. The absorption processes started with a zero-order process with a duration of 0.119 days (2.86 hours), followed by a first first-order process

starting 0.0837 days (2.01 hours) after injection with an absorption rate constant of 1.57 once per day. Then, 1.72 days after injection, a new first-order process began with an absorption rate constant of 0.0441 once per day. Finally, the last first-order absorption process started 26.9 days after injection with an absorption rate constant of 0.0175 once per day.

For each PR formulation, the fraction of the dose going into each absorption process was different, as follows.

- For triptorelin pamoate PR 3 month: 20.0% of the dose for the zero-order absorption process (F2), 51.6% of the dose for the first first-order absorption process (F1), 15.0% of the dose for the second first-order absorption process (F3), and 13.4% of the dose for the third first-order absorption process (F4).
- For triptorelin acetate PR 1 month: 18.6% of the dose for the zero-order absorption process (F2), 11.8% of the dose for the first first-order absorption process (F1), 38.4% of the dose for the second first-order absorption process (F3), and 31.2% of the dose for the third first-order absorption process (F4).

The fraction of the dose going through the zero-order process seemed to be similar between the two formulations, while the majority of the dose was absorbed via the first first-order process for triptorelin pamoate PR 3 month and the second first-order process for triptorelin acetate PR 1 month.

Model-simulated triptorelin concentration–time profiles are illustrated in Supplementary Fig. 1a. Simulations, based on the design of this study, were performed using the population values of the PK parameters without taking into account interindividual variability. In Supplementary Fig. 1a, the dashed line represents the LLOQ value (0.01 ng/mL).

The final PK model was used to predict the individual PK parameters after the first injection for all patients who received triptorelin (Table 5). This model was also used to predict the individual PK

parameters after the second and last injection for all patients who received triptorelin pamoate PR 3 month (Supplementary Table 5). Of note, PK parameters reported in the tables listed above are in the same magnitude as those obtained after the noncompartmental analysis (NCA) performed on patients from the PK/PD subgroup.

PD Results

Only an exploratory graphical analysis was performed to compare the two triptorelin formulations on the PD biomarker data expressed as percentage change from baseline for all patients (Supplementary Fig. 1). Overall, when looking at the evolution over time for the three PD biomarkers, only small differences were observed between the two formulations, with a more sustained effect of triptorelin pamoate PR 3 month injection on E2 levels and no transient increase in E2 levels observed thereafter. The evolution of LH and FSH levels in function of time were very similar between the two formulations.

Conclusions

A relatively complex pop PK model was developed to satisfactorily describe triptorelin concentrations from the two formulations used in this study. Based on the current PK analysis, it seemed that the absolute bioavailability for triptorelin pamoate PR 3 month was slightly higher than for triptorelin acetate PR 1 month (0.439 and 0.334, respectively). The higher drug exposure, after dose correction, of triptorelin pamoate PR 3 month was consistent with the results from the NCA performed in the PK/PD subgroup.

Overall, when looking at the profile of the E2, LH, and FSH biomarkers over time, the profiles were similar for the administration of triptorelin pamoate PR 3 month and triptorelin acetate PR 1 month. Based on E2 levels, overall, patients reached castration levels between 21 days and 168 days after the first injection for both formulations, with few differences observed between the hormone profiles for both formulations. Once castration levels were achieved after the first injection, no transient increase of E2 levels was observed thereafter. Following the end of the dosing period at

day 168, triptorelin pamoate PR 3 month appeared to sustain castration levels for a longer period than triptorelin pamoate PR 1 month, which had a faster return to baseline levels of E2.

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