Annex 29
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)

Non-Clinical Study Report

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)
1) type of the medicinal product, registration of which was conducted or planned	Medicinal product with complete dossier (stand-alone dossier) (new active substance)
2) conducted studies	X yes ☐ no if no, justify
2. Pharmacology:	
1) primary pharmacodynamics	Binding affinity of TAK-385 for GnRh receptors (Study No:SD2LE2006-MK-007); Antagonistic activity of TAK-385 for human GnRh receptor-expressing CHO cell system (Study No:SD2LE2006-MK-001); Antagonistic activity of TAK-385 for monkey GnRh receptor in a monkey GnRh receptor-expressing CHO cell system (Study No:SD2LE2006-MK-002); Suppression of a LH release by single oral administration of a novel non-peptid GnRh antagonist TAK-385, in castrated cynomolgus monkeys (Study No:SD2LE2006-MK-003); Suppression of the HPG axis by a novel orally active GnRh antagonist TAK-385, in female human GnRh receptor knock-in mice (Study No:SD2LE2006-MK-009); Suppression of the HPG axis by a novel orally active GnRh antagonist TAK-385, in male human GnRh receptor knock-in mice (Study No:SD2LE2006-MK-008)
2) secondary pharmacodynamics	In vitro pharmacological diversity profile of TAK-385 MDS Pharma services pharmacology data report (MDSPS PT: 1083670)
3) safety pharmacology	Effects on the central nerves system in rats (Study No:BA06114); Effects on the Respiratory System in rats (Study No:BA06115); Effects on the Cardiovascular System in Conscious Monkeys (Study No:BA06116); Effects on hERG Current (Study No:B060607)
4) pharmacodynamic interactions	-
3. Pharmacokinetic properties:	
1) analytical procedures and reports on their validation	Validation for the determination of T-1331285 in Rabbit plasma by HPLC/MS (Study No:JCL053761); Validation of a HPLC Method for the determination of TAK-385 (Study No:3776VA, 385VA); Validation of a HPLC Method for the determination of T-1331285 (Study No:3476VA); Validation for the determination of T-1331285 in Mouse plasma by HPLC/MS (Study No:JCL053741); Validation for the determination of T-1331285 in Rat plasma by HPLC/MS (Study No:JCL053721); Validation for the determination of T-1331285 in Monkey plasma by HPLC/MS (Study No:JCL053751)

2) absorption	MVT-601Clearence and volume of distribution in rats and monkeys following I.V.; Plasma concentrations of TAK-385 in rats after single oral ang I.V. (TAK-385/00076); Plasma concentrations of TAK-385 in monkey after single oral ang I.V. (TAK-385/00077); Plasma concentrations of radioactivity in rats after single oral administration of 14C-TAK (TAK-385/00078); Plasma concentrations and excretion of radioactivity in monkey after single oral and I.V. administration of 14C-TAK (TAK-385/00079); Plasma concentrations and urinary excretion of radioactivity in monkey after single oral and I.V. administration of 14C-TAK (TAK-385/00080); Permeability study of 14C-TAK across Caco-2 cells (GE-0660-G); Absorption site of 14C-TAK in rats (TAK-385-12451); Lymphatic absorption of radioactivity in rats after single oral administration of 14C-TAK (TAK-385-12452); Portal transfer of radioactivity in rats after jejunal administration of 14C-TAK (TAK-385-12709); Linearity in the plasma concentration time profiles of TAK-385 in rats after single oral and I.V. administration (TAK-385-12713); Linearity in the plasma concentration time profiles of TAK-385 in monkey after single oral administration (TAK-385-12714); Plasma concentration time profiles of TAK-385 in rats after repeated oral administration (TAK-385-12723)
3) distribution	Potencial effects of TAK-385 on in vitro plasma protein binding of concomitant drugs in humans (St.No:15-805-053); Concentrations of radioactivity in the tissues of rats after single oral administration of 14C-TAK-385 (TAK-385/00085); Concentrations of radioactivity in the tissues of female rats after single oral administration of 14C-TAK-385 (TAK-385/00082); Concentrations of radioactivity in the tissues of pigmented rats after single oral administration of 14C-TAK-385 (TAK-385/00083); In vitro plasma protein binding of 14C-TAK-385 in rats, mice, monkey and humans (TAK-385/00084); Whole body autoradiography in male rats after single oral administration of 14C-TAK-385 (TAK-385-12448); Whole body autoradiography in female rats after single oral administration of 14C-TAK-385 (TAK-385-12449); In vitro distribution of 14C-TAK-385 in rats, mice, monkey and humans (TAK-385-12450); Feto-placental transfer of radioactivity of pregnant rats after single oral administration of 14C-TAK-385 (TAK-385-12711)
4) metabolism	MVT-601 Metabolite Characterization in Human Hepatocytes (MVT-601-9027); Indetification of TAK-385 Metabolite, Metabolite B in rats (S-TAK-385-072); In vitro metabolism of 14C-TAK-385 by Hepatic microsomes from Humans and Animals (A871-385-021); Indetification of CYP-450 Isoforms involved the in vitro Metabolism of 14C-TAK-385 by CYP expressing microsomes (A871-385-022); Indetification of CYP-450 Isoforms involved the in vitro Metabolism of 14C-TAK-385 by Correlation Analizys (A871-385-023); Characterization of TAK-385 Metabolites (TAK-385/00085); Metabolite profile in rat plasma after single oral administration of 14C-TAK-385 (TAK-385/00086); Metabolite profile in monkey plasma after single oral administration of 14C-TAK-385 (TAK-385/00087); Metabolite profile in rat urine, feces and bile plasma after single oral administration of 14C-TAK-385 (TAK-385/00088);

	Metabolite profile in monkey urine, feces and bile plasma after single oral administration of 14C-TAK-385 (TAK-385/00089); Investigation of Gut Microbiota-Mediated Metabolism of TAK-385 with Select Antibiotic Drugs (TAK-385-12402); Metabolite profiles in the portal plasma, jejunum and jejunal contents after jejunal administration of [14C]TAK-385 to rats (TAK-385-12710); Metabolite profiles in the milk and plasma after single oral administration of [14C]TAK-385 to lactating rats (TAK-385-12715); A Pharmacokinetic Study of TAK-385 After a Single Oral Administration to Normal and Pseudo Germ-Free Male Sprague-Dawley Rats (TAK-385-12974); In Vitro Determination of Relative Contributions of Major Cytochrome P450 Isozymes to the Microsomal Metabolism of [14C]TAK-385 Using Cytochrome P450 Isozyme-Selective Chemical Inhibitors (TAK-385-13009); Formation of Metabolite-B on the in Vitro Metabolism of [14C]TAK-385 by Human Liver Microsomes and CYP2C8-expressing Microsomes (TAK-385-13393)
5) excretion	Urinary, fecal and expiratory excretion of radioactivity in rats after a single oral administration of [14C]TAK-385 (TAK-385/00074); Biliary excretion of radioactivity in rats after a single oral administration of [14C]TAK-385 (TAK-385/00075); Lacteal secretion of [14C]TAK-385 in rats (TAK-385-12712)
6) pharmacokinetic interactions (non-clinical)	A Pharmacokinetic Study of TAK-385 after a Single Oral or Intravenous Administration to Male Sprague-Dawley Rats With or Without Elacridar (RPT-03023); Inhibitory Effects of TAK-385 on Cytochrome P450 Activities (Study No.: 817/AD); Evaluation of CYP3A Induction by TAK-385 in Human Hepatocytes (TAK-385/00015); Inhibitory Effect of TAK-385 on [3H]Digoxin Transport across Caco-2 Cells (TAK-385-10183); Inhibitory Effects of TAK-385 on CYP Activities in Human Liver Microsomes (Study No. B131136); Determination of P-gp Kinetic Parameters for TAK-385 in Caco-2 Cells (TAK-385-12581); In vitro evaluation of CYP induction by TAK-385 in human hepatocytes (TAK-385 12716); Inhibition Study of TAK-385 using OATP1B1/1B3, OAT1/3, OCT2, MATE1/2-K and BCRP Expressing Cells (TAK-385-13265); Evaluation of 14C-TAK-385 as a Substrate of Human Drug Transporters OATP1B1 and OATP1B3 (TAK-385-13267); Assessment of Inhibitory Effect of TAK-385 on the BSEP Using Human BSEP-Expressing Membrane Vesicles (Study No. 14-160/su)
7) other pharmacokinetic studies	-
4. Toxicology:	
1) single dose toxicity	Effects of T-1331285 (TAK-013 backup compound) on plasma ALT and AST during single oral dosing to monkeys (Study No. 04-015 / ac); Preliminary oral gavage single dose toxicokinetic study of T-1331285 in mice (35-344/tk); Oral gavage single dose toxicity study of TAK-385 in rats (06-158/SU); Preliminary intravenous single dose toxicity study of TAK-385 in rats (06-220/ac); Acut oral gavage escalating dose toxicity study of TAK-385 in monkeys (BA06113); Intravenous single dose toxicity study of TAK-385 in rats (06-157/AC)

2) repeated dose toxicity	Preliminary two week oral gavage toxicity study of T-1331285 in monkeys (05-190/su); Preliminary two week oral gavage toxicity study of T-1331285 in rats (04-118/su); Preliminary two week oral gavage toxicity study of T-1361888 in monkeys (04-245/su); Four week oral gavage range-finding toxicity study of TAK-385 in mice (06-283/ca); Four week oral gavage toxicity study of TAK-385 in monkeys (BA06118); Four week oral gavage toxicity study of TAK-385 in rats (06-160/su); Thirteen week oral gavage range-finding toxicity study of TAK-385 in mice (B061815-1); Thirteen week oral gavage range-finding toxicity study of TAK-385 in rats (B-6100); Thirty-nine-week oral gavage toxicity study of TAK-385 in monkeys (BA07043); Twenty-six-week oral gavage toxicity study of TAK-385 in rats (B-6137)
3) genotoxicity: in vitro	Cytogenetic Assay with TAK-385 in Chinese Hamster Lung Cells (06-166/GE); Bacterial Reversion Assay with TAK-385 (Study No.: B060605); Micronucleus Assay with TAK-385 in Rats (Study No.: B060606)
in vitro (including additional toxicokinetics assessment)	-
4) carcinogenicity:	
long-term studies	Twenty-four-month oral gavage carcinogenicity study of TAK-385 in mice (B-6137); Twenty-four-month oral gavage carcinogenicity study of TAK-385 in rats (B-6555);
short-term studies or mid-term studies	4.2.3.4.2 SHORT- OR MEDIUM-TERM STUDIES All short- and medium-term repeat dose toxicity studies are included in Module 4.2.3.2, Repeat-Dose Toxicity. No additional short- or medium-term toxicity study reports are included in Module 4.2.3.4.2.
additional studies	-
5) reproductive and developmental toxicity:	
effect on fertility and early embryonic development	Preliminary study for effects of TAK-385 on the estrous cycle in rats (06-161/fe); Effects of TAK-385 on Fertility and Early Embryonic Development to Implantation in Rats (Study Number: SBL010-039)
embryotoxicity	Range-finding study for effects on TAK-385 on embryo-fetal development in rats (06-162/te); Range-finding study for effects on TAK-385 on embryo-fetal development in rabbits (06-163/te); Effects of TAK-385 on Embryo-Fetal Development in Rats (Study Number: SBL010-038); Effects of TAK-385 on Embryo-Fetal Development in Rabbits (Study Number: SBL010-040)
prenatal and postnatal toxicity	Effects of TAK-385 on Pre- and Postnatal Development in rats (Study Number: 300136)
studies in which the drug is administered to the offspring (juvenile animals) and/or late effect is assessed	4.2.3.5.4 STUDIES IN WHICH THE OFFSPRING (JUVENILE ANIMALS) ARE DOSED AND/OR FURTHER EVALUATED No specific toxicity studies were conducted in juvenile animals. A waiver for use in paediatric populations (<18 years of age) was granted for the combination of relugolix, estradiol and

