Appendix 1. List of Independent Ethics Committees and Institutional Review Boards

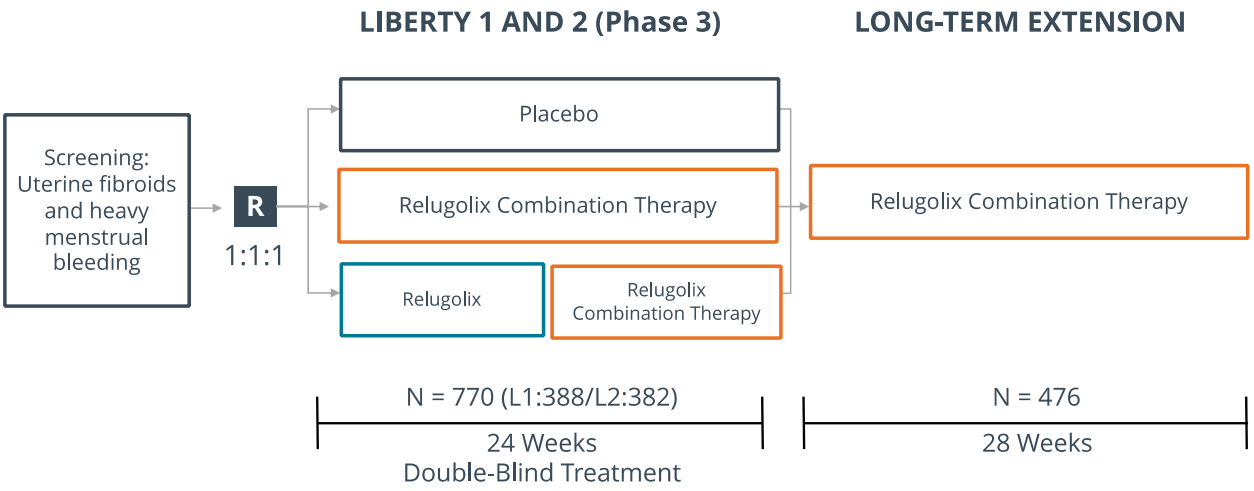
IEC/IRB	Principal Investigator	Site
United States		
Schulman Associates Institutional Review Board 4445 Lake Forest Drive Suite 300 Cincinnati, OH 45242	Central IRB	
Western Institutional Review Board 1019 39th Avenue SE Suite 120 Puyallup, WA 98374	Andrew Kaunitz, MD	1045
Chesapeake Institutional Review Board 6940 Columbia Gateway Drive Suite 110 Columbia, MD 21046	David F. Archer, MD	1103
Western Institutional Review Board 1019 39th Avenue SE Suite 120 Puyallup, WA 98374	Kelli Braun, MD	1239
Rest of World		
Belgium		
UZ Gent Ghent University Hospital C Heymanslaan 10, B-9000 Ghent, Belgium	Central IEC	
Brazil		
Comissão Nacional de Ética em Pesquisa – CONEP SEPN 510 Norte, Bloco A, 3º andar – Edifício Ex-INAN – Unidade II – Ministério da Saúde – CEP 70750-521 – Brasília – DF	Central IEC	
Comitê de Ética em Pesquisa da Faculdade de Medicina do ABC Avenida Lauro Gomes, 2000 – Prédio CEPES – 2º andar – CEP 09060-780 – Santo André/SP - Brazil	Emerson de Oliveira	1099
Comitê de Ética e Pesquisa do Centro de Referência da Saúde da Mulher Comitê de Ética em Pesquisa da Pontifícia Avenida Brigadeiro Luis Antônio, 683, 2º andar, Bela Vista, São Paulo/SP, 01317-000, Brazil	Luciano Gibran	1142

IEC/IRB	Principal Investigator	Site
Universidade Católica do Rio Grande do Sul – PUCRS Av. Ipiranga 6681, Prédio 50, Sala 703 - CEP: 90619-900, Porto Alegre- RS, Brazil	Carlos Isaia Filho	1167
Chile		
Comité ético Científico del Servicio de Salud Metropolitano Central Victoria Subercaseaux N° 381, 4° Piso, zip code 8320143, Santiago, Chile	Claudio Andrés Villarroel Quintana Cristian Jesam Gaete	1112 1148
Comite Ético Científico de Seguridad CChC Guardia Vieja 181, oficina 207, zip code 7510186 Providencia, Santiago, Chile	Guillermo Galan Chiappa	1116
Comité ético Científico del Servicio de Salud Metropolitano Sur Oriente Concha y Toro 3459, Puente Alto, Santiago, Chile	Marco Levancini Alvarez	1246
Czech Republic		
Fakultní Nemocnice Brno, Multicentrická etická komise Jihlavská 20 625 00 Brno Czech Republic	Central IEC	
Hungary		
Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottság Széchenyi István tér 7-8, 1051 Budapest, Hungary	Central IEC	
Italy		
Comitato Etico Policlinico Gemelli Segreteria tecnico Scientifica COMITATO ETICO Policlinico Gemelli Segreteria Tecnico- Scientifica Largo Gemelli, 8 00168 Roma	Central IEC	
COMITATO ETICO DELL'UNIVERSITA' CATTOLICA DEL SACRO CUORE E ANNESSO POLICLINICO "A.GEMELLI" COMITATO ETICO Policlinico Gemelli Segreteria Tecnico- Scientifica Largo Gemelli, 8 00168 Roma	Fiorenzo, De Cicco Nardone	1091

IEC/IRB	Principal Investigator	Site
"COMITATO ETICO Azienda Ospedaliera Universitaria Senese COMITATO ETICO REGIONE TOSCANA - AREA VASTA SUD EST Viale Bracci 16 53100 Siena Italy	Vincenzo De Leo, MD	1093
COMITATO ETICO DELL'UNIVERSITA' "SAPIENZA" Viale Del Policlinico, 155 00161 ROMA Italy	Maria Grazia Porpora	1101
Poland		
Komisja Bioetyczna przy Lubleskiej Izbie Lekarskiej ul. Chmielna 4, 20-079 Lublin, Poland	Central IEC	
Komisja Bioetycznaprzy Okręgowej Radzie Lekarskiej Wielkopolskiej Izby Lekarskiej ul. Nowowiejskiego 51, 61-734 Poznań, Poland	Central IEC	1085 1087 1088 1110 1244
South Africa		
South African Medical Association Research Ethics Committee (SAMAREC) Block F, Castle Walk Office Park, Nossob Street, Erasmuskloof Ext 3, Pretoria 0181, South Africa	Central IEC	
United Kingdom		
East Midlands - Leicester South REC The Old Chapel, Royal Standard Court, Nottingham, NG1 6FS	Central IEC	

Abbreviations: IEC = Independent Ethics Committee; IRB = Institutional Review Board.

Appendix 2. LIBERTY long-term extension study design.



