Annex 30
to Procedure for Conducting Expert Evaluation of Materials Pertinent to Medicinal Products, which are Submitted for State Registration (Re-Registration), as well as the Expert Evaluation of Materials about Introduction of Changes to the Registration Documents during the Validity Period of Registration Certificate
(paragraph 4, section IV)

Clinical Trial Report № 11

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate 40 mg/1 mg/0.5 mg film-coated tablet)
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	A Study to Determine the Effect of Rifampin on the Pharmacokinetics of Relugolix in Healthy Adult Subjects. **(MVT-601-1004)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 16.01.2017. to 21.03.2017.
8. Countries where the clinical trial was conducted	This study was conducted at a single center in the United States.
9. Number of subjects	planned: 18 actual: 18
10. Purpose and secondary objectives of the clinical trial	Primary objective was to compare plasma PK parameters of single-dose oral relugolix alone and after repeat-dose oral rifampin administration. Secondary objective was to determine the safety and tolerability of single-dose oral relugolix alone and after repeat-dose oral rifampin.
11. Clinical trial design	Open-label, single-sequence, cross-over, drug-drug interaction study
12. Key inclusion criteria	A subject was eligible for inclusion in this study only if all of the following criteria applied: 1.Was healthy as determined by a responsible and experienced investigator, based on a medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring. 2. Male or female between 18 and 55 years of age inclusive, at the time of signing informed consent. 3. A male subject was willing to adhere to the contraception requirements 4. A female subject was eligible to participate if she was of: • Non-childbearing potential • Child-bearing potential and agreed to use one of the contraception methods 5. Body weight ≥50 kg for men and ≥45 kg for women and body mass index within

	the range 18.5-32.0 kg/m2 (inclusive). 6. Capable of giving written informed consent.
13. Investigational medicinal product, method of administration, strength	Relugolix 40-mg Tablets
14. Comparator, method of administration, strength	Rifampin 300 mg Capsules /600 mg (2 capsules) oral/
15. Concomitant therapy	Acetaminophen at doses of ≤ 2 grams/day was permitted for use any time during the study. Non-sedating antihistamines and decongestants were administered on an as needed basis. Other concomitant medication was considered on a case-by-case basis by the investigator for treatment of a medical need in consultation with the study director.
16. Efficacy evaluation criteria	Not applicable
17. Safety evaluation criteria	Symptoms and signs, vital signs, ECGs, clinical laboratory assessments and adverse events.
18. Statistical methods	Plasma concentrations of relugolix were determined by the bioanalytical laboratory (QPS, Newark, DE) using a validated analytical procedure (liquid chromatography/tandem mass spectrometry [LC/MS/MS]) The effect of rifampin on the plasma PK of relugolix was analyzed using a mixed effect model with treatment as a fixed effect and subject as a random effect. The PK parameters was natural log-transformed prior to analysis. The geometric least squares mean ratios and 90% CIs were estimated between the relugolix + rifampin treatment (Test) and the relugolix alone treatment (Reference) for AUC0-∞, AUC0-t, and Cmax by taking the exponential of mean differences and the corresponding 90% CIs.
19. Demographic data of the study population (gender, age, race, etc.)	The median age of subjects in this study was 32.5 years (range 19 to 55 years). The majority of subjects were male (13 of 18 subjects [72.2%]), were mostly White (14 of 18 subjects [77.8%]), with ethnicity evenly distributed between Hispanic and not Hispanic or Latino (each with 9 of 18 subjects [50.0%])
20. Efficacy outcomes	Not applicable.
21. Safety outcomes	• There were no severe treatment-emergent adverse events, serious adverse events, or deaths reported during the study. • In general, the number and frequency of treatment-emergent adverse events were similar following a single oral dose of relugolix 40 mg and following co-administration of a single dose of relugolix 40 mg with rifampin 600 mg QD followed by rifampin 600 mg QD for 4 days, but were greatest in number and frequency following rifampin 600 mg QD for 7 days. • Safety assessments including vital signs, physical examinations, clinical laboratory tests, and ECG data were overall unremarkable. • One partner pregnancy was reported, with estimated conception approximately 2 months after the last dose of relugolix and rifampin.
22. Conclusion (summary)	In this population of 18 healthy male and female subjects treated with relugolix 40 mg alone, relugolix 40 mg co-administered with rifampin 600 mg, and rifampin 600 mg alone, the study data support the following conclusions: • The geometric mean relugolix Cmax was 23% lower and the AUC0-∞ was 55% lower when pretreated and co-administered with rifampin compared to relugolix alone.

	• The elimination half-life of relugolix was similar with and without pretreatment and co-administration with rifampin.
Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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(paragraph 4, section IV)

Clinical Trial Report № 12

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate 40 mg /1 mg/0.5 mg film-coated tablet)
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	A Phase 1, open-label study to evaluate the pharmacokinetic drug-drug interaction between multiple doses of TAK-385 and a panel of Cytochrome P-450 substrates administered concomitantly as an indiana cocktail in healthy subjects. **(TAK-385-102)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 28.07.2008. to 29.08.2008.
8. Countries where the clinical trial was conducted	This study was conducted at a single center in the United States.
9. Number of subjects	planned: 16 actual: 16
10. Purpose and secondary objectives of the clinical trial	The primary objective of this study was to evaluate the effects of multiple doses of TAK-385 (20 mg) on the pharmacokinetic profiles of key cytochrome P-450 (CYP) isoenzyme probe substrates (caffeine, tolbutamide, dextromethorphan, and midazolam) and their metabolites administered concomitantly as a drug cocktail. The secondary objective of this study was to evaluate the safety and tolerability of multiple doses of TAK-385 administered alone and in the presence of the drug cocktail in healthy subjects.
11. Clinical trial design	This was a phase 1, open-label, single sequence study.
12. Key inclusion criteria	Healthy Adult Men and Women
13. Investigational medicinal product, method of administration, strength	Relugolix 20-mg Tablets oral
14. Comparator, method of administration, strength	Not applicable

15. Concomitant therapy	Indiana Drug Cocktail Caffeine 200 mg Tablet Oral Dextromethorphan 30 mg Gelcap Oral Midazolam 4 mg Solution Oral Tolbutamide 500 mg Tablet Oral
16. Efficacy evaluation criteria	Not applicable
17. Safety evaluation criteria	Physical examination findings, vital sign measurements, 12-lead ECGs, clinical laboratory tests, and adverse event monitoring was used for safety monitoring. Summary statistics were used in the analysis of adverse events, laboratory test variables, and vital signs.
18. Statistical methods	A mixed analysis of variance model was used to assess equivalence between Day 1 and Day 10 pharmacokinetic profiles for each CYP probe substrate. Steady state analysis of TAK-385 was performed using the natural logarithms of Ctrough by using a mixed analysis of variance model. All safety assessments were presented in data listings and summarized using descriptive statistics, where deemed appropriate.
19. Demographic data of the study population (gender, age, race, etc.)	Participants were healthy women (10) and men (6) with a the mean age of 34.9 years, and a mean weight of 72.04 kg. There were 12 White and 4 African American.
20. Efficacy outcomes	Not applicable.
21. Safety outcomes	A total of 24 adverse events were reported by 11 of 16 subjects (68.8%) during the study. Of the 11 subjects who experienced adverse events, 9 subjects experienced 1 or more adverse events that were considered possibly, probably, or definitely related to study drug. No serious adverse events were reported and no deaths occurred during the study. All reported adverse events were rated as of mild intensity.
22. Conclusion (summary)	Multiple dosing with TAK-385 (20 mg QD) for 7 days does not have a clinically relevant effect on the pharmacokinetic profiles of key CYP isoenzyme substrates (caffeine [1A2], tolbutamide [2C9], dextromethorphan [2D6], and midazolam [3A4]) and their metabolites administered concomitantly as a drug cocktail. Multiple doses of TAK-385 administered alone and in the presence of the drug cocktail to healthy subjects were well tolerated. All adverse events were mild and no subject discontinued from the study. There were no clinically relevant changes in laboratory test results, vitals signs, or ECG. Given the marginal extent of the pharmacokinetic interactions observed in this study between TAK-385 and the CYP isoenzyme substrates in the drug cocktail, TAK-385 is unlikely to show clinically significant pharmacokinetic interactions with other CYP 1A2, 2C9, 2D6, and 3A4 substrates.

Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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Clinical Trial Report № 13

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate from 40 mg/1 mg/0.5 mg film-coated tablet)
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	A Phase I, Double-Blind, Randomized, Placebo-Controlled, Sequential-Panel, Ascending Single- and Multiple-Dose Study to Evaluate the Effect of TAK-385 (relugolix) on Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics in Healthy Premenopausal Women. **(TAK-385/CPH-001)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 29.08.2007. to 12.08.2008.
8. Countries where the clinical trial was conducted	This study was conducted at a single center in Japan.
9. Number of subjects	planned: 144 actual: 169
10. Purpose and secondary objectives of the clinical trial	The study objective was to evaluate the safety, pharmacokinetics, and pharmacodynamic effects of TAK-385 (relugolix) in healthy Japanese adult premenopausal women following single and 14-day repeated (once daily) oral doses in a double-blind, placebo-controlled manner. In addition, the effects of food on the safety and pharmacokinetics of TAK-385 (relugolix) were determined in a crossover manner.
11. Clinical trial design	Randomized, double-blind, placebo-controlled, parallel-group, single/multiple-dose design open-label, crossover design
12. Key inclusion criteria	Healthy Japanese adult premenopausal women
13. Investigational medicinal product, method of administration, strength	Relugolix from 1 mg to 80 mg Tablets oral
14. Comparator, method of administration, strength	Placebo
15. Concomitant therapy	Any prescribed and OTC drugs, vitamins, Chinese herbal medicines, and supplements (including St. John's Wart, Korean ginseng, kava-kava, gingko, and melatonin) were prohibited from 28 days prior to the

