Clinical Trial Results Disclosure Synopsis

Name of Sponsor: Takeda Pharma GmbH
Viktoriaallee 3 – 5
52066 Aachen / Germany

Title of Study: 3 Months, Open-Label, Parallel-Group Study of the Pharmacodynamics, Pharmacokinetics and Safety of TAP-144SR 1-month Depot Gelatine-Free vs. Gelatine-Containing Formulation in Female Patients with Uterine Fibroids

Phase of Development: Phase II

Name of Active Ingredient: 5-oxo-L-prolyl-L-histidyl-tryptophyl-L-seryl-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide monoacetate (leuprorelin acetate)

Name of Finished Product: TAP-144SR (Leuprorelin acetate) gelatine-free (GF) 1 Month-Depot

Investigators: 10 principal investigators in Germany enrolled subjects for screening:

Study Sites: 7 sites in Germany enrolled subjects into the open-label treatment period

Publications Based on the Study (Citations) at Time of Study Completion: None

Study Period:

Date first subject signed informed consent form: 21 September 2006

Date of last subject's last visit/contact (from the Clinical database): 12 June 2008

Objectives:

To compare Leuprorelin Acetate Sustained Release (TAP-144SR) gelatine free (GF) with the existing TAP-144SR gelatine containing (GC) formulation, with respect to safety, tolerability, pharmacokinetics and pharmacodynamics.

Safety and tolerability:

Safety and tolerability were to be assessed by recording vital signs, results of physical examinations, any adverse events and laboratory safety variables.

Pharmacokinetics:

Pharmacokinetic parameters were to be computed from the individual serum concentration vs. time curves of leuprorelin.

Pharmacodynamics:

Serum concentrations of oestradiol, progesterone, luteinising hormone (LH) and follicle stimulating hormone (FSH) were to be measured.

Methodology:

This study was randomised, open-label, and parallel-group in design. 80 female patients were to be allocated to one of 2 groups of 40. On Day 0, 40 subjects were to receive a single subcutaneous (s.c.) dose of TAP- 144SR (GF) and 40 subjects were to receive a single s.c. dose of TAP-144SR (GC). Subjects had to receive a second injection of the study drug on Day 28, and a third injection on Day 56. They had then to return on Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77 and 84 for pharmacokinetic and pharmacodynamic blood sampling.

Number of Subjects:

Planned: 80 subjects (40 per treatment group)
Screened: 149 subjects
Enrolled in the open-label treatment period: 85 subjects
Analyzed: Full Analysis Set and Safety Set: 85 subjects; Per Protocol Set: 83 subjects

Diagnosis and Main Criteria for Inclusion:

1. Female patients with measurable uterine fibroids confirmed by vaginal or abdominal ultrasound, deemed otherwise healthy.
2. Age at least 18 years and premenopausal.
3. A body mass index (Quetelet index) in the range 18-28. Body Mass Index (BMI) = weight [kg]/(height [m])^2
4. Ability to understand the nature of the study and any hazards of participating in it. Ability to comply with the requirements of the entire study.
5. Willingness to give written consent to participate after reading the Consent Form, and after having the opportunity to discuss the study with an investigator or his deputy.
6. Oestradiol, progesterone, luteinising hormone (LH), follicle stimulating hormone (FSH) results within the range of normal ovarian function (17ß-oestradiol (E2): 44 – 300 pg/mL, progesterone (P): 0 – 30 ng/mL, FSH: 1.5 – 45.0 mU/mL; LH: 0 – 30 mU/mL). Progesterone values > 30 ng/mL were allowed if pregnancy or a corpus luteum cyst could be ruled out as the cause.)
7. Regular menstruation (except for symptoms of fibroids).

8. Willingness to use barrier contraception throughout the study. This did not apply to patients who had undergone tubal ligation.

Duration of Treatment: Active treatment: approximately 3 months; Prestudy phase: 1 to 28 days.

Test Product, Dose and Mode of Administration, and Lot Number:

Study Medication	Product Dose Strength and Form	Study Dosage	Mode of Administration	Drug Product Lot Number
TAP-144SR (GF)	1 Month-Depot 3.75 mg	3.75 mg / month	subcutaneous injection	Z397D011

Patients had to receive a single subcutaneous injection of TAP-144SR (GF) 1 Month-Depot at baseline (Day 0) and on Study Days 28 and 56.

Reference Therapy, Dose and Mode of Administration, and Lot Number:

Study Medication	Product Dose Strength	Study Dosage	Mode of Administration	Drug Product Lot Number
TAP-144SR (GC)	1 Month-Depot 3.75 mg (contains 0.65 mg purified gelatine)	3.75 mg / month	subcutaneous injection	S385/1

Patients had to receive a single subcutaneous injection of TAP-144SR (GC) 1 Month-Depot at baseline (Day 0) and on Study Days 28 and 56.

