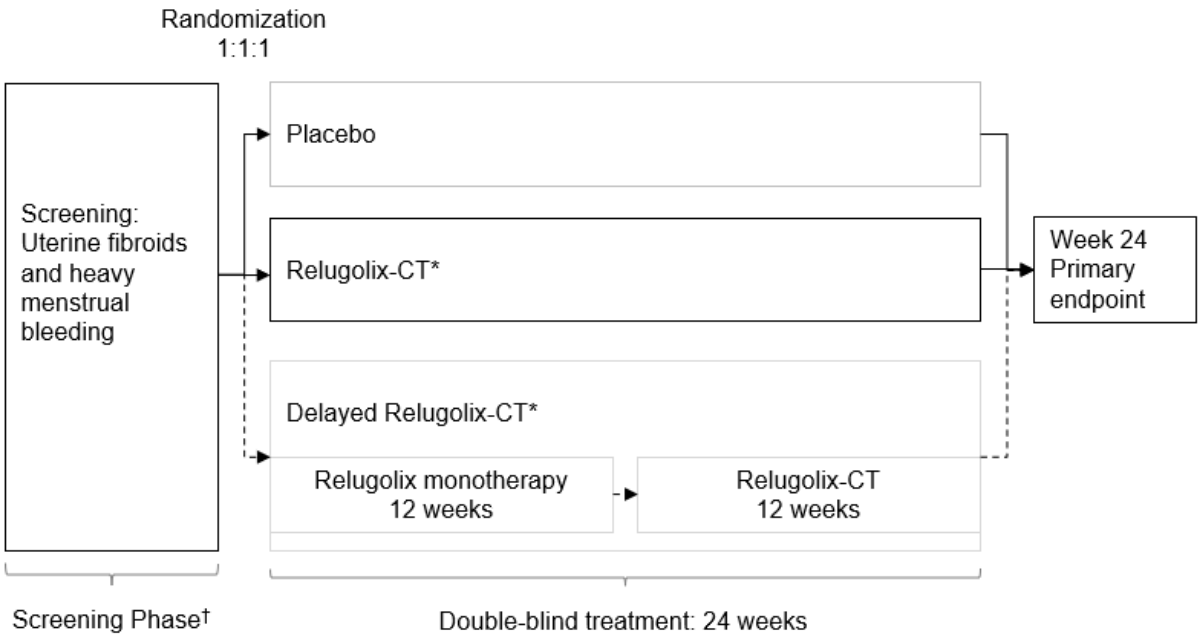
Appendix 1. Study Design: LIBERTY 1 and LIBERTY 2

Primary endpoint at week 24 was defined as both a volume of menstrual blood loss of less than 80 mL and a reduction of at least 50% from the baseline volume of menstrual blood loss, as measured by the alkaline hematin method, over the last 35 days of the treatment period. *The purpose of the delayed Relugolix-CT group was to evaluate the safety of relugolix monotherapy; since this regimen was not intended for clinical practice, only results on pain endpoints for the Relugolix-CT and placebo groups are described. †UF-associated pain scores were collected during the screening phase using the eDiary. The number of pain score days obtained from each woman during the screening phase (serving also as the baseline) was variable and could be shorter than 7 days or as long as 70 days. Relugolix-CT, relugolix combination therapy (relugolix 40 mg + estradiol 1 mg + norethindrone acetate 0.5 mg); UF, uterine fibroid; eDiary, electronic diary; NRS, Numerical Rating Scale.



Stewart EA, Lukes AS, Venturella R, Arjona Ferreira JC, Li Y, Hunsche E, et al. Relugolix combination therapy for uterine leiomyoma–associated pain in the LIBERTY randomized trials. Obstet Gynecol 2022;139.
The authors provided this information as a supplement to their article.
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Appendix 2. List of Independent Ethics Committees and Institutional Review Boards for LIBERTY 1 and LIBERTY 2

LIBERTY 1

IEC/IRB	Principal Investigator
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
Chesapeake Institutional Review Board 6940 Columbia Gateway Drive Suite 110 Columbia, MD 21046	David F. Archer, MD
Trinity Hospitals Institutional Review Board One Burdick Expressway West Minot, ND 58701	David Billings, MD
Western Institutional Review Board 1019 39th Avenue SE Suite 120 Puyallup, WA 98374	Kelli Braun, MD
Rest of World	
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	
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
Comitê de Ética em Seres Humanos do Hospital de Clinicas de Curitiba Rua Pe. Camargo nº 285 – térreo – Alto da Glória – Curitiba/PR - CEP 80060-240 – Brazil	Rosires de Andrade
Comitê de Ética e Pesquisa do Centro de	Luciano Gibran