	initiation of the study drug administration until completion of the post-study observation period in each Step. However, when the investigator or subinvestigator recognized the necessity for treatment of adverse events etc., administration of the above drugs was permitted. In addition, single use of acetaminophen for algomenorrhea etc. was permitted.
16. Efficacy evaluation criteria	Not applicable
17. Safety evaluation criteria	Adverse events, vital signs, body weight, ECG, ophthalmological examination and laboratory tests.
18. Statistical methods	Descriptive statistics were used to summarize the continuous data of vital signs, body weight, 12-lead ECG findings, ophthalmological findings, and laboratory test variables. The changes from baseline were also summarized. The categorical data of those were summarized with cross-tabulations. Shifts from baseline were summarized for each dose group. Descriptive statistics were used to summarize the plasma and urinary concentrations of TAK-385 at each scheduled time point by treatment group. The concentration-time profiles (individual plot and mean with standard deviation plot) were provided by treatment group. Pharmacokinetic parameters of TAK-385 were determined for each subject in the pharmacokinetics population. Descriptive statistics were used to summarize the pharmacokinetic parameters by treatment group.
19. Demographic data of the study population (gender, age, race, etc.)	Volunteers were healthy Japanese adult premenopausal women, mean age was 27.1 years, mean BMI was 20.87.
20. Efficacy outcomes	Not applicable.
21. Safety outcomes	The adverse events that were commonly observed through the whole study were menstruation irregular. The incidence of adverse events was not clearly different among the administration under fasted condition, after breakfast, and before breakfast. Mild blood potassium increased observed in 1 subject taking 40 mg after breakfast in the multiple-dose phase was an adverse event leading to discontinuation of the study drug administration, but returned to normal after the discontinuation. No serious adverse event and no death were reported in the whole study.
22. Conclusion (summary)	The single oral dose up to 80 mg and the 14-day repeated oral dose up to 40 mg of TAK-385 (relugolix) were well tolerated in the healthy Japanese premenopausal women. There were no clinically significant changes or abnormalities observed in the safety assessments performed. The pharmacokinetics of TAK-385 (relugolix) was over dose proportional over a dose range of 1 mg to 80 mg under fasted conditions, however, it was dose proportional from 10 mg to 40 mg in after breakfast administration. TAK-385 (relugolix) accumulated in the body with 14-day repeated dose, however the concentrations of TAK-385 (relugolix) attained to steady state within 7 days. The urinary excretion ratio of TAK-385 (relugolix) was less than 3.5% of dose. Food intake reduced plasma TAK-385 (relugolix) concentrations. TAK-385 (relugolix) reduced serum LH, E2, FSH, and progesterone concentrations. Serum E2 concentrations were maintained below a menopausal level during 14-day repeated dose of TAK-385 (relugolix)

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Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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(paragraph 4, section IV)

Clinical Trial Report № 14

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate 40 mg/1 mg/0.5 mg film-coated tablet)
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	A Phase 1, Open-label, Drug-drug Interaction Study to Evaluate the Effects of Multiple Oral Doses of Erythromycin on the Pharmacokinetics of a Single Oral Dose of TAK-385 (relugolix) in Healthy Adult Male and Female Subjects **(TAK-385/CPH-010)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 29.05.2012. to 12.07.2012.
8. Countries where the clinical trial was conducted	Subjects were enrolled in the Treatment Period at one site in Japan.
9. Number of subjects	planned: 20 actual: 20
10. Purpose and secondary objectives of the clinical trial	The primary objective of this study was to investigate the effect of erythromycin on the pharmacokinetics of a single oral dose of TAK-385 (relugolix) in healthy Japanese adult male and female subjects. Secondary Objective was to investigate the effects of erythromycin on the safety and tolerability of a single oral dose of TAK-385(relugolix) in healthy Japanese adult male and female subjects.
11. Clinical trial design	This was a phase 1, open-label, drug-drug interaction study.
12. Key inclusion criteria	Healthy Japanese Adult Men and Women
13. Investigational medicinal product, method of administration, strength	Relugolix 20-mg Tablets oral
14. Comparator, method of administration, strength	Not applicable
15. Concomitant therapy	Erythromycin 100-mg tablet 1200 mg/day (300 mg each 4 times daily) Oral
16. Efficacy evaluation criteria	Not applicable
17. Safety evaluation criteria	Adverse events (AEs), vital signs, weight, electrocardiogram (ECG), and clinical laboratory tests

18. Statistical methods	(1) Plasma concentration The plasma concentrations of TAK-385 (relugolix) was summarized by each administration condition (TAK-385 (relugolix) alone, and in combination with erythromycin), over each scheduled sampling interval using descriptive statistics. Plot of time profiles for TAK-385 (relugolix) plasma concentrations (individual data, and for arithmetic means with standard deviation (SD) data for each) were generated by each administration condition. The pharmacokinetic (PK) parameters [excluding AUMC(0-tlqc) and AUMC(0-inf)] were summarized by each period using descriptive statistics. Two-sided confidence intervals (CIs) (confidence coefficient level; 90% and 95%) of the ratio between the administration condition (combination / alone) were calculated, based on analysis of variance (ANOVA) with natural log-transformed AUC(0-inf), AUC(0-120), AUC(0-tlqc), and Cmax of TAK-385 (relugolix) as dependent variables and administration condition as fixed effects. The above analysis was also performed without log-transformation, for reference. The log-transformed Tmax, MRT, and λz were also to be evaluated in the same way, as required. In addition, some analyses relating to gender were performed. (2) Urinary excretion ratio The cumulative urinary excretion ratios of TAK-385 (relugolix) (% of dose) were summarized by each administration condition over each scheduled sampling interval, using descriptive statistics. Plots of time profiles for TAK-385 (relugolix) cumulative urinary excretion ratios (individual data, and arithmetic means with SD data for each) were generated by each administration condition.
19. Demographic data of the study population (gender, age, race, etc.)	A total of 48 subjects were screened for this study. Of these, 20 subjects received the study drug. In the PK analysis set, the age (mean ± SD) was 27.8 ± 3.88 years in the male subjects, 24.4 ± 3.44 years in the female subjects and 26.1 ±3.97 years in the combined male/female subjects; the height was 170.1 ± 3.54 cm, 157.5 ± 4.33 cm and 163.8 ± 7.52 cm, respectively; the weight was 65.34 ± 6.014 kg, 50.25 ± 6.470 kg and57.80 ± 9.843 kg, respectively; the BMI was 22.49 ± 1.488 kg/m2, 20.17 ± 1.947 kg/m2 and 21.33 ± 2.064 kg/m2, respectively, showing no significant differences between male and female subjects except for height and weight.
20. Efficacy outcomes	Not applicable.
21. Safety outcomes	In the safety analysis set, the incidence of TEAEs was 35% (7/20 subjects, 7 events) in all of the subjects. The incidence of TEAEs of each treatment period was 5% (1/20 subjects, 1 event) in the relugolix -alone period, 0% (0/20 subjects, 0 events) in the erythromycin-alone period, and 30% (6/20 subjects, 6 events) in the combination period. All the TEAEs were reported only in the female subjects (70%, 7/10 subjects, 7events). The details were menstruation irregular (50%, 5/10 female subjects), metrorrhagia (10%, 1/10 female subjects), and diarrhoea (10%, 1/10 female subjects). Any of these TEAEs were considered related to the study drug, mild in severity, and recovered without any treatment. No clinically significant changes in clinical laboratory tests (serum chemistry, hematology, and urinalysis), vital signs, weight, and ECG results were observed in any subjects.
22. Conclusion (summary)	When TAK-385 (relugolix) was administered in combination with erythromycin, the exposure of TAK-385 (relugolix) in plasma was

	increased by about 6 times. There was no difference in T1/2 and renal clearance (CLr) between the combination period and the -relugolix alone period.
Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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Clinical Trial Report № 15

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate 40 mg /1 mg/0.5 mg film-coated tablet)
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	An Open-Label, Single-Centre, Two Part Phase 1 Mass Balance Study to Assess the Absorption, Distribution, Metabolism, Excretion and Absolute Bioavailability of Orally Administered [^{14C}]-TAK-385 in Healthy Male Subjects (Mass Balance Phase). **(TAK-385/1009)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	01.10.2014.
8. Countries where the clinical trial was conducted	This study was conducted at a single center in the United Kingdom.
9. Number of subjects	planned: 12 actual: 12
10. Purpose and secondary objectives of the clinical trial	The objectives of this study were: (a) Mass balance of total radioactivity in urine and fecal samples will be assessed (b) Percent recovery of total dosed radioactivity excreted in urine and feces.
11. Clinical trial design	This was a two-part phase 1, open-label, single centre, absorption, distribution, metabolism, excretion (ADME) and absolute bioavailability (AB) study.
12. Key inclusion criteria	Healthy Adult Men
13. Investigational medicinal product, method of administration, strength	relugolix ([^{14}C]-TAK-385) 80 mg solution, oral relugolix 40 mg tablets, oral relugolix ([^{14}C]-TAK-385) 80 μg infusion, intravenous
14. Comparator, method of administration, strength	Not applicable
15. Concomitant therapy	Not applicable
16. Efficacy evaluation criteria	Not applicable