Criteria for Evaluation:

Efficacy:

Efficacy had to be assessed in terms of:

- Primary efficacy criterion was to demonstrate the non-inferiority of the GF formulation compared to the GC formulation in the suppression of oestradiol levels ≤ 30 pg/mL.
- Secondary:
  - Serum concentrations of oestradiol
  - LH
  - FSH
  - and progesterone measured using a validated radio-immuno assay (RIA) method
  - Serum concentration of TAP-144SR measured using a validated RIA method

Safety:

Safety had to be assessed in terms of:

- Adverse events
- Routine laboratory values (white blood cells (WBC), red blood cells (RBC), Haemoglobin, Haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), Platelets, Differential (Neutrophiles, Lymphocytes, Monocytes, Eosinophiles, Basophiles), Albumin, Alkaline Phosphatase, alanine aminotransferase (ALT) (GPT), aspartate aminotransferase (AST) (GOT), Bilirubin total, blood urea nitrogen (BUN) / Urea, Calcium, Chloride, Cholesterol total, creatinine kinase (CK), gamma-glutamyltransferase (γ-GT), Glucose, Phosphorous, Potassium, Sodium, Total Protein, Triglycerides, Uric Acid)
- Vital signs (blood pressure and heart rate)
- Physical examination results

Statistical Methods:

The primary endpoint was the percentage of measured 17β-oestradiol (E2) concentrations ≤ 30 pg/mL from Day 35 to the end of the study (Day 35 to Day 84, weekly measurements). The threshold level of 30 pg/mL is accepted by the Federal Institute for Drugs and Medical Devices of Germany. The primary objective of the study was to demonstrate the non-inferiority of the test formulation (GF) compared to the reference formulation (GC) in terms of the primary endpoint. The non-inferiority margin was determined to be 12.5% (absolute). The primary endpoint was to be evaluated confirmatorily in the per-protocol analysis (PP) (primary analysis). Additionally, the same evaluation was to be performed in the intention-to-treat analysis (exploratory).

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

The majority of patients were of Caucasian origin (39/41 (95.1%) and 43/44 (97.7%) in the GF and GC group). The average age overall was 42.4 ± 5.2 [43.0] (mean ± SD [median]) and was comparable across both treatment groups (42.4 ± 5.4 [43.0] GF vs. 42.5 ± 5.0 [43.0] GC). Height, weight and BMI were also comparable across the two treatment groups (height (cm): 166.6 ± 5.6 [167.0] GF vs. 166.0 ± 5.7 [166.0] GC; weight (kg): 66.9 ± 8.5 [65.0] GF vs. 68.0 ± 6.9 [67.0] GC; BMI (kg/m^2): 24.10 ± 2.62 [23.50] GF vs. 24.67 ± 2.18 [24.50] GC).

Prior medications were reported in 2/41 (4.9%) and 3/44 (6.8%) patients in the GF and GC group. At the screening ultrasound anteflexio uteri was observed in 38/41 (92.7%) and 36/44 (81.8%) patients in the GF and GC group, whereas a retroflexio was observed in 3/41 (7.3%) and 6/44 (13.6%) patients, respectively. The volume of the uterus at screening was assessed as

160.00 ± 84.59 [147.93] and 155.27 ± 95.89 [131.52] cm3 in the GF and GC group. The volume of the myoma at screening was assessed as 18.54 ± 28.37 [5.78] and 39.25 ± 72.12 [8.78] cm3 in the GF and GC group. Disease symptoms at screening were reported in 15/41 (36.6%) and 18/44 (40.9%) patients in the GF and GC group. At screening, FSH levels amounted to 4.60 ± 2.24 [3.90] and 4.78 ± 3.54 [3.80] mU/mL in the GF and GC group and LH amounted to 4.55 ± 4.00 [3.30] and 5.01 ± 3.99 [4.30] mU/mL, respectively.

Subject Disposition:

85 patients enrolled in the study were assigned to one of the two treatment groups according to the randomisation plan (41 patients to the gelatine-free (GF) and 44 patients to the gelatine-containing (GC) group). 85 patients received study medication at least once and provided at least one E2 level after the first injection. They were thus eligible for the safety analysis and included in the full analysis set (FAS) that was analysed according to the intention-to-treat principle. Two patients were excluded from the PP set that comprised 83 patients, 41 patients in the GF and 42 patients in the GC group.

Efficacy Results:

Primary efficacy variable:

The confirmatory primary endpoint was evaluated in the PP analysis (primary analysis). The average rate of oestradiol measurements ≤ 30 pg/mL over the observed period from Day 35 until Day 84 comprising 8 measurements amounted to 94.38 ± 13.26 [100.00] (mean ± [median]) and 85.06 ± 23.09 [100.00] % in the GF and GC group, respectively.