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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	
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
Comitê de Ética em Pesquisa do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da USP Avenida Bandeirantes, 3900 – Campus Universitário s/n – Monte Alegre – Subsolo - 14048-900 – Ribeirão Preto/SP – Brazil	Rui Ferriani
Germany	
Ethikkommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster Gartenstrasse 210-214, 48147 Muenster, Germany	
Ethik-Kommission der Ärztekammer Hamburg Weidestrasse 122 b 22083 Hamburg, Germany	Klaus Peters
Landesamt für Gesundheit und Soziales Geschäftsstelle der Ethik-Kommission des Landes Berlin Fehrbelliner Platz 1 10707, Berlin, Germany	Christiane Buenemann-Buschmann
Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster Gartenstrasse 210-214, 48147 Muenster, Germany	Sebastian Schäfer
Ethikkommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster Berliner Allee 20 30175 Hannover, Germany	Heiner Frommeyer
Italy	
Comitato Etico Policlinico Gemelli Segreteria tecnico Scientifica COMITATO ETICO Policlinico Gemelli Segreteria Tecnico-Scientifica Largo Gemelli, 8 00168 Roma	
COMITATO ETICO DELL'UNIVERSITA'	Fiorenzo, De Cicco Nardone

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CATTOLICA DEL SACRO CUORE E ANNESSO POLICLINICO "A.GEMELLI" COMITATO ETICO Policlinico Gemelli Segreteria Tecnico-Scientifica Largo Gemelli, 8 00168 Roma	
COMITATO ETICO REGIONALE DELLA LIGURIA (SEZIONE N. 2) Largo Rosanna Benzi, 10 16132 GENOVA Italy	Valentino Remorgida
"COMITATO ETICO Azienda Ospedaliera Universitaria Senese COMITATO ETICO REGIONE TOSCANA - AREA VASTA SUD EST Viale Bracci 16 53100 Siena Italy	Vincenzo De Leo, MD
COMITATO ETICO DELL'UNIVERSITA' "SAPIENZA" Viale Del Policlinico, 155 00161 ROMA Italy	Maria Grazia Porpora
Comitato Etico Indipendente di Area Vasta Emilia Centro (CE-AVEC) della Regione Emilia- Romagna C/O Azienda Ospedaliero – Universitaria di Bologna, Policlinico S.Orsola- Malpighi Albertoni, 15 40138 BOLOGNA Italy	Renato Seracchioli
COMITATO ETICO INDIPENDENTE Azienda Ospedaliero Universitaria di Cagliari P.O. San Giovanni di Dio Ospedale 54 – 09124 Cagliari Italy	Gian Benedetto Melis
Comitato Etico dell'Università Federico II Sergio Pansini 5 80131 Napoli Italy	Carmine Nappi
Poland	
Komisja Bioetyczna przy Lubleskiej Izbie Lekarskiej ul. Chmielna 4, 20-079 Lublin, Poland	Central IEC
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

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United Kingdom	
East Midlands - Leicester South REC The Old Chapel, Royal Standard Court, Nottingham, NG1 6FS	Central IEC

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

LIBERTY 2

IEC/IRB	**Principal Investigator**
United States	
Schulman Associates Institutional Review Board 4445 Lake Forest Drive Suite 300 Cincinnati, OH 45242	Central IRB
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
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
Comite Ético Científico de Seguridad CChC Guardia Vieja 181, oficina 207, zip code 7510186 Providencia, Santiago, Chile	Guillermo Galan Chiappa
Comité ético Científico del Servicio de Salud Metropolitano Sur Oriente Concha y Toro 3459, Puente Alto, Santiago, Chile	Marco Levancini Alvarez
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	Central IEC