17. Safety evaluation criteria	Not applicable
18. Statistical methods	Not applicable
19. Demographic data of the study population (gender, age, race, etc.)	All subjects were male in the study, as dictated by the study entry criteria. In Part 1, the mean age of subjects was 40.5 years, mean weight was 82.00 kg, and mean BMI was 27.30 kg/m2; all subjects but one were White. In Part 2, mean age of subjects was 44.5 years, mean weight was 90.70 kg, and mean BMI was 28.42 kg/m2; all subjects were White. Demographics were similar between subjects in Part 1 and Part 2 of the study.
20. Efficacy outcomes	Not applicable.
21. Safety outcomes	Not applicable
22. Conclusion (summary)	• Following administration of a single oral dose of [^{14}C]-TAK-385 80 mg solution, the mean (SD) cumulative recovery was 87.1% (6.2%) of the administered radioactivity. The time course of excretion of total radioactivity showed that material was predominantly excreted in feces, with <5.5% of the radioactivity excreted in urine. • Following administration of a single oral dose of [^{14}C]-TAK-385 80 mg solution, distribution of [^{14}C]-TAK-385 into red blood cells was limited, with a mean blood-to-plasma ratio of 0.78 (%CV, 8%). • Following administration of an IV microtracer dose of [^{14}C]-TAK-385 80 µg, the mean concentration-time profile of total radioactivity showed a rapid distribution phase followed by a prolonged terminal elimination phase, with a mean $t_{1/2z}$ of approximately 111 hours (~4.6 days) in plasma. Mean plasma CL of TAK-385 was 29.4 L/hr, with low intersubject variability (range, 24.0-34.5 L/hr). • The mean estimate of absolute bioavailability (F) of TAK-385 was 11.6% (range, 6.0%-24.8%). • Following administration of a single dose of [^{14}C]-TAK-385 80 mg solution, approximately 42% to 68%, 2% to 4%, and 1% to 5% of the radioactivity in plasma was associated with TAK-385, Metabolites A and B, and Metabolite C, respectively, over a 72-hour sampling period. In human feces, TAK-385 and Metabolite C were the major components, accounting for 4.2% (mean) and 40.6% of the dose, respectively. In urine, TAK-385 accounted for 2.2% of the dose, and none of the metabolites were detected. The remaining radioactivity in both urine and feces was comprised of a number of unidentified metabolites and background radioactivity, with each unidentified metabolite accounting for <3% of the dose. • Following administration of an IV microtracer dose of [^{14}C]-TAK-385 80 µg, mean recovery of radioactivity up to 72 hours postdose was approximately 26% (range, 14%-42%) in feces, which is indicative of biliary excretion and/or intestinal secretion, and approximately 13% (range, 10%-17%) in urine.

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	• Single oral and IV doses of TAK-385 were safe and well tolerated as administered to healthy male subjects in this study.
Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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Clinical Trial Report № 16

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate 40 mg/1 mg/0.5 mg film-coated tablet)
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	A Phase 1, Randomized, Open-label, Crossover Study to Assess Food Effect on Single Oral Dose Administration of TAK-385 Final Formulation in Premenopausal Healthy Adult Women. **(TAK-385-1011)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 04.07.2016. to 31.08.2016.
8. Countries where the clinical trial was conducted	This study was conducted at a single study site in Japan.
9. Number of subjects	planned: 34 actual: 12
10. Purpose and secondary objectives of the clinical trial	Primary objective of this study was to evaluate food effect on the pharmacokinetics of a single oral dose of TAK-385 in Japanese premenopausal healthy adult women. Secondary Objective was to evaluate food effect on the safety of a single oral dose of TAK-385 in Japanese premenopausal healthy adult women.
11. Clinical trial design	This was a phase 1, randomized, open-label, crossover study.
12. Key inclusion criteria	Premenopausal healthy adult women
13. Investigational medicinal product, method of administration, strength	Relugolix 40 mg Tablets, oral, single-dose
14. Comparator, method of administration, strength	NA
15. Concomitant therapy	Subjects were instructed not to take any medications including over-the-counter products, without first consulting with the investigator.
16. Efficacy evaluation criteria	Efficacy was not assessed in this study.

17. Safety evaluation criteria	The safety endpoints included AEs, vital signs, weight, ECG findings, and laboratory test results.
18. Statistical methods	For the plasma concentration of unchanged TAK-385, descriptive statistics at each protocol specified blood sampling time point were calculated for each dosing condition (fasted conditions without breakfast, before breakfast, and after breakfast), and the concentration (individual subjects and mean/SD) versus time plots under these dosing conditions were provided. For the pharmacokinetic parameters of unchanged TAK-385, the descriptive statistics were calculated for each dosing condition. For AUC120, AUClast, AUC∞, and Cmax, geometric means and coefficients of variation were also calculated for each dosing condition. For the pharmacokinetic parameters except for AUC120, AUClast, AUC∞, Cmax, and tmax, coefficients of variation were also calculated for each dosing condition. In addition, based on a mixed effect model with natural log-transformed AUC120, AUClast, AUC∞, and Cmax of unchanged TAK-385 as dependent variables, group, treatment period, and dosing conditions as fixed effects, and subjects as a random effect, the differences between dosing conditions (value after breakfast-value in fasted conditions without breakfast, and value before breakfast-value in fasted conditions without breakfast) and corresponding two-sided CIs (confidence coefficient: 90%, 95%) were calculated. The Satterthwaite method was used to adjust the degrees of freedom.
19. Demographic data of the study population (gender, age, race, etc.)	Mean age was 28.0 years (between 20 and 42 years) and mean BMI was 20.73 kg/m^2. All volunteers were Japanese women.
20. Efficacy outcomes	Efficacy was not assessed in this study.
21. Safety outcomes	Overall, 9 TEAEs were reported in 5 subjects (41.7%) after administration under fasted conditions, 9 TEAEs in 5 subjects (41.7%) after administration before breakfast, and 5 TEAEs in 3 subjects (27.3%) after administration after breakfast. The most common TEAEs (reported in at least 2 subjects under any of the dosing conditions) by SOC were gastrointestinal disorders, nervous system disorders, and reproductive system and breast disorders. The common TEAEs (reported in at least 2 subjects) after administration under fasted conditions were metrorrhagia and diarrhoea, which were reported in 3 subjects (25.0%) and 2 subjects (16.7%), respectively. The common TEAE after administration before breakfast was metrorrhagia, which was reported in 3 subjects (25.0%). The common TEAE after administration after breakfast was abdominal pain lower, which was reported in 2 subjects (18.2%). All the TEAEs were considered related to the study drug and were mild in severity. The reported outcomes were "recovered/resolved" for all the TEAEs. No deaths, other SAEs, or TEAEs leading to study drug discontinuation were reported during the study. No TEAEs indicating LFT abnormalities were reported in this study.
22. Conclusion (summary)	The mean AUCs and Cmax of TAK-385 final formulation tablet (40 mg) after administration after breakfast were markedly lower than those after administration under fasted conditions. No obvious differences were noted in the mean AUCs or Cmax of TAK-385 final formulation tablet (40 mg) between administration before breakfast and administration under fasted conditions. Administration of a single dose of TAK-385 final formulation tablet was well tolerated under fasted conditions without breakfast and under fed

	conditions, ie, before and after breakfast. The safety profile of TAK-385 was not affected by the dosing conditions.

Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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(paragraph 4, section IV)

Clinical Trial Report № 17

1. Name of the medicinal product (Registration certificate number, if any)	**Ryeqo** Relugolix+Estradiol+Norethisterone acetate 40 mg /1 mg/0.5 mg film-coated tablets
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Dose, Inpatient and Outpatient Study in Healthy Men to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy for Testosterone Lowering of TAK-385, an Oral Gonadotropin-Releasing Hormone (GnRH) Antagonist. **(C27001)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 18.10.2011. to 18.10.2012.
8. Countries where the clinical trial was conducted	United Kingdom (2)
9. Number of subjects	Part 1: planned: 32, actual: 32 | Part 2: planned:56, actual:40 | Part 3: planned: 66, actual: 66 | Part 4: planned 80, actual: 38
10. Purpose and secondary objectives of the clinical trial	Part 1, Inpatient, Single Dose *Primary Objectives:* • To evaluate the safety and tolerability of TAK-385 in healthy male subjects following a single dose administration of TAK-385. • To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) (testosterone and luteinizing hormone [LH]) of TAK-385 in healthy male subjects following a single dose *Secondary Objectives:* • To assess the effect of a single dose of TAK-385 on serum dihydrotestosterone (DHT) and follicle-stimulating hormone (FSH) • To preliminarily assess the effect of food on the PK of TAK-385 in healthy male subjects (Cohort 3 only) Part 2, Inpatient, 14-Day, Multiple Dose *Primary Objectives:*

	• To evaluate the safety and tolerability of TAK-385 in healthy male subjects following multiple dosing • To assess the effect of multiple doses of TAK-385 on serum testosterone and LH *Secondary Objectives:* • To evaluate the PK of TAK-385 in healthy male subjects following multiple dosing and to relate PK to hormone PD responses (PK/PD) • To identify the dose range across which medical castration (average testosterone levels < 0.69 nmol/L) occurs during the second week of dosing • To evaluate the effects of TAK-385 on FSH and DHT Part 3, Outpatient, 28-Day, Multiple Dose *Primary Objectives:* • To evaluate the safety and tolerability of 1 or more dose levels of TAK-385 achieving maximal suppression of testosterone in men receiving an oral GnRH antagonist • To confirm 1 or more TAK-385 dose levels that achieve sustained medical castration during the final 2 weeks of dosing *Secondary Objectives:* • To assess the relationship between TAK-385 and serum androgen concentrations • To further evaluate the PK of TAK-385 in healthy male subjects following multiple dosing and to relate PK to hormone PD responses (PK/PD) Part 4, Outpatient, 28-Day, Multiple Dose *Primary Objective:* • To further evaluate the safety, tolerability, and efficacy for testosterone lowering of daily or weekly dosing regimens of TAK-385 *Secondary Objectives:* • To further assess the relationship between TAK-385 and serum androgen concentrations • To evaluate the PK of TAK-385 in healthy male subjects following multiple daily or weekly dosing and to relate PK to hormone PD responses (PK/PD)
11. Clinical trial design	This was a 4-part, randomized, double-blind, placebo-controlled, single and multiple dose, inpatient and outpatient, phase 1 study.
12. Key inclusion criteria	Healthy male subjects
13. Investigational medicinal product, method of administration, strength	Relugolix 20, 40 and 80 mg tablets, oral
14. Comparator, method of administration, strength	Placebo
15. Concomitant therapy	Not applicable
16. Efficacy evaluation criteria	Not applicable
17. Safety evaluation criteria	Safety was based on AEs, SAEs, vital signs, physical examination findings, clinical laboratory results, and 12-lead electrocardiograms (ECGs).
18. Statistical methods	Pharmacokinetics: Individual TAK-385 plasma and urine concentration-time data obtained in Parts 1 and 2 were analyzed using noncompartmental methods (WinNonlin Enterprise version 5.2) to characterize the single- and multiple-dose PK of TAK-385 and to evaluate the effect of food on TAK-385 PK. Individual plasma and/or