	norethisterone acetate. This waiver can be found in Module 1.10. No study reports are included in Module 4.2.3.5.4.
6) local tolerance	4.2.3.6 LOCAL TOLERANCE No specific local tolerance studies were conducted for relugolix as the route of administration was the same in repeat-dose toxicity studies (oral) as the intended oral dose (see Section 3.1.6 of Module 2.4, Nonclinical Overview). No study reports are included in Module 4.2.3.6.
7) additional toxicity studies:	
antigenicity (antibody production)	-
immunotoxicity	-
mechanistic study	Evaluation of Di-docosahexaenoyl (22:6)-bis(monoacylglycerol) Phosphate as a Biomarker of Phospholipidosis in a 4-Week Study of TAK-385 Administered via Oral Gavage to Male Sprague-Dawley Rats (TAK-385-13010)
drug dependence	-
toxicity of metabolites	-
toxicity of impurities	Bacterial reversion assay with TAK-385 U-2 (39-163/ge); Computational mutagenicity analysis of Relugolis related substances (MVT-6019025); In Silico Assessment of the Mutagenic Potential of U-7 and U-7 precursor in TAK-385 (Takeda Study: PCD-DS-385-09A); The mutagenic potential of related substances for TAK-385 (TAK-385/10002); The mutagenic potential of related substances for TAK-385, U-6 (TAK-385/10009); Bacterial reversion assay with TAK-385 U-2 (B090400); Single dose oral gavage toxicokinetic study of TAK-385 U-2 in mice (09-167/tk); Bacterial reversion assay with TAK-385 U-2 Calf serum (39-146/ge); Bacterial reversion assay with TAK-385 U-2 Bovine serum (39-176/ge); Cytogenetic Assay with TAK-385 U-2 in Chinese Hamster Lung (CHL) Cells (Study No.: B090578); Single dose oral gavage toxicokinetic study of TAK-385 U-2 in rats (09-168/tk); *IN VITRO* HPRT GENE MUTATION ASSAY WITH TAK-385 U-2 IN CHINESE HAMSTER LUNG (V79) CELLS (Study Code No. K08-0005); Bacterial reversion assay with TAK-385 U-2 Human S9 mix (B742); Micronucleus Assay with TAK-385 U-2 in Rats (Study No.: B090577); In vivo / in vitro UDS assay with TAK-385 U-2 in Rat hepatocytes (B090579); In vivo lacZ-mutation assay with TAK-385 U-2 in Muta™Mice (Study Number 8212684); Bacterial reversion assay with TAK-385 U-2 Rat S9 mix (39-181/ge);
others	3T3 NRU Phototoxicity test of T-1331285 (05-281/pt); Structure elucidation of TAK-385 reference standard (TAK-385/00036); SINGLE-DOSAGE PHOTOTOXICITY STUDY TO DETERMINE THE EFFECTS OF ORAL (GAVAGE) ADMINISTRATION OF T-1331285 ON SKIN IN HAIRLESS MICE SPONSOR'S (STUDY NUMBER: 05-356/CO)
5. Conclusions on non-clinical study	An extensive nonclinical development program was conducted for the new chemical entity relugolix. Additionally, as part of the proposed combination therapy, an assessment of nonclinical pharmacology, pharmacokinetics and safety for E2 and NETA were evaluated based on reviews of published literature in context of co-

	administration with relugolix as part of the proposed combination therapy. Nonclinical data for relugolix indicate it is a potent and selective antagonist of the human GnRH receptor, and in pharmacologically-relevant (monkeys and human GnRH receptor knock-in mice) animal models, results in suppression of LH concentrations with functional decreases in sex steroid hormones (ie, estrogen) and associated phenotypic effects. These data support the proposed clinical mechanism of action whereby relugolix antagonizes GnRH receptors in the pituitary, resulting in the suppression of LH and FSH secretion and decreases in endogenous sex steroid hormones levels (ie, estrogen, progesterone and testosterone). Undesirable pharmacodynamic interactions based on primary or secondary pharmacology are not expected for the components of the proposed combination. Although relugolix, E2, and NETA are all extensively metabolized prior to excretion, no significant PK interactions were observed between components of the combination that impact the safety or efficacy profiles. There were no nonclinical toxicology signals that might indicate the potential for adverse additive or synergistic interactions with respect to general toxicity, genotoxicity and carcinogenicity, or reproductive toxicology. Further, for the new chemical entity, relugolix, the systemic exposures at the NOAEL in animal toxicity studies are, in general, significantly higher than the expected clinical exposures. The comprehensive nonclinical package presented here, taken together with clinical data for relugolix alone, clinical data with the combination including pivotal phase 3 safety and efficacy studies, and available clinical and nonclinical information available in published literature for E2 and NETA, support the safe and effective use of the therapeutic combination of relugolix (40 mg) with E2 (1 mg) and NETA (0.5 mg) for the treatment of symptoms associated with uterine fibroids.

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

Додаток 29
до Порядку проведення експертизи реєстраційних матеріалів на лікарські засоби, що подаються на державну реєстрацію (перереєстрацію), а також експертизи матеріалів про внесення змін до реєстраційних матеріалів протягом дії реєстраційного посвідчення (пункт 4 розділу IV)

Звіт про доклінічні дослідження

1. Назва лікарського засобу (за наявності - номер реєстраційного посвідчення)	Рієко (Релуголікс+естрадіол+норетистерону ацетат, 40 мг/1 мг/0,5 мг, таблетки, вкриті плівковою оболонкою)
1) тип лікарського засобу, за яким проводилася або планується реєстрація	Лікарський засіб за повним досьє (автономним досьє) (нова діюча речовина)
2) Проведені дослідження:	X так ☐ ні якщо ні, обґрунтувати
2. Фармакологія:	
1) первинна фармакодинаміка	Афінність зв'язування ТАК-385 з рецепторами ГнРГ (Дослідження №: SD2LE2006-MK-007); Антагоністична активність ТАК-385 до системи клітин СНО людини, що експресує рецептори ГнРГ (Дослідження №: SD2LE2006-MK-001); Антагоністична активність ТАК-385 до системи клітин СНО мавп, що експресує рецептори ГнРГ (Дослідження №: SD2LE2006-MK-002); Пригнічення вивільнення ЛГ при одноразовому пероральному введенні нового непептидного антагоніста ГнРГ ТАК-385 у кастрованих яванських макак (Дослідження №: SD2LE2006-MK-003); Пригнічення осі ГГЛ новим перорально активним антагоністом ГнРГ ТАК-385 у самок мишей з нокінгом рецепторів ГнРГ людини (Дослідження №: SD2LE2006-MK-009); Пригнічення осі ГГЛ новим перорально активним антагоністом ГнРГ ТАК-385 у самців мишей з нокінгом рецепторів ГнРГ людини (Дослідження №: SD2LE2006-MK-008).
2) вторинна фармакодинаміка	Профіль фармакологічного різноманіття ТАК-385 in vitro: Звіт про фармакологічні дані MDS Pharma Services (MDSPS PT: 1083670).
3) фармакологія безпеки	Вплив на центральну нервову систему у щурів (Дослідження №: BA06114); Вплив на дихальну систему у щурів (Дослідження №: BA06115); Вплив на серцево-судинну систему у свідомих мавп (Дослідження №: BA06116); Вплив на тік hERG (Дослідження №: B060607).
4) фармакодинамічні взаємодії	-
3. Фармакокінетика:	
1) аналітичні методики та звіти щодо їх валідації	Валідація визначення Т-1331285 у плазмі кроликів методом ВЕРХ/МС (Дослідження №: JCL053761); Валідація методу ВЕРХ для визначення ТАК-385 (Дослідження №: 3776VA, 385VA); Валідація методу ВЕРХ для визначення Т-1331285 (Дослідження №: 3476VA); Валідація для визначення Т-1331285 у плазмі мишей методом ВЕРХ/МС (Дослідження №: JCL053741); Валідація для визначення Т-1331285 у плазмі щурів методом ВЕРХ/МС (Дослідження №:

	JCL053721); Валідація на визначення Т-1331285 у плазмі мавп методом ВЕРХ/МС (Дослідження №: JCL053751).
2) всмоктування	MVT-601 Кліренс та об'єм розподілу у щурів і мавп після внутрішньовенного введення; Концентрації ТАК-385 у плазмі крові щурів після одноразового перорального та внутрішньовенного введення (ТАК-385/00076); Концентрації ТАК-385 у плазмі мавп після одноразового перорального та внутрішньовенного введення (ТАК-385/00077); Концентрації радіоактивності в плазмі щурів після одноразового перорального введення 14С-ТАК (ТАК-385/00078); Концентрація в плазмі та виділення радіоактивності у мавп після одноразового перорального та внутрішньовенного введення 14С-ТАК (ТАК-3 85/00079); Концентрація в плазмі та виділення з сечею радіоактивності у мавп після одноразового перорального та внутрішньовенного введення 14С-ТАК (ТАК-385/00080); Дослідження проникності 14С-ТАК через клітини Caco-2 (GE-0660-G); Місце всмоктування 14С-ТАК у щурів (ТАК-385-12451); Лімфатична абсорбція радіоактивності у щурів після одноразового перорального введення 14С-ТАК (ТАК-385-12452); Портальне проникнення радіоактивності у щурів після введення 14С-ТАК (ТАК-385-12709); Лінійність у профілях "концентрація в плазмі/час" ТАК-385 у щурів після одноразового перорального та внутрішньовенного введення (ТАК-385-12713); Лінійність у профілях "концентрація в плазмі/час" ТАК-385 у мавп після одноразового перорального введення (ТАК-385-12714); Профілі "концентрація в плазмі/час" ТАК-385 у щурів після багаторазового перорального введення (ТАК-385-12723).
3) розподіл	Потенційний вплив ТАК-385 на зв'язування супутніх препаратів з білками плазми у людини in vitro (Дослідження №: 15-805-053); Концентрації радіоактивності в тканинах щурів після одноразового перорального введення 14С-ТАК-385 (ТАК-385/00085); Концентрації радіоактивності в тканинах самок щурів після одноразового перорального введення 14С-ТАК-385 (ТАК-385/00082); Концентрації радіоактивності в тканинах пігментованих щурів після одноразового перорального введення 14С-ТАК-385 (ТАК-385/00083); Зв'язування 14С-ТАК-385 з білками плазми у щурів, мишей, мавп та людей in vitro (ТАК-385/00084); Ауторадіографія всього тіла у самців щурів після одноразового перорального введення 14С-ТАК-385 (ТАК-385-12448); Ауторадіографія всього тіла у самок щурів після одноразового перорального введення 14С-ТАК-385 (ТАК-385-12449); Розподіл 14С-ТАК-385 у щурів, мишей, мавп та людей in vitro (ТАК-3 85-12450); Фето-плацентарне проникнення радіоактивності у вагітних щурів після одноразового перорального введення 14С-ТАК-385 (ТАК-385-12711).
4) метаболізм	MVT-601 Характеристика метаболітів у гепатоцитах людини (MVT-601-9027); Ідентифікація метаболіту ТАК-385, метаболіту В у щурів (S-ТАК-385-072); Метаболізм 14С-ТАК-385 мікросомами печінки