Non-inferiority of the GF formulation compared to the GC formulation in the suppression of oestradiol levels was confirmed using the Hodges-Lehmann estimator for the difference of medians. The lower bound of the (non-parametric, two-sided 95%) confidence interval for the difference of the test group minus reference group was 0.0 and thus greater than - δ (i.e. -0.125). The primary objective was also confirmed using the supportive two sample test for means with ADDPLAN software. All test results were reproduced in the intent-to-treat (ITT) analysis.

Secondary efficacy variables:

Both groups showed a "flare", a pronounced increase in oestradiol during the first 14 days after the first injection of the study drug on Day 0. However, 21 days after the first injection mean oestradiol levels were already suppressed below ≤ 30 pg/mL, especially in the GF group (8.20 ± 20.17 [3.19] and 23.59 ± 51.63 [4.64] pg/mL in the GF and GC group).

LH levels started to be clearly suppressed on Day 14 (V3) post injection. Compared to screening, LH levels were reduced by -2.36 ± 4.13 [-1.30] and -2.76 ± 3.88 [-2.30] mU/mL in the GF and GC group at Day 14. LH levels remained reduced until Day 84 (V13) (-4.34 ± 4.14 [-3.20] and -4.85 ± 4.11 [-3.80] mU/mL, respectively, difference compared to screening).

FSH levels started to be clearly reduced at Day 14 (V3) post injection. Compared to screening, FSH levels were reduced by -2.01 ± 2.74 [-1.80] and -1.87 ± 4.12 [-1.20] mU/mL in the GF and GC group on Day 14. FSH levels remained reduced compared to screening until approximately Day 56 (V9) when the initial values were reached again (0.02 ± 2.62 [0.50] and 0.27 ± 4.52 [1.35] mU/mL, respectively, difference compared to screening).

Progesterone levels started to be clearly reduced already on Day 0. Compared to screening, progesterone levels were reduced by -9.28 ± 7.16 [-9.02] and -9.43 ± 6.16 [-8.62] ng/mL in the GF and GC group on Day 0. Progesterone levels remained reduced compared to screening until the end of study on Day 84 (V13) (-9.70 ± 7.17 [-8.69] and -9.81 ± 6.24 [-10.14] ng/mL, respectively, difference compared to screening).

Pharmacokinetics of leuprorelin acetate:

Leuprorelin acetate levels showed a peak on Day 35 (V6) in both groups (236.18 ± 127.63 [201.50] and 188.74 ± 93.58 [167.00] pg/mL in the GF and GC group and remained on a comparable level until Day 84 (V13) (177.30 ± 85.59 [175.50] and 147.93 ± 90.33 [145.00] pg/mL, respectively.

This profile demonstrated that there was no uncontrolled accumulation of the study drug. On the contrary, after the second and third injection a steady state of leuprorelin acetate serum levels was observed without accumulation.

The area under curve (AUC) of leuprorelin was calculated using the linear trapezoidal rule. The arithmetic mean ± SD of the $AUC_{Day\ 28\text{-}84}$ was 11073.76 ± 4004.09 and 9088.90 ± 3323.08 pg/mL*day in the GF and GC group. The AUC of the GF formulation was clearly higher than the AUC the GC formulation (mean ratio GF/GC: 121.3 [112.9, 130.4] 90% confidence interval (CI)). Thus, the 90% confidence interval was outside the limits 80% and 125% for accepting equivalence. It should be remembered that bioequivalence based on drug concentration is a surrogate for bioequivalence based on pharmacodynamics.

Other efficacy variables:

Compared to screening, the size of myoma decreased by approximately 50% in both groups, from 18.54 ± 28.37 [5.78] and 39.25 ± 72.12 [8.78] cm^3 in the GF and GC group to 8.24 ± 15.38 [2.57] and 16.64 ± 35.84 [1.81] cm^3, respectively, on Day 84 (Visit 13).

Except for one patient in the GC group with persistent moderate pelvic tenderness, all symptoms (dysmenorrhoea, dyspareunia, pelvic pain and pelvic tenderness) vanished until Visit 13.

Safety Results:

Starting with the first administration of study medication, 81 adverse events (AEs) were observed in 31/41 (75.6%) patients in the GF and 85 AEs were observed in 33/44 (75.0%) patients in the GC group during the course of the trial. The most frequently affected system organ class (SOC) was vascular disorders (17 AEs in 16/41 (39.0%) and 20 AEs in 17/44

(38.6%) patients in the GF and GC group). Most frequent preferred terms were hot flush (16 AEs in 15/41 (36.6%) and 18 AEs in 16/44 (36.4%), patients, respectively) and headache (12 AEs in 8/41 (19.5%) and 20 AEs in 12/44 (27.3%) patients, respectively).