	urine concentrations and single- and multiple-dose PK parameters of TAK-385 were listed and summarized descriptively by study part, study day, and dose level. Dose-proportionality of PK parameters of TAK-385 after single and multiple dosing was first explored graphically by plotting individual dose-normalized exposure parameters: dose-adjusted maximum observed plasma concentration (Cmax/D), dose-adjusted area under the plasma concentration-time curve from time 0 to the last quantifiable concentration (AUC0-tlqc/D) and dose adjusted area under the plasma concentration-time curve from time 0 to infinity (AUC0-∞/D), or dose adjusted area under the plasma concentration-time curve over the dosing interval (AUC0-tau/D) versus dose. Then, a formal assessment was performed using both analysis of variance (ANOVA) and power model approaches. In Part 1 (Cohort 3), ANOVA was performed on ln-transformed PK parameters [area under the plasma concentration-time curve from time 0 to the last quantifiable concentration (AUC0-tlqc), area under the plasma concentration-time curve from time 0 to infinity (AUC0-inf), and maximum observed plasma concentration (Cmax)] of TAK-385 to assess the effect of food on TAK-385 oral bioavailability. In Part 2, steady state attainment was determined based on visual inspection of mean observed predose plasma concentration during multiple dosing (Ctrough) versus time profiles at each dose level. Noncompartmental analyses of Part 3 and 4 data were not planned given the limited number of postdose samples collected per subject on Days 1 and 28. ***Pharmacodynamics:*** Pharmacodynamic measures included serum concentrations of testosterone, DHT, LH, and FSH. In Part 2, the number and percentage of subjects with average testosterone levels < 0.69 nmol/L occurring during the second week of dosing, together with the associated 95% binomial absolute confidence interval, were tabulated. In Parts 3 and 4, the number and percentage of subjects with testosterone levels consistently < 0.69 nmol/L from Day 14 through Day 28, together with the associated 95% binomial absolute confidence interval (CI), were tabulated.
19. Demographic data of the study population (gender, age, race, etc.)	In Part 1, subjects in the study were White (75.0%), Black (18.8%), and Asian (6.3%). The median age was 27.5 years (range 19 to 50 years). The median body weight and body mass index (BMI) were 82.10 kg and 25.10 kg/m^2, respectively, and were similar across all dose cohorts. In Part 2, subjects in the study were White (92.5%), Black (5.0%), and Asian (2.5%). The median age was 50.0 years (range 41 to 69 years). The median body weight and BMI were 78.65 kg and 25.75 kg/m^2, respectively, and were similar across all dose cohorts. In Part 3, subjects in the study were White (89.4%), Other (4.5%), Asian (3.0%), and Black (3.0%); 9.1% were Hispanic or Latino (all in the placebo group). The median age was 53.0 years (range 45 to 75 years). The median weight and BMI were 80.10 kg and 25.80 kg/m^2, respectively, and were similar across all dose cohorts. In Part 4, subjects in the study were White (92.1%) and Asian, Black, and Other (2.6%, respectively). The median age was 53.0 years (45 to 71 years). The median weight and BMI were 78.80 kg and 26.25 kg/m^2, respectively, and were similar across all dose cohorts.
20. Efficacy outcomes	Not applicable.

21. Safety outcomes	TAK-385 was well tolerated, with no AEs of symptomatic significance unless directly related to the effects of acute medical castration. Mild to moderate transaminase elevations were observed without symptoms or changes in total bilirubin. Observed changes in QT/QTc intervals appeared to be consistent with those described in the literature with other medical castration agents. Longer term dosing is required to assess the significance of these findings.
22. Conclusion (summary)	TAK-385 was readily absorbed in plasma following single and multiple oral administration. After attaining Cmax, plasma TAK-385 concentrations declined in a multi-exponential manner with a mean disposition phase half-life of approximately 36 to 65 hours across the 20 to 180-mg QD dose range. Moderate to large interindividual variability in TAK-385 systemic exposures was apparent across all study parts. □ At steady-state, AUC0-tau increased in a dose-proportional manner following multiple doses of TAK-385 over the dose range of 20 to 180 mg QD, while Cmax increased slightly more than dose-proportionately. Steady-state conditions were reached within 11 to 14 days and TAK-385 systemic exposure increased approximately 2-fold following QD dosing. □ Co-administration with food decreased TAK-385 systemic exposure (Cmax and AUC0-∞) by approximately 50% and delayed absorption when compared to fasting conditions. □ Less than 4% of TAK-385 was excreted unchanged in urine after single and repeat dosing. □ Effective medical castration was consistently achieved at maintenance doses of 80, 160, and 180 mg QD. Only loading doses of 180 mg or greater led to testosterone levels below the castration limit of 1.73 nmol/L within 24 to 48 hours. While a large variability in the PD response was apparent across cohorts, higher doses of TAK-385 produced more robust testosterone suppression. The recommended safe and effective dose regimen based on this study would be ≥ 80 mg QD TAK-385 for sustained castration during the treatment period.
Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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(paragraph 4, section IV)

Clinical Trial Report № 18

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate 40 mg/1 mg/0.5 mg film-coated tablet)
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	An Open-Label, Single-Dose Study to Assess the Effect of Moderate Renal Impairment on the Pharmacokinetics of Relugolix. **(MVT-601-040)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 07.12.2018. to 18.02.2019.
8. Countries where the clinical trial was conducted	This study was conducted at a single center in the United States.
9. Number of subjects	planned: 24 actual: 24
10. Purpose and secondary objectives of the clinical trial	Primary objective of this study was to assess the effect of moderate renal impairment on the pharmacokinetics of relugolix. Secondary objectives were to assess the safety and tolerability after administration of a single 40-mg dose of relugolix in study participants with moderate renal impairment and demographically matched study participants with normal renal function.
11. Clinical trial design	This was a single-dose, open-label study to assess the effect of moderate renal impairment on the pharmacokinetic of relugolix
12. Key inclusion criteria	A study participant was eligible for inclusion in this study only if the following criteria applied: 1. Study participant was a male or female between the age of 18 and 80 years. 2. Study participant had a body weight ≥ 45 kg and Body Mass Index (BMI) of 17 to 40 kg/m^2, 3. Study participant's renal function was defined (Healthy Study participants with normal renal function or Study participants with moderate renal impairment)
13. Investigational medicinal product, method of administration, strength	Relugolix 40 mg Tablets , oral, single-dose

14. Comparator, method of administration, strength	NA
15. Concomitant therapy	Acetaminophen at doses of ≤2 g/day were permitted for use any time during the study. Non-sedating antihistamines and decongestants could also be administered on an as-needed basis. Other concomitant medication was considered on a case-by-case basis by the Investigator for treatment of a medical need in consultation with the sponsor medical monitor. Any concomitant medication was recorded in the study records, including the doses administered, the dates and times of administration and the reason for administration.
16. Efficacy evaluation criteria	NA
17. Safety evaluation criteria	Safety was monitored throughout the study by repeated assessments of clinical laboratory tests, vital sign measurements, and evaluation of adverse events. Study participants returned to the clinic approximately 10 days after administration of study drug on Day 1 (2 days after the last blood sample was collected) for a follow-up visit.
18. Statistical methods	Log-transformed AUC0-∞, AUC0-t, and Cmax for relugolix were analyzed by analysis of variance (ANOVA) with cohort as fixed effect. The point estimates of the geometric least squares mean ratio (GMR; moderate renal impairment/normal renal function) and the associated 90% confidence intervals (CIs) for the AUC0-∞, AUC0-t, and Cmax of relugolix were provided for cohort comparisons.
19. Demographic data of the study population (gender, age, race, etc.)	Each of the 12 healthy participants with normal renal function (Cohort 1) were demographically matched with the 12 participants with moderate renal impairment (Cohort 2) according to the protocol-specified criteria of sex (9 males and 3 females in each cohort), race (11 White and 1 Black/African American in each cohort), age (mean of 64.5 years and 62.5 years, respectively), and weight (mean of 88.73 kg and 84.93 kg, respectively).
20. Efficacy outcomes	NA
21. Safety outcomes	A total of 4 healthy participants with normal renal function (Cohort 1) reported 4 adverse events. No adverse events were reported by participants with moderate renal impairment (Cohort 2). All adverse events were rated by the investigator to be mild (grade 1/mild) and resolved without intervention. Three of the four adverse events were considered by the investigator to be drug-related (two adverse events of somnolence and one adverse event of dry mouth). No deaths, serious adverse events or adverse events leading to withdrawal were reported during the study. No clinically significant abnormal findings were observed in clinical laboratory tests or vital sign measurements.
22. Conclusion (summary)	The total exposure (AUC0-∞) and maximum concentration (Cmax) of relugolix was increased by about 1.5-fold in participants with moderate renal impairment compared with healthy participants with normal renal function. Because the terminal half-life estimates were the same for both cohorts, the increases in exposure and Cmax are likely attributable to an increase in absorption, rather than a decrease in elimination. o The GMR (moderate renal impairment /normal renal function) and 90% CI for the AUC0-inf and Cmax of relugolix was 1.4521 (0.9812, 2.1491) and 1.4732 (0.8550, 2.5386), respectively. o The mean t½ of 56.3 hours was estimated for both participants with moderate renal impairment and healthy participants with normal renal function. Administration of a single 40-mg dose of relugolix was generally safe and well-tolerated.

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Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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(paragraph 4, section IV)

Clinical Trial Report № 19

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo Relugolix+Estradiol+Norethisterone acetate 40 mg /1 mg/0.5 mg film-coated tablets
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	An Open-Label, Single Treatment Group Study to Assess the Effect of Co-administration of Relugolix, Estradiol, and Norethindrone Acetate on the Potential to Suppress Ovarian Activity in Healthy Premenopausal Women. **(MVT-601-046)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 03.04.2019. to 14.11.2019.
8. Countries where the clinical trial was conducted	This study was conducted at a single center in Germany.
9. Number of subjects	planned: 80 actual: 71
10. Purpose and secondary objectives of the clinical trial	Primary objectif was to assess the effect of co-administration of relugolix 40 mg, est (NETA) 0.5 mg (Activelle®) QD for 84 consecutive days on the potential to suppress ovarian activity. Secondary objectives were: -To estimate the proportion of women who satisfy the Landgren criterion in each treatment period; -To characterize the duration of time required to return to ovulation following the 84-day treatment period; -To estimate the proportion of women who demonstrate a return to ovulation within 36 days following the study treatment period; -To characterize the LH, FSH, E2, and P concentration-time profiles during the study treatment periods and the Post-Treatment Period; -To determine the pharmacokinetics of relugolix, E1, E2 and NET at steady state; -To assess the safety and tolerability of co-administration of relugolix 40 mg, E2 1 mg, and NETA 0.5 mg (Activelle®) QD for 84 days.