	людей і тварин in vitro (A871-385-021); Ідентифікація ізоформ CYP-450, включаючи метаболізм 14C-TAK-385 мікросомами, що експресують CYP, in vitro (A871-385-022); Ідентифікація ізоформ CYP-450, включаючи метаболізм 14C-TAK-385 in vitro методом кореляційного аналізу (A871-385-023); Характеристика метаболітів TAK-385 (TAK-385/00085); Профіль метаболітів в плазмі щурів після одноразового перорального введення 14C-TAK-385 (TAK-385/00086); Профіль метаболітів в плазмі мавп після одноразового перорального введення 14C-TAK-385 (TAK-385/00087); Профіль метаболітів в сечі, калі та плазмі жовчі щурів після одноразового перорального введення 14C-TAK-385 (TAK-385/00088); Профіль метаболітів в сечі, калі та плазмі жовчі мавп після одноразового перорального введення 14C-TAK-385 (TAK-3 85/00089); Дослідження метаболізму TAK-385, опосередкованого мікробіотою кишечника, за допомогою окремих антибіотиків (TAK-385-12402); Профілі метаболітів у портальній плазмі, тонкій кишці та вмісті тонкої кишки після введення [14C]TAK-385 щурам (TAK-385-12710); Профілі метаболітів у молоці та плазмі після одноразового перорального введення [14C]TAK-385 лактуючим самкам щурів (TAK-385-12715); Фармакокінетичне дослідження TAK-385 після одноразового перорального введення нормальним і псевдо-вільним від мікробів самцям щурів Спраг-Доулі (TAK-385-12974); Визначення відносного внеску основних ізоферментів цитохрому P450 у мікросомальний метаболізм [14C]TAK-385 з використанням ізоферментно-селективних хімічних інгібіторів цитохрому P450 in vitro (TAK-385-13009); Утворення метаболіту-B при метаболізмі [14C]TAK-385 мікросомами печінки людини та мікросомами, що експресують CYP2C8, in vitro (TAK-385-13393).
5)виведення	Виділення радіоактивності з сечею, калом та на видоху у щурів після одноразового перорального введення [14C]TAK-385 (TAK-385/00074); Виведення радіоактивності з жовчю у щурів після одноразового перорального введення [14C]TAK-385 (TAK-385/00075); Виділення [14C]TAK-385 з молоком у щурів (TAK-385-12712).
6) фармакокінетичні взаємодії (доклінічні)	Фармакокінетичне дослідження TAK-385 після одноразового перорального або внутрішньовенного введення самцям щурів Спраг-Доулі з елакридаром або без нього (RPT-03023); Інгібуючий вплив TAK-385 на активність цитохрому P450 (Дослідження №: 817/AD); Оцінка індукції CYP3A TAK-385 у гепатоцитах людини (TAK-385/00015); Інгібуючий вплив TAK-385 на транспорт [3H]дигоксину у клітинах Caco-2 (TAK-385-10183); Інгібуючий вплив TAK-385 на активність CYP в мікросомах печінки людини (Дослідження №: B131136); Визначення кінетичних параметрів P-gp для TAK-385 в клітинах Caco-2 (TAK-385-12581); Оцінка індукції CYP TAK-385 у гепатоцитах людини in vitro (TAK-385 12716); Дослідження інгібування TAK-385 з використанням клітин, що експресують OATP1B1/1B3, OAT1/3,

	OCT2, MATE1/2-K та BCRP, in vitro (TAK-385-13265); Оцінка 14C-TAK-385 як субстрату переносників лікарських засобів людини OATP1B1 та OATP1B3 (TAK-385-13267); Оцінка інгібуючого впливу TAK-385 на BSEP з використанням мембранних везикул, що експресують BSEP, людини (Дослідження №: 14-160/su).
7) інші фармакокінетичні дослідження	-
4. Токсикологія:	
1) токсичність у разі одноразового введення	Вплив T-1331285 (резервна сполука TAK-013) на АЛТ та АСТ у плазмі під час одноразового перорального введення мавпам (Дослідження №: 04-015/ac); Попереднє токсикокінетичне дослідження одноразової дози T-1331285 у мишей після перорального введення через зонд (35-344/tk); Дослідження токсичності одноразової дози TAK-385 у щурів після перорального введення через зонд (06-158/SU); Попереднє дослідження токсичності однієї дози TAK-385 у щурів після внутрішньовенного введення (06-220/ac); Дослідження гострої токсичності TAK-385 при підвищенні доз у мавп після перорального введення через зонд (BA06113); Дослідження токсичності однієї дози TAK-385 у щурів після внутрішньовенного введення (06-157/AC)
2) токсичність у разі повторних введень	Попереднє 2-тижневе дослідження токсичності T-1331285 у мавп після перорального введення через зонд (05-190/su); Попереднє 2-тижневе дослідження токсичності T-1331285 у щурів після перорального введення через зонд (04-118/su); Попереднє 2-тижневе дослідження токсичності T-1361888 у мавп після перорального введення через зонд (04-245/su); 4-тижневе дослідження для визначення діапазону токсичності TAK-385 у мишей після перорального введення через зонд (06-283/ca); 4-тижневе дослідження токсичності TAK-385 у мавп після перорального введення через зонд (BA06118); 4-тижневе дослідження токсичності TAK-385 у щурів після перорального введення через зонд (06-160/su); 13-тижневе дослідження для визначення діапазону токсичності TAK-385 у мишей після перорального введення через зонд (B061815-1); 13-тижневе дослідження для визначення діапазону токсичності TAK-385 у щурів після перорального введення через зонд (B-6100); 39-тижневе дослідження токсичності TAK-385 у мавп після перорального введення через зонд (BA07043); 26-тижневе дослідження токсичності TAK-385 у щурів після перорального введення через зонд (B-6137).
3) генотоксичність: in vitro	Цитогенетичний аналіз TAK-385 у клітинах з легенів китайського хом'ячка (06-166/GE); Аналіз бактеріальної реверсії при введенні TAK-385 (Дослідження №: B060605); Мікроядерний аналіз при введенні TAK-385 у щурів (Дослідження №: B060606).
in vivo (включаючи додаткову оцінку з токсикокінетики)	-
4) канцерогенність:	
довгострокові дослідження	24-тижневе дослідження канцерогенності TAK-385 у

	мишей після перорального введення через зонд (B-6137); 24-тижневе дослідження канцерогенності ТАК-385 у щурів після перорального введення через зонд (B-6555);
короткострокові дослідження або дослідження середньої тривалості	4.2.3.4.2 КОРОТКОСТРОКОВІ ДОСЛІДЖЕННЯ АБО ДОСЛІДЖЕННЯ СЕРЕДНЬОЇ ТРИВАЛОСТІ Всі короткострокові дослідження токсичності або дослідження середньої тривалості зазначені у Модулі 4.2.3.2 «Токсичність у разі повторних введень». Інші короткострокові дослідження токсичності або дослідження середньої тривалості до Модулю 4.2.3.4.2 не включені.
додаткові дослідження	-
5) репродуктивна токсичність та токсичний вплив на розвиток потомства:	
вплив на фертильність і ранній ембріональний розвиток	Попереднє дослідження впливу ТАК-385 на естральний цикл у щурів (06-161/fe); Вплив ТАК-385 на фертильність і ранній ембріональний розвиток до імплантації у щурів (Дослідження №: JSBL010-039).
ембріотоксичність	Дослідження для визначення діапазону впливу ТАК-385 на ембріональний розвиток у щурів (06-162/te); Дослідження для визначення діапазону впливу ТАК-385 на ембріональний розвиток у кроликів (06-163/te); ВпливТАК-385 на ембріональний розвиток у щурів (Дослідження №: SBL010-038); ВпливТАК-385 на ембріональний розвиток у кроликів (Дослідження №: SBLO10-040)
пренатальна і постнатальна токсичність	Вплив ТАК-385 на пре- і постнатальний розвиток у щурів (Дослідження №: 300136)
дослідження, при яких препарат уводиться потомству (нестатевозрілим тваринам) та/або оцінюється віддалена дія	4.2.3.5.4 ДОСЛІДЖЕННЯ, ПРИ ЯКИХ ПРЕПАРАТ УВОДИТЬСЯ ПОТОМСТВУ (НЕСТАТЕВОЗРІЛИМ ТВАРИНАМ) ТА/АБО ОЦІНЮЄТЬСЯ ВІДДАЛЕНА ДІЯ Спеціальні дослідження токсичності у нестатевозрілих тварин не проводились. Звільнення від застосування у педіатричній популяції (віком <18 років) була надана щодо комбінації релуголіксу, естрадіолу та норетистерону ацетату. Це звільнення наведене у Модулі 1.10. Жодні звіти про дослідження до Модулю 4.2.3.5.4. не включені.
6) місцева переносимість	4.2.3.6 МІСЦЕВА ПЕРЕНОСИМІСТЬ Спеціальні дослідження місцевої переносимості релуголіксу не проводились, оскільки спосіб застосування є таким же, як і в дослідженнях токсичності у разі повторних введень (перорально) (див. розділ 3.1.6 Модуля 2.4 «Доклінічний огляд Жодні звіти про дослідження до Модулю 4.2.3.6 не включені.
7) додаткові дослідження токсичності:	
антигенність (утворення антитіл)	-
імунотоксичність	-
дослідження механізмів дії	Оцінка ди-докозагексаеноіл (22:6)-біс(моноацилгліцерол) фосфату як біомаркера фосфоліпідозу під час 4-тижневого дослідження ТАК-385 у самців щурів Спраг-Доулі після перорального

	введення через зонд (ТАК-385-13010).
лікарська залежність	-
токсичність метаболітів	-
токсичність домішок	Аналіз бактеріальної реверсії при введенні ТАК-385 U-2 (39-163/ge); Розрахунковий аналіз мутагенності домішок релуголіксу (MVT-6019025); Оцінка мутагенного потенціалу прекурсора U-7 та U-7 в ТАК-385 in silico (Дослідження Takeda: PCD-DS-385-09A); Мутагенний потенціал домішок ТАК-385 (ТАК-385/10002); Мутагенний потенціал домішок ТАК-385, U-6 (ТАК-385/10009); Аналіз бактеріальної реверсії при введенні ТАК-385 U-2 (B090400); Токсикокінетичне дослідження однієї дози ТАК-385 U-2 у мишей після перорального введення через зонд (09-167/tk); Аналіз бактеріальної реверсії при введенні ТАК-385 U-2 у телячій сироватці (39-146/ge); Аналіз бактеріальної реверсії при введенні ТАК-385 U-2 у бичачій сироватці (39-176/ge); Цитогенетичний аналіз ТАК-385 U-2 у клітинах з легенів китайського хом'ячка (КЛКХ) (Дослідження №: B090578); Токсикокінетичне дослідження однієї дози ТАК-385 U-2 у щурів після перорального введення через зонд (09-168/tk); Дослідження мутації гена HPRT при введенні ТАК-385 U-2 у клітинах з легенів китайського хом'ячка (v79) in vitro (Дослідження №: K08-0005); Аналіз бактеріальної реверсії при введенні ТАК-385 U-2 у суміші S9 людини (B742); Мікроядерний аналіз при введенні ТАК-385 у щурів (Дослідження №: B090577); Аналіз UDS при введенні ТАК-385 U-2 в гепатоцитах щурів in vivo/in vitro (B090579); Аналіз мутації lacZ при введенні ТАК-385 U-2 у мишей Muta™ in vivo (Дослідження №: 8212684); Аналіз бактеріальної реверсії при введенні ТАК-385 U-2 у суміші S9 щурів (39-181/ge);
інше	3T3 NRU Випробування фототоксичності Т-1331285 (05-281/pt); З'ясування структури еталонного стандарту ТАК-385 (ТАК-385/00036); Дослідження фототоксичності одноразової дози для визначення впливу перорального (через зонд) введення Т-1331285 на стан шкіри безшерстих мишей (Дослідження №: 05-356/CO)
5. Висновки щодо доклінічного вивчення	Була проведена широка програма доклінічної розробки нової хімічної речовини релуголікс. Крім того, в рамках запропонованої комбінованої терапії була проведена оцінка доклінічної фармакології, фармакокінетики та безпеки Е2 та НЕТА на основі оглядів опублікованої літератури в контексті одночасного застосування з релуголіксом як частини запропонованої комбінованої терапії. Доклінічні дані щодо релуголіксу вказують на те, що він є потужним і селективним антагоністом рецепторів ГнРГ людини, а на фармакологічно релевантних (мавпи та миші з нокінгом рецепторів ГнРГ людини) тваринних моделях призводить до пригнічення концентрації ЛГ із функціональним зниженням рівня статевих стероїдних гормонів (тобто естрогену) і пов'язаних фенотипових ефектів. Ці дані підтверджують запропонований клінічний механізм