Al-Hendy A, Lukes AS, Poindexter A, Venturella R, Villarroel C, McKain L, et al. Long-term relugolix combination therapy for symptomatic uterine leiomyomas. Obstet Gynecol 2022;140.
The authors provided this information as a supplement to their article.

Appendix 3. Supplemental Methods

Methodology:

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). All patients received oral relugolix 40 mg once a day co-administered with estradiol (E2) 1 mg and norethindrone acetate (NETA) 0.5 mg for up to 28 weeks.

The objectives of the study were to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including the 24 weeks of treatment during the parent study) with relugolix + E2/NETA. Eligible patients completed participation in one of the parent studies and consented to participate in this extension study. Screening and baseline procedures were performed at the same visit for this extension study (referred to as the Week 24/Baseline visit in this study), which coincided with the Week 24 visit of the parent study. The Week 24/Baseline visit included vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), dual-energy x-ray absorptiometry (DXA), patient-reported outcome assessments, transvaginal ultrasound, and endometrial biopsy (if required). When Week 24 procedures in the parent study were completed, the investigator assessed patient eligibility for participation in the open-label extension study. The eligibility assessment was based on data available at the Week 24/Baseline visit. No MVT-601-3003 study procedures were performed until the informed consent form (ICF) for this extension study was signed.

Patients received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and received their first dose of study drug for this extension study in the clinic after being deemed eligible for and providing informed consent to participate in this extension study. The administration of the first dose of study drug for MVT-601-3003 defined enrollment in this study. Patients then took the open-label study treatment (relugolix 40 mg co-administered with E2 1 mg and NETA 0.5 mg) orally once a day for up to 28 weeks.

At the Week 36 visit and Week 52/Early Termination visit, each patient had an assessment of bone mineral density (BMD) by DXA. Quality-of-life questionnaires were also completed.

Safety was assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, BMD by DXA, and transvaginal ultrasound.

Patients with a BMD loss > 3% at the lumbar spine (L1 – L4) or total hip at their Week 52/Early Termination visit relative to the parent study baseline measurement underwent a follow-up bone densitometry scan at 6 (± 1) months. If these follow-up scans showed bone loss of > 1.5% at the lumbar spine and/or > 2.5% at total hip compared with pretreatment baseline, a second follow-up DXA scan was scheduled at 12 months, and any patients who had ≥ 3% bone loss at any site were referred to a bone specialist.

The status of menstruation recovery was documented at the Follow-up visit. Patients whose menses had not returned as of the Follow-up visit for whom there was no explanation for the lack of resumption (eg, medical procedure or medications) were contacted by telephone 3 (± 0.5) months after the Follow-up visit to determine if menses had resumed and were asked about factors that may have affected the resumption of menses.

If the patient enrolled directly into another relugolix clinical study upon completion of the Week 52 visit, then the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (± 1) months and status of menstruation recovery could have been waived.

Number of Participants (planned and analyzed):

It was estimated that approximately 600 patients (75% of the total of 780 patients who were randomized into the parent studies) would participate in this study.

A total of 477 patients were enrolled to receive open-label relugolix + E2/NETA, which represents approximately 60% of patients randomized in the parent studies and > 75% of patients who completed those studies. One patient (Patient 116301) was enrolled in error and did not receive treatment.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria:

Completed 24 weeks of study drug treatment and study participation in either MVT-601-3001 or MVT-601-3002;

Voluntarily signed and dated the ICF prior to initiation of any screening or study-specific procedures for MVT-601-3003;

Note: Procedures conducted as part of the parent study that also served as baseline procedures for this study could have been performed under the ICF for the parent study.

Was not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the study period, including during the Safety Follow-up period;

Had a negative urine pregnancy test at the Week 24/Baseline visit;

Agreed to continue to use acceptable nonhormonal contraceptive methods consistently during the Open-Label Treatment period and for at least 30 days after the last dose of study drug. However, the patient was not required to use the specified nonhormonal contraceptive methods if any of the following applied:

- Had a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods, such as Essure™), at least 4 months prior to the Week 24/Baseline visit (patients with Essure had to have prior confirmation of tubal occlusion by hysterosalpingogram) and there had to be no evidence of post-Essure syndrome;
- Had a non-hormonal intrauterine device (eg, Paragard®) placed in the uterus;
- Was not sexually active with men; periodic sexual relationships with men required the use of nonhormonal contraception, as noted above;
- Practiced total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence was not acceptable.

Exclusion Criteria:

Had undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, or endometrial ablation for abnormal uterine bleeding at any time during the parent study (MVT-601-3001 or MVT-601-3002);

Had a weight that exceeded the weight limit of the DXA scanner or had a condition that precluded an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement, spinal hardware in the lumbar spine);

Had a Z-score < 02.0 or had a ≥ 7% decrease in BMD from the parent study baseline at lumbar spine, total hip, or femoral neck, based on the parent study Week 24 DXA assessment of BMD;

Had any contraindication to treatment with E2/NETA, including the following:

- Known, suspected, or history of breast cancer;
- Known or suspected estrogen-dependent neoplasia;
- Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
- History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
- Known anaphylactic reaction or angioedema or hypersensitivity to E2 or NETA;
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorder, including Factor V Leiden;
- Migraine with aura;
- History of porphyria;

Was inappropriate for participation in this study because of conditions that may have interfered with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, subinvestigator, or medical monitor;

Met a withdrawal criterion in the parent study (MVT-601-3001 or MVT-601-3002).

Study Interventions, Dose, Mode of Administration, and Batch Numbers:
Open-label relugolix 40-mg tablet plus an E2/NETA 1 mg/0.5 mg over-encapsulated tablet administered orally.

Duration of Study Intervention: Study treatment was administered once a day for 28 weeks.

Objectives and Endpoints:

Objectives	Endpoints
Primary Efficacy	
• 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 wees, 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.	• Proportion of women who achieved or maintained an MBL < 80 mL and at least a 50% reduction from parent study baseline to the last 35 days of treatment, as measured by the alkaline hematin method.
Secondary Efficacy	
• 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: o Achievement/maintenance of amenorrhea; o Hemoglobin; o Changes in symptom severity and quality-of-life related to uterine fibroids, as measured by the UFS-QoL; o Impact of heavy menstrual bleeding on social, leisure, and physical activities, as measured by the MIQ; o Uterine volume; o Uterine fibroid volume.	• Change from parent study baseline to Week 52 in MBL volume; • Proportion of women who achieved or maintained amenorrhea over the last 35 days of treatment; • Proportion of women with a hemoglobin concentration below the lower limit of normal at parent study baseline who achieved an increase of ≥ 1 g/dL from parent study baseline at Week 52; • Proportion of women with a hemoglobin concentration ≤ 10.5 g/dL at parent study Baseline who achieve an increase of > 2 g/dL from parent study Baseline at Week 52; • Change from parent study baseline to Week 52 in hemoglobin concentration; • Change from parent study baseline to Week 52 in UFS-QoL symptom severity scale; • Change from parent study baseline to Week 52 in UFS-QoL subscales and total score; • Change from parent study baseline to Week 52 in uterine volume; • Change from parent study baseline to Week 52 in uterine fibroid volume.
Safety	
To evaluate the safety of relugolix 40 mg once a day co-administered with E2/NETA for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent	Incidence of adverse events; Percent change from parent study baseline to Week 52 in BMD at the lumbar spine (L1 - L4), femoral neck, and total hip, as assessed by DXA.

studies (MVT-601-3001 or MVT-601-3002), including the following: • Adverse events; • Changes in BMD.	
Pharmacodynamic	
To evaluate the pharmacodynamic effects 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 estradiol concentration.	Change from parent study baseline to Week 52 in predose concentrations of serum estradiol.