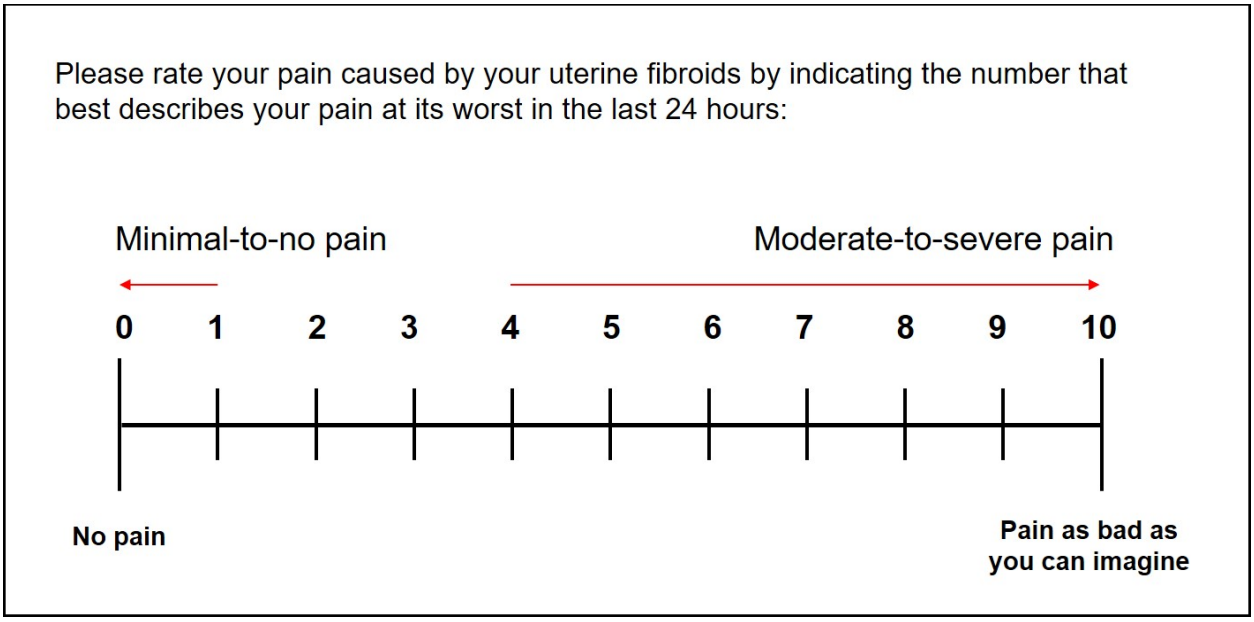
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Széchenyi István tér 7-8, 1051 Budapest, Hungary	
Poland	
Komisja Bioetycznaprzy Okręgowej Radzie Lekarskiej Wielkopolskiej Izby Lekarskiej ul. Nowowiejskiego 51, 61-734 Poznań, Poland	Central IEC
South Africa	
South African Medical Association Research Ethics Committee (SAMAREC) Block F, Castle Walk Office Park, Nossob Street, Erasmuskloof Ext 3, Pretoria 0181, South Africa	Central IEC

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

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Appendix 3. Numerical rating scale.



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Appendix 4. Demographic and Baseline Characteristics of the Pain Subpopulations for LIBERTY 1 and 2

Baseline characteristic	LIBERTY 1 (n = 127)		LIBERTY 2 (n = 150)	
	Relugolix-CT (n = 58)	Placebo (n = 69)	Relugolix-CT (n = 68)	Placebo (n = 82)
Age (y)	42.3±5.0	43.0±5.4	42.7±4.8	41.9±5.5
Race, n (%)				
American Indian/Alaska native	1 (1.7)	1 (1.4)	0	1 (1.2)
Asian	0	1 (1.4)	0	1 (1.2)
Black/African American	27 (46.6)	36 (52.2)	33 (48.5)	43 (52.4)
White	28 (48.3)	30 (43.5)	33 (48.5)	35 (42.7)
None of the above	2 (3.4)	0	1 (1.5)	1 (1.2)
Multiple	0	1 (1.4)	1 (1.5)	0
Not reported	0	0	0	1 (1.2)
Region				
North America	46 (79.3)	54 (78.3)	50 (73.5)	58 (70.7)
Rest of world	12 (20.7)	15 (21.7)	18 (26.5)	24 (29.3)
BMI (kg/m^2)	32.7±8.6	32.3±7.4	31.4±7.4	31.5±7.6
MBL volume (mL)	244.6±171.6	218.4±123.7	246.0±199.5	198.1±105.6
Index UF volume (cm^3)	76.1±149.2	83.0±144.8	63.6±131.1	76.6±130.2
Uterine volume (cm^3)	381.2±293.9	414.7±288.4	406.4±371.8	365.4±341.7
Hemoglobin (g/dL)	11.3±1.7	11.4±1.4	11.4±1.5	11.1±1.5
Maximum NRS score for UF-associated pain ≥4,	7.4 (1.9)	7.0 (1.9)	7.1 (2.2)	7.0 (1.9)
Timing of maximum NRS score ≥4				
On menstrual bleeding days only	23 (39.7)	35 (50.7)	38 (55.9)	42 (51.2)
On non-menstrual bleeding days only	3 (5.2)	1 (1.4)	6 (8.8)	5 (6.1)
On both menstrual bleeding and non-menstrual bleeding days	32 (55.2)	33 (47.8)	24 (35.3)	35 (42.7)

Data are mean±SD, or n (%). Relugolix-CT, relugolix combination therapy; y, years; BMI, body mass index; MBL, menstrual blood loss; UF, uterine fibroid; NRS, Numerical Rating Scale; SD, standard deviation.

Stewart EA, Lukes AS, Venturella R, Arjona Ferreira JC, Li Y, Hunsche E, et al. Relugolix combination therapy for uterine leiomyoma–associated pain in the LIBERTY randomized trials. Obstet Gynecol 2022;139.
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