	дії, згідно з яким релуголікс антагонізує рецептори ГнРГ в гіпофізі, призводячи до пригнічення секреції ЛГ і ФСГ, а також зниження рівня ендогенних статевих стероїдних гормонів (тобто естрогену, прогестерону та тестостерону). Небажані фармакодинамічні взаємодії на основі первинної або вторинної фармакології для компонентів запропонованої комбінації не очікуються. Хоча релуголікс, Е2 і НЕТА інтенсивно метаболізуються до виведення, значущих фармакокінетичних взаємодій між компонентами комбінації, які впливали б на профілі безпеки або ефективності, не спостерігалось. Жодних доклінічних токсикологічних сигналів, які могли б вказувати на ймовірність несприятливих адитивних або синергічних взаємодій з точки зору загальної токсичності, генотоксичності та канцерогенності або репродуктивної токсичності, отримано не було. Крім того, системні експозиції нової хімічної речовини релуголіксу за NOAEL (рівень відсутності виявлених небажаних явищ) у дослідженнях токсичності на тваринах загалом є значно вищими, ніж очікувані клінічні показники. Наданий повний пакет доклінічної документації, разом із клінічними даними щодо релуголіксу окремо, клінічними даними щодо комбінованого препарату, включаючи основні дослідження безпеки та ефективності фази 3, а також наявні клінічні та доклінічні дані, доступні в опублікованій літературі щодо Е2 та НЕТА, підтверджують безпечність та ефективність застосування терапевтичної комбінації релуголіксу (40 мг) з Е2 (1 мг) і НЕТА (0,5 мг) для лікування симптомів, пов'язаних з міомою матки.

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CLINICAL STUDY REPORT
MVT-601-042

Study Title:	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
Study Intervention:	Relugolix
Trade Name:	N/A
Indication:	Heavy Menstrual Bleeding Associated with Uterine Fibroids
Brief Description:	Open-label, single-dose bioequivalence study
Study Sponsor:	Myovant Sciences GmbH
IND Number:	076642
Study Phase:	Phase 1
Study Initiation Date:	11 Mar 2019
Study Completion Date:	21 Jun 2019
Report Date:	15 Nov 2019
Original:	

This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Council on Harmonisation (ICH) Harmonised Tripartite Guideline.

SYNOPSIS

Name of Sponsor/Company: Myovant Sciences GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Study Intervention: Relugolix 40-mg tablet	Volume:	
Trade Name: Not applicable	Page:	

Title of Study: 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

Study Number: MVT-601-042

Study Phase: Phase 1

PIP and/or PSP Number (if applicable): Not applicable

Number of Study Centers and Countries: This study was conducted at a single center in the United States.

Publications (reference): Not applicable

Studied Period (years):	**Phase of development:** 1
Date first participant enrolled: 11 Mar 2019 Date last participant completed: 21 Jun 2019	

Methodology: This was an open-label, randomized, two-treatment, three-sequence, three-period crossover and partial replicate, single-dose study in 90 healthy postmenopausal women to establish bioequivalence between the relugolix/estradiol (E2)/ norethindrone acetate (NETA) (40 mg/1 mg/0.5 mg) FDC tablet and co-administration of a relugolix 40-mg tablet and an E2/NETA (1 mg/0.5 mg; Activella) tablet. The study consisted of three treatment periods (Treatment Periods 1, 2 and 3). Study participants were randomized to order in which they received study treatment (relugolix/E2/NETA FDC tablet [test {T}]; co-administration [relugolix + Activella] [reference {R}]) in a crossover manner according to one of three treatment sequences (n = 30 per treatment sequence) with co-administration administered in two of the three treatment periods within each treatment sequence (Appendix 16.1.1, Protocol Section 4.2).

On Day 1 of each treatment period, after fasting from all food and drink, except water, for at least 10 hours, study participants received their assigned study treatment with 240 mL of room temperature water and continued to fast for 4 hours postdose. Additionally, water was restricted 1 hour prior to and after study drug administration. The dosing conditions were consistent with those recommended in the FDA guidance on bioequivalence (Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations, Mar 2014).

Blood sampling was collected up to 168 hours postdose for determination of relugolix plasma concentrations and up to 72 hours postdose for determination of norethindrone (NET) plasma concentrations and estradiol (E2), estrone (E1), and total E1 serum concentrations. There was a 10-day washout interval between study drug administration in each treatment period.

Number of Participants (planned and analyzed): Ninety participants were planned and were enrolled in the study and 86 participants completed the study. The Safety Population included all of the 90 participants who were enrolled and received at least one dose of study drug. All 90 participants were included in the Pharmacokinetic Concentration Pharmacokinetic Parameter Populations. Participants or specific pharmacokinetic parameters for each analyte excluded from the statistical analysis for assessment of bioequivalence is provided in Section 5.1.

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Clinical Trial Report

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(Relugolix+Estradiol+Norethisterone acetate 40 mg/1 mg/0.5 mg film-coated tablet)

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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 № 1

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	LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids. **(study number: MVT-601-3001)**
6. Phase of the clinical trial	Phase 3
7. Time frame of the clinical trial	From 07.03.2017. to 29.04.2019.
8. Countries where the clinical trial was conducted	80 centers globally including North America, Brazil, Italy, Poland, South Africa, and the United Kingdom.
9. Number of subjects	planned: 390 actual: 388
10. Purpose and secondary objectives of the clinical trial	**Primary objective:** The objective of this study was to determine the benefit of relugolix 40 mg once a day co-administered with E2 1 mg and NETA 0.5 mg compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids **Secondary objective:** To determine the benefit of 24 weeks of relugolix 40 mg once a day co-administered with either 12 or 24 weeks of E2 and NETA (1 mg/0.5 mg) compared with placebo for 24 weeks on the following: • Achievement of amenorrhea; • Change in hemoglobin; • Impact of uterine fibroids symptoms, activities, and health-related quality-of-life as measured by components of the Uterine Fibroid Symptom and Health-Related Quality-of-Life (UFS-QoL); • Patient global assessment (PGA) for function and symptoms as measured by the PGA for function and symptoms;

	• Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire (MIQ); • Pain associated with uterine fibroids; • Uterine volume; • Uterine fibroid volume.
11. Clinical trial design	This was an international Phase 3, randomized, double-blind, placebo-controlled study.
12. Key inclusion criteria	Heavy Menstrual Bleeding Associated with Uterine Fibroids.
13. Investigational medicinal product, method of administration, strength	Relugolix 40 mg tablet, oral, E2/NETA 1 mg/0.5 mg over-encapsulated tablet, oral
14. Comparator, method of administration, strength	Relugolix placebo tablet, oral and E2/NETA placebo capsule, oral.
15. Concomitant therapy	Concomitant medications taken during the study treatment period were summarized for all patients in the Safety population by treatment group as treated. Medications were considered concomitant if exposure occurred during the Treatment- Period. Prohibited drug categories are provided in the protocol (CSR MVT-601-3001 Appendix 16.1.1).
16. Efficacy evaluation criteria	Proportion of women in the relugolix + E2/NETA group versus the placebo group who achieve an MBL (menstrual bleeding loss) volume of < 80 mL AND at least a 50% reduction from baseline MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method.
17. Safety evaluation criteria	• Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and ECGs; • Percent change from baseline to Week 12 in bone mineral density (BMD) at the lumbar spine (L1 - L4) in the relugolix + E2/NETA group compared with the relugolix + delayed E2/NETA group, as assessed by dual-energy x-ray absorptiometry DXA; • Percent change from baseline to Week 24 in BMD at the lumbar spine (L1 - L4), total hip, and femoral neck, as assessed by DXA; • Incidence of vasomotor symptoms.
18. Statistical methods	The statistical analyses performed in this study were for the prespecified endpoints in the SAP, which was finalized prior to database lock and unblinding of the data. All statistical analyses were conducted using SAS® Version 9.2 or higher. Statistical tests for the primary and secondary efficacy endpoints were assessed at a two-sided $\alpha = 0.05$ significance level, and all CIs were reported as two-sided, unless otherwise stated.
19. Demographic data of the study population (gender, age, race, etc.)	Overall, demographic characteristics were generally similar among treatment groups. The mean(SD) age for all patients in this study was 42.0 (5.38) years with the mean ages being similar among treatment groups. There were numerically more patients in the relugolix + delayed E2/NETA group < 40 years compared with the other two treatment groups.

	The two predominant racial representations in the study were Black or African American (191 patients [49.4%]) and White (173 patients [44.7%]). There were fewer Black or African American patients randomized to the relugolix + E2/NETA group (59 patients [46.1%]) than to the relugolix + delayed E2/NETA and placebo groups (67 patients [50.8%] and 65 patients (51.2%], respectively). There were more White patients randomized to the relugolix + E2/NETA (64 patients [50.0%]) than to the relugolix + delayed E2/NETA and placebo groups (53 patients [40.2%] and 56 patients [44.1%], respectively). Over 75% of patients in each treatment group were enrolled in North America.
20. Efficacy outcomes	This international Phase 3, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of oral relugolix + E2/NETA for 24 weeks met the primary efficacy endpoint of demonstrating superiority in improvement of heavy menstrual bleeding associated with uterine fibroids when compared with placebo. In the relugolix + E2/NETA group, 73.44% of patients achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment compared with 18.90% in the placebo group ($p < 0.0001$). The robustness of the primary efficacy analysis result was supported by sensitivity analyses and subgroup analyses. Results from these analyses confirmed the results of the primary endpoint analyses (ie, 24 weeks of treatment with relugolix + E2/NETA) demonstrated a comprehensive and significant improvement in MBL volume that was generally consistent across the subgroups analyzed.
21. Safety outcomes	In this study, relugolix combination therapy was generally well-tolerated, and no safety concerns were identified. The incidence of adverse events, both serious and nonserious, was overall balanced between combination relugolix + E2/NETA and placebo treatment groups. The most frequently reported adverse events were headache and hot flush; only hot flush was reported more frequently in the relugolix + E2/NETA group than in the placebo group (11% versus 8%). As expected, vasomotor symptoms were reported more frequently in patients who received relugolix + delayed E2/NETA. Bone mass was preserved in the combination relugolix + E2/NETA group. Data from the relugolix + delayed E2/NETA group indicated that E2/NETA mitigates the hypoestrogenic symptoms observed with relugolix monotherapy, including hot flushes and loss of BMD.
22. Conclusion (summary)	This international Phase 3, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of oral relugolix + E2/NETA for 24 weeks met the primary efficacy endpoint of demonstrating superiority in improvement of heavy menstrual bleeding associated with uterine fibroids when compared with placebo. In this study, relugolix combination therapy was generally well-tolerated, and no safety concerns were identified. Bone mass was preserved in the combination relugolix + E2/NETA group.

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

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 № 2

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	LIBERTY 2: An International Phase 3 Randomized, Double-Blind Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids **(MVT-601-3002)**
6. Phase of the clinical trial	Phase 3
7. Time frame of the clinical trial	From 03.05.2017. to 10.07.2019
8. Countries where the clinical trial was conducted	99 centers globally, including centers in North America (United States), Belgium, Brazil, Chile, Czech Republic, Hungary, Poland, and South Africa.
9. Number of subjects	planned: 390 actual: 382
10. Purpose and secondary objectives of the clinical trial	Primary: • To determine the benefit of relugolix 40 mg once a day co-administered with estradiol (E2) 1 mg and norethindrone acetate (NETA) 0.5 mg compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids. Secondary: • To determine the benefit of 24 weeks of relugolix 40 mg once a day co-administered with either 12 or 24 weeks of E2 and NETA (1 mg/0.5 mg) compared with placebo for 24 weeks on the following: • Achievement of amenorrhea; • Change in hemoglobin; • Impact of uterine fibroids symptoms, activities, and health-related quality-of-life as measured by components of the

	Uterine Fibroid Symptom and Health-Related Quality-of-Life (UFS-QoL); • Patient global assessment for function and symptoms as measured by the patient global assessment (PGA) for function and symptoms; • Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire (MIQ); • Pain associated with uterine fibroids; • Uterine volume; and • Uterine fibroid volume.
11. Clinical trial design	This was an international phase 3, randomized, double-blind, placebo-controlled study.
12. Key inclusion criteria	Heavy Menstrual Bleeding Associated with Uterine Fibroids.
13. Investigational medicinal product, method of administration, strength	Relugolix 40 mg tablet, oral, E2/NETA 1 mg/0.5 mg over-encapsulated tablet, oral
14. Comparator, method of administration, strength	Relugolix placebo tablet, oral and E2/NETA placebo capsule, oral.
15. Concomitant therapy	A total of 360 patients (94.5%) received concomitant medications during the study, including 120 patients (95.2%) in the relugolix + E2/NETA group, 118 patients (93.7%) in the relugolix + delayed E2/NETA group, and 122 patients (94.6%) in the placebo group.
16. Efficacy evaluation criteria	The primary efficacy endpoint for this study was the proportion of women who achieved an MBL (menstrual bleeding loss) volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method, referred to as responder rate. The primary efficacy analysis was the comparison of the relugolix + E2/NETA group with the placebo group with respect to responder rate.
17. Safety evaluation criteria	Safety was evaluated by monitoring: • adverse events, • BMD (bone mineral density) • clinical laboratory data, • 12-lead ECGs, • vital signs, • physical examinations, • visual acuity examinations, • endometrial biopsies, • menstrual bleeding patterns, • pregnancy, and overdose
18. Statistical methods	The primary hypothesis tested in this study was whether relugolix + E2/NETA was superior to placebo in the primary endpoint defined as the percentage of women who achieved both an MBL volume of < 80 mL and at least a 50% reduction in MBL volume over the last 35 days of treatment as compared with baseline. The point estimate and two-sided 95% CI of the difference in the proportions were calculated between relugolix + E2/NETA and placebo. The between-treatment comparison was performed using the Cochran-Mantel-Haenszel method stratified by randomization stratification factors (geographic region and mean screening MBL volume).

	The primary endpoint was tested at a two-sided 0.05 significance level. The primary endpoint was met if the treatment effect observed in the relugolix + E2/NETA group compared with that observed in the placebo group was statistically significant with a two-sided p-value of < 0.05.
19. Demographic data of the study population (gender, age, race, etc.)	Overall, demographic characteristics were generally similar among treatment groups. The mean (SD) age for all patients in this study was 42.1 (5.29) with the mean ages being similar among treatment groups. There were numerically more patients in the placebo group < 40 years compared with the other two treatment groups. The two predominant racial representations in the study were Black or African American (202 patients [53.0%]) and White (157 patients [41.2%]). There were more Black or African American patients randomized to placebo (74 patients [57.4%]) than to the relugolix + E2/NETA and relugolix + delayed E2/NETA groups (62 patients [49.6%] and 66 patients [52.0%], respectively). There were more White patients randomized to relugolix + E2/NETA (58 patients [46.4%]) than to the relugolix + delayed E2/NETA and placebo groups (50 patients [39.4%] and 49 patients [38.0%], respectively). At least 74.0% of patients in each treatment group were enrolled in North America while approximately 26.0% were enrolled outside of North America.
20. Efficacy outcomes	The study met its primary endpoint. In the relugolix + E2/NETA group, 89 patients (71.20%) achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment compared with 19 patients (14.73%) in the placebo group. The observed difference between the two groups was 56.47% (95% CI: 46.45% to 66.49%) in favor of the relugolix + E2/NETA group and was statistically significant ($p < 0.0001$). Across all subgroups, treatment differences were consistent with the primary analysis with a higher proportion of patients who received relugolix + E2/NETA meeting the definition for responder than patients who received placebo, as indicated by the point estimate and lower bound of the 95% CI for the odds ratios being above 1 favoring relugolix + E2/NETA over placebo. The magnitude of the responses across these subgroups was generally consistent with that observed in the analysis of the primary efficacy endpoint in the overall population, especially in the subgroups with larger sample sizes. Treatment effect was slightly higher in the rest of world than in North America and in White patients compared with Black or African American patients. Small sample sizes in Asian and other racial groups made it difficult to make robust comparisons. Smaller treatment differences were observed in the subgroups of women with larger uterine volumes ($\geq 300\ cm^3$) relative to the rest of the subgroups; however, the odds ratio (95% CI) in these subgroups was still in favour of relugolix + E2/NETA.
21. Safety outcomes	In this study, relugolix combination therapy was generally well-tolerated, and no safety concerns were identified. The incidence of adverse events, both serious and nonserious, was overall balanced between combination relugolix + E2/NETA and placebo treatment groups. The most frequently reported adverse events were headache and hot flush; only hot flush was reported more frequently in the relugolix + E2/NETA group than in the placebo group (33.3% vs.

	3.9%). As expected, vasomotor symptoms were reported more frequently in patients who received relugolix + delayed E2/NETA. Bone mass was preserved in the combination relugolix + E2/NETA group. Data from the relugolix + delayed E2/NETA group indicated that E2/NETA mitigates the hypoestrogenic symptoms observed with relugolix monotherapy, including hot flushes and loss of BMD.
22. Conclusion (summary)	This international phase 3, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of oral relugolix + E2/NETA for 24 weeks met the primary efficacy endpoint of demonstrating superiority in improvement of heavy menstrual bleeding associated with uterine fibroids when compared with placebo. In the relugolix + E2/NETA group, 71.20% of patients achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment compared with 14.73% in the placebo group ($p < 0.0001$).
Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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Clinical Trial Report № 3

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	LIBERTY EXTENSION: An International Phase 3 Open-Label, Single-Arm, Long-Term Efficacy and Safety Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids.**(MVT-601-3003)**
6. Phase of the clinical trial	Phase 3
7. Time frame of the clinical trial	From 05.12.2017. to 24.01.2020.
8. Countries where the clinical trial was conducted	This study was conducted at 149 centers in the United States, Belgium, Brazil, Chile, the Czech Republic, Hungary, Italy, Poland, and South Africa.
9. Number of subjects	planned: 600 actual: 477
10. Purpose and secondary objectives of the clinical trial	The objectives of this extension study were to evaluate the long-term efficacy and safety of relugolix + E2/NETA for up to 52 weeks of treatment (including the 24 weeks of treatment during either parent study, MVT-601-3001 or MVT-601-3002).
11. Clinical trial design	This was a multinational phase 3, open-label, single-arm, long-term efficacy and safety extension study that enrolled eligible patients who completed participation in one of the phase 3, randomized, placebo-controlled parent studies (MVT-601-3001 or MVT-601-3002).
12. Key inclusion criteria	Heavy Menstrual Bleeding Associated with Uterine Fibroids.
13. Investigational medicinal product, method of administration, strength	Relugolix 40 mg tablet, oral, E2/NETA 1 mg/0.5 mg over-encapsulated tablet, oral
14. Comparator, method of administration, strength	Relugolix placebo tablet, oral and E2/NETA placebo capsule, oral.
15. Concomitant therapy	A total of 464 patients (97.5%) received concomitant medications during the study, including

	160 patients (98.2%) in the relugolix + E2/NETA group, 144 patients (96.6%) in the relugolix + delayed E2/NETA group, and 160 patients (97.6%) in the placebo group.
16. Efficacy evaluation criteria	The primary efficacy endpoint for this study was the proportion of women who achieved an MBL volume < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method, referred to as a responder rate.
17. Safety evaluation criteria	Safety was evaluated by: • monitoring adverse events, • clinical laboratory data, • 12-lead ECGs, • vital signs, • physical examinations, • assessments of BMD, • endometrial biopsies, • menstrual bleeding patterns, • pregnancy, and overdose.
18. Statistical methods	All statistical analyses were conducted using SAS® Version 9.2 or higher. Where appropriate, variables were summarized descriptively by study visit. For categorical variables, the count and proportions of each possible value were tabulated by parent study treatment group. For continuous variables, the number of patients with non-missing values, mean, median, standard deviation (SD), minimum, and maximum values were tabulated.
19. Demographic data of the study population (gender, age, race, etc.)	In general, demographic and baseline characteristics were consistent with those observed in the parent studies. The majority of patients were in their later reproductive years (40+ years of age), approximately half were Black or African American, and most were overweight or obese by BMI. The baseline characteristics of the overall enrolled population were consistent with a high burden of symptomatic uterine fibroids, including a mean MBL volume of 234.33 mL that far exceeded the 80 mL threshold for heavy menstrual bleeding (with some patients exceeding 1000 mL of MBL volume); anemia with a mean hemoglobin concentration of 11.22 g/dL; mean index uterine fibroid volume of 81.57 cm3 that exceeded the minimum threshold required for eligibility; mean uterine volume of 409.24 cm3 that was greater than a gravid uterus at 12 weeks gestation (Sheth et al. 2017).
20. Efficacy outcomes	To evaluate the long-term efficacy of relugolix 40 mg once a day co-administered with low-dose E2 and NETA for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or

	MVT-601-3002), on heavy menstrual bleeding associated with uterine fibroids. To evaluate the long-term efficacy of relugolix 40 mg once a day co-administered with low-dose E2 and NETA for up to 52 weeks, among patients who previously completed on of the parent studies (MVT-601-3001 or MVT-601-3002), on the following: – Achievement/maintenance of amenorrhea; – Hemoglobin; – Changes in symptom severity and quality-of-life related to uterine fibroids, as measured by the UFS-QoL; -Impact of heavy menstrual bleeding on social, leisure, and physical activities, as measured by the MIQ; – Uterine volume; – Uterine fibroid volume.
21. Safety outcomes	Safety was evaluated by: • monitoring adverse events, • clinical laboratory data, • 12-lead ECGs, • vital signs, • physical examinations, • assessments of BMD, • endometrial biopsies, • menstrual bleeding patterns, • pregnancy, and overdose.
22. Conclusion (summary)	This multi-national Phase 3, extension study, designed to evaluate long-term efficacy and safety with relugolix + E2/NETA, demonstrated that the improvement of heavy menstrual bleeding associated with uterine fibroids was sustained through 52 weeks of treatment. In the relugolix + E2/NETA group, 87.73% of patients met the primary endpoint, an MBL volume of < 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment.
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 № 4

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 Two-Part, Open-Label, Randomized, Two-Treatment, Two-Sequence, Two-Period Crossover Single-Dose Study to Assess the Effects of Food on the Relugolix/Estradiol/Norethindrone Acetate (40 mg/1 mg/0.5 mg) Fixed-Dose Combination Tablet in Healthy Postmenopausal Women (Part 1) and the Relugolix 40-mg Tablet in Healthy Premenopausal Women (Part 2).**(MVT-601-041)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 15.05.2019. to 11.10.2019.
8. Countries where the clinical trial was conducted	US
9. Number of subjects	planned: NA actual: 48
10. Purpose and secondary objectives of the clinical trial	Part 1: To assess the effect of food on a single relugolix/ E2/ NETA (40 mg/1 mg/0.5 mg) FDC tablet following consumption of a high-fat meal Part 2: To assess the effect of food on a single relugolix 40-mg tablet (T4B formulation) following consumption of a high-fat meal.
11. Clinical trial design	A Two-Part, Open-Label, Randomized, Two-Treatment, Two-Sequence, Two-Period Crossover Single-Dose Study.
12. Key inclusion criteria	Healthy Postmenopausal Women (Part 1) and Healthy Premenopausal Women (Part 2).
13. Investigational medicinal product, method of administration, strength	Part 1: Relugolix/estradiol/norethindrone acetate (40 mg/1 mg/0.5 mg) FDC tablet Part 2: Relugolix 40 mg
14. Comparator, method of administration, strength	NA
15. Concomitant therapy	Concomitant medications administered in Part 1 of the study included acetaminophen for 2 participants.

	Concomitant medications administered in Part 2 included triple antibiotic ointment; loratadine, hydrocortisone cream, and prednisone; acetaminophen; ibuprofen; Vitamin B, biotin, ascorbic acid, and collagen.
16. Efficacy evaluation criteria	Efficacy was not a part of the study design.
17. Safety evaluation criteria	Safety was monitored throughout the study by repeated measurement of vital signs and clinical laboratory tests and evaluations of adverse events. Study participants returned to the CRU for a Follow-Up visit ten days after administration of study drug on Day 1 of Treatment Period 2.
18. Statistical methods	Log-transformed pharmacokinetic parameters AUC0-∞, AUC0-t, and Cmax were analyzed separately for each study part (Part 1 and Part 2) by a mixed-effect model based on the two-treatment (fed or fasted), two-sequence, two-period crossover design of the study. Only participants with non-missing pharmacokinetic parameters for both treatments (fed and fasted) were included in the model. This model included treatment, sequence, and period as fixed effects and study participant as a random effect. For each of the log-transformed pharmacokinetic parameters (AUCs and Cmax for relugolix, baseline-adjusted and unadjusted AUCs and Cmax for unconjugated E2, baseline-adjusted and unadjusted AUCs and Cmax for unconjugated E1, baseline-adjusted and unadjusted AUCs and Cmax for total E1, and AUCs and Cmax for NET), the point estimate and the associated 90% confidence interval (CI) were constructed for the difference in log-transformed means for the following comparison: • Part 1: Relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet fed versus fasted; • Part 2: Relugolix 40-mg tablet fed versus fasted. Point estimates and the corresponding 90% CIs for the differences were exponentiated to obtain the the ratios of geometric least-squares means (GMR; fed/fasted) and the 90% CIs on the original scale. In addition, a nonparametric analysis was performed to assess the median difference in tmax between fed and fasted treatments separately for each study part (Part 1 and Part 2), with the fasted treatment as the reference treatment.
19. Demographic data of the study population (gender, age, race, etc.)	In Part 1 of the study, the mean age of study participants was 56.9 years (range: 48 to 64 years), with a mean BMI of 26.823 kg/m2 (range: 22.78 to 29.54 kg/m2). All participants were healthy postmenopausal women. Twenty-one of the 24 participants (88%) were White; 2 of the 24 participants (8%) were Black or African American; and 1 of the 24 participants (4%) was American Indian or Alaska Native. Fifteen of the 24 participants (63%) were Hispanic or Latino, and 9 of the 24 participants (38%) were not Hispanic or Latino. In Part 2 of the study, the mean age of study participants was 39.2 years (range: 18 to 50 years), with a mean BMI of 27.655 kg/m2 (range: 21.71 to 31.44 kg/m2). All participants were healthy White Hispanic or Latino premenopausal women.
20. Efficacy outcomes	Efficacy was not a part of the study design.
21. Safety outcomes	In both Part 1 and Part 2 of the study, there were no remarkable findings for clinical laboratory values or vital sign measurements.

	There were no deaths or serious adverse events reported and no study participants were discontinued due to an adverse event.
22. Conclusion (summary)	Part 1 • After administration of the relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet following consumption of a high-fat, high-calorie meal, the total exposure (AUC0-∞) and Cmax of relugolix were decreased by 38% and 55%, respectively. The baseline-adjusted Cmax of unconjugated E2 was decreased by 11%. The baseline-adjusted AUC0-∞ and Cmax of total E1 were decreased by 13% and 40%, respectively. The AUC0-∞ of NET was increased by 1.26-fold. The baseline-adjusted AUC0-∞ of unconjugated E2 and the Cmax of NET remained unchanged after consumption of a high-calorie, high-fat meal. o The GMR (fed/fasted) and the 90% CI for the AUC0-∞ and Cmax of relugolix were 0.6211 (0.5096, 0.7570) and 0.4535 (0.3349, 0.6140), respectively; o The GMR and the 90% CI for the baseline-adjusted AUC0-∞ and Cmax of unconjugated E2 were 0.9799 (0.8071, 1.1896) and 0.8907 (0.7922, 1.0015), respectively; o The GMR and the 90% CI for the baseline-adjusted AUC0-∞ and Cmax of total E1 were 0.8705 (0.8282, 0.9149) and 0.5953 (0.5438, 0.6516), respectively; and The GMR and the 90% CI for the AUC0-∞ and Cmax of NET were 1.2556 (1.2021, 1.3115) and 0.9568 (0.8505, 1.0765), respectively. • Administration of a single relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablet in the fasted state or following consumption of a high-fat, high-calorie meal to healthy postmenopausal women was generally safe and well tolerated. Part 2 • After administration of a 40-mg tablet T4B formulation of relugolix following consumption of a high-fat, high-calorie meal, the total exposure (AUC0-∞) and Cmax of relugolix were decreased by 41% and 65%, respectively. o The GMR (fed/fasted) and the 90% CI for the AUC0-∞ and Cmax of relugolix were 0.5946 (0.4890, 0.7230) and 0.3539 (0.2666, 0.4698), respectively. • Administration of a single 40-mg relugolix tablet (T4B formulation) in the fasted state or following consumption of a high-fat, high-calorie meal to healthy premenopausal women was generally safe and well tolerated.
Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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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 № 5

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 2, Randomized, Open-Label, Parallel Group Study Evaluating the Safety and Efficacy of TAK-385, an Oral Gonadotropin-Releasing Hormone (GnRH) Antagonist, for Patients With Localized Prostate Cancer Requiring Neoadjuvant and Adjuvant Androgen Deprivation Therapy With External Beam Radiation Therapy (EBRT). **(C27003)**
6. Phase of the clinical trial	Phase 2
7. Time frame of the clinical trial	From 13.06.2014. to 14.12.2015.
8. Countries where the clinical trial was conducted	UK and US
9. Number of subjects	planned: NA actual: 108
10. Purpose and secondary objectives of the clinical trial	**Primary Objective** To evaluate the efficacy of TAK-385 for achieving and maintaining testosterone suppression (<50 ng/dL [1.73 nmol/L]). **Secondary Objectives** To evaluate the safety and tolerability of TAK-385. To evaluate prostate gland size reduction 8 to 12 weeks after starting study drug. To determine the time to achieve castration levels of testosterone (<50 ng/dL [1.73 nmol/L] and <20 ng/dL [0.69 nmol/L]). To determine time to testosterone recovery (TTR) during 12 weeks following the discontinuation of ADT. To evaluate the efficacy of PSA lowering including rate of reduction at 12 weeks, at the end of treatment (EOT) (24 weeks), and PSA levels during the 12 weeks following study drug discontinuation. To evaluate the population PK of TAK-385 in patients with prostate cancer.

	To determine the effects of TAK-385 on other endocrine markers. To evaluate quality of life (QoL) related to ADT and recovery from ADT using the Aging Males' Symptoms (AMS) scale, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30, and the EORTC-QLQ-PR25.
11. Clinical trial design	This was a phase 2, randomized, open-label, parallel group study.
12. Key inclusion criteria	Localized Prostate Cancer
13. Investigational medicinal product, method of administration, strength	Relugolix 40 or 80 mg film-coated tablet, oral
14. Comparator, method of administration, strength	Degarelix 20 or 40 mg/mL formulations subcutaneous
15. Concomitant therapy	Medications used by the patient and therapeutic procedures completed by the patient were recorded in the eCRF from the beginning of Screening until 30 days after the last dose of TAK-385 or 4 weeks plus 30 days after the last degarelix injection.
16. Efficacy evaluation criteria	• Testosterone Assessment • PSA (prostate-specific antigen) Assessment • Prostate Gland Assessment • PK Measurements • PD Measurements
17. Safety evaluation criteria	Adverse events (AEs) were assessed, and laboratory values, vital signs, physical examinations (including slit-lamp examination of the eye), and 12-lead electrocardiograms (ECGs) were obtained to evaluate the safety and tolerability of TAK-385.
18. Statistical methods	No formal statistical differences were sought or hypothesized between TAK-385 and degarelix. The primary objective of this study was to demonstrate sustained castration (testosterone <50 ng/dL [1.73 nmol/L] in > 90% of patients in the TAK-385 dosing arm beginning after 4 weeks of TAK-385 treatment and extending through the 24-week treatment period. The castration rate was estimated using 2-sided 95% CI. There were no statistical decision rules in this study.
19. Demographic data of the study population (gender, age, race, etc.)	Demographics were similar between the treatment groups. The majority of patients were white (89% in the TAK-385 group, 82% in the degarelix group) and not Hispanic or Latino (95% in the TAK-385 group and 92% in the degarelix group). The mean (Std Dev) age of patients was 70.2 (5.65) years in the TAK-385 group and 70.3 (6.97) years in the degarelix group.
20. Efficacy outcomes	TAK-385 (120 mg QD, preceded by a loading dose on Day 1) demonstrated rapid testosterone-lowering effects similar to injectable loading- and maintenance-dose degarelix, with most patients experiencing medical castration (testosterone <50 ng/dl) by the end of 7 days treatment. The findings are consistent with the GnRH receptor antagonism mechanism of action, compared with the testosterone flare and relatively later onset of castration associated with GnRH agonist therapy. □ Effective castration was achieved and maintained between the Week 5, Day 1 Visit and the Week 25, Day 1 Visit for both treatment groups (TAK-385: 95%; degarelix: 89%).

	□ The proportion of patients who achieved testosterone levels <20 ng/dl (0.69 nmol/L) at Week 25, Day 1 in the TAK-385 group (82%) was at least as large as the degarelix group (68%). □ The time course, intensity, and overall pattern of PSA response (waterfall plots, reduction in PSA by ≥50% or ≥90%, absolute values, and nadir) were similar between the TAK-385 and degarelix groups. □ Percent reductions in prostate gland size over 8 to 12 weeks (mean 25% to 30%) were similar in the 2 treatment groups and consistent with previous studies of neoadjuvant ADT. □ Following discontinuation of treatment at Week 25, Day 1, mean testosterone values and associated CIs were higher in the TAK-385 group at the EOT, Follow-up, and EOS visits. The recovery time course appeared to approach 'steady state' for TAK-385 by 8 weeks following discontinuation of dosing. For both treatment groups, AMS total scores had positive mean percent changes from Baseline above 15% at each study visit, indicating worsening of symptoms. AMS total mean scores steadily increased from Baseline to the Week 25, Day 1 visit and were not significantly different between TAK-385 and degarelix. □ Global QoL scores from the EORTC QLQ-C30 at Week 25, Day 1 were similar with mean changes of Baseline of -10.1 points (TAK-385) and -7.5 points (degarelix). Multiple domains measured by EORTC-QLQ-PR25, particularly the sexual activity domain and the hormonal treatment-related symptoms domain, were adversely affected by both treatments. □ From EOT through the EOS, QoL such as AMS and sexual activity scores appeared to improve more in the TAK-385 than the degarelix group, consistent with the observed pattern of testosterone recovery. □ Observed TAK-385 trough concentrations at 120 mg QD reached steady state during the first week; trough concentrations throughout the 24 weeks of treatment remained on average approximately 2 fold above the target level of 4 ng/mL for effective castration.
21. Safety outcomes	A higher proportion of patients in the degarelix group than the TAK-385 group experienced any AE (97% vs 86%), a grade 3 or higher AE (11% vs 2%), a grade 3 or higher AE related to study drug (3% vs 0%), or any SAE (8% vs 2%). A total of 50 patients (77%) in the TAK-385 group and 28 patients (74%) in the degarelix group experienced an AE related to study drug. Two patients (3%) in the TAK-385 group and no patient in the degarelix group experienced an AE resulting in drug dose modification. There were no drug-related SAEs, AEs leading to study drug discontinuation, or deaths in either treatment group.
22. Conclusion (summary)	In this study of 24 weeks neoadjuvant/adjuvant ADT to EBRT of localized intermediate risk prostate cancer, the oral GnRH receptor antagonist TAK-385 (relugolix) was well tolerated and demonstrated efficacy for rapidly achieving and then maintaining effective castration over the 24-week treatment period. The pattern and overall efficacy of testosterone-lowering was similar and at least as effective as that of the active comparator, degarelix, an approved injectable 1-month depot peptide analog GnRH receptor antagonist. Upon discontinuation of treatment after 24 weeks, testosterone recovered more rapidly in patients receiving TAK-385. QoL measures suggested that this may

	provide potential additional benefit in patients receiving limited duration ADT.
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 № 6

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 Fluconazole and Atorvastatin on the Pharmacokinetics of a Single Oral Dose of TAK-385 in Healthy Subjects. **(C27005)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 13.03.2014. to 19.04.2014.
8. Countries where the clinical trial was conducted	The study was conducted at a single center in the United States (Celerion, Inc [Tempe, AZ]).
9. Number of subjects	planned: 40 actual: 40
10. Purpose and secondary objectives of the clinical trial	The primary objectives are: Arm 1: To assess the effect of multiple doses of fluconazole on the PK of a single oral dose of TAK-385 (relugolix) Arm 2: To assess the effect of multiple doses of atorvastatin on the PK of a single oral dose of TAK-385 (relugolix) The secondary objective is: To further evaluate the safety and tolerability of a single dose of TAK-385 administered to healthy subjects before and after multiple oral doses of fluconazole or atorvastatin.
11. Clinical trial design	This was a nonrandomized, open-label, fixed-sequence, 2-arm study.
12. Key inclusion criteria	Healthy adult male or female in good health.
13. Investigational medicinal product, method of administration, strength	Relugolix 40 mg film-coated tablet, oral Atorvastatin 80-mg tablets and fluconazole 200-mg tablets, oral

14. Comparator, method of administration, strength	It was a Drug-Drug Interaction Study, there wasn't any comparator.
15. Concomitant therapy	No subjects received oral or systemic concomitant medications during this study. Two subjects (1 in each treatment arm) developed pruritus during the study and received 2% diphenhydramine cream as treatment; no other subjects received concomitant medications.
16. Efficacy evaluation criteria	Not applicable
17. Safety evaluation criteria	Safety was assessed by periodic physical examinations, 12-lead ECGs, clinical laboratory assessments, and monitoring of AEs and SAEs.
18. Statistical methods	Demographic and baseline characteristics were summarized, including gender, age as of informed consent date, race, weight, height, and BMI as appropriate. Descriptive statistics were calculated for continuous demographic variables (age, weight, height, and BMI) and frequency counts were to be tabulated for categorical demographic variables (gender, race, and ethnicity). No inferential statistics were carried out.
19. Demographic data of the study population (gender, age, race, etc.)	The mean age (SD) for all subjects was 38.8 (9.72) years, ranging from 21 to 55 years of age. An equal number of men and women were enrolled in each treatment arm (10 subjects [50%] each). Subjects were primarily white (34 subjects [85%]) and Hispanic or Latino (31 subjects [78%]). Demographics were similar between Arm 1 and Arm 2.
20. Efficacy outcomes	Not applicable.
21. Safety outcomes	No deaths or SAEs were reported in this study. • One subject discontinued the study (withdrew consent on Day 3 because of a personal emergency) after receiving a single 40 mg dose of TAK-385 on Study Day 1. The remaining subjects received all doses of study treatment as scheduled. • Overall, TEAEs were similar for TAK-385 alone and dosed concomitantly with atorvastatin or fluconazole. The most commonly reported TEAEs, occurring in > 5% of subjects in the fluconazole or atorvastatin arms, respectively, were pruritus (0 [0%], 3 [15%]); rash papular (0 [0%], 2 [10%]); erythematous rash (0 [0%], 3 [15%]); and arthropod bite (2 [10%], 1 [5%]). • Three subjects experienced 4 events that were considered to be related to TAK-385. One subject reported the events of somnolence and dizziness, and 2 subjects reported events of hypoaesthesia that were considered by the investigator to be related to TAK-385. All 4 events were Grade 1 in severity and had no associated objective or physical examination findings. • No clinically meaningful trends over time in laboratory values were noted. No trends over time were seen for vital signs or ECG findings.
22. Conclusion (summary)	• Co-administration of a single 40 mg dose of TAK-385 with the moderate CYP3A inhibitor fluconazole (200 mg QD) resulted in a modest increase in TAK-385 systemic exposure (Cmax: 44%; AUC0-inf 19%), but not to a clinically relevant extent when viewed in the context of overall variability in TAK-385 exposure. • Co-administration of a single 40 mg dose of TAK-385 with the weak CYP3A inhibitor atorvastatin (80 mg QD) did not result in a clinically meaningful interaction. • These results support the lack of a major contribution of CYP3A metabolism to the disposition of TAK-385.

	• Single 40 mg doses of TAK-385, administered with or without fluconazole or atorvastatin, were well tolerated. Co-administration of a single 40 mg dose of TAK-385 with fluconazole or atorvastatin did not result in a clinically significant influence on the safety profile of TAK-385 compared to administration of TAK-385 alone. No new safety signals were observed.
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 № 7

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 Two-Part, Open-Label, Fixed-Sequence, Two-Period Crossover Study to Assess the Effects of Voriconazole on the Pharmacokinetics of Relugolix in Healthy Adult Men and Women. **(MVT-601-043)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 18.02.2019. to 23.04.2019.
8. Countries where the clinical trial was conducted	USA
9. Number of subjects	planned: 32 actual: 32
10. Purpose and secondary objectives of the clinical trial	The primary objective was to assess the effect of voriconazole on the pharmacokinetics of relugolix after co-administration of relugolix and voriconazole. Secondary objectives were: • To characterize voriconazole and the N-oxide metabolite concentrations at steady state. • To assess the safety and tolerability after administration of relugolix alone and upon co- administration of relugolix and voriconazole in healthy adult men and women.
11. Clinical trial design	This was a two-part, open-label, fixed-sequence, two-period crossover drug interaction study.
12. Key inclusion criteria	Healthy Adult Men and Women
13. Investigational medicinal product, method of administration, strength	Relugolix 40 mg and 120 mg tablets, oral Voriconazole 200 mg tablets, oral

14. Comparator, method of administration, strength	There wasn't any comparator.
15. Concomitant therapy	Acetaminophen at doses of < 2 g/day was 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 medical monitor. Use of concomitant medications was recorded in the eCRF, including the name of the concomitant medication, dose(s) administered, dates and times of administration and the reason for administration.
16. Efficacy evaluation criteria	Not applicable
17. Safety evaluation criteria	Safety was monitored throughout the study by repeated measurement of vital signs and clinical laboratory tests and evaluation of adverse events. Study participants returned to the CRU approximately 10 days after the last dose of study drug in Treatment Period 2 for a follow-up visit.
18. Statistical methods	Log-transformed pharmacokinetic parameters (AUC0-∞, AUC0-t, and Cmax) for relugolix were analyzed separately for each study part (Part 1 and Part 2) using a mixed-effects model with treatment as a fixed effect and participants as a random effect, the point estimate and corresponding 90% CI from which would be the same as the results obtained from two one-sided paired t-tests (if equivalence limits are given). The point estimates and the corresponding 90% CIs for the differences on the log-scale were exponentiated to obtain the GMRs (co-administration [voriconazole + relugolix] / relugolix alone) and the 90% CIs on the original scale. The between-subject and within-subject CV% from the mixed-effects model were also reported. Only participants with non-missing parameter results for both co-administration (voriconazole + relugolix) and relugolix alone were included in the model.
19. Demographic data of the study population (gender, age, race, etc.)	The majority of participants were women (81.3%), White (93.8%) and were of Hispanic or Latino ethnicity (87.5%). The mean age was 41.3 years and ranged from 20 to 56 years. The mean BMI was 27.21 kg/m2 and all study participants had a BMI of ≤30 kg/m^2.
20. Efficacy outcomes	Not applicable.
21. Safety outcomes	Overall in Part 1 of the study, 11 of 16 participants (68.8%) reported a total of 20 adverse events. Almost all adverse events were rated by the investigator as mild or moderate in severity, with the exception of 1 serious adverse event that was rated as severe. All adverse events were reported in Treatment Period 2 either after administration of voriconazole alone or co-administration of relugolix 40 mg and voriconazole and were considered by the investigator to be drug-related. One participant reported adverse events of clinical interest ALT increased (grade 2/moderate) and AST increased (grade 2/moderate) after co-administration of relugolix 40 mg and voriconazole. One participant reported a serious adverse event of acute cholecystitis (grade 3/severe) after co-administration of relugolix 40 mg and voriconazole. No deaths or adverse events leading to discontinuation were reported. Part 2 Overall in Part 2 of the study, 12 of 16 participants (75.0%) reported a total of 19 adverse events. All adverse events were rated by the investigator as mild or moderate in severity, were transient in nature and resolved without intervention. All adverse events were reported in Treatment Period 2 either after administration of voriconazole alone or

	co-administration of relugolix 120 mg and voriconazole and were considered by the investigator to be drug-related. No deaths, serious adverse events, or adverse events leading to discontinuation were reported.
22. Conclusion (summary)	Part 1 (relugolix 40 mg): • After co-administration of relugolix with voriconazole, a strong CYP3A4 inhibitor, a modest and variable increase in exposure to relugolix, which were considered not to be clinically meaningful, was observed. • Overall, administration of a single 40-mg dose of relugolix alone and administration of voriconazole 400 mg Q12H x 1 day and 200 mg Q12H x 12 days with co-administration of relugolix 40 mg on Day 8 to healthy adult men and women was generally safe and well-tolerated. o Reversible nonserious grade 2 transaminase elevations (ALT and AST) that reached ≥3 x the upper limit of normal (protocol-specified adverse event of clinical interest) were reported in a single participant after co-administration of relugolix in Treatment Period 2. The events were assessed as drug-related by the investigator and led to withdrawal of study drug administration. Part 2 (relugolix 120 mg): • After co-administration of relugolix with voriconazole, a strong CYP3A4 inhibitor, small and considerably variable changes in exposure to relugolix, which were considered not to be clinically meaningful, were observed. • Administration of a single 120-mg dose of relugolix alone and administration of voriconazole 400 mg Q12H x 1 day and 200 mg Q12H x 12 days with co-administration of relugolix 120 mg on Day 8 to healthy adult men was generally safe and well-tolerated.
Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine

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 № 8

1. Name of the medicinal product (Registration certificate number, if any)	Ryeqo (Relugolix+Estradiol+Norethisterone acetate 40 mg 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 Two-Part, Open-Label, Fixed-Sequence, Two-Period Crossover Study to Assess the Effects of Relugolix on the Pharmacokinetics of Midazolam in Healthy Adult Men and Women. **(MVT-601-044)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 14.03.2019. to 24.07.2019.
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 was: • To assess the effects of relugolix on the pharmacokinetic parameters of midazolam after co-administration of relugolix and midazolam. Secondary objectives were: • To assess the pharmacokinetics of relugolix at steady state after QD administration for 14 day. • To assess the safety and tolerability of a single administration of midazolam alone and after multiple-dose administration in healthy adult men and women (Part 1) and in healthy adult men (Part 2).
11. Clinical trial design	This was a two-part, open-label, fixed-sequence, two-period crossover study.
12. Key inclusion criteria	Healthy Adult Men and Women
13. Investigational medicinal product, method of administration, strength	Relugolix 40-mg Tablets and Relugolix 120-mg Tablets
14. Comparator, method of administration, strength	Not applicable