11. Clinical trial design	This was an open-label, nonrandomized (single treatment group) pharmacokinetic, pharmacodynamic, safety and tolerability study
12. Key inclusion criteria	Healthy adult premenopausal women.
13. Investigational medicinal product, method of administration, strength	Relugolix 40 mg Tablets, oral and Activelle® tablets, containing E2 1 mg and NETA 0.5 mg, oral
14. Comparator, method of administration, strength	NA
15. Concomitant therapy	All concomitant medications used during the study were recorded, including the drug generic or trade name as appropriate (e.g., multivitamins), dose amount, route of administration, start date, and stop date. However, the medication, dose and/or dosing regimen for any medically indicated treatment did not alter as a result of participation in the current study.
16. Efficacy evaluation criteria	Not applicable
17. Safety evaluation criteria	The safety and tolerability of the study treatment was evaluated by safety assessments including physical and gynecological examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), clinical laboratory tests, and reporting of adverse event.
18. Statistical methods	Frequency analysis of Hoogland-Skouby scores over the entire 84-day treatment period and descriptive statistics on dominant follicle sizes over time. Proportion (%) of study participants who were in the completers population and who demonstrated inhibition of ovulation during the entire 84-day treatment period. For all proportions, the associated 95% confidence intervals (Clopper-Pearson, exact) was provided. Frequency analysis Kaplan Meier estimate Frequency analysis Descriptive statistics Descriptive statistics of relugolix, E1, E2, and NET at steady-state; Frequency analysis and descriptive summary statistics
19. Demographic data of the study population (gender, age, race, etc.)	All participants were healthy adult premenopausal women, with a mean age of 29.2 years (range: 18 to 35 years) and a mean BMI of 23.57 kg/m2. All study participants had a BMI between 18.5 and 30 kg/m2, as required by the study protocol. The majority of study participants were White (61 of 70 [87.14 %]). All other participants were Asian (1.43 %), Black or African American (1.43 %), multiracial (2.86 %) or other (7.14 %).
20. Efficacy outcomes	Not applicable.
21. Safety outcomes	Overall, 68 of 70 participants (97.14%) reported a total of 524 adverse events. Approximately the same number of adverse events were considered by the investigator to be study drug-related as those judged not related to study drug. The most commonly reported adverse events were categorized as nervous system disorders and infections and infestations with headache and nasopharyngitis reported most frequently. Most reported adverse events were rated as mild or moderate in severity. In the majority of adverse events (99.81 %) no adaptation of study drug administration was necessary with the exception of 1 case in which study drug was withdrawn. One case of serious adverse event was documented in this study, the participant (# 755) experienced severe back pain (grade 3) requiring hospitalization after the visit on Day 27 of Treatment Period 3, which was considered by the investigator not related to the study drug.

22. Conclusion (summary)	Ovulation was inhibited in 100% of participants during the 84-day treatment period (co-administration of relugolix 40 mg, E2/NETA (1 mg/ 0.5 mg; Activelle®)). • Ovarian activity, as evidenced by the degree of follicular growth, was markedly suppressed during the 84-day treatment period (co-administration of relugolix 40 mg, E2/NETA (1 mg/ 0.5 mg; Activelle®)). The follicular suppression was pronounced for the majority of the study population and was shown to be superior to that during cyclic administration of oral combined hormonal contraceptives. • The mean duration of time to return to ovulation after cessation of treatment was 23.5 days. • The return to ovulation during the 36-day post treatment period was almost complete with 97.01 % (65 out of 67 participants) having a confirmed ovulation within the 36-day post treatment period which is comparable to rates observed after combined contraceptive treatment. An additional participant ovulated on Day 43 and another participant, who was unavailable for evaluation from Day 24 to Day 36, began menstruating on Day 39. As a result, for 66 out of 67 study participants a return of ovulation and for 1 participant a return of menses after discontinuation of treatment was confirmed. • Pituitary secretion of FSH and LH as well as ovarian production of E2 and P were consistently suppressed during the entire treatment period. Mean serum E2 concentrations were in the optimal range for an effective and safe treatment of endometriosis- and fibroid-related symptoms, and indicated that exogenous administration of a 1-mg dose of E2 was sufficient. • The suppression of endometrial proliferation during treatment was pronounced for the majority of the study population, with mean endometrial thickness being consistently maintained between 4-5 mm. • The number of bleeding and spotting days during treatment was generally low with only 9.52% and 2.25% of evaluable days during the 84-day treatment period reported as “spotting” and “bleeding” respectively.

Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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Clinical Trial Report № 20

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate 40 mg/1 mg/0.5 mg film-coated tablet)
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	A Randomized, Double-Blind, Placebo- and Positive-Controlled (Open-Label Moxifloxacin), 4-Arm Parallel-Group Study to Evaluate the Effect of TAK-385 on Cardiac Repolarization in Healthy Subjects. **(TAK-385-106)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 06.09.2013. to 20.10.2013.
8. Countries where the clinical trial was conducted	This study was conducted at a single center in the United States.
9. Number of subjects	planned: 280 actual: 280
10. Purpose and secondary objectives of the clinical trial	**Primary objective** of this study was to determine the effects of TAK-385 relative to placebo on ECG intervals as the measure of cardiac repolarization following single oral doses in healthy subjects The **secondary objectives** of the study were as follows: • To characterize the pharmacokinetic profiles of TAK-385 after administration of 60 and 360 mg single doses of TAK-385. • To evaluate the safety and tolerability of TAK-385 60 and 360 mg following single dose administration in healthy subjects. • To confirm assay sensitivity to the response in the QT/QTc interval following a single dose of moxifloxacin 400 mg in healthy adult subjects.
11. Clinical trial design	This was phase 1, double-blind (open-label for moxifloxacin), randomized, placebo- and positive-controlled, parallel-group, single-site study.
12. Key inclusion criteria	Healthy Subjects
13. Investigational medicinal product, method of administration, strength	Relugolix 60 mg and 360 mg Tablets, oral, single-dose

14. Comparator, method of administration, strength	Moxifloxacin 400 mg
15. Concomitant therapy	Concomitant medication use was recorded throughout the study. All medications (other than study drug) used at any time from Screening through the Follow-up Phone Call, including vitamin supplements, OTC medications, and oral herbal preparations, were recorded in the eCRF as concomitant medications.
16. Efficacy evaluation criteria	NA
17. Safety evaluation criteria	The safety measurements were adverse events, clinical laboratory evaluations, vital signs, ECGs, and physical examinations.
18. Statistical methods	Descriptive statistics were used to summarize demographic and other baseline variables by treatment group and overall: N, mean, SD, median, minimum, and maximum for continuous variables such as age and weight, and N and percentage of subjects within each category for categorical variables such as gender and race. N and percentage of subjects were also used to summarize subject disposition by treatment group and overall.
19. Demographic data of the study population (gender, age, race, etc.)	Of the 280 randomized subjects, 144 (51.4%) were male and 136 (48.6%) were female. The mean age of subjects was 35.1 years. Most subjects were White (254/280 [90.7%]) and of Hispanic or Latino ethnicity (216/280 [77.1%]).
20. Efficacy outcomes	NA
21. Safety outcomes	No deaths, other SAEs, discontinuation due to TEAEs, pregnancies, or overdoses occurred. No subjects had clinical laboratory test results, vital signs, or ECG results that were reported as adverse events, and no abnormal LFT results or clinically significant changes from Baseline in physical examination findings occurred. Overall, 11.4% (32/280 subjects) had TEAEs that were considered by the investigator to be related to study drug. The percentage of subjects with drug-related TEAEs was higher in all active treatment groups than in the placebo group and slightly higher in the TAK-385 360 mg group and TAK-385 60 mg groups than in the moxifloxacin or placebo groups: 8.6%(6/70 subjects), 12.9% (9/70 subjects), 14.3% (10/70 subjects), and 10.0% (7/70 subjects), in the placebo, TAK-385 60 mg, TAK-385 360 mg, and moxifloxacin groups, respectively. The most frequently reported drug-related TEAE (>2% of subjects in any treatment group) was headache (3.2% [9/280 subjects]), which was reported for a higher percentage of subjects in the TAK-385 360 mg group than in the other 3 groups. The majority of drug-related TEAEs of headache were considered by the investigator to be mild in intensity; none were severe in intensity. TEAEs in the reproductive system and breast disorders SOC were reported for 2.9% [8/280 subjects]). The percentage of subjects with TEAEs in this SOC was higher in the TAK-385 360 mg group than in the other 3 groups: 5.7% (4/70 subjects) vs 1.4% (1/70 subjects) each in the placebo and moxifloxacin groups, and 2.9% (2/70 subjects) in the TAK-385 60 mg group. All of TEAEs in this SOC were considered by the investigator to be related to study drug and mild in intensity.

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22. Conclusion (summary)	• Administration of single doses of TAK-385 60 or 360 mg in healthy subjects did not prolong QT/QTc intervals. • Assay sensitivity was demonstrated in this study by confirming the QT prolongation effect of moxifloxacin 400 mg. • As administered in this study, single doses of TAK-385 (60 and 360 mg) were well tolerated in healthy subjects.

Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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Clinical Trial Report № 21

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate 40 mg/1 mg/0.5 mg film-coated tablet)
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	A Double-Blind, Randomized, Placebo-Controlled, Sequential-Panel, Ascending Single- and Multiple-Dose Study to Evaluate the Effect of TAK-385 on Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics in Healthy Premenopausal Women. **(TAK-385-101)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 24.08.2007. to 16.07.2008.
8. Countries where the clinical trial was conducted	This study was conducted in the United States.
9. Number of subjects	planned: 120 actual: 120
10. Purpose and secondary objectives of the clinical trial	**Primary:** To evaluate the safety, tolerability, and pharmacokinetics of TAK-385 in healthy premenopausal women following single and multiple dosing phases. **Secondary:** • Evaluate the pharmacodynamic effect of TAK-385 at steady-state on ovarian and gonadotropin steroidogenesis (Cohorts 8 to 10 only). • Determine the effect of food on the pharmacokinetics of TAK-385 (Cohort 7 only). • Assess the effect of TAK-385 on cytochrome P-450 (CYP) 3A4 induction.
11. Clinical trial design	This was a phase 1, double-blind, randomized, placebo-controlled, sequential-panel, ascending single- and multiple-dose study.
12. Key inclusion criteria	Healthy Premenopausal Women
13. Investigational medicinal product, method of administration, strength	Relugolix 1-mg, 5 mg and 20 mg Tablets

14. Comparator, method of administration, strength	Placebo
15. Concomitant therapy	Medications taken within 28 days prior to Screening and stopped prior to Screening were recorded in the medication history CRF. Medications taken during or after Screening were considered as concomitant medications. Medications started prior to Screening and continued after Screening were also be considered as concomitant medications.
16. Efficacy evaluation criteria	Not applicable
17. Safety evaluation criteria	Adverse events, clinical laboratory test results (including hematology, serum chemistry, and urinalysis), vital signs, ECG characteristics, ophthalmic evaluations, and physical examination findings.
18. Statistical methods	**Pharmacokinetic Measures:** To assess the dose proportionality following single dosing in Cohorts 1 to 6, regression analysis of natural logarithm (log) transformed Cmax, AUC(0-tlqc), and AUC(0-inf) was performed on log(dose). The 90% confidence interval (CI) of the slope estimate equals 1 is presented. To assess the food effect, an analysis of variance was performed using Cohort 7 log(Cmax), log(area under the plasma concentration-time curves [AUCs]) as dependent variable; treatment, sequence, period as fixed effects; and subject (seq) as a random effect. The least squares means ratio of TAK-385 fed (test) to TAK-385 fasted (reference) and the corresponding 90% CI is presented for Cmax, AUC(0-tlqc), and AUC(0-inf). To assess the dose proportionality following multiple dosing in Cohorts 8 to 10, regression analysis of log transformed Cmax, Cmin, and AUC(0-tau) was performed on log(dose). The 90% CI of the slope estimate equals 1 is presented. **Pharmacodynamic Measures:** Descriptive statistics (number of subjects, mean, SD, SE, percent coefficient of variation [%CV], median, minimum, and maximum) were used to summarize pharmacodynamic parameters: serum concentrations of E2, FSH, LH, and urine 6β-hydroxycortisol to cortisol ratios (Q). Safety: All safety assessments (adverse events, clinical laboratory evaluations, ophthalmic examination, 12-lead ECG, physical examination, and vital signs) were summarized for each dose group with descriptive statistics, where appropriate, and presented in data listings.
19. Demographic data of the study population (gender, age, race, etc.)	A total of 120 female subjects (age range of 19 to 49 years), were randomly assigned to treatment in the study. Race: 108 White, 5 American Indian or Alaska native, 1 Asian and 6 Black or African American.
20. Efficacy outcomes	Not applicable.
21. Safety outcomes	TAK-385 appears to be safe and well tolerated following TAK-385 at single doses up to 80 mg and multiple doses up to 40 mg QD for 14 days, in healthy premenopausal women. · Overall, the frequency of adverse events was similar between the placebo and TAK-385 dose groups in both the SRD and MRD portions of the study with no apparent dose relationship. However, the frequency of drug-related adverse events were higher after the highest single dose (80 mg) and the highest multiple dosing dose (40

	mg QD) than in the comparable dose groups, with the increased frequency being spread over several system organ classes.
22. Conclusion (summary)	• TAK-385 pharmacokinetic parameters increased moderately supraproportionally over the dose range studied when TAK-385 was given as either single or multiple QD doses. Steady state was achieved after 6 to 7 days of dosing, and the pharmacokinetics of TAK-385 appear to be time-independent (no autoinduction or autoinhibition of its metabolism). However, this analysis may be confounded by the different dosing conditions with respect to food in the SRD and MRD portions of the study. TAK-385 AUC(0-tau) doubled between Day 1 and Day 14 with QD dosing. • T1/2 was not dependent on dose and was approximately 14 to 16 hours potentially supporting a QD dosage regimen. • • CLr was not a substantial pathway of TAK-385 elimination since less than 3% of the dose was excreted in the urine. CLr was independent of dose or time. • TAK-385 appears to be safe and well tolerated following TAK-385 at single doses up to 80 mg and multiple doses up to 40 mg QD for 14 days, in healthy premenopausal women. • TAK-385 pharmacokinetic parameters increased moderately supraproportionally over the dose range studied when TAK-385 was given as either single or multiple QD doses. Steady state was achieved after 6 to 7 days of dosing, and the pharmacokinetics of TAK-385 appear to be time-independent (no autoinduction or autoinhibition of its metabolism). However, this analysis may be confounded by the different dosing conditions with respect to food in the SRD and MRD portions of the study. TAK-385 AUC(0-tau) doubled between Day 1 and Day14 with QD dosing. • T1/2 was not dependent on dose and was approximately 14 to 16 hours potentially supporting a QD dosage regimen. • CLr was not a substantial pathway of TAK-385 elimination since less than 3% of the dose was excreted in the urine. CLr was independent of dose or time. • A marked food effect was observed. Food intake prior to dosing reduced TAK-385 Cmax and AUC by approximately 60% and 45%, respectively. Notably, the increased exposure associated with fasted dosing of TAK-385 is an important finding for the clinical development program overall. Following consideration of the food effect data, it is now intended that dosage regimens used in future clinical studies will be based upon dosing prior to food intake, so as to ensure that the TAK-385 safety evaluation includes circumstances in which potential exposure is maximized for the study subjects. • TAK-385 suppressed mean concentrations of endogenous E2, LH, and FSH following single doses in a dose-related manner. Multiple doses of TAK-385 also suppressed E2, LH, FSH, and progesterone concentrations in a dose related manner. The natural endogenous increase in progesterone expected postovulation was not observed in subjects receiving multiple doses of TAK-385, suggesting that TAK-385 QD prevented

	ovulation. There was no apparent effect of TAK-385 on endogenous GH, PRL, thyrotropin, and ACTH. • TAK-385 at single doses up to 80 mg and multiple doses up to 40 mg QD does not appear to inhibit or induce CYP34A as determined by 6β-hydroxycortisol to cortisol ratios.

Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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Clinical Trial Report № 22

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate 40 mg/1 mg/0.5 mg film-coated tablet)
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	A 3-Part, Open-Label, Randomized, Crossover, Single-Dose Biocomparability Study to Assess the Pharmacokinetic Performance of Relugolix/Estradiol/Norethindrone Acetate (40 mg/1 mg/0.5 mg) Fixed-Dose Combination Tablet Formulations in Healthy Postmenopausal Women. **(MVT-601-036)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 28.08.2018. to 23.10.2018.
8. Countries where the clinical trial was conducted	This study was conducted at a single center in the United States.
9. Number of subjects	planned: actual: 24
10. Purpose and secondary objectives of the clinical trial	*Primary objective* was to assess the pharmacokinetics of relugolix, baseline-adjusted total E1, and NET after single-dose administration of the L2 relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet and co-administration of corresponding doses of relugolix and Activella. *Secondary objectives* were: 1. To assess the pharmacokinetics of unconjugated E1 and unconjugated E2 after administration of the L2 relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet and co-administration of corresponding doses of relugolix and Activella. 2. To assess the safety and tolerability of single-dose administration of the L2 relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet and co-administration of corresponding doses of relugolix and Activella.
11. Clinical trial design	A 3-Part, Open-Label, Randomized, Crossover, Single-Dose Biocomparability Study

12. Key inclusion criteria	Healthy Postmenopausal Women
13. Investigational medicinal product, method of administration, strength	Administration of a single L2 relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet (Lot No. CBCKF) orally
14. Comparator, method of administration, strength	Co-Administration (Relugolix + Activella) (Reference 1): First co-administration of a single relugolix 40 mg tablet (Lot No. 1583860) and a single Activella tablet (1 mg E2/0.5 mg NETA) (Lot No. GF72150) orally. Co-Administration (Relugolix + Activella)(Reference 2): Second co-administration of a single relugolix 40 mg tablet (Lot No. 1583860) and a single Activella tablet (1 mg E2/0.5 mg NETA) (Lot No. GF72150) orally.
15. Concomitant therapy	Acetaminophen at doses of $\leq$ 2 g/day was permitted for use any time during the study. Non-sedating antihistamines and decongestants may have also been administered on an as-needed basis. A note-to-file had been generated to list the concomitant medications and treatments approved by the principal investigator and the sponsor medical monitor. Other concomitant medication may have been administered on a case-by-case basis by the principal investigator or sub-investigator for treatment of a medical need in consultation with the medical monitor. Any concomitant medication was recorded in the study records, including the doses administered, the dates and times of administration, and the reason for administration.
16. Efficacy evaluation criteria	NA
17. Safety evaluation criteria	A complete physical examination included, at minimum, assessment of the cardiovascular, respiratory, gastrointestinal and neurological systems, thyroid and head, eyes, ears, nose, and throat (HEENT), and skin. Height and weight were also measured and recorded at the screening visit only.
18. Statistical methods	Log-transformed pharmacokinetic parameters were analyzed by a generalized linear model based on the partial replicate design study with the exception of Relugolix Cmax that was analyzed using a reference-scaled approach for bioequivalence.
19. Demographic data of the study population (gender, age, race, etc.)	All participants were postmenopausal women; the mean age was 59.1 years and ranged from 46 to 65 years. The mean BMI was 26.549 kg/m^2 and all study participants had a BMI of less than 30 kg/m^2. All participants were White; 12 of 24 (50%) were Hispanic or Latino and 12 of 24 (50%) participants were not Hispanic or Latino.
20. Efficacy outcomes	NA
21. Safety outcomes	There were no deaths or serious adverse events reported and no study participants were discontinued due to adverse events in this study. Eleven of the 24 (45.8%) study participants who had at least 1 adverse event reported a total of 17 adverse events. Five participants reported 5 adverse events after administration of the L2 FDC tablet, 5 participants reported 8 adverse events after the first co-administration of relugolix and Activella, and 4 participants reported 4 adverse events after the second co-administration of relugolix and Activella. Fourteen adverse events reported by 8 participants were considered by the investigator to be drug-related. Three study participants reported 3 adverse events (1 each) considered by the investigator to be drug-related after administration of the FDC tablet, 4 participants reported 7 drug-related adverse events after the first co-administration of relugolix and Activella, and 4 participants reported 4 drug-related adverse events after