One serious AE (abdominal wall abscess) was observed during the treatment phase in a GC patient.

During the treatment phase, 48, respectively 57 AEs of mild intensity were observed in 24/41 (58.5%) and 23/44 (52.3%) patients in the GF and GC group. 31 AEs and 26 AEs of moderate intensity in the GF and GC group, respectively, affected 17/41 (41.5%) and 18/44 (40.9%) patients, respectively.2 AEs of severe intensity in each group were observed in 2/41 (4.9%) patients in the GF group (viral infection, arthritis) and 2/44 (4.5%) patients in the GC group (abdominal wall abscess, headache).

The majority of AEs were assessed as recovered in outcome (79 AEs in 30/41 (73.2%) and 83 AEs in 32/44 (72.7%) patients in the GF and GC group). 1 AE in 1/41 (2.4%) and 2 AEs in 2/44 (4.5%) patients in the GF and GC group were considered as not yet recovered at the end of the study, whereas the outcome was unknown in one patient in the GF group.

36 AEs in 17/41 (41.5%) and 36 AEs in 17/44 (38.6%) patients in the GF and GC group were classified as having no or unlikely causal relationship to the study drug. 7 AEs in 4/41 (9.8%) and 4 AEs in 4/44 (9.1%) patients in the GF and GC group with a definite causal relationship to the study medication were observed. This concerned a total of 6 cases of injection site swelling or reaction and 5 cases of hot flush. 23 AEs in 17/41 (41.5%) and 28 AEs in 20/44 (45.5%) patients in the GF and GC group were assessed as probably related to the study medication, while 15 AEs in 9/41 (22.0%) and 17 AEs in 9/44 (20.5%) patients, respectively, with possible causality were observed.

Clinically relevant deviations of safety laboratory parameters from the normal range were observed in one patient in the GF group (CK increase) and two patients in the GC group (increases of transaminases and bilirubin). Vital signs were comparable in both groups and showed marginal changes during the study. The only change in the number of patients with abnormal physical exam findings was one patient in the GF group on Day 0 with additional abnormal findings of the skin and adnexa.

Conclusion:

TAP-144SR (GF) 1M-Depot generated a stable and therapeutically effective serum concentration of leuprorelin. The primary objective, non-inferiority of the GF formulation compared to the GC formulation in the suppression of oestradiol levels was confirmed using the Hodges-Lehmann estimator for the difference of medians. Decrease of progesterone, LH and FSH levels was comparable in both treatment groups. Shrinking of myomas was comparable in both groups and symptoms of the disease vanished almost completely in both groups. Serum concentrations of

leuprorelin acetate were slightly but significantly higher in the GF compared to the GC group. Safety and tolerability was comparable in both formulations. No unexpected events from GC experience was observed after GF treatment. The GF formulation is at least as effective as the GC formulation and both formulations have a comparable safety profile. No clinically relevant differences were found, and thus both formulations are interchangeable.

Significant Changes During Study:

There were four amendments to the protocol which implemented the following changes: editorial changes regarding the exclusion criteria (including the gynaecologic conditions acute pelvioperitonitis, ovarian cysts, persistent corpus luteum; history of bilateral oophorectomy and hysterectomy or hypophysectomy), measurement of oestradiol (liquid chromatography-mass spectrometry/ mass spectrometry ((LC-MS/MS) method), performance of pregnancy urine test (human chorionic gonadotropin (ß-HCG)), examination of urine for the presence of leucocytes, the option to replace patient withdrawn from the study was removed, storing and processing of blood samples, additional analysis of LH and FSH hormone levels, requirement of non-hormonal contraceptives, the role of the case report form (CRF) as source document and data protection. Further, the CRF was intended to be the source document for demographic data, vital signs and time of taking the blood samples, it was specified that a complete physical examination should only take place at Visit S and 1, the normal ranges for E2 and progesterone (P) were redefined and the condition to conduct visits on Days 7, 14, 21, 35, 49, 63, 70 and 77 (± 1 day) only in the morning was omitted, the condition to conduct the visit on Day 0 only in the morning was omitted, the normal ranges for LH and FSH were redefined and the condition to take samples during the mid-luteal phase was omitted, the requirement to perform the screening visit during the mid-luteal phase was omitted, however, visit should not take place during menstruation.

Study ID Number:

ENG K001 GF

Other Study ID Number(s):

2005-005641-19 [EudraCT Number]

EC 406 [Takeda ID]

U1111-1114-2217 [Registry ID: WHO]

DATE OF DISCLOSURE SYNOPSIS: 13 June 2012