15. Concomitant therapy	Midazolam hydrochloride syrup 2-mg/mL
16. Efficacy evaluation criteria	Not applicable
17. Safety evaluation criteria	Physical examinations, vital sign measurements, clinical laboratory tests, ECGs, and adverse events.
18. Statistical methods	Natural-log (ln)-transformed AUC0-∞, AUC0-t, and Cmax for midazolam were analyzed by an analysis of variance (ANOVA) model with treatment (midazolam alone or co-administration of midazolam and relugolix) as a fixed effect. The point estimates of the geometric least squares mean ratio (GMR; co-administration [midazolam + relugolix]/midazolam alone) and the associated 90% confidence intervals (CIs) for the AUC0-∞, AUC0-t , and Cmax of midazolam were provided for comparisons.
19. Demographic data of the study population (gender, age, race, etc.)	In Part 1 of the study, the mean age of study participants was 41.2 years (range: 29 to 58 years), with a mean BMI of 26.2 kg/m2 (range: 22.3 to 29.9 kg/m2). Participants were healthy men (25%) and women (75%). All participants were White; 9 of 12 (75%) were Hispanic or Latino.
20. Efficacy outcomes	Not applicable.
21. Safety outcomes	In both Part 1 and Part 2 of the study, there were no remarkable findings for vital sign measurements. With the exception of ALT increased and AST increased in 1 participant in Part 2 of the study, no clinically significant alterations in clinical laboratory test results were observed. There were no deaths or serious adverse events reported and no study participants were discontinued due to adverse events in Part 1 or Part 2 of this study.
22. Conclusion (summary)	The weak inductive effect of relugolix on CYP3A-mediated metabolism does not appear to be dose-related and is not considered to be clinically meaningful.
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 № 9

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 Two-Part, Open-Label, Fixed-Sequence, Two-Period Crossover Study to Assess the Effects of Relugolix on the Pharmacokinetics of Rosuvastatin in Healthy Adult Men and Women. **(MVT-601-045)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 13.05.2019. to 31.07.2019.
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 was: to assess the effects of relugolix on the pharmacokinetics of rosuvastatin after co-administration of rosuvastatin and relugolix. Secondary objectives were:To characterize the pharmacokinetics of relugolix at steady state after once daily administration for 14 days. To assess the safety and tolerability of a single administration of rosuvastatin alone and upon co-administration with relugolix following administration of relugolix once daily for 14 days in healthy adult men and women.
11. Clinical trial design	This was a two-part, open-label, fixed-sequence, two-period crossover study
12. Key inclusion criteria	Healthy Adult Men and Women
13. Investigational medicinal product, method of administration, strength	Relugolix 40-mg Tablets and Relugolix 120-mg Tablets, Oral
14. Comparator, method of administration, strength	Not applicable
15. Concomitant therapy	Rosuvastatin 10-mg Tablet, Oral
16. Efficacy evaluation criteria	Not applicable
17. Safety evaluation criteria	A full physical examination included, at a minimum, assessment of the

	cardiovascular, respiratory, gastrointestinal and neurological systems, thyroid, head, eyes, ears, nose and throat (HEENT), and skin. Height and weight were also measured and recorded at the screening visit only. A brief physical examination included, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Symptom-directed physical examinations conducted per principal investigator or sub-investigator discretion during the study focused on signs and symptoms reported by the participant to assess for clinically significant changes from baseline.
18. Statistical methods	Natural-log (ln)-transformed AUC0-∞, AUC0-t, and Cmax for rosuvastatin were analyzed by an analysis of variance (ANOVA) model with treatment (rosuvastatin alone or co-administration of rosuvastatin and relugolix) as a fixed effect. The point estimates of the geometric least-squares mean ratio (GMR; co-administration [rosuvastatin + relugolix]/ rosuvastatin alone) and the associated 90% confidence intervals (CIs) for the AUC0-∞, AUC0-t, and Cmax of rosuvastatin were provided for comparisons.
19. Demographic data of the study population (gender, age, race, etc.)	In Part 1 of the study, participants were healthy women (67%) and men (33%) with ahe mean age of 41.3 years (range: 23 to 58 years), and a mean BMI of 26.4 kg/m^2 (range: 21.9 to 30.5 kg/m2). Participants were healthy women (67%) and men (33%). All participants were White; and all were Hispanic or Latino.
20. Efficacy outcomes	Not applicable.
21. Safety outcomes	In general, administration of a single 10-mg dose of rosuvastatin alone and administration of 120-mg doses of relugolix once daily for 17 days with co-administration of rosuvastatin 10 mg on Day 15 to healthy adult men was generally safe and well-tolerated. Three of 12 participants reported nonserious asymptomatic and reversible elevations in transaminase and GGT values. In 2 participants, the elevations were rated as mild (grade 1/mild) and in 1 participant, the elevations were rated as severe (grade 3/severe) and met protocol-specific criteria for adverse events of clinical interest (ALT or AST ≥ 3x ULN). The transaminase and GGT elevations in all 3 participants were considered by the investigator to be possibly related to rosuvastatin and relugolix. Overall, there was a slightly greater decrease in exposure to rosuvastatin upon co-administration with relugolix following administration of 120-mg doses compared with 40-mg doses of relugolix once daily for 14 days.
22. Conclusion (summary)	There was a slightly greater decrease in exposure to rosuvastatin upon co-administration with relugolix following administration of 120-mg doses compared with 40-mg doses of relugolix once daily for 14 days. The general safety and tolerability after administration of a single 10-mg dose of rosuvastatin alone or administration of 40-mg or 120-mg doses of relugolix once daily for 17 days with co-administration of rosuvastatin 10 mg on Day 15 was similar, noting that 3 of 12 participants reported reversible transaminase and GGT increases with the 120-mg dose of relugolix whereas none of 12 participants reported such elevations with the 40-mg dose of relugolix.
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 № 10

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, Fixed-Sequence, 2-Period Crossover Drug Interaction Study to Assess the Effect of Relugolix on the Pharmacokinetics of Estradiol and Norethindrone in Healthy Postmenopausal Women. **(MVT-601-039)**
6. Phase of the clinical trial	Phase 1
7. Time frame of the clinical trial	From 19.10.2018. to 06.12.2018.
8. Countries where the clinical trial was conducted	USA
9. Number of subjects	planned: 24 actual: 24
10. Purpose and secondary objectives of the clinical trial	Primary objective was • to assess the effects of relugolix on the pharmacokinetic parameters of unconjugated E2, total E1 and NET after co-administration of relugolix and E2/NETA. Secondary objectives were: 1. To assess the effect of relugolix on pharmacokinetic parameters of unconjugated E1 after co-administration of relugolix and E2/NETA 2. To assess the effect of relugolix on pharmacokinetic parameters of estrone sulfate (E1S) after co-administration of relugolix and E2/NETA 3. To assess the pharmacokinetics of relugolix at steady state (after once daily administration for 14 days)

	4. To assess the safety and tolerability of administration of a single dose of E2/NETA alone and after multiple-dose administration of relugolix in healthy postmenopausal women.
11. Clinical trial design	This was an open-label, fixed-sequence, 2-period crossover drug interaction study.
12. Key inclusion criteria	Healthy postmenopausal women.
13. Investigational medicinal product, method of administration, strength	Treatment A: E2/NETA (1-mg/0.5-mg) tablet Treatment B: Co-administration of a E2/NETA (1 mg/0.5 mg) tablet and a 40-mg dose of relugolix.
14. Comparator, method of administration, strength	Treatment A: E2/NETA (1-mg/0.5-mg) tablet Treatment B: Co-administration of a E2/NETA (1 mg/0.5 mg) tablet and a 40-mg dose of relugolix.
15. Concomitant therapy	Acetaminophen at doses of ≤ 2 g/day was permitted for use any time during the study. Non-sedating antihistamines and decongestants could also be administered on an as needed basis. Administration of other concomitant medications for treatment of a medical need were considered on a case-by-case basis by the Investigator in consultation with the medical monitor. Use of concomitant medications was recorded in the eCRF, including the doses administered, the dates and times of administration and the reason for administration.
16. Efficacy evaluation criteria	Not applicable
17. Safety evaluation criteria	The safety and tolerability of relugolix were evaluated by safety assessments including physical examinations, vital sign measurements, 12-lead ECGs, clinical laboratory tests, and reporting of adverse experiences.
18. Statistical methods	Log-transformed pharmacokinetic parameters (baseline-adjusted and unadjusted AUC0-∞, AUC0-t, and Cmax for unconjugated E2, unconjugated E1, total E1, and E1S; AUC0-∞, AUC0-t, and Cmax for NET) were analyzed using a mixed-effects model with treatment as a fixed effect and participant as a random effect. Point estimates and the corresponding 90% CIs for the differences on the log-scale were exponentiated to obtain the GMRs (co-administration [relugolix + E2/NETA] / E2/NETA alone) and the 90% CIs on the original scale. The within-subject CV% from the mixed-effects model were also reported. Only participants with non-missing parameter results for both the co-administration (relugolix + E2/NETA) and the E2/NETA alone treatments were included in the model.
19. Demographic data of the study population (gender, age, race, etc.)	All participants were postmenopausal women, with a mean age of 57.3 years (range: 48 to 65 years) and a mean BMI of 27.83 kg/m2 (range of 22.5 to 29.9 kg/m2). The majority of participants were White (23 of 24 [95.8%]) and of Hispanic ethnicity (20 of 24 [83.3%]).
20. Efficacy outcomes	Not applicable.
21. Safety outcomes	Overall, 15 of 24 participants (62.5%) reported a total of 35 adverse events. All adverse events were rated as mild (grade 1/mild) in severity, transient in nature and were resolved by the end of study. Of the total adverse events, 32 adverse events reported for 13 participants were considered by the investigator to be drug-related.
22. Conclusion (summary)	After co-administration of E2/NETA (1 mg/0.5 mg; Activella) with relugolix, following administration of 40-mg doses of relugolix once daily for 14 days, small decreases in the exposure-related

	pharmacokinetic parameters (AUCs and C_{max}) for unconjugated E2 and other estrogen-related endpoints (unconjugated and total E1 and E1S) were observed; no appreciable differences in the exposure to NET were identified. With the exception of the baseline-adjusted $AUC_{0-\infty}$ for E2 and the baseline-adjusted C_{max} for E1S, the 90% CIs for the Geometric least-squares mean ratios (GMRs) (coadministration [E2/NETA + relugolix] / E2/NETA alone) for all other endpoints for unconjugated E2, unconjugated and total E1, E1S, and NET were contained within 0.8000 to 1.2500, meeting the acceptance criterion used to rule out a drug interaction. Although the lower bound of the 90% CI for the GMR for the baseline-adjusted $AUC_{0-\infty}$ of unconjugated E2 was below 0.8000, the decrease is relatively small (19%) and is not considered to be clinically meaningful, particularly in the context of the development program for relugolix. With respect to the baseline-adjusted C_{max} for E1S, the observed small decrease (17%) is unlikely to be clinically meaningful considering E1S represents the estrogenic pool, for which AUC is likely a better measure of physiologic effects. Upon once daily administration of relugolix (40 mg), steady state was achieved by Day 12. Administration of a single dose of E2/NETA (1 mg/0.5 mg; Activella) alone or administration of 40-mg doses of relugolix once daily for 17 days (Day 1 to 17) with co-administration of E2/NETA (1 mg/0.5 mg; Activella) on Day 15 to healthy adult postmenopausal women was generally safe and well-tolerated.
Applicant (Registration certificate Holder)	Dr. Jakubovics István Head of Representative office «Richter Gedeon Nyrt» in Ukraine