Statistical Methods:

Descriptive assessments of efficacy and safety were made between the parent study baseline and the end of the open-label extension study (Week 52) on the extension study population, defined as patients who enrolled in MVT-601-3003 (ie, who received at least one dose of study drug in the open-label extension study), separately for the following treatment groups originally randomized in the parent studies:

Relugolix + E2/NETA: Randomized to 24 weeks of oral relugolix 40 mg once daily co-administered with 1 mg E2 and 0.5 mg NETA in the parent study;

Relugolix + delayed E2/NETA: Randomized to 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1 mg E2 and 0.5 mg NETA in the parent study;

Placebo: Randomized to placebo in the parent study.

The parent study baseline was, in general, used as the reference point for the extension study for all change from baseline-related endpoints, unless otherwise specified.

No formal treatment comparisons were performed for this extension study.

Sample Size:

Because this was an extension study, the sample size was determined by the numbers of patients who completed either parent study (MVT-601-3001 or MVT-601-3002) and who were eligible and willing to participate in this study. It was estimated that approximately 600 patients (75% of 780 patients who were randomized into the parent studies) would participate in this extension study.

Efficacy

Efficacy assessments included MBL volume assessed by the alkaline hematin method, quality of life questionnaires (UFS-QoL, MIQ, and EQ-5D-5L), and uterine and uterine fibroid volume.

Safety:

Safety data included adverse events, vital signs, clinical laboratory tests, 12-lead ECGs, endometrial biopsies, and assessments of BMD. Safety data were analyzed using descriptive statistics, unless otherwise specified.

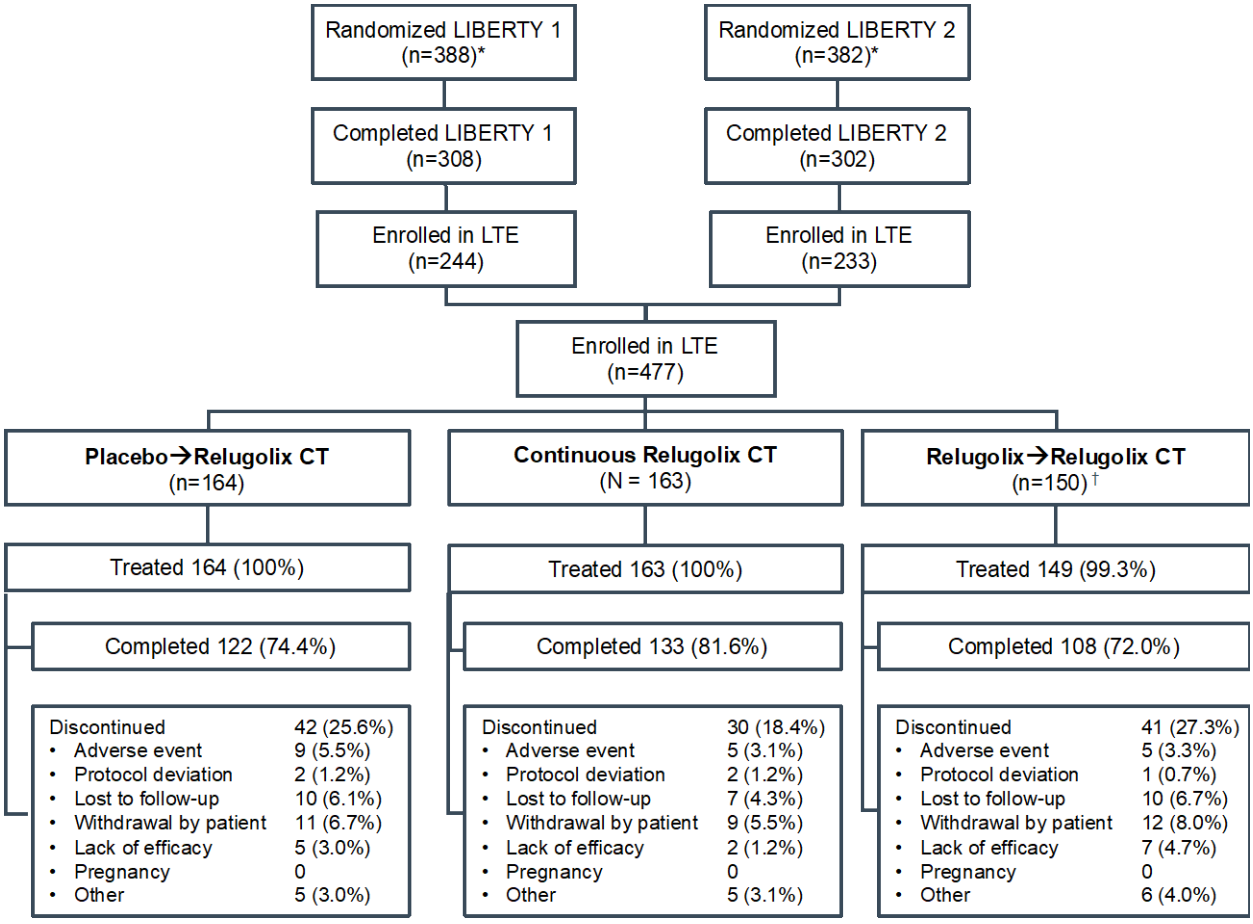
The severity of all adverse events was evaluated by the investigator based on Common Terminology Criteria for Adverse Events (CTCAE) and were coded to preferred term and system organ class using MedDRA (version 22.0 or higher). Adverse events were classified as "related" to study treatment if the relationship was rated by the investigator as possibly related or probably related. Adverse events related to any study drug component (relugolix or placebo and E2/NETA or placebo) were considered as related to study drug.

Laboratory values were also classified by toxicity grade based on the CTCAE. Shift tables summarizing baseline toxicity grade versus worst post-baseline toxicity grade throughout the parent and open-label extension studies were provided.

Corrected BMD data (corrected to account for changes in scanner calibration) were used for analysis, as determined by the central radiology laboratory in the three pre-specified anatomical locations: lumbar spine (L1 - L4), total hip, and femoral neck. Bone mineral density (measured at the Baseline, Week 12, and Week 24 visits in the parent studies and at the Week 36 and Week 52 visits in the extension study) was summarized descriptively by parent study treatment group and each measure anatomical location for all patients in the extension safety population. Percentage changes from baseline along with 95% CIs for mean percentage changes from baseline were also summarized by parent study treatment group and anatomical location. Mean percentage change from baseline with corresponding 95% CI was plotted by visit, parent study treatment group, and anatomical location. A mixed-effects model with repeated measures was used to assess BMD at 12, 24, 36, and 52 weeks. Categorical representation of percentage change from baseline to 12, 24, 36, and 52 weeks of treatment were presented by the number and proportion of patients who had BMD declines of ≤ 2%, > 2% to 3%, > 3% to 5%, > 5% to 8%, and > 8% by parent study treatment group and anatomical location. Z-scores were summarized by parent study treatment group, visit, and anatomical location with descriptive statistics, including 95% CIs, and the number and percentage of patients with a Z-score < -2.0 were presented by parent study treatment group, visit, and anatomical location. Percentage changes from baseline in BMD were also summarized by intrinsic factors (eg, age, race, body mass index [BMI]) and extrinsic factors (eg, geographic region). Subgroups included but were not limited to geographic region (North America versus Rest of World), age category (< 40 versus ≥ 40), Race (Black or African America versus Not Black or African American), ethnicity (Hispanic or Latino versus Not Hispanic or Latino), and BMI at baseline (< 30 versus ≥ 30 kg/m^2).

The protocol-specified endometrial biopsy procedure was performed at the Week 52/Early Termination visit in the extension study. All endometrial biopsy results available at the time of the analysis were summarized. Primary diagnosis from pathologist evaluation were categorized by medical monitor's review for biopsies performed in the parent studies. Extension study biopsies were summarized according to primary diagnosis categories provided by the pathologist evaluation. Endometrial biopsies performed in the parent studies and the extension study at Week 52 or at the time of early termination were summarized in separate tables, as different pathology laboratories were used for the parent and extension studies. All endometrial biopsy data were also provided in a by-patient listing, including visits in both the parent study and extension study.

Appendix 4. Patient disposition. *One patient randomized but not dosed. †One patient enrolled, but not treated (ie, 149 patients treated). LTE, long-term extension. Additional information on the patient disposition for LIBERTY 1 and LIBERTY 2 studies has been previously published (Al-Hendy A, et al. N Engl J Med. 2021;384:630-642).



Appendix 5. LIBERTY Long-term Extension Principal Investigators and Study Sites

Investigator Name	Facility Name
Samuel Alexander, MD	Southern Clinical Research Associates
Mark Firestone, MD	South Florida Medical Research
Dana Shipp, MD	Medical Center for Clinical Research
Andrea Lukes, MD	Carolina Women's Research and Wellness Center
R Garn Mabey, MD	Rex Garn Mabey, Jr, MD Chartered
Steven Sussman, MD	Lawrence OB/GYN Clinical Research, LLC
Stephen Gene Swanson, MD	Women's Clinic of Lincoln, PC
Arthur Waldbaum, MD	Downton Women's Health Care
Ronald Ackerman, MD	Comprehensive Clinical Trials, LLC
Robert E Deck Jr., MD	Clinical Trials Management, LLC
Robert Smith Jr., MD	Suncoast Clinical Research
Cynthia Goldberg, MD	Visions Clinical Research - Tucson
Ernesto Gomez, MD	Mesa Obstetricians and Gynecologists
Debra Walland, MD	Fellows Research Alliance, Inc.
Gwang-Yi Hwang, MD	Physicians' Research Options, Red Rocks Ob/Gyn
Edmond Pack, MD	Office of Edmond E. Pack
Khadra Osman, MD	KO Clinical Research, LLC
Michael Swor, MD	Physician Care Clinical Research, LLC
Alfred Poindexter, III, MD	Advances in Health
Samuel Simha, MD	Research Memphis Associates, LLC
Pouru Bhiwandi, MD	Wake Research Associates, LLC
Sandra Hurtado, MD	The Woman's Hospital of Texas Clinical Research Center
Stuart Weprin, MD	HWC Women's Research Center, LLC
Albert Tydings, MD	Clinical Trials Management, LLC
Edward Zbella, MD	Women's Medical Research Group, LLC
Kevin Fleishman, MD	Clinical Physiology Associates
Patricia Thompson, MD	Fellows Research Alliance, INC
Ivonne Reynolds, DO	South Florida Clinical Research Institute
Charles Newlin, MD	DCOL Center for Clinical Research
Ronald Surowitz, DO	Health Awareness, Inc.
James Simon, MD	James A. Simon, MD, PC

Investigator Name	Facility Name
Andrew Kaunitz, MD	UF College of Medicine-Jacksonville, Dept. of Obstetrics and Gynecology
Guillermo Lievano, DO	Genoma Research Group
Kathryn Moore, MD	Vista Clinical Research
Nasiruddin Rana, MD	Affinity Clinical Research Institute
Sharifa Fazili, MD	Upstate Clinical Research Associates, LLC
Winifred Soufi, MD	Agile Clinical Research Trials
Vaughn Whittaker, MD	New York Clinical Trials - Manhattan (NYCT, A Member of the Alliance, Inc.)
Juana Cuevas, MD	New York Clinical Trials- Brooklyn (NYCT, A Member of the Alliance, Inc.)
Brian MacGillivray, MD	Stone Oak, LLC dba Discovery Clinical Trials
Charles E Miller, MD	The Advanced Gynecologic Surgery Institute
Andrew Wagner, MD	Saginaw Valley Medical Research Group, LLC
Danilo Herrera, MD	Coastal Clinical Research
Sandra Nieto, MD	Futura Research Inc.
Rovena Reagan, MD	Women's Health Care Research Corp.
John Whitfield, MD	Signature Gyn Services
Lydie L. Hazan, MD	Axis Clinical Trials (ACTCA, A Member of the Alliance, Inc.)
Jody Jones, MD	ClinSite, LLC
Clifton Nicholson-Uhl, MD	Praetorian Pharmaceutical Research, LLC
Dominique Smith, MD	Soapstone Center for Clinical Research
Franklin Morgan, Jr., MD	Tidewater Physicians for Women
Ronald Hardy, MD	North Spokane Women's Health Research
James Roth, MD	Advanced Clinical Research/Old Farm Obstetrics& Gynecology
David F. Archer, MD	Eastern Virginia Medical School
Ladynez Espinal, MD	Clinovation Research, LLC
Antoinette Pragalos, MD	CTI Clinical Research Center
Kirk Brody, MD	Chattanooga Medical Research
Hugo Perez, MD	Suncoast Clinical Research
Nelson Uzquiano, MD	UAG Innovation Women Research, LLC
Michael A. Wells, MD	SEC Clinical Research
Parke Hedges, MD	Clinical Trials of Texas, Inc.,
Delbert "Alan" Johns, MD	Texas Health Care, PLLC
Marigene Salazar Sharma, MD	Albuquerque Clinical Trials, Inc.
Danielle A. "Dee-Dee" Shiller, DO	Pharmasite Research, Inc.

Investigator Name	Facility Name
Jay Berman, MD	C.S. Mott Center- Wayne State University
Gordon B. Clark, MD	GTC Research
Suzanne L. Fussell, MD	Long Beach Clinical Trial Services, Inc.
Arthur Schatz, MD	Ideal Clinical Research
Anthony Adams, MD	Paramount Research Solutions/Apogee Womens Health
Kwabena Ayesu, MD	Omega Research Consultants, LLC
Eric Brown, MD	Medisense, Inc
Fred Newton, MD	Lynn Institute of the Ozarks
Robert Littleton, MD	Unified Women's Clinical Research-Raleigh
Silpa Senchani, MD	ONCOVA Clinical Research, Inc.
Hugh A. Wilkinson, MD	Axcess Medical Research
Gioi Smith-Nguyen, MD	Grossmont Center for Clinical Research
Kurt Barnhart, MD	Department of Obstetrics and Gynecology, University of Pennsylvania School of Medicine
Aparna Tamirisa, MD	Houston Center for Clinical Research
Clark Griffith, MD	DCT - HCWC, LLC, dba Discovery Clinical Trials
Amber G. Hatch, MD	Unified Women's Clinical Research d/b/a Lyndhurst Clinical Research
David DeAtkine, Jr., MD	Central Research Associates, Inc.
Juan P. Frias, MD	National Research Institute
Todd B. Chappell, MD	Adams Patterson GYN/Wake Research Associates
Vicki Schnell, MD	Center for Reproductive Medicine
Molly Katz, MD	Katz and Kade, Inc.
Yamirka Duardo Guerra, MD	LCC Medical Research Institute, LLC
Mara Rabin (fka Epstein), MD	Wasatch Clinical Research
Ronnie M Givens II, MD	Clinical Trials of South Carolina
Elliot E Cazes, MD	New Tampa Ob/GYN (Stedman Clinical Trials)
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David Montaldi, DO	One Health Research Clinic, Inc.
Kelli Braun, MD	Augusta University Medical Center
Issam Daya, MD	Continental Clinical Solutions, LLC
Bradley Block, MD	Oviedo Medical Research
Keila Hoover, MD	Miami Clinical Research

Investigator Name	Facility Name
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Gregory P. Moore, II, MD	Clinical Research Partners, LLC
Hessam Aazami, MD	Hope Clinical Research
Ronald Ackerman, MD	Comprehensive Clinical Trials, LLC
Keila Hoover, MD	Miami Clinical Research
Sandra Hurtado, MD	The Woman's Hospital of Texas Clinical Research Center
Andrea Lukes, MD	Carolina Women's Research and Wellness Center
Godson Oguchi, MD	Midland Florida Clinical Research Group
Stephen Blank, MD	Mount Vernon Clinical Research, LLC/
Marquita Anderson, MD	Gadolin Research LLC
Duane Anderson, MD	Excel Clinical Research
Jean-Luc Squifflet	Cliniques Universitaires Saint-Luc
Wim Decleer	Algemeen Ziekenhuis Jan Palfijn Gent
Stefan Cosyns	Universitair Ziekenhuis Brussel
Michaël De Brucker	Centre Hospitalier Universitaire de Tivoli
Sonia Debbio, MD	Centro Paulista de Investigação Clinica
Maria Celeste Wender, MD, PhD, ScD	Hospital de Clínicas de Porto Alegre
Carlos Isaia Filho	Unidade de Pesquisa Clínica - Centro de Medicina Reprodutiva Dr. Carlos Isaia Filho
Emerson de Oliveira	Centro Multidisciplinar de Estudos Clínicos Unidade Santo André
Luciano Gibran	Hospital Pérola Byington - Centro de Referência da Saúde da Mulher
Carlos Isaia Filho	Unidade de Pesquisa Clínica - Centro de Medicina Reprodutiva Dr. Carlos Isaia Filho
Claudio Andrés Villarroel Quintana	Hospital Clinico San Borja Arriaran
Guillermo Galan Chiappa	Centro de Capacitación e Investigaciones Clínicas
Cristian Jesam Gaete	Instituto Chileno de Medicina Reproductiva
Marco Levancini Alvarez	Hospital Padre Hurtado
Aleš Skrivánek	G-CENTRUM
Olga Hlavácková	Centrum Gynekologické Rehabilitace
Aleš Roztocil	Nemocnice Jihlava
Petr Sák, MD, PhD	MUDr. Petr Sák
János Zatik	Szent Anna Nogyógyászati, Szülészeti és Ultrahang Magánrendelo

Investigator Name	Facility Name
Károly Pap, MD	Szabolcs-Szatmár-Bereg Megyei Kórházak és Egyetemi Oktatókórház
Tamás Nyirády	Mediroyal
Ferenc Racz	Csongrád Megyei Dr. Bugyi István Kórház
Márta Rákos	Synexus Magyarország Egészségügyi Szolgáltató Kft. - Affiliated Site Gyula
József Nemes	Synexus Magyarország
Fiorenzo, De Cicco Nardone	Fondazione Policlinico Universitario Agostino Gemelli
Vincenzo De Leo, MD	Azienda Ospedaliera Universitaria Senese
R. Venturella	Azienda Ospedaliera “Pugliese Ciaccio” di Catanzaro
M. Bau	Azienda Ospedaliero Universitaria “Citta della Salute e dell Scienza” di Torino – Ospedale Sant Anna
F. Petraglia	Azienda Ospedaliero Universitaria Careggi
Jacek Szamatowicz	ARTEMIDA Centrum Ginekologii Endokrynologii i Medycyny Rozrodu
Krzysztof Szymanowski	Examen
Tomasz Rechberger, Prof	Niepubliczny Zaklad Opieki Zdrowotnej NOVITA Specjalistyczne Gabinety Lekarskie
Zoulikha Jabiry-Zieniewicz	NZOZ Zieniewicz Medical
Krzysztof Wilk	Wielospecjalistyczna Poradnia Lekarska Synapsis
Slawomir Jedrzejczyk	Niepubliczny Zaklad Opieki Zdrowotnej JORDAN Slawomir Jedrzejczyk
K. Oronowicz	Twoja Przychodnia – Szczecińskie Centrum Medyczne
Tobias De Villiers	Clintrials Projects cc
Victor Hulme	Life Vincent Pallotti Hospital
Nyda Fourie	Iatros International
Lynette Reynders	Office Of Lynette Reynders, MB CHB
Sagaren Naidu	Dr S Naidu O and G Clinical Trials
Elmarie Wypkema	Life Wilgeheuwel Hospital
Daniel Malan	Phoenix Pharma

Appendix 6. Summary of Patients Who Met the Bone Mineral Density Decrease Exclusion Criteria for LIBERTY Extension Study

		LIBERTY 1		LIBERTY 2		Total
		≥ 7 change BMD	Z-score < -2.0	≥ 7 change BMD	Z-score < -2.0	
Relugolix CT	Lumber Spine	0	0	1	2	11
	Total Hip	0	0	0	0	
	Femoral Neck	3	0	4	1	
Relugolix→ Relugolix CT	Lumber Spine	3	0	6	1	21
	Total Hip	0	0	0	0	
	Femoral Neck	7	1	3	0	
Placebo→ Relugolix CT	Lumber Spine	1	0	0	0	8
	Total Hip	0	0	0	0	
	Femoral Neck	4	0	3	0	
Total		18	1	17	4	40

Abbreviations: BMD = bone mineral density; CT = combination therapy; NETA = norethindrone acetate.

[a] if the same subject were excluded due to meeting both BMD and Z-score criteria, only the BMD criterion was included in the total to avoid double-counting.

Appendix 7. Baseline Characteristics for the Pivotal LIBERTY Studies, the Long-term Extension, and the Long-term Extension Study Completers

Baseline Characteristic		Pooled Pivotal LIBERTY Studies (N = 768)		Long-Term Extension Study (N = 476)		Long-Term Extension Study Completers (N = 363)	
Age, Mean years (SD)		42.1	(5.3)	42.2	(5.4)	42.3	(5.3)
Race n (%)	Black	393	(51.2)	238	(50.0)	178	(49.0)
	White	330	(43.0)	207	(43.5)	162	(44.6)
	Other*	45	(5.9)	31	(6.5)	23	(6.3)
Region n (%)	North America	580	(75.5)	334	(70.2)	245	(67.5)
	Rest of World†	188	(24.5)	142	(29.8)	118	(32.5)
Body Mass Index, Mean kg/m^2 (SD)		31.5	(7.1)	31.7	(7.0)	31.2	(6.8)
MBL Volume, Mean mL (SD)		228.8	(154.3)	234.3	(161.8)	227.7	(148.3)
Uterine Volume, Mean cm^3 (SD)		408.0	(367.3)	409.2	(347.6)	401.6	(326.0)
Volume of largest fibroid, Mean cm^3 (SD)		77.45	(134.3)	81.6	(137.0)	84.8	(143.3)
Hemoglobin, Mean g/dL (SD)		11.2	(1.5)	11.2	(1.5)	11.3	(1.6)
< 10.5, n (%)		240	(31.3)	145	(30.5)	108	(29.8)
UFS-QoL Symptom Severity Scale, Mean Score (SD)		59.4	(20.8)	60.1	(19.8)	59.7	(19.8)
UFS-QoL BPD Scale, Mean Score (SD)		69.9	(21.7)	70.8	(20.1)	69.9	(19.9)
UFS-QoL Total HRQoL Scale, Mean Score (SD)		36.8	(21.4)	35.9	(20.6)	37.4	(21.1)

Data shown by randomization treatment assignment. *Other includes American Indian or Alaska Native, Asian, other, multiple, and not reported. †Rest of World includes Africa, Europe and South America. CT = Combination Therapy; MBL = menstrual blood loss; SD = standard deviation.

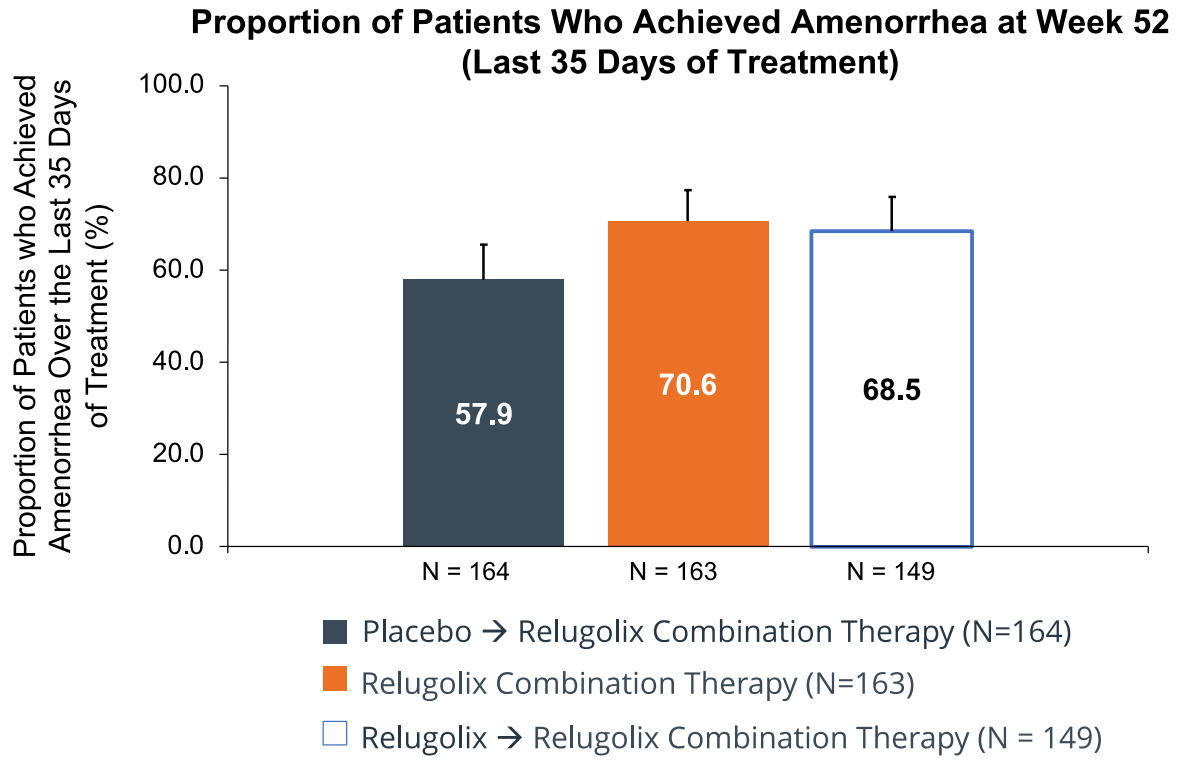
Appendix 8. Subgroup Analysis for Primary Endpoint