	the second co-administration of relugolix and Activella. The most frequently reported adverse event was the MedDRA Preferred Term (PT) feeling hot, reported by 3 of 24 participants, including 1 participant after administration of the FDC tablet and 2 participants after co-administration of relugolix and Activella.
22. Conclusion (summary)	The relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet was considered to be biocomparable to co-administration of relugolix and Activella in this pilot study, based on the following assessments: The GMR (FDC tablet/co-administration [relugolix + Activella]) and 90% CI for the AUC0-∞ (based on a generalized linear model) was 0.9037 (0.8048, 1.0147) and the GMR and upper bound of the 95% CI for the Cmax of relugolix (based on a reference-scaled approach) was 0.8910 (0.0159). The GMR (FDC tablet/co-administration [relugolix + Activella]) and 90% CI for the AUC0-∞ and Cmax of baseline-adjusted total E1 were 0.9964 (0.9552, 1.0393) and 0.8655 (0.8063, 0.9290), respectively. The GMR (FDC tablet/co-administration [relugolix + Activella]) and 90% CI for the AUC0-∞ and Cmax of NET were 1.0031 (0.9761, 1.0310) and 0.8226 (0.7709, 0.8779), respectively. The GMR (FDC tablet/co-administration [relugolix + Activella]) and 90% CI for the AUC0-∞ and Cmax of baseline-adjusted unconjugated E1 were 0.9996 (0.9562, 1.0450) and 1.0277 (0.9729, 1.0856), respectively. The GMR (FDC tablet/co-administration [relugolix + Activella]) and 90% CI for the AUC0-∞ and Cmax of baseline-adjusted unconjugated E2 were 1.0428 (0.9759, 1.1143) and 1.1496 (1.0697, 1.2355), respectively.

Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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(paragraph 4, section IV)

Clinical Trial Report № 23

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate 40 mg/1 mg/0.5 mg film-coated tablet)
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	An Open-Label, Randomized, Two-Treatment, Three-Sequence, Three-Period Crossover and Partial Replicate, Single-Dose Study to Demonstrate Bioequivalence Between the Relugolix/Estradiol/Norethindrone Acetate (40 mg/1 mg/0.5 mg) Fixed-Dose Combination Tablet and Co-administration of a Relugolix 40-mg Tablet and Estradiol/Norethindrone Acetate (1 mg/0.5 mg; Activella®) in Healthy Postmenopausal Women. **(MVT-601-042)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 11.03.2019. to 21.06.2019.
8. Countries where the clinical trial was conducted	This study was conducted at a single center in the United States.
9. Number of subjects	planned: 90 actual: 90
10. Purpose and secondary objectives of the clinical trial	*Primary objective* was to demonstrate bioequivalence between the relugolix/estradiol (E2)/norethindrone acetate (NETA) (40 mg/1 mg/0.5 mg) fixed-dose combination (FDC) tablet and co-administration of relugolix (40 mg) and E2/NETA (1 mg/0.5 mg; Activella). *Secondary objective* was to assess safety and tolerability of single dose administration of the relugolix/E2/NETA 40 mg/1 mg/0.5 mg) FDC tablet and co-administration of relugolix (40 mg) and Activella (1 mg/0.5 mg).
11. Clinical trial design	This was an open-label, randomized, two-treatment, three-sequence, three-period crossover and partial replicate, single-dose study
12. Key inclusion criteria	Healthy Postmenopausal Women
13. Investigational medicinal product, method of administration, strength	Relugolix/Estradiol/ Norethindrone Acetate (40 mg/1 mg/0.5 mg) Fixed-Dose Combination Tablet, oral

14. Comparator, method of administration, strength	Relugolix 40-mg Tablet and Estradiol/Norethindrone Acetate (1 mg/0.5 mg; Activella®), oral
15. Concomitant therapy	There was no use of prior medications by any study participant. Use of concomitant medications was reported in 4 study participants as follows: • Participant #1076 received a single dose of ibuprofen on Day 9 of Treatment Period 3 for an upper respiratory infection after co-administration of relugolix and Activella on Day 1. • Participant #1078 received 5 days of ciprofloxacin beginning on Day 1 of Treatment Period 2 for a urinary tract infection after co-administration of relugolix and Activella. •Participant #1079 received acetaminophen on Day 2 of Treatment Period 2 andazithromycin on Day 6 to Day 8 of Treatment Period 2 for a molar abscess afteradministration of the FDC tablet on Day 1. •Participant #1058 received ciprofloxacin during the follow-up period for an infectionrelated to a fall that occurred on Day 7 of Treatment Period 3 after administration of theFDC tablet on Day 1.
16. Efficacy evaluation criteria	NA
17. Safety evaluation criteria	Adverse event reporting, physical examinations, vital sign measurements, ECGs and clinical laboratory tests.
18. Statistical methods	Log-transformed pharmacokinetic parameters were analyzed by either standard average bioequivalence (ABE) method or reference-scaled average bioequivalence (RSABE) method, depending on the within-subject coefficient of variation (CVWR%) of that parameter. When CVWR% < 30%, the ABE method was used, and a mixed-effects model was used based on the replicate design study.
19. Demographic data of the study population (gender, age, race, etc.)	All participants were postmenopausal women, with a mean age of 55.9 years (range: 41 to 65 years) and a mean BMI of 28.29 kg/m2. All study participants had a BMI of ≤ 32 kg/m2, as required by the study protocol. The majority of study participants were White (82 of 90 [91.1%]). All participants were of Hispanic or Latino ethnicity.
20. Efficacy outcomes	NA
21. Safety outcomes	Overall, 15 of 90 participants (16.7%) reported a total of 18 adverse events. The most commonly reported adverse events were categorized as nervous system disorders and gastrointestinal disorders with headache and abdominal pain occurring most frequently. One participant was discontinued for a nonserious adverse event of tooth abscess considered by the investigator not to be related to study drug administration. No clinically significant abnormal findings were observed in vital sign measurements or clinical laboratory tests. No deaths, serious adverse events, or adverse events of clinical interest were reported during the study.
22. Conclusion (summary)	Based on statistical analysis of all pre-specified primary and secondary endpoints, bioequivalence between the relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet and co-administration of relugolix (40 mg) and an E2/NETA tablet (1 mg/0.5 mg; Activella) was demonstrated. Specifically, bioequivalence was established based on the following pre-specified primary endpoints: • The GMR (FDC tablet/co-administration [relugolix + Activella]) and the upper bound of the 95% confidence interval for the RSABE method for the AUC0-∞

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	(CVWR% of 37.6%) and Cmax (CVWR% of 59.2%) of relugolix were 1.0111 (-0.0826) and 1.0209 (-0.1875), respectively; • The GMR (FDC tablet/co-administration [relugolix + Activella]) and 90% CI of the GMR (ABE method) for the AUC0-∞ and Cmax of baseline-adjusted unconjugated E2 were 1.0031 (0.9531, 1.0558) and 1.0634 (1.0115, 1.1180), respectively; • The GMR (FDC tablet/co-administration [relugolix + Activella]) and 90% CI of the GMR (ABE method) for the AUC0-∞ and Cmax of baseline-adjusted total E1 were 0.9845 (0.9589, 1.0107) and 0.8919 (0.8573, 0.9278), respectively; • The GMR (FDC tablet/co-administration [relugolix + Activella]) and 90% CI of the GMR (ABE method) for the AUC0-∞ and Cmax of NET were 0.9957 (0.9754, 1.0165) and 0.8488 (0.8137, 0.8854), respectively.

Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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Clinical Trial Report № 24

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate 40 mg/1 mg/0.5 mg film-coated tablet)
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	A Phase 2, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Study of the Efficacy and Safety of TAK-385 10, 20, and 40 mg (p.o.) in the Treatment of Uterine Fibroids. **(TAK-385/CCT-001)**
6. Phase of the clinical trial	Phase 2
7. Time frame of the clinical trial	From 02.11.2011. to 03.09.2012.
8. Countries where the clinical trial was conducted	36 Japan sites enrolled subjects in the Double-Blind Treatment Period.
9. Number of subjects	planned: 220 actual: 216
10. Purpose and secondary objectives of the clinical trial	This was a phase 2, multicenter, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of 3 dose levels (10, 20, and 40 mg) of TAK-385 administered orally for 12 weeks, compared with placebo in women with uterine fibroids. In addition, the pharmacodynamic and pharmacokinetic (PK) effects of TAK-385 were to be assessed.
11. Clinical trial design	A Phase 2, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Study.
12. Key inclusion criteria	Women with uterine fibroids
13. Investigational medicinal product, method of administration, strength	Relugolix/Estradiol/ Norethindrone Acetate (10 mg, 20 mg and 40 mg/1 mg/0.5 mg) Tablet, oral
14. Comparator, method of administration, strength	Placebo