Subgroups	Category	Treatment	n	Responder n (%)	Responder rate (95% CI)
Geographic region	NORTH AMERICA	Relugolix CT	113	97 (85.8 %)	(78.03%, 91.68%)
		Relugolix→Relugolix CT	104	85 (81.7 %)	(72.95%, 88.63%)
		Placebo→Relugolix CT	117	86 (73.5 %)	(64.55%, 81.23%)
	REST OF WORLD	Relugolix CT	50	46 (92.0 %)	(80.77%, 97.78%)
		Relugolix→Relugolix CT	45	37 (82.2 %)	(67.95%, 92.00%)
		Placebo→Relugolix CT	47	40 (85.1 %)	(71.69%, 93.80%)
MBL volume at baseline	< 225 mL	Relugolix CT	107	98 (91.6 %)	(84.63%, 96.08%)
		Relugolix→Relugolix CT	88	76 (86.4 %)	(77.39%, 92.75%)
		Placebo→Relugolix CT	109	86 (78.9 %)	(70.04%, 86.13%)
	≥ 225 mL	Relugolix CT	56	45 (80.4 %)	(67.57%, 89.77%)
		Relugolix→Relugolix CT	61	46 (75.4 %)	(62.71%, 85.54%)
		Placebo→Relugolix CT	55	40 (72.7 %)	(59.04%, 83.86%)
Age	< 40 years	Relugolix CT	38	31 (81.6 %)	(65.67%, 92.26%)
		Relugolix→Relugolix CT	47	39 (83.0 %)	(69.19%, 92.35%)
		Placebo→Relugolix CT	48	35 (72.9 %)	(58.15%, 84.72%)
	≥ 40 years	Relugolix CT	125	112 (89.6 %)	(82.87%, 94.35%)
		Relugolix→Relugolix CT	102	83 (81.4 %)	(72.45%, 88.40%)
		Placebo→Relugolix CT	116	91 (78.4 %)	(69.85%, 85.54%)
Race	Black	Relugolix CT	70	58 (82.9 %)	(71.97%, 90.82%)
		Relugolix→Relugolix CT	82	67 (81.7 %)	(71.63%, 89.38%)
		Placebo→Relugolix CT	89	65 (73.0 %)	(62.58%, 81.90%)

Subgroups	Category	Treatment	n	Responder n (%)	Responder rate (95% CI)
	White	Relugolix CT	85	78 (91.8 %)	(83.77%, 96.62%)
		Relugolix→Relugolix CT	52	43 (82.7 %)	(69.67%, 91.77%)
		Placebo→Relugolix CT	71	57 (80.3 %)	(69.14%, 88.78%)
	Asian	Relugolix CT	1	1 (100.0 %)	(2.50%, 100.00%)
		Relugolix→Relugolix CT	3	2 (66.7 %)	(9.43%, 99.16%)
		Placebo→Relugolix CT	0	0 (0.0%)	
	Others	Relugolix CT	4	3 (75.0 %)	(19.41%, 99.37%)
		Relugolix→Relugolix CT	10	8 (80.0 %)	(44.39%, 97.48%)
		Placebo→Relugolix CT	3	3 (100.0 %)	(29.24%, 100.00%)
Largest fibroid volume at baseline	< 25 cm3	Relugolix CT	81	74 (91.4 %)	(83.00%, 96.45%)
		Relugolix→Relugolix CT	58	51 (87.9 %)	(76.70%, 95.01%)
		Placebo→Relugolix CT	73	55 (75.3 %)	(63.86%, 84.68%)
	≥ 25 cm3	Relugolix CT	81	69 (85.2 %)	(75.55%, 92.10%)
		Relugolix→Relugolix CT	90	70 (77.8 %)	(67.79%, 85.87%)
		Placebo→Relugolix CT	91	71 (78.0 %)	(68.12%, 86.03%)
Uterine volume at baseline	< 300 cm3	Relugolix CT	96	89 (92.7 %)	(85.55%, 97.02%)
		Relugolix→Relugolix CT	69	58 (84.1 %)	(73.26%, 91.76%)
		Placebo→Relugolix CT	82	61 (74.4 %)	(63.56%, 83.40%)
	≥ 300 cm3	Relugolix CT	67	54 (80.6 %)	(69.11%, 89.24%)
		Relugolix→Relugolix CT	80	64 (80.0 %)	(69.56%, 88.11%)
		Placebo→Relugolix CT	82	65 (79.3 %)	(68.89%, 87.43%)

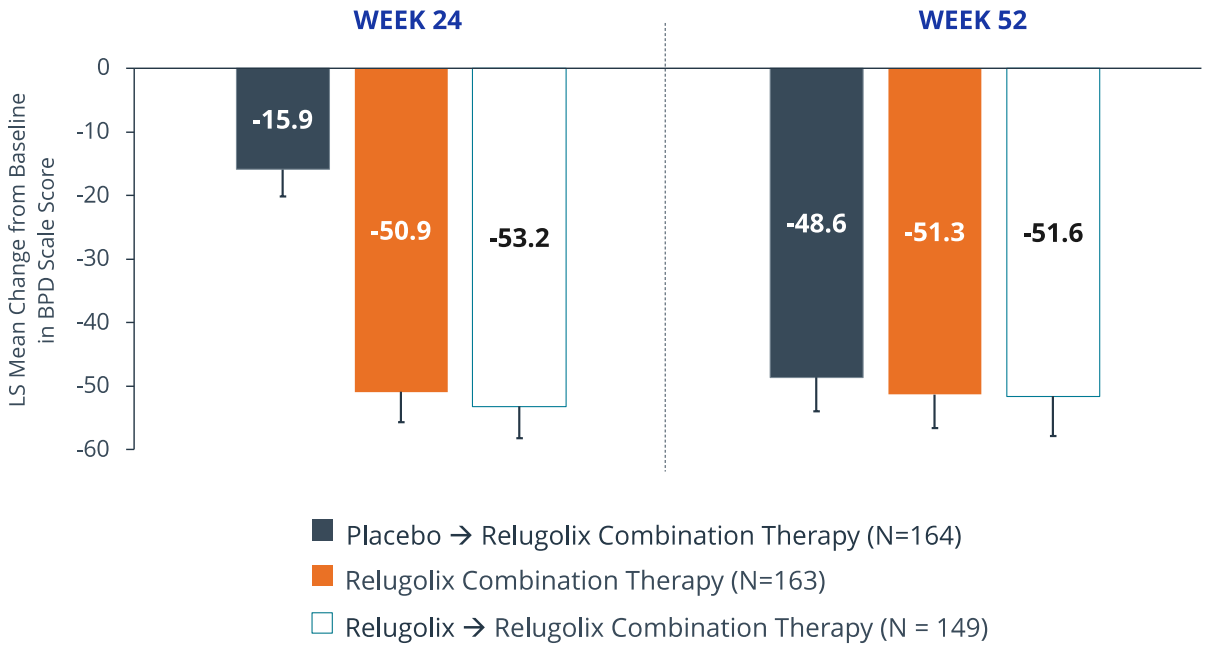
Subgroups	Category	Treatment	n	Responder n (%)	Responder rate (95% CI)
BMI at baseline	< 30 kg/m^2	Relugolix CT	70	64 (91.4 %)	(82.27%, 96.79%)
		Relugolix→Relugolix CT	70	59 (84.3 %)	(73.62%, 91.89%)
		Placebo→Relugolix CT	71	54 (76.1 %)	(64.46%, 85.39%)
	≥ 30 kg/m^2	Relugolix CT	92	78 (84.8 %)	(75.79%, 91.42%)
		Relugolix→Relugolix CT	79	63 (79.7 %)	(69.20%, 87.96%)
		Placebo→Relugolix CT	93	72 (77.4 %)	(67.58%, 85.45%)
Maximum NRS pain score at baseline	< 4	Relugolix CT	49	43 (87.8 %)	(75.23%, 95.37%)
		Relugolix→Relugolix CT	42	32 (76.2 %)	(60.55%, 87.95%)
		Placebo→Relugolix CT	32	23 (71.9 %)	(53.25%, 86.25%)
	≥ 4	Relugolix CT	113	99 (87.6 %)	(80.09%, 93.06%)
		Relugolix→Relugolix CT	107	90 (84.1 %)	(75.79%, 90.46%)
		Placebo→Relugolix CT	130	102 (78.5 %)	(70.40%, 85.19%)

Appendix 9. Proportion of patients who achieved amenorrhea at week 52 (last 35 days of treatment). *Error bars* show upper 95% CIs.



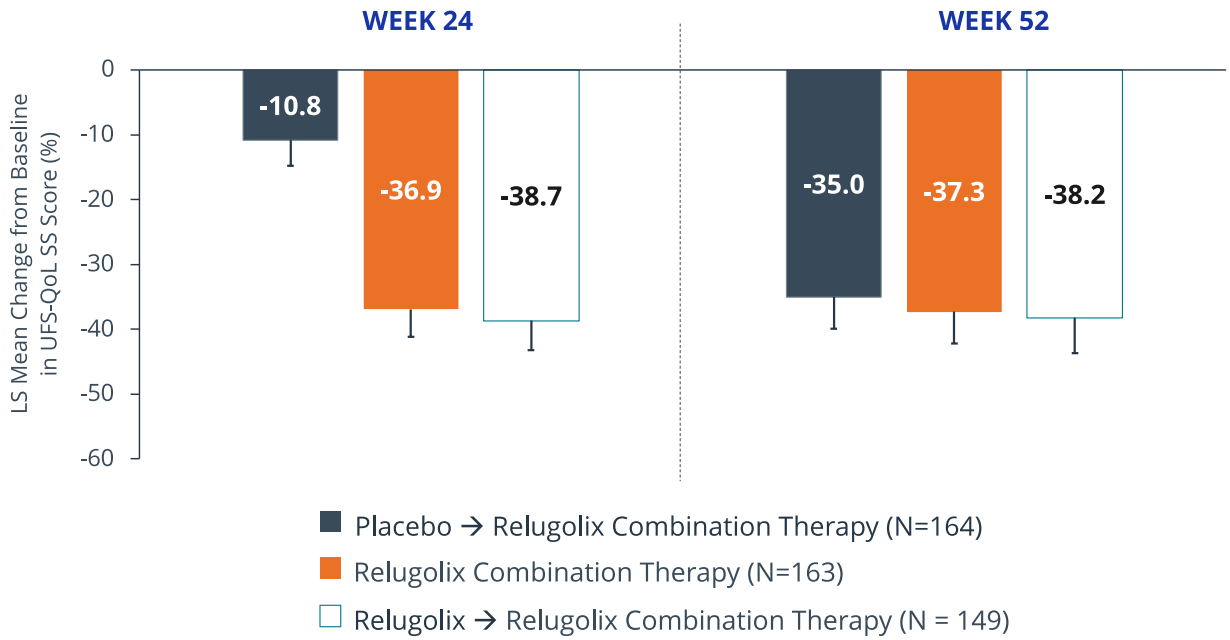
Al-Hendy A, Lukes AS, Poindexter A, Venturella R, Villarroel C, McKain L, et al. Long-term relugolix combination therapy for symptomatic uterine leiomyomas. Obstet Gynecol 2022;140.
The authors provided this information as a supplement to their article.

Appendix 10. Change from Baseline in Bleeding and Pelvic Discomfort (BPD) scale score at week 24 and week 52. *Error bars* show lower 95% confidence interval. CT, combination therapy; LS, least squares.



Al-Hendy A, Lukes AS, Poindexter A, Venturella R, Villarroel C, McKain L, et al. Long-term relugolix combination therapy for symptomatic uterine leiomyomas. Obstet Gynecol 2022;140.
The authors provided this information as a supplement to their article.

Appendix 11. Change in symptom severity at week 24 and week 52. *Error bars* show lower 95% CI. CT, combination therapy; LS, least squares; SS, Symptom Severity; UFS-QoL SS, Uterine Fibroid Symptom-Quality of Life Symptom Severity.



Al-Hendy A, Lukes AS, Poindexter A, Venturella R, Villarroel C, McKain L, et al. Long-term relugolix combination therapy for symptomatic uterine leiomyomas. Obstet Gynecol 2022;140.
The authors provided this information as a supplement to their article.

Appendix 12. Lumbar Spine and Total Hip Bone Mineral Density Results Over 52 Weeks

	Placebo→Relugolix CT (N = 164)	Relugolix CT (N = 163)	Relugolix→Relugolix CT (N = 149)
Lumbar spine (L1 - L4)			
Week 12			
n	146	145	137
LS mean percent change (95% CI)	0.40 (-0.081, 0.887)	-0.37 (-0.812, 0.076)	-2.27 (-2.728, -1.819)
Week 24			
n	156	153	144
LS mean percent change (95% CI)	0.24 (-0.234, 0.716)	-0.23 (-0.693, 0.236)	-2.18 (-2.631, -1.727)
Week 36			
n	138	145	120
LS mean percent change (95% CI)	-0.25 (-0.791, 0.298)	-0.73 (-1.233, -0.219)	-2.11 (-2.623, -1.589)
Week 52			
n	120	132	108
LS mean percent change (95% CI)	-0.78 (-1.325, -0.226)	-0.80 (-1.358, -0.250)	-2.05 (-2.575, -1.516)
Total hip			
Week 12			
n	145	146	131
LS mean percent change (95% CI)	0.47 (0.092, 0.838)	0.07 (-0.335, 0.466)	-0.95 (-1.315, -0.585)
Week 24			
n	156	155	142
LS mean percent change (95% CI)	0.61 (0.204, 1.015)	0.03 (-0.361, 0.423)	-1.01 (-1.366, -0.655)
Week 36			
n	137	147	122
LS mean percent change (95% CI)	0.19 (-0.202, 0.576)	-0.22 (-0.612, 0.169)	-0.99 (-1.396, -0.575)
Week 52			
n	121	129	105
LS mean percent change (95% CI)	-0.07 (-0.477, 0.347)	-0.15 (-0.615, 0.309)	-0.84 (-1.298, -0.386)

Abbreviations: CI = confidence interval; E2 = estradiol; LS = least squares; n = number of patients in subset; N = number of patients; CT = combination therapy.