15. Concomitant therapy	Concomitant medication was any drug given in addition to the study drug. These were prescribed by a physician or obtained by the subject over the counter. At each study visit, subjects were asked whether they had taken any medication other than the study drug used from signing of informed consent through the end of the study (including vitamin supplements, over-the-counter medications, and herbal medicines).
16. Efficacy evaluation criteria	Primary Endpoint Decrease in menstrual blood loss Proportion of subjects with a total PBAC score of <10 from Week 6 to 12 Secondary Endpoints Decrease in menstrual blood loss Proportion of subjects with a total PBAC score of <10 from Week 2 to 6 Proportion of subjects with a total PBAC score of <10 from Week 2 to 12 Amenorrhea Proportion of subjects with a total PBAC score of 0 from Week 6 to 12 Proportion of subjects with a total PBAC score of 0 from Week 2 to 6 Proportion of subjects with a total PBAC score of 0 from Week 2 to 12 Change in menstrual blood loss Change in the total PBAC score relative to baseline from Week 6 to 12 Myoma and uterine volumes Blood concentration of hemoglobin (Hb) Pain symptoms, other clinical symptoms, and quality of life (QOL) Numerical Rating Scale (NRS) score, Uterine Fibroid Symptom and Quality of Life (UFS-QOL) score Hematocrit (Ht), serum iron (Fe), and serum ferritin The use of analgesic medications during the treatment period
17. Safety evaluation criteria	Bone mineral density (BMD), adverse events (AEs), vital signs, weight, 12-lead electrocardiogram (ECG), clinical laboratory tests, and biochemical bone metabolism markers (serum type I collagen cross-linked N-telopeptide [NTx] and bone-specific alkaline phosphatase [BAP]).
18. Statistical methods	The proportion of subjects with a total PBAC score of <10 from Week 6 to 12 were summarized by treatment group. The point estimate and 2-sided 95% confidence interval of the difference were calculated between each TAK-385 group and placebo group (TAK-385 group – placebo group). Comparison between the treatment groups were also performed using the closed testing procedure given below. The chi-square test was used to compare the proportion of subjects with a total PBAC score of <10 from Week 6 to 12 between the TAK-385 40-mg group and placebo group. When TAK-385 40-mg group was found superior in comparison with placebo group, TAK-385 20-mg group was compared with placebo group. Similarly, when TAK-385 20-mg group was found superior in comparison with placebo group, TAK-385 10-mg group was compared with placebo group.
19. Demographic data of the study population (gender, age, race, etc.)	A total of 216 female subjects were randomized in the study from 307 subjects who were screened. The mean age of subjects who were randomized ranged between 41years and 43 years, the mean height ranged between 158 cm and 160 cm, and the mean weight ranged between 55 kg and 61 kg in all the treatment groups.
20. Efficacy outcomes	In the efficacy evaluation, as the primary endpoint in this study, a statistically significant difference in proportion of

	subjects with a total PBAC score of < 10 from Week 6 to 12 between each TAK-385 group and placebo group was observed, and the superiority of each TAK-385 group to placebo group was confirmed. The proportion was highest in TAK-385 40- mg group, suggesting a dose-response relationship. The decrease in menstrual blood loss in other time frames of the treatment period, and achievement of amenorrhea, being ones of the secondary endpoints in this study, showed higher proportion of subjects at higher dose levels of TAK-385. The mean of total PBAC score was lower at higher dose levels of TAK-385. In addition, a tendency toward improvement was seen also in myoma and uterine volumes, blood concentration of Hb, and pain symptoms. Therefore, it was indicated that the oral administration of TAK-385 at dose of 10 mg, 20 mg and 40 mg would improve the clinical symptoms of patients with uterine fibroids.
21. Safety outcomes	In the safety evaluation, the major TEAEs reported during the study period were considered to have been caused by the pharmacological effect of TAK-385. The incidence of these events was higher in accordance with the dose levels among the 10 mg, 20 mg and 40 mg groups of TAK-385, but there were no clinically significant TEAEs related to the study drug. The percent change of BMD in this study was considered to be the same level or less compared to the percent change of BMD that has previously been reported to occur with the use of leuprolide acetate 3.75 mg. As for the recovery of menstruation, it was considered there are no clinically significant issues overall.
22. Conclusion (summary)	It was therefore considered that there would be no clinically significant issues in the safety of TAK-385 administered to patients with uterine fibroids at dose levels up to 40 mg, and the tolerability thereof would be favorable. It was therefore concluded, that administration of TAK-385 up to 40mg in patients with uterine fibroids would be favorable from an efficacy, tolerability and safety aspect

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Clinical Trial Report № 25

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate 40 mg/1 mg/0.5 mg film-coated tablet)
2. Applicant	Gedeon Richter Plc. Hungary
3. Manufacturer	**Gedeon Richter Plc., Hungary** (primary packaging, secondary packaging, quality control, batch release), **Pateon Inc., Canada** (in bulk product manufacturing, quality control)
4. Conducted studies:	X yes ☐ no if no, justify
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
5. Full title of the clinical trial, code number of the clinical trial	A Phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy and safety of TAK-385 10, 20, and 40 mg (p.o.) in the treatment of endometriosis. **(TAK-385/CCT-101)**
6. Phase of the clinical trial	Phase 2
7. Time frame of the clinical trial	From 03.12.2011. to 30.09.2013.
8. Countries where the clinical trial was conducted	101 Japan sites enrolled subjects in the Double-Blind Treatment Period.
9. Number of subjects	planned: 495 actual: 487
10. Purpose and secondary objectives of the clinical trial	This was a phase 2, multicenter, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of 3 dose levels (10 mg, 20 mg, and 40 mg) of TAK-385 administered orally for 12 weeks compared with placebo in women with endometriosis. In addition, the pharmacokinetic and pharmacodynamic effects of TAK-385 were to be assessed. Leuplin was used as a reference to explore the clinical context of TAK-385.
11. Clinical trial design	This was a phase 2, multicenter, randomized, double-blind, parallel-group study.
12. Key inclusion criteria	Endometriosis
13. Investigational medicinal product, method of administration, strength	Relugolix 10, 20 and 40 mg Tablets, oral
14. Comparator, method of administration, strength	Placebo
15. Concomitant therapy	About 78 to 90% of the subjects were administered some concomitant medications during the treatment period in each treatment group. The major concomitant medications were loxoprofen sodium hydrate (29 to 54%), sodium ferrous citrate (20 to 35%), and acetaminophen (16 to 28%).

16. Efficacy evaluation criteria	Primary Endpoint: (1) Efficacy □ Change from baseline in mean of visual analogue scale (VAS) score for pelvic pain at the end of treatment period Secondary Endpoints: (1) Efficacy □ VAS score for pelvic pain during the treatment period □ VAS score for dyspareunia during the treatment period Additional Endpoints: □ Pelvic pain - Modified B&B (M-B&B) score for pelvic pain during the treatment period - B&B score for pelvic pain during the treatment period □ Dyspareunia - M-B&B score for dyspareunia during the treatment period - B&B score for dyspareunia during the treatment period □ Use of pain killer during the treatment period □ Decrease in menstrual blood loss and achievement of the amenorrheic state □ QOL (Endometriosis Health Profile-30 [EHP-30])
17. Safety evaluation criteria	Bone mineral density (BMD), adverse events (AEs), vital signs, weight, 12-lead electrocardiogram (ECG), clinical laboratory tests, and biochemical bone metabolism markers (serum type I collagen cross-linked N-telopeptide [NTx] and bone-specific alkaline phosphatase [BAP]).
18. Statistical methods	A statistical analysis plan (SAP) was prepared and finalized prior to unblinding of subject's treatment assignment. This document provided further details regarding the definition of analysis variables and analysis methodology to address all study objectives.
19. Demographic data of the study population (gender, age, race, etc.)	The mean age of randomized subjects ranged between 35.1 and 36.1 years, the mean height between 158.6 and 160.8 cm, and the mean weight between 51.3 and 56.5 kg in all the treatment groups. There seemed to be no clinically significant differences among the treatment groups.
20. Efficacy outcomes	The efficacy and safety of orally administered TAK-385 were investigated in patients with endometriosis at doses of 10 mg, 20 mg and 40 mg for 12 weeks, compared with an administration of placebo, and of leuprorelin acetate as an active reference. In the efficacy evaluation, with respect to the primary endpoint in this study, "the change from baseline in mean of VAS score for pelvic pain at the end of the treatment period", a statistically significant difference was observed between each TAK-385 treatment group and placebo group. The change from baseline in mean of VAS score for pelvic pain in TAK-385 40-mg group was comparable to that in Leuprorelin group. The change from baseline in mean of VAS score by visit for pelvic pain and dysmenorrhea, both being secondary endpoints, increased in a time-dependent manner from early stage of treatment in higher dose levels of TAK-385. In the additional endpoints, the proportion of days using pain killer and the amount of menstrual bleeding decreased, and the proportion of subjects who achieved amenorrhea increased in a time-dependent manner depending on the dose levels of TAK-385. The concentration of CA125, a biochemical endometriosis marker, decreased at higher dose

	levels of TAK-385 dose, and the concentration in TAK-385 40-mg group was approximately the same as in Leuprorelin group.
21. Safety outcomes	In the safety evaluation, the major TEAEs such as hot flush, metrorrhagia, and menorrhagia that occurred in TAK-385 groups in the treatment period were considered to be due to the pharmacological effects of TAK-385, with higher incidences in accordance with higher dose levels, which were also observed in another study in patients with uterine fibroids (TAK-385/CCT-001 study). No apparent difference in TAK-385 40-mg group was observed in incidence or timing of onset of TEAEs in comparison with the group administered leuprorelin acetate. One serious TEAE, liver function test abnormal, occurred in TAK-385 20-mg group. The overall changes from baseline for liver function-related laboratory test results at the end of treatment period were slightly larger at higher dose levels of TAK-385, and change profile in TAK-385 40-mg group was similar to that in Leuprorelin group. BMD decreases were seen in TAK-385 groups, and the percent change and time-profile of BMD were approximately the same as those in the TAK-385/CCT-001 study carried out with uterine fibroid patients. A similar effect on BMD decrease was observed at the TAK-385 40-mg dose to that of leuprorelin acetate administration.
22. Conclusion (summary)	On the basis of the efficacy and safety findings in this study, 40 mg of TAK-385 is considered to be an effective dose for treating endometriosis.

Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine