PROTOCOL

PROTOCOL TITLE:	**A PHASE II, SINGLE-ARM STUDY OF GIREDESTRANT IN PATIENTS WITH GRADE 1 ENDOMETRIAL CANCER**
PROTOCOL NUMBER:	CO44195
VERSION NUMBER:	1
TEST COMPOUND:	Giredestrant (RO7197597)
STUDY PHASE:	Phase II
EUDRACT NUMBER:	To be determined
IND NUMBER:	162,936
NCT NUMBER:	To be determined
MEDICAL MONITOR:	Victor Khor, Ph.D.
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL ACCEPTANCE FORM

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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE: **A PHASE II, SINGLE-ARM STUDY OF GIREDESTRANT IN PATIENTS WITH GRADE 1 ENDOMETRIAL CANCER**

STUDY RATIONALE

The purpose of this study is to assess the efficacy, safety, and pharmacokinetics of giredestrant in participants with Grade 1 endometrioid endometrial carcinoma (EC).

OBJECTIVES AND ENDPOINTS AND ESTIMANDS

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020) in Section 3.

Primary Objective	Corresponding Endpoints/Estimands
• To evaluate the efficacy of giredestrant by regression rate by the Month 6 assessment	• Population: Participants who have received any amount of study drug and have had a histological assessment at baseline, i.e., before the first exposure to any amount of study drug. Participants who do not have any post-baseline assessment will be excluded. • Variable: Participants who have regression, defined as participants who have a decrease in the proportion of cancer in the EMB or have an increase of non-cancer/non-atypical hyperplasia (%) by the Month 6 assessment (preferably after the completion of Cycle 6) compared with baseline • Treatment: giredestrant 30 mg • Intercurrent Events – Participants without a post-baseline assessment – Withdrawal of Consent/Lost to Follow-Up – Death • Handling of intercurrent events: – Withdrawal of Consent/Lost to Follow-Up/Death: Such events are expected to be very rare. Participants will be excluded if death or withdrawal is irrelevant to disease; if death or withdrawal occurs after assessment, the results from assessment will be used; if death or withdrawal is disease-related and no assessment was done, this will be excluded. – Summary measure: Proportion of participants who have regression by the Month 6 assessment

Primary Objective	Corresponding Endpoints/Estimands
	• Population: Participants who have received any amount of study drug and have had a histological assessment at baseline, i.e., before the first exposure to any amount of study drug. Participants who do not have any post-baseline assessment will be excluded. • Variable: Participants who have regression, defined as participants who have a decrease in the proportion of cancer in the EMB or have an increase in non-cancer/non-atypical hyperplasia (%) by the Month 6 assessment (preferably after the completion of Cycle 6) compared with baseline • Treatment: giredestrant 30 mg • Intercurrent Events – Participants without a post-baseline assessment – Withdrawal of Consent/Lost to Follow-Up – Death • Handling of intercurrent events: – Withdrawal of Consent/Lost to Follow-Up/Death: Such events are expected to be very rare. Participants will be excluded if death or withdrawal is irrelevant to disease; if death or withdrawal occurs after assessment, the results from assessment will be used; if death or withdrawal is disease--related and no assessment was done, this will be excluded. – Summary measure: Proportion of participants who have regression by the Month 6 assessment
Primary Safety Objective	**Corresponding Endpoints/Estimands**
• To evaluate the safety and tolerability of giredestrant by regression rate by Month 6	• Occurrence and severity of adverse events with severity determined according to the NCI CTCAE v5.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results • All participants who received at least 1 dose of study treatment will be included in safety analysis
Secondary Objectives	**Corresponding Endpoints/Estimands**
• To evaluate the efficacy of giredestrant by complete regression rate by the Month 6 assessment	• Variable: Complete regression rate, defined as participants having an assessment of 100% of non-cancer/non-atypical hyperplasia by the Month 6 assessment • Population, Treatment, Intercurrent Events and Handling are the same as the primary objective • Summary measure: Proportion of participants who have complete regression

Secondary Objectives	Corresponding Endpoints/Estimands
• To evaluate the efficacy of giredestrant by duration of regression	• Variable: Time from the first regression to time of the first relapse – Regression is defined as: Decrease in the proportion of cancer in the EMB (%) compared with baseline. or Increase in non-cancer/non-atypical hyperplasia when compared with baseline. – Relapse is defined as: Increase in the proportion of cancer in the EMB (%) when compared with its nadir. or Increase in the proportion of cancer in the EMB and atypical hyperplasia (%) compared with its nadir. • Population: Participants who have regression • Treatment, Intercurrent Events and Handling are the same as the primary objective • Summary measure: median of time from first regression to first worsening
• To evaluate the efficacy of giredestrant by time to regression	• Variable: the time from the first study treatment to the first regression – Regression is defined as Decrease in the proportion of cancer in the EMB (%) compared with baseline. or Increase in non-cancer/non-atypical hyperplasia when compared with baseline. • Population, Treatment, Intercurrent Events and Handling are the same as the primary objective • Summary measure: median of time from first study treatment to first regression
• To evaluate the efficacy of giredestrant by time to relapse or loss of clinical benefit	• Variable: Time to relapse or loss of clinical benefit, defined as the time from the first study treatment to relapse or loss of clinical benefit, whichever occurred first – Relapse defined as: Increase in the proportion of cancer in the EMB (%) when compared with baseline. or Increase in the proportion of cancer in the EMB and atypical hyperplasia (%) when compared with baseline. – Loss of clinical benefit per the investigator

Secondary Objectives	Corresponding Endpoints/Estimands
	• Population, Treatment, Intercurrent Events and Handling are the same as the primary objective • Summary measure: mean of time from first study treatment to relapse or loss of clinical benefit Increase in the proportion of cancer in the EMB and atypical hyperplasia (%) when compared with baseline. – Loss of clinical benefit per the investigator • Population, Treatment, Intercurrent Events and Handling are the same as the primary objective • Summary measure: mean of time from first study treatment to relapse or loss of clinical benefit

EMB = endometrial biopsy; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

OVERALL DESIGN

Overview of Study Design

This Phase II, global, single-arm study is designed to evaluate the efficacy, safety, and pharmacokinetics of giredestrant monotherapy in participants with Grade 1 endometrioid EC. Participants must not have had prior treatment for complex endometrial hyperplasia, endometrial intraepithelial neoplasia (EIN), or endometrial cancer.

This study will enroll approximately 45 participants across all sites.

After providing informed consent, participants will undergo screening procedures as outlined in the schedule of activities.

Confirmation of Grade 1 endometrioid histology at the study's Central Laboratory is required for study entry for all candidate participants. Participants with endometrial samples that are not confirmed by the Central Study Laboratory will not be eligible for the study.

Participants enrolled in the study will receive giredestrant 30 mg taken orally (PO) once a day (QD) on Days 1–28 of each 28-day cycle for 6 cycles. After completion of 6 cycles, the participant and investigator can choose to continue study therapy or discontinue study therapy and receive investigator-determined care. After 6 months, participants can discontinue study treatment and undergo surgery or continue to receive study treatment for up to 18 additional cycles, per shared decision-making by the participant and physician. Participants will undergo endometrial sampling at baseline and every 3 months (Q3M) for a minimum of 6 months. Participants that are treated beyond the minimum of 6 cycles will continue to undergo endometrial sampling Q3M. Representative tissue from each endometrial sampling timepoint must be submitted to the Central Study Laboratory.

After initiation of study treatment, all adverse events will be reported according to the adverse event reporting period. In addition, the Sponsor will be notified if the investigators become aware of any serious adverse events or adverse events of special interest that are believed to be related to prior treatment with study drug(s). These events should be reported using the Adverse Event electronic Case Report Form (eCRF). The investigator will follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or protocol-related procedures until they are resolved or no further changes in the event's status are expected.

NUMBER OF PARTICIPANTS

Approximately 45 participants with Grade 1 endometrioid EC will be enrolled in this study.

STUDY TREATMENT

Participants will receive open-label giredestrant 30 mg PO QD on Days 1–28 of each 28-day cycle, beginning on Day 1 of Cycle 1.

DURATION OF PARTICIPATION

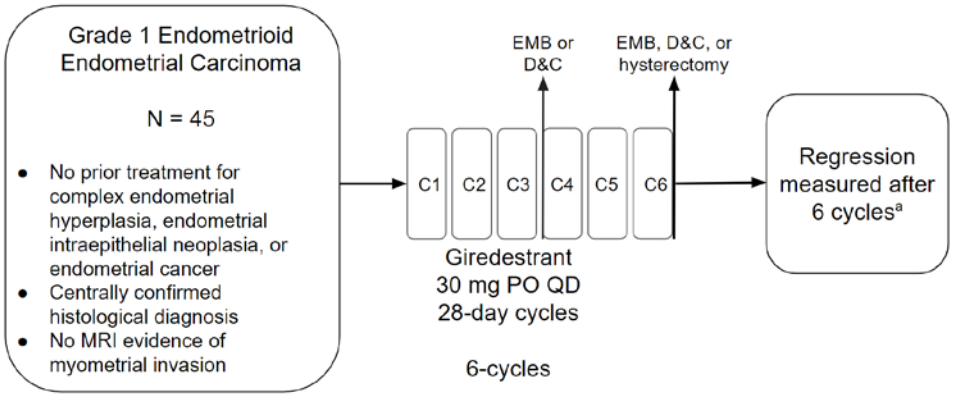
The total duration of study participation for each individual is expected to be approximately 8–26 months.

INDEPENDENT DATA MONITORING COMMITTEE

An independent Data Monitoring Committee iDMC is not being used.

1.2 STUDY SCHEMA

Figure 1 Study Schema



C = cycle; EMB = endometrial biopsy; D&C = dilation and curettage; MRI = magnetic resonance imaging; N = number of participants; PO = orally; QD = once a day.

[a] After 6-cycles and sample collected for regression, participants can continue study treatment for an additional 18 cycles, plan for surgery, or continue with off-study treatment.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities

Day(s) (Window)	Protocol Reference	Screening [a]		Treatment Cycles (28-day Cycles)		Every 3 Months (±14 days)	Treatment Completion/ Discontinuation [b]
				Cycles 1–3	Cycles 4 and Beyond		
		–28 to –1	–7 to –1	Day 1 of Each Cycle (±3 days)	Day 1 of Each Cycle (±3 days)		30 Days after Final Dose (±3 days)
Informed consent	8	x					
Demographics	8	x					
Medical history and baseline conditions	8	x					
Vital signs	8.2.2	x		x	x		x
Weight	–	x					x
Height	–	x					x
Complete physical examination	8.2.1	x					
Limited physical examination	8.2.1			x	x		x
Pelvic examination	–	x				x	x
12-Lead ECG	8.2.3	x		x	x		
Hematology [c]	Appendix 2		x	x	x		x
Fasting lipid panel [d]	Appendix 2		x				x
Coagulation [e]	Appendix 2		x	x	x		x
Chemistry [f]	Appendix 2		x	x	x		x
FSH and Estradiol [g]	Appendix 2		x	x	x		x
Pregnancy test [h]	Appendix 2		x	x	x		x

Table 1 Schedule of Activities

Day(s) (Window)	Protocol Reference	Screening [a]		Treatment Cycles (28-day Cycles)		Every 3 Months (±14 days)	Treatment Completion/ Discontinuation [b]
				Cycles 1–3	Cycles 4 and Beyond		
		–28 to –1	–7 to –1	Day 1 of Each Cycle (±3 days)	Day 1 of Each Cycle (±3 days)		30 Days after Final Dose (±3 days)
Urinalysis [i]	Appendix 2			x			
Study drug administration [j]	6.1			Administered at clinic visits or self-administered by participants			
Medication diary [k]	6.4			x	x		
Screening tumor sample [l]	8.1.1	x					
MRI / CT-scan [m]	5.1	x					
Bone density scan	–	x					
On-study tumor sample [n]	8.1.1						
Plasma PK sample	8.4			Please see Table 2 for PK samples			
Biomarker samples [o]	8.7 8.10.2			Please see Table 2 for biomarker samples			
Concomitant medications	6.8.3	x	x	x	x		x
Adverse events	8.3 Appendix 3 Appendix 4	x	x	x	x		x

CT = computed tomography; D&C = dilation and curettage; EMB = endometrial biopsy; LHRH = leutinizing hormone-releasing hormone; MRI = magnetic resonance imaging; PK = pharmacokinetic; PO = orally; Q3M = every 3 months; QD = once a day; WES = whole-exome sequencing; WGS = whole-genome sequencing.

Table 1 Schedule of Activities

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. For PK samples, please see Table 2 for timing of collection.

[a] Results of standard-of-care assessments performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such assessments do not need to be repeated for screening.

[b] Participants who complete the treatment period will return to the clinic for a treatment completion visit at 30 (+3) days after their final dose of study treatment. Participants who discontinue study drug prematurely will return to the clinic for a treatment discontinuation visit 30 (+3) days after their final dose of study drug.

[c] Complete blood count should be available for review prior to dosing to inform dosing decisions.

[d] Perform after >8 hours of fasting.

[e] Perform if clinically indicated.

[f] Blood urea nitrogen, creatinine, total bilirubin, ALP, ALT, and AST counts should be available for review prior to dosing to inform dosing decisions.

[g] Applicable for pre-and peri-menopausal women (as defined in Section 5.1), and women receiving an LHRH agonist. For participants with therapy induced amenorrhea or oophorectomy, serial measurement of FSH is needed to ensure postmenopausal status. For participants <60 applicable only at screening to ensure postmenopausal status.

[h] Pregnancy test should be available for review prior to dosing to inform dosing decisions. For months where there are no planned site visits, the participants will be required to carry out the urine pregnancy test (supplied by the site) at home and record the result in their participant diary log. In the case of a positive result, the participant is required to inform the site within 1 business day. Pregnancy tests should be performed within 24 hours prior to endometrial biopsy.

[i] Urinalysis should be performed as clinically indicated during study treatment.

[j] Participants will receive giredestrant 30 mg PO QD (Days 1–28 of each cycle). On clinic visit days, participants should take their study treatment in the clinic, and the date and time of dose should be accurately recorded. See Section 6.1 and Section 6.4 for more details on study treatment.

[k] Participants will receive and should be instructed to complete a medication diary. The medication diary, unused study drug, and study drug containers (used or unused) should be collected and reviewed on Day 1 of each cycle for drug accountability.

[l] Samples up to 2 months days prior to enrollment will be accepted.

[m] Magnetic resonance imaging confirmation of non-deeply invasive tumor in uterus at screening is required. An MRI or CT with contrast of the chest and abdomen is required for confirmation of no extrauterine disease

Table 1 Schedule of Activities

[n] Endometrial specimen can be collected by EMB or D&C at Month 3 (e.g., concurrent at the Cycle 4 visit) and at Month 6 (e.g., coincident with the end of Cycle 6). If the participant undergoes a hysterectomy within 28 days of completing the cycle, a representative portion of the hysterectomy sample can be used as the Month 6 histologic specimen. If study treatment is continued after Cycle 6, the endometrial specimen should be collected Q3M (±14 days) (i.e., before Cycles 10, 13, 16, etc.)

[o] Not applicable for a site that has not been granted approval for WGS or WES.

Table 2 Schedule of Pharmacokinetic and Biomarker Samples

Visit	Timepoint	Sample Type
Screening (Day – 28 to Day – 1)	NA	Giredestrant biomarker (tumor biopsy [a])
Day 1 of Cycle 1	Predose	Giredestrant PK (plasma)
		Giredestrant biomarker (blood [b], plasma and serum)
	3–4 hours post-dose	Giredestrant PK (plasma)
Day 1 of Cycle 2	Predose [c]	Giredestrant PK (plasma)
		Giredestrant biomarker (plasma and serum)
	3–4 hours post-dose	Giredestrant PK (plasma)
Day 1 of Cycle 3	Predose [c]	Giredestrant PK (plasma)
		Giredestrant biomarker (plasma and serum)
Day 1 of Cycle 4	Predose	Giredestrant biomarker (plasma and serum)
Every 3 months	NA	Giredestrant biomarker (tumor biopsy [a])
Day 1 of Cycle 6	Predose [c]	Giredestrant PK (plasma)
		Giredestrant biomarker (plasma and serum)
Treatment discontinuation visit	NA	Giredestrant PK (plasma)
		Giredestrant biomarker (plasma and serum)
		Giredestrant biomarker (tumor biopsy [a])

NA = not applicable; PK = pharmacokinetic; WES = whole-exome sequencing; WGS = whole-genome sequencing.

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ± 3 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] See Section 8.7 for details on tumor tissue sample requirements.

[b] Not applicable for a site that has not been granted approval for WGS or WES (see Section 8.10.2). If missed for this timepoint, this blood sample for WGS or WES can be collected at any point in the study.

[c] The predose biomarker and PK sample should be taken on the same day as treatment administration (within 2 hours prior to dosing). Date and actual time of dose and PK sample collections should be accurately recorded to the minute.

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to assess the efficacy, safety, and pharmacokinetics of giredestrant in participants with Grade 1 endometrioid endometrial carcinoma (EC).

2.2 BACKGROUND

Cancer of the uterine corpus is the most prevalent gynecologic malignancy in women in the United States with over 60,000 new cases expected in 2023 and accounts for nearly 11,000 deaths. Endometrial carcinomas account for the greatest number of these cases (25.7/100,000 women per year) and the peak ages of diagnosis are between ages 55 and 64 years (median 62 years) (Sherman and Devesa 2003; Ueda et al. 2008). Endometrioid carcinomas compose more than 83% of uterine cancers (Creasman et al. 2006) serving as the prototype for the World Health Organization (WHO) 2014 classification of type 1 endometrial cancers (Murali et al. 2014). Type 1, low-grade endometrioid carcinomas are generally still confined to the uterus when they are diagnosed because most women present with abnormal uterine bleeding, and a histologic diagnosis is readily taken. Early detection and active management are thus important to maximize the chances of favorable prognoses (Pessoa et al. 2014; Tzur et al. 2017).

Type II diabetes and insulin resistance, anovulation, amenorrhea, infertility, and obesity, are consistently associated with increased risks for EC (Navaratnarajah et al. 2008). In fact, endometrial cancer is twice as common in overweight women and more than three times as common in obese women (Onstad et al. 2016). Pathogenesis of most ECs begins with uninterrupted endometrial proliferation, hormonally stimulated by endogenous (including peripheral conversion in adipocytes) or exogenous estrogen (e.g., tamoxifen) unopposed by progesterone or progestins, progressing through states of simple to complex forms of endometrial hyperplasia (EH). Given the hormonal etiology, endometrial intraepithelial neoplasia (EIN) and ECs usually express estrogen and progesterone receptors (ER and PR, respectively) (Conlon et al. 2014; Lax 2017).

Surgical staging with total hysterectomy, bilateral salpingo-oophorectomy, lymph node evaluation and evaluation for extrauterine disease is the standard approach to women with newly diagnosed endometrial cancer (Magrina et al. 1999; Malur et al. 2001; Bell et al. 2008; Boggess et al. 2008; Malzoni et al. 2009).

However, reproductive-age women with low-risk EC may be candidates for fertility preservation, most commonly with progestin therapy, thus deferring surgical management until after completion of childbearing.

Giredestrant is a potent, orally bioavailable, small molecule therapeutic agent that is being developed for the treatment of patients with ER-positive breast cancer and endometrial cancer. Giredestrant antagonizes the effects of estrogens via competitive

binding to the ligand binding domain (LBD) of both wild-type and mutant ER, with nanomolar potency (Liang et al. 2021). Upon binding, giredestrant induces an inactive conformation to the ER LBD, as measured by displacement of co-activator peptides. In addition to its direct antagonist properties, the mechanism of action of giredestrant includes reducing levels of ERα protein through proteasome-mediated degradation. Giredestrant enables full suppression of ER signaling, which is not achieved by first-generation ER therapeutics such as tamoxifen that display partial agonism. Giredestrant potently inhibits the proliferation of multiple ER-positive breast cancer cell lines in vitro, including cells engineered to express clinically relevant mutations in ER.

2.2.1 Nonclinical Data

Nonclinical studies comparing drug exposure and in vitro potency of giredestrant versus fulvestrant demonstrated that human steady-state total drug exposure of giredestrant at 30 mg once a day (QD) is approximately 10-fold higher than the steady-state exposure of fulvestrant 500 mg intramuscular (IM) monthly. Furthermore, the lower plasma protein binding of giredestrant provides a higher free concentration of giredestrant than fulvestrant. With in vitro and biochemical assays, giredestrant exhibited up to 10-times higher potency than fulvestrant both in wild-type and ER-1 (*ESR1*)-mutant contexts.

In vivo, giredestrant exhibited dose-dependent anti-tumor activity in xenograft models of ER-positive breast cancer, including in a patient-derived xenograft model that harbors an activating *ESR1* mutation (ER.Y537S). The efficacious dose range was 0.1–10 mg/kg/day, and all doses were well-tolerated. On the basis of in vivo xenograft models, maximal activity of giredestrant occurs at human dose equivalents $>$10 mg. In three patient-derived xenograft models, no further ER depletion nor inhibition of ER transcriptional activity was observed with the increase of dose from 20–80 mg/kg, corresponding to clinical exposures of 30 mg and 100 mg, respectively. Fulvestrant, when dosed according to a clinically relevant dosing scheme, was less efficacious than giredestrant in the assessed xenograft models. Taken together, giredestrant data demonstrated robust nonclinical activity in ER-positive breast cancer models of both *ESR1*-wild type and *ESR1*-mutation-bearing disease.

Refer to the Giredestrant Investigator's Brochure for details on toxicology and safety pharmacology studies.

2.2.2 Clinical Data

As of the clinical cutoff date (CCOD) of 17 September 2021, 175 patients in Study GO39932 (advanced or metastatic ER+/human epidermal growth factor receptor 2 [HER2]− breast cancer) had received treatment as follows: 111 patients had been treated with single-agent giredestrant at doses of 10 mg, 30 mg, 90/100 mg, and 250 mg (±leutinizing hormone-releasing hormone [LHRH] agonist), and 64 patients had been treated with giredestrant 100 mg in combination with palbociclib 125 mg (±LHRH agonist) (given Days 1–21 with 7 days off). Overall, patients had received a

median of 226 doses of giredestrant (range: 15–1054 doses) and remained on giredestrant treatment for a median of 8.8 months (range: 0–36 months).

Clinical benefit, as measured by either radiographic partial response or at least 6 months of stable disease, was observed at all 4 single-agent giredestrant doses tested. All of the 41 patients treated in the single-agent giredestrant 30-mg cohort were considered clinical benefit-evaluable patients (defined as patients with a confirmed complete response, partial response, or patients who discontinued from study, or patients staying on the treatment for at least 24 weeks since Cycle 1, Day 1 of giredestrant). The clinical benefit rate (CBR) was 53.7% (22 of 41 clinical benefit-evaluable patients). The CBR was similar to that observed in patients treated at higher doses (e.g., at 90/100 mg the CBR was 50.9% [95% CI: 37.07% to 64.65%] in 28 of 55 clinical benefit-evaluable patients).

Furthermore, pharmacodynamic (PD) modulation of specified marker ER, PR, and proliferative index (Ki67) could not be differentiated by dose because treatment changes during the study were similarly observed.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of giredestrant may be found in the Giredestrant Investigator's Brochure.

2.2.2.1 Adverse Events, Regardless of Attribution

Of the 87 patients treated with single-agent giredestrant at doses ranging from 10–250 mg, adverse events, regardless of attribution and occurring in 10% or more patients, included the following: fatigue (23%), back pain (18%), nausea and arthralgia (17% each), diarrhea (15%), constipation and pain extremity (14% each) and cough (12 %). Adverse events of bradycardia/sinus bradycardia were reported in 7 patients (8%) in single-agent giredestrant (all at doses $\geq$90 mg). No bradycardia adverse events have been reported with the use of the 30 mg dose, although asymptomatic changes have been observed, with a mean maximum decrease of 4 beats per minute (bpm) and 13 bpm in patients with baseline resting heart rates of $<$60 bpm and $\geq$60 bpm, respectively. No other adverse events were reported to the Cardiac Disorders System Organ Class, other than 1 case of Grade 1 palpitations from the 90/100 mg cohorts.

Of the 22 patients treated with single-agent giredestrant 30 mg, the following adverse events occurred in 10% or more patients: nausea (27%), myalgia (23%), fatigue, constipation, back pain, and vomiting (18% each), diarrhea, pain in extremity, gastroesophageal reflux disease, dyspepsia, and arthralgia (14% each).

Grade $\geq$3 adverse events, regardless of attribution and occurring in more than 1 patient in single-agent giredestrant cohorts were: diarrhea, decreased appetite, and fatigue (2 patients [2.3%] each).

One death was reported with single-agent giredestrant. One patient in the giredestrant 100 mg dose group (+LHRH agonist) experienced a Grade 5 duodenal ulcer perforation considered by the investigator as not related to giredestrant.

2.2.2.2 Adverse Events Attributed to Study Treatment

Of the 87 patients treated with single-agent giredestrant at doses ranging from 10–250 mg, adverse events attributed to giredestrant have been mostly Grade 1 or 2 in severity.

In the single-agent giredestrant 30 mg cohort, the adverse events attributed to giredestrant occurring in 10% or more patients included: nausea (23%), and fatigue, diarrhea, dyspepsia, or myalgia (14% each). No patients in this cohort experienced any Grade 3 adverse events considered related to giredestrant.

No patients were withdrawn from treatment because of adverse events associated with single-agent giredestrant.

Overall, giredestrant was well-tolerated at all dose levels with no trend for an increase in frequency or severity of adverse events, with the exception of dose-dependent Grade 1 asymptomatic bradycardia/heart rate decrease.

See Appendix 4 for information on anticipated risks for giredestrant and risk mitigation measures, including guidelines for managing adverse events associated with giredestrant.

Detailed information on giredestrant is provided in the Giredestrant Investigator's Brochure.

2.3 BENEFIT–RISK ASSESSMENT

Women that present with atypical hyperplasia or Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) Stage I/II EC are typically treated by total hysterectomy and bilateral salpingo-oophorectomy. However, there has been an increasing trend for conservative treatment for women with low-risk Grade 1 EC. Nonsurgical treatment is particularly important for morbidly obese women with high surgical risks and pre- or peri-menopausal women who wish to maintain fertility. Progestins, which counteracts the effect of estrogen in the endometrium, is the standard treatment for women that elect for conservative treatment. While initially largely effective in leading to tumor regression, unwanted side effects and lack of durable response leads to discontinuation of the treatment and high rates of relapse.

Giredestrant is a potent, orally bioavailable ERα antagonist and inducer of ERα degradation that competes with estrogens for binding to the ER, with low nanomolar potency; it is being developed for the treatment of patients with ER-positive breast cancer and endometrial cancer. Giredestrant has demonstrated robust nonclinical

activity in ER-positive breast cancer models of *ESR1* wild type and *ESR1*-mutation bearing disease. Giredestrant has also demonstrated anti-estrogenic activity in rodent uterus models. Fulvestrant, an approved selective ER degrader (SERD) molecule, when dosed according to a clinically relevant dosing scheme was less efficacious than giredestrant in xenograft models. As described in Section 2.2.2, giredestrant was well-tolerated in safety pharmacology studies.

The proposed Phase II study (CO44195) is designed to provide proof of concept of giredestrant monotherapy for Grade 1, Stage 1 endometrioid EC. Endometrioid ECs are driven by excess estrogen relative to progesterone. Both nonclinical and clinical studies have shown giredestrant to have an anti-estrogenic response in breast cancer and in the uterus, and may represent a potentially efficacious treatment option for patients with endometrioid EC. Results from Studies GO39932 and WO42312 with giredestrant monotherapy or in combination have shown giredestrant to be well-tolerated.
Taken together, giredestrant provides a reasonable benefit-risk balance for patients with endometrioid EC.

The present study has incorporated key design elements that are critical to an adequate assessment of benefit versus risk for giredestrant in a single Phase II study.
The eligibility criteria are designed to minimize the potential risks of giredestrant (Sections 5.1 and 5.2). Participants will be evaluated every 3 months (Q3M) of treatment to monitor endometrial tumor histology. Evaluation of tumor histology will be assessed by a central laboratory. After 6 cycles of treatment, participants and investigators will decide whether to continue study treatment or seek alternative treatment options.

See Appendix 4 for information on anticipated risks for giredestrant and risk mitigation measures, including guidelines for managing adverse events associated with giredestrant.

Refer to the Giredestrant Investigator's Brochure for details on nonclinical and clinical studies.

2.3.1 COVID-19 Benefit-Risk Assessment

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, participants with comorbidities, including those with cancer, are a more vulnerable population.
Infection with severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) has been associated with higher morbidity and mortality in patients with cancer in some retrospective analyses. It is unclear whether or how cancer therapies such as endocrine therapy can impact the incidence or severity of COVID-19. It is not known whether any of the agents being investigated in this study will increase the risk of infection with SARS-CoV-2. Participants with a serious infection requiring IV antibiotics within 7 days prior to initiation of study treatment or any active infection that, in the opinion of the

investigator, could impact participant safety will be excluded from study participation, and participants will be carefully monitored for infections during the study.

3. OBJECTIVES AND ENDPOINTS AND ESTIMANDS

This study will evaluate the efficacy, safety, and pharmacokinetics of giredestrant in participants with Grade 1 endometrioid EC. Table 3 presents the primary, secondary, and exploratory objectives for the study expressed using the estimand framework in accordance with the International Council for Harmonisation (ICH) E9(R1) statistical principles for clinical trials (U.S. Food and Drug Administration 2020). Table 4 lists the remaining pharmacokinetic (PK) and exploratory biomarker objectives.

Table 3 Objectives and Endpoints and Estimands

Primary Objective	Corresponding Endpoints/Estimands
• To evaluate the efficacy of giredestrant by regression rate by the Month 6 assessment	• Population: Participants who have received any amount of study drug and have had a histological assessment at baseline, i.e., before the first exposure to any amount of study drug. Participants who do not have any post-baseline assessment will be excluded. • Variable: Participants who have regression, defined as participants who have a decrease in the proportion of cancer in the EMB or have an increase in non-cancer/non-atypical hyperplasia (%) by the Month 6 assessment (preferably after the completion of Cycle 6) compared with baseline • Treatment: giredestrant 30 mg • Intercurrent Events – Participants without a post-baseline assessment – Withdrawal of Consent/Lost to Follow-Up – Death • Handling of intercurrent events: – Withdrawal of Consent/Lost to Follow-Up/Death: Such events are expected to be very rare. Participants will be excluded if death or withdrawal is irrelevant to disease; if death or withdrawal occurs after assessment, the results from assessment will be used; if death or withdrawal is disease-related and no assessment was done, this will be excluded. – Summary measure: Proportion of participants who have regression by the Month 6 assessment

Table 3 Objectives and Endpoints and Estimands

Primary Objective	Corresponding Endpoints/Estimands
	• Population: Participants who have received any amount of study drug and have had a histological assessment at baseline, i.e., before the first exposure to any amount of study drug. Participants who do not have any post-baseline assessment will be excluded. • Variable: Participants who have regression, defined as participants who have a decrease in the proportion of cancer in the EMB or have an increase in non-cancer/non-atypical hyperplasia (%) by the Month 6 assessment (preferably after the completion of Cycle 6) compared with baseline • Treatment: giredestrant 30 mg • Intercurrent Events – Participants without a post-baseline assessment – Withdrawal of Consent/Lost to Follow-Up – Death • Handling of intercurrent events: – Withdrawal of Consent/Lost to Follow-Up/Death: Such events are expected to be very rare. Participants will be excluded if death or withdrawal is irrelevant to disease; if death or withdrawal occurs after assessment, the results from assessment will be used; if death or withdrawal is disease--related and no assessment was done, this will be excluded. – Summary measure: Proportion of participants who have regression by the Month 6 assessment
Primary Safety Objective	**Corresponding Endpoints/Estimands**
• To evaluate the safety and tolerability of giredestrant by regression rate by Month 6	• Occurrence and severity of adverse events with severity determined according to the NCI CTCAE v5.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results • All participants who received at least 1 dose of study treatment will be included in safety analysis
Secondary Objectives	**Corresponding Endpoints/Estimands**
• To evaluate the efficacy of giredestrant by complete regression rate by the Month 6 assessment	• Variable: Complete regression rate, defined as participants having an assessment of 100% of non-cancer/non-atypical hyperplasia by the Month 6 assessment • Population, Treatment, Intercurrent Events and Handling are the same as the primary objective • Summary measure: Proportion of participants who have complete regression

Table 3 Objectives and Endpoints and Estimands

Secondary Objectives	Corresponding Endpoints/Estimands
• To evaluate the efficacy of giredestrant by duration of regression	• Variable: Time from the first regression to time of the first relapse – Regression is defined as: Decrease in the proportion of cancer in the EMB (%) compared with baseline. or Increase in non-cancer/non-atypical hyperplasia when compared with baseline. – Relapse is defined as: Increase in the proportion of cancer in the EMB (%) when compared with its nadir. or Increase in the proportion of cancer in the EMB and atypical hyperplasia (%) compared with its nadir. • Population: Participants who have regression • Treatment, Intercurrent Events and Handling are the same as the primary objective • Summary measure: median of time from first regression to first worsening
• To evaluate the efficacy of giredestrant by time to regression	• Variable: the time from the first study treatment to the first regression – Regression is defined as Decrease in the proportion of cancer in the EMB (%) compared with baseline. or Increase in non-cancer/non-atypical hyperplasia when compared with baseline. • Population, Treatment, Intercurrent Events and Handling are the same as the primary objective • Summary measure: median of time from first study treatment to first regression
• To evaluate the efficacy of giredestrant by time to relapse or loss of clinical benefit	• Variable: Time to relapse or loss of clinical benefit, defined as the time from the first study treatment to relapse or loss of clinical benefit, whichever occurred first – Relapse defined as: Increase in the proportion of cancer in the EMB (%) compared with baseline. or Increase in the proportion of cancer in the EMB and atypical hyperplasia (%) when compared with baseline. – Loss of clinical benefit per the investigator

Table 3 Objectives and Endpoints and Estimands

Secondary Objectives	Corresponding Endpoints/Estimands
	• Population, Treatment, Intercurrent Events and Handling are the same as the primary objective • Summary measure: mean of time from first study treatment to relapse or loss of clinical benefit Increase in the proportion of cancer in the EMB and atypical hyperplasia (%) compared with baseline. – Loss of clinical benefit per the investigator • Population, Treatment, Intercurrent Events and Handling are the same as the primary objective • Summary measure: mean of time from first study treatment to relapse or loss of clinical benefit
Exploratory Efficacy Endpoints	**Corresponding Endpoints/Estimands**
• To evaluate the efficacy of giredestrant by regression rate by Month 9	• Variable: Participants who have regression which is defined as participants who have a decrease in the proportion of cancer in the EMB or have an increase in non-cancer/non-atypical hyperplasia (%) within 9 months compared with baseline • Population, Treatment, Intercurrent Events and Handling, and summary measure are the same as the primary objective
• To evaluate the efficacy of giredestrant by regression rate by Month 12	• Variable: Participants who have regression, defined as participants who have a decrease in the proportion of cancer in the EMB or have an increase in non-cancer/non-atypical hyperplasia (%) within 12 months compared with baseline • Population, Treatment, Intercurrent Events and Handling, and summary measure are the same as the primary objective
• To evaluate the efficacy of giredestrant by sensitive regression rate by the Month 6 assessment	• Population: Participants who have received any amount of study drug and have had a histological assessment at baseline • Variable, Treatment, Intercurrent Events and Handling, and summary measure are the same as the primary objective
• To evaluate the efficacy of giredestrant by durable regression	• Variable: Participants who have had at least two consecutive regressions. Regression is defined as a decrease in the proportion of cancer in the EMB or an increase in non-cancer/non-atypical hyperplasia (%) when compared with baseline • Population, Treatment, Intercurrent Events and Handling, and summary measure are the same as the primary objective

Table 3 Objectives and Endpoints and Estimands

Exploratory Efficacy Endpoints	Corresponding Endpoints/Estimands
• To evaluate the efficacy of giredestrant by regression by the Month 6 assessment as determined by the pathologist	• Variable: Participants who have regression, as determined by the pathologist, from assessments by the Month 6 assessment • Summary measure: Proportion of regression, as determined by the pathologist, by the Month 6 assessment • Population, Treatment, Intercurrent Events and Handling are the same as the primary objective

EMB = endometrial biopsy; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 4 Pharmacokinetic and Biomarker Objectives and Endpoints

Pharmacokinetic Objective	Corresponding Endpoints/Estimands
• To characterize the giredestrant PK profile	• Plasma concentration of giredestrant at specified timepoints
Biomarker Objective	**Corresponding Endpoints/Estimands**
• To identify and/or evaluate biomarkers that are predictive of response to giredestrant (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to giredestrant, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of giredestrant activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety or pharmacokinetics	• Relationship between biomarkers in blood, plasma, serum and tumor tissue and efficacy, safety, PK, disease biology, or other biomarker endpoints

ER = estrogen receptor; Ki67 = proliferative index; PK = pharmacokinetic; PR = progesterone receptor.

4. STUDY DESIGN

4.1 OVERALL DESIGN

4.1.1 Overview of Study Design

This Phase II, global, single-arm study is designed to evaluate the efficacy, safety, and pharmacokinetics of giredestrant monotherapy in participants with Grade 1 endometrioid EC. Participants must not have had prior treatment for complex EH, EIN, or endometrial cancer.

This study will enroll approximately 45 participants across all sites.

After providing informed consent, participants will undergo screening procedures as outlined in the schedule of activities.

Confirmation of Grade 1 endometrioid histology at the study's Central Laboratory is required for study entry for all candidate participants. Participants with endometrial samples that are not confirmed by the Central Study Laboratory will not be eligible for the study.

Participants enrolled in the study will receive giredestrant 30 mg taken orally (PO) QD on Days 1–28 of each 28-day cycle for 6 cycles. After completion of 6 cycles, the participant and investigator can choose to continue study therapy or discontinue study therapy and receive investigator-determined care. After 6 months, participants can discontinue study treatment and undergo surgery or continue to receive study treatment for up to 18 additional cycles, per shared decision-making by the participant and physician. Participants will undergo endometrial sampling at baseline and Q3M for a minimum of 6 months. Participants that are treated beyond the minimum of 6 cycles will continue to undergo endometrial sampling Q3M. Representative tissue from each endometrial sampling timepoint must be submitted to the Central Study Laboratory.

After initiation of study treatment, all adverse events will be reported according to the adverse event reporting period. In addition, the Sponsor will be notified if the investigators become aware of any serious adverse events or adverse events of special interest that are believed to be related to prior treatment with study drug(s).
These events should be reported using the Adverse Event electronic Case Report Form (eCRF). The investigator will follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or protocol-related procedures until they are resolved or no further changes in the event's status are expected.

A study schema is provided in Section 1.2 (see Figure 1). A schedule of activities and a sample collection schedule are provided in Section 1.3 (see Table 1 and Table 2).

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

This study will enroll participants with Grade 1 low-risk endometrioid EC with no radiographic evidence of a deeply invasive tumor. Endometrial carcinoma with endometrioid histology is driven by hormonal imbalances. Generally, the first consideration for women with this disease is a total hysterectomy and bilateral salpingo-oophorectomy. However, women who choose a conservative route, which is particularly important for morbidly obese women with high surgical risks and pre- or peri-menopausal women who wish to maintain fertility, hormone therapy is an option. Progestins, which counteract the effect of estrogen in the endometrium, is the standard treatment for women that elect for conservative treatment. However, while initially effective in leading to tumor regression, progestin therapy can lead to unwanted side effects and a lack of durable response which leads to discontinuation of the treatment and high rates of relapse. Additional effective treatment options are needed for women that choose conservative therapy.

In this study, histologic regression within 6 months will be used as the primary endpoint. This study will test the hypothesis that treatment with giredestrant will lead to pathologic regression of endometrioid ECs. Histologic specimens collected at screening, Month 3, and Month 6 by endometrial biopsy (EMB) or dilation and curettage (D&C), will be analyzed by central pathologic review by a certified pathologist. Pathologic regression will be defined as a decrease in the percentage of cancerous portion or an increase in non-cancer/non-atypical hyperplasia. Regression by 6 months was chosen as the primary endpoint given previous benefits seen by 6 months with progestin therapy, and will allow participants to continue with giredestrant or other treatment options if desired (Yamazawa et al. 2007).

4.2.2 Rationale for Biomarker Assessments

Endometrioid EC is a heterogeneous disease (Cancer Genome Atlas Network 2013). Therefore, all participants may not be equally likely to benefit from treatment with giredestrant. Predictive biomarker samples will be assessed in an effort to identify those participants who are most likely to respond to giredestrant.
Pharmacodynamic biomarkers will be assessed to demonstrate evidence of biologic activity of giredestrant in participants. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored. Biomarker data will not inform clinical decisions or participant management.

Baseline tumor tissue samples will be collected from all participants, preferably by means of a biopsy performed at study entry. Tumor tissue to be collected during study treatment will be requested if deemed clinically feasible by the investigator, for immunohistochemistry (IHC) assays, DNA and RNA extraction for exploratory next-generation sequencing (NGS) or other research on non-inherited biomarkers

(including, but no limited to, cancer-related genes and biomarkers associated with common molecular and biological pathways).

Tumor tissue may be assessed for ER, progesterone-receptor, and Ki67. In addition, tumor tissue may enable assessment of ER pathway activity using RNA analysis of ER target genes (Guan et al. 2019). Next-generation sequencing techniques such as targeted exome sequencing may offer a unique opportunity to identify biomarkers of response and/or resistance to giredestrant in tumor tissue. For example, mutations in the *ESR1* gene are more prevalent in metastatic ER-positive breast cancer tumors, and have been correlated with resistance to anti-estrogen therapies (Robinson et al. 2013; Toy et al. 2013; Jeselsohn et al. 2014). *ESR1* mutations in the ligand binding domain are found in 5.8% of primary endometrial cancers with endometrioid histology (The Cancer Genome Atlas Research Network 2013; Backes et al. 2016; Gibson et al. 2016). The presence of *ESR1* mutations is associated with obesity-independent endometrial cancer, and patients with *ESR1* mutations trend toward worse prognosis when compared to patients with wild-type *ESR1* tumors (Backes et al. 2016). Sequencing of other cancer-related genes may result in the identification of biomarkers of response and/or resistance to giredestrant. The collection of tissue samples may also support future diagnostic development.

Tissue samples will be collected for DNA extraction to enable whole-genome sequencing (WGS) or whole-exome sequencing (WES) to identify variants that are predictive of response to study drug. Additionally, these variants are associated with progression to a more severe disease state, acquired resistance to study drug, and susceptibility to developing adverse events. This information can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Genomics is increasingly informing researchers' understanding of disease pathobiology. Both WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

Circulating tumor DNA (ctDNA) is a sensitive method for monitoring cancer activity and stratifying patients that are likely to respond 30 to therapy. There is increasing evidence that ctDNA obtained from blood specimens of patients with cancer may be representative of the DNA and mutational status of tumor cells. Circulating tumor DNA has a clinical utility in early detection and recurrence of endometrial cancer (Pereira et al. 2016). Circulating tumor DNA has been detected in 18% of primary ECs using NGS (Bolivar et al. 2019). Furthermore, *ESR1* amplification is reported in early

precursor lesions of endometrial cancer and has also been suggested as a mechanism of resistance to endocrine therapy (Lebeau et al. 2008; Tomita et al. 2009). To gain insight into potential causal relationships between the clinical activity of giredestrant and resistance mechanisms, mutational status of signaling genes, may be monitored in ctDNA isolated from plasma. Assessment of genes related to signaling genes and endocrine resistance may result in the identification of biomarkers of response and/or resistance to giredestrant.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

This study will evaluate giredestrant 30 mg PO QD on Days 1–28 of each 28-day cycle beginning on Day 1 of Cycle 1. The selected dose was based on both nonclinical and clinical data as described in Sections 2.2.1 and 2.2.2, respectively.

The Phase Ia/b Study GO39932 evaluated escalating doses of giredestrant from 10–250 mg PO QD (see Section 2.2.2). Overall, giredestrant was well-tolerated at all dose levels with no clear trend for an increase in frequency or severity of events, except bradycardia/heart rate decrease that was dose-related. Nonclinical in vivo xenograft models revealed that the maximal activity is saturated at doses above 10 mg human dose equivalents. Human steady-state total drug exposure of giredestrant at 30 mg QD is approximately 10-fold higher than the steady-state exposure of fulvestrant 500 mg IM monthly, with higher in vitro potency (see Section 2.2.1 for other nonclinical data).

Based on the totality of the available nonclinical and clinical data, giredestrant 30 mg administered PO QD has been selected as the most appropriate dose and schedule to maximize efficacy while ensuring tolerability.

Refer to the Giredestrant Investigator's Brochure for additional information.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last visit/last scheduled procedure shown in the schedule of activities (see Section 1.3).

The end of this study is defined as the date of the last visit of the last participant in the study or the date at which the last data point required for statistical analysis (regression rate by Month 6) or safety follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur approximately 6 months after the last participant is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to be approximately 8–26 months.

5. STUDY POPULATION

Approximately 45 participants with Grade 1 endometrioid EC will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Potential participants are eligible to be included in the study only if all of the following criteria apply:

- Signed Informed Consent Form
- Age ≥ 18 years at the time of signing Informed Consent Form
- Life expectancy ≥ 12 weeks
- Ability to comply with the study protocol
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Confirmed Grade 1 EC of endometrioid histology for which participants are willing to receive 6-cycles of study therapy. An EMB or D&C sample must be provided within 2 months of enrollment to a central laboratory for histologic confirmation to determine eligibility.
- Magnetic resonance imaging (MRI)-confirmation of non-deeply invasive tumor
- MRI or computed tomography (CT)-confirmation of no extrauterine disease
- Willing to undergo a minimum of 6 continuous cycles of therapy before decision on surgery
- No prior treatment for complex EH, EIN, or endometrial cancer
- Able and willing to take oral medications
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to enrollment:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor (G-CSF) support
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9 g/dL)

    Participants may be transfused to meet this criterion.

- PT (or INR) and aPTT (or PTT) $< 1.5 \times$ upper limit of normal (ULN)

  This applies only to participants who are not receiving therapeutic anticoagulation. Participants receiving therapeutic anticoagulation should be on a stable dose.
- AST, ALT, and ALP $\leq 2.5 \times$ ULN
- Total bilirubin $\leq 1.5 \times$ ULN:

  Participants with known Gilbert disease: bilirubin $\leq 3 \times$ ULN.

  Estimated creatinine clearance ≥ 15 mL/min and calculated per institutional guidelines.

- Negative HIV test at screening
- For female participants of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agree to refrain from donating eggs, as defined below:

  Female participants must remain abstinent or use non-hormonal contraceptive methods with a failure rate of $<$ 1% per year during the treatment period and for 10 days after the final dose of giredestrant.

  Participants must refrain from donating eggs during this same period.

  A female participant is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a female participant with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of non-hormonal contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. Luteinizing hormone-releasing hormone agonists are not adequate contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

5.2 EXCLUSION CRITERIA

Potential participants are excluded from the study if any of the following criteria apply:

- Pregnancy or breastfeeding, or intention of becoming pregnant during the study or within 10 days after the final dose of giredestrant or within the time period specified per local prescribing guidelines after the final dose of the investigator's choice of endocrine therapy

  Female participants of childbearing potential must have a negative urine pregnancy test result within 14 days prior to initiation of study treatment.
- Participants with non-endometrioid histologies, such as serous, clear cell, and mixed
- Treatment with investigational therapy within 28 days prior to initiation of study enrollment
- Treatment for cancer including but not limited to, chemotherapy, immunotherapy, cyclin-dependent kinase (CDK)4/6i, endocrine therapy, biologic therapy, or herbal therapy within 28 days prior to the initiation of study enrollment
- Any gastrointestinal condition causing malabsorption or obstruction (e.g., celiac sprue, gastric bypass surgery, strictures, adhesions, history of small bowel resection, blind loop syndrome)
- Has been on any hormonal treatment (including progestin-containing intrauterine device [IUD]) for complex atypical hyperplasia (CAH)/EIN or Grade 1 EC in the last 3 months
- Use hormone replacement therapy (including systemic or topical estrogen, progesterone, or testosterone based medication) or/and phytoestrogen supplements (i.e., black cohosh) or has been on progestin (including progestin-containing IUD), tamoxifen or aromatase inhibitor within the prior 3 months
- Known hypersensitivity to giredestrant or its excipients
- Known intercurrent illness or psychiatric illness/social situations that will limit compliance with study requirements
- Evidence or high suspicion of metastatic/extrauterine disease at enrollment
- Unwilling or unable to comply with study-related procedures, including all endometrial sampling/biopsies
- Planned surgery, either for the treatment of cancer or any other surgery, during the study treatment period and up to 9 days after the completion of study treatment
- Serious infections requiring IV antibiotics within 7 days prior to initiation of study treatment or any active infection that, in the opinion of the investigator, could impact participant safety

  In the setting of a pandemic or epidemic, screening for active infections should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology [ASCO] or European Society for Medical Oncology [ESMO]).

- Participants who have clinically significant liver disease consistent with Child-Pugh Class B or C, including active hepatitis (e.g., hepatitis B virus [HBV] or hepatitis C virus [HCV]), current alcohol abuse, cirrhosis, or positive test for viral hepatitis, as defined below:

  Active infection is defined as requiring treatment with antiviral therapy or presence of positive test results for hepatitis B (hepatitis B surface antigen and/or total hepatitis B core antibody [HBcAb]) or HCV antibody. Unless required by local regulations, participants are not required to have HBV or HCV assessments at screening if these assessments have not been previously performed.

  Participants who are positive for HCV serology are eligible only if testing for HCV RNA is negative
- Substance abuse within 12 months prior to screening
- Any serious medical condition or abnormality in clinical laboratory tests that precludes the participant's safe participation in and completion of the study
- History of other malignancy within 5 years prior to screening, except for those with an expected negligible risk for metastases or death (e.g., 5-year overall survival 90%) after curative treatment
- Active tuberculosis
- Severe infection per investigator judgment at the time of enrollment, including but not limited to, use of systemic antibiotics, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact participant safety
- Significant cardiovascular disease, such as cardiac disease New York Heart Association Class II or greater, myocardial infarction, or cerebrovascular accident within 3 months prior to enrollment, unstable arrhythmias, or unstable angina
- Participants with known coronary artery disease, congestive heart failure not meeting the above criterion or with a left ventricular ejection fraction 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate
- Major surgical procedure other than for diagnosis within 28 days prior to enrollment or anticipation of need for a major surgical procedure during the study
- Prior allogeneic bone marrow transplantation or solid organ transplant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the participant at high risk for treatment complications Illnesses or conditions that interfere with the participant's capacity to understand, follow, and/or comply with study procedures

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for 1 re-screening opportunities (for a total of 2 screenings per individual) at the investigator's discretion. Individuals must re-sign the consent form prior to re-screening. The investigator will maintain a record of reasons for screen failure (see Section 8).

6. STUDY TREATMENT, OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN, AND CONCOMITANT THERAPY

The investigational medicinal product (IMP) for this study is giredestrant. Appendix 7 identifies all investigational and non-IMPs for this study.

6.1 STUDY TREATMENT ADMINISTERED

Table 5 provides a description of assigned study treatments for this study.

Table 5 Study Treatment Description

	Giredestrant
Use	Experimental
Drug form	Capsule
Unit dose strength(s)	30 mg/capsule
Dosage level(s)	30 mg QD
Formulation(s)	Refer to the Giredestrant Investigator's Brochure
Packaging	Plastic bottle; fill count 30 capsules per bottle
Labeling	Per local requirements
Route of administration	Oral
Source	Sponsor

QD = once a day.

Participants will receive open-label giredestrant 30 mg PO QD on Days 1–28 of each 28-day cycle, beginning on Day 1 of Cycle 1.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 4.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel e.g., pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using an interactive voice or Web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

Investigational medicinal products will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the Giredestrant Investigator's Brochure for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT

6.3.1 Treatment Assignment

This is a non-randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and

eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from an IxRS.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision.

When participants self-administer study treatment at home, compliance with study treatment will be assessed.

At the beginning of Cycle 1, site study staff will provide the participant with detailed instructions and training for the handling and administration of study drugs. At each cycle, participants will receive and should be instructed to complete a medication diary.

The medication diary, unused study drug, and study drug containers (used or unused) should be collected and reviewed for drug accountability at the beginning of each cycle.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration eCRF. Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Appendix 3.

6.5 DOSE MODIFICATION

Reduction of the giredestrant dose is not permitted. Please note that the investigator should always exercise their clinical judgement based on the nature of the adverse event, recovery status and benefit-risk to the participant when assessing the interruption time required (if needed). In case of frequent treatment interruptions, possible discontinuation of study treatment should be discussed with the participant.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not have any plans to provide Roche IMP (giredestrant) or any other study treatments to participants who have completed the study. The Sponsor may evaluate whether to continue providing giredestrant in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

https://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose of giredestrant. Cases of

medication error, including overdoses, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities until resolution
3. Obtain a plasma sample for pharmacokinetic analysis within 7 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)

Decisions regarding dose interruptions or modifications will be made by the investigator on the basis of clinical evaluation of the participant. The Medical Monitor is available to advise as needed.

6.8 CONCOMITANT THERAPY

Any medication and vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by a participant in addition to protocol–mandated treatment from 7 days prior to initiation of study treatment to treatment discontinuation must be recorded on the Concomitant Medications eCRF along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.1 Permitted Therapy/Other Permitted Therapy

In general, investigators may manage a participant's care (including preexisting conditions) through use of supportive therapies, as clinically indicated and per local standard practice, with the exception of prohibited therapies defined in Section 6.8.3 and taking into account cautionary therapies defined in Section 6.8.2. All concomitant medication and/or therapies should be documented in the participant's eCRF.

Participants with treatment-induced bone loss or osteoporosis should be managed in accordance with local practice and/or based on treatment algorithms for managing bone health during cancer treatment recommended by international guidelines (Coleman et al. 2014; Trémolières et al. 2017). Treatment of this condition with bisphosphonates or receptor activator of nuclear factor κ-B ligand (RANK) ligands, if required, is permitted.

6.8.2 Cautionary Therapy

The following guidelines on cautionary therapy apply only to participants receiving giredestrant.

6.8.2.1 Medications Associated with Bradycardia

Investigators should use medical judgment and exercise caution when considering initiation of concomitant medication known to cause decreases in heart rate, including but not limited to, β-blockers and calcium-channel antagonists. An alternative therapy should be used when possible. Participants on stable dose of a β-blocker or calcium-channel antagonist for preexisting baseline conditions (e.g., hypertension) are permitted during the study but should be monitored closely in case dose modification is warranted.

6.8.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

6.8.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited during study treatment as described below:

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment, during study treatment, and up to 9 days after the completion of study treatment.
- Any concomitant therapy intended for the treatment of cancer (other than protocol mandated study treatment), including but not limited to, chemotherapy, immunotherapy CDK4/6i, endocrine therapy, biologic therapy, or herbal therapy is prohibited for various time periods prior to starting study treatment and during study treatment, until disease recurrence and unacceptable toxicity is documented and the participant has discontinued study treatment

  These therapies should be stopped 28 days prior to the initiation of study treatment.
- Hormone replacement therapy, megestrol acetate, and selective ER modulators (e.g., raloxifene) are prohibited
- Topical hormonal therapy is prohibited unless required to treat adverse events for which all other feasible therapeutic options have been exhausted

Enrolled participants who subsequently require the use of any prohibited therapies (with the exception of topical estrogens [including any intra-vaginal preparations] and selective ER modulators to treat adverse events) must be discontinued from study treatment as outlined in Section 7.1.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. See the schedule of activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow--up evaluations that need to be completed.

Participants must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Intolerable toxicity related to study treatment determined by the investigator to be unacceptable given the potential for treatment benefit and the severity of the event
- Pregnancy
- Use of an anti-cancer therapy not required per protocol
- Persistent noncompliance with protocol-specified drug administration and follow-up tests
- Development of metastatic disease while on therapy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants who complete the treatment period or discontinue study treatment prematurely will return to the clinic for a treatment completion/early discontinuation visit 28 days after their final dose of study drug.

See the schedule of activities in Section 1.3 (see Table 1) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study treatment is required by the investigator when a study participant meets abnormal liver tests, considered related to giredestrant, as outlined in

Section A3–7.6, or if the investigator believes that it is in the best interest of the participant when abnormal liver chemistries do not meet protocol-specified stopping rules.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. Withdrawal from the study also means withdrawal from study treatment, if it has not already been completed or discontinued.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3). See the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

If a participant withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing

address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a detailed record of all participants screened, to document eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., complete blood count) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the timeframe defined in the schedule of activities.

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, will be recorded at screening. Any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant within 7 days prior to initiation of study treatment will be recorded. Demographic data, including age, and self-reported race or ethnicity, will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be

acceptable. Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

8.1 EFFICACY ASSESSMENTS

8.1.1 Response Evaluation

Study participants will have provided an EC tissue samples from their diagnostic EMB or D&C. As part of the study, participants will undergo EMB (or D&C) at Month 3 (e.g., concurrent at the Cycle 4 visit) and Month 6 (e.g., coincident with the end of Cycle 6). If the participant undergoes hysterectomy within 28 days of completing the cycle, a representative portion of the hysterectomy sample can be used as the Month 6 histologic specimen. If the participant continues treatment past 6 cycles, endometrial sampling by EMB or D&C should continue Q3M at the closest clinical visit while receiving study drug and at study drug discontinuation or study drug completion (if not within 28 days of last sample collected). These specimens will be sent to and analyzed by a central pathology lab and reviewed by a certified pathologist. Pathologic regression will be defined as a decrease in the cancerous component and/or an increase in non-cancer/non-atypical hyperplasia component compared with baseline.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, dermatologic, respiratory, gastrointestinal, and genitourinary (gynecological) systems. A pelvic examination will be performed, including a bimanual examination at screening and every 3 cycles. Any abnormality identified prior to the first dose of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom directed and gynecological physical examinations should be performed at specified post-baseline visits and as clinically indicated.
Investigators should pay special attention to clinical signs related to previous serious illnesses and gynecological symptoms. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities (a worsening in the character, frequency, or severity of a known condition) should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Temperature, heart or pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and heart or pulse rate measurements will be assessed while the participant is in a seated position with a completely automated device.
Manual techniques will be used only if an automated device is not available.

Blood pressure and heart or pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute).

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the schedule of activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures RR interval, QRS interval, QT interval, and QT interval corrected through use of Fridericia's formula (QTcF)/QT interval, PR duration.

All ECG recordings must be performed through use of a standard high-quality, high-fidelity digital electrocardiograph machine. Lead placement should be as consistent as possible. Electrocardiogram recordings must be performed after the participant has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre−ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site. Digital recordings will be stored at the investigational site. The following should be recorded on the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$ 500 ms and/or $>$ 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard of care treatment may be instituted at the investigator's discretion. If a PK sample is not scheduled for that

timepoint, an PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Appendix 3. The investigator should also evaluate the participant for potential concurrent risk factors (e.g., electrolyte abnormalities, concomitant medications known to prolong the QT interval, severe bradycardia).

8.2.4 Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF (see Appendix 3).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days of the final dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report (CSR).

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 2.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment (see Section 7).

It is important that adverse events are collected in a uniform manner. This also includes collection of adverse events that are well understood and managed, and that are in line with the expected safety profile of giredestrant.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported (see Appendix 3). All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 28 days after the final dose of study treatment at the timepoints specified in the schedule of activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts.
All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the participant is lost to

follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB) or Ethics Committees, and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Giredestrant	Giredestrant Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Giredestrant Investigator’s Brochure and will notify the IRB/Ethics Committee, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the

study or within 10 days after the final dose of giredestrant (or for the period of time specified in the local prescribing information).

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

8.3.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 3.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.6)
- Suspected transmission of an infectious agent by a study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.
- Grade ≥3 hepatitis or elevations in AST or ALT
- Grade ≥3 acute kidney injury, creatinine increases, or renal toxicity
- Grade ≥2 bradycardia
- Grade ≥2 thromboembolic event

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 4.

8.3.9 Medical Monitors and Emergency Medical Contacts

Contact Information for All Sites

Medical Monitor:	Victor Khor, Ph.D. (Primary)
Mobile Telephone No.:	+1 407 580 9047
Email:	Khor.Victor@gene.com

Medical Monitor:	Marcela Castro, M.D. (Secondary)
Mobile Telephone No.:	+1 650 822 3055
Email	castro.marcela@gene.com
Medical Monitor:	Yvonne G. Lin, M.D. (Secondary)
Mobile Telephone No.:	+1 650 291 9683
Email	Lin-Liu.Yvonne@gene.com

To ensure the safety of study participants, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Plasma samples will be collected for measurement of plasma concentrations of giredestrant as specified in the schedule of activities (see Section 1.3).

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of giredestrant.
Samples collected for analyses of giredestrant plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these plasma samples.
Participant confidentiality will be maintained. At visits during which plasma samples for the determination of giredestrant will be taken, one sample of sufficient volume can be used.

Pharmacokinetic samples will be destroyed no later than 5 years after the final CSR has been completed to allow for assay development and validation (if needed).

8.5 PHARMACODYNAMICS

See Section 8.7 for information on PD biomarkers.

8.6 GENETICS

See Section 8.7 and Appendix 6 for information on genetic biomarkers.

8.7 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Blood, plasma, serum, and tumor tissue samples for exploratory research on biomarkers, including biomarker assay development
- Newly collected tumor tissue sample obtained at baseline for exploratory research on biomarkers (including but not limited to: RNA, DNA, IHC for ER, PR, Ki67), including biomarker assay development

  A representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or 20 slides containing unstained, freshly cut, serial sections must be submitted along with an associated de-identified pathology report prior to study enrollment.

  Tumor tissue should be of good quality, as determined on the basis of total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells (preferably 500 tumor cells) that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via EMB, D&C, or surgery specimen from hysterectomy (for end of treatment sample) are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), is not acceptable.

Exploratory biomarker research may include, but will not be limited to, analysis of ctDNA, analysis of expression of *ESR1* and ER target genes, Ki67, signatures associated with endometrial cancer subtypes, immune-related genes and signaling genes (e.g., *CTNNB1, KRAS, PTEN, PIK3CA)*. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of gene and/or protein expression; analysis of mutations, copy number, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of NGS of a comprehensive panel of genes. Tumor tissue, serum, plasma and blood samples may be used for future research and/or development of disease-related tests or tools.

Genomic research with a focus on somatic variants may be conducted by comparing DNA extracted from blood with DNA extracted from tissue to distinguish somatic variants from germline variants. Genomic profiling may include WGS or WES of blood samples, with a focus on somatic variants. Whole-genome sequencing or WES of samples with a focus on germline variants may also be conducted, but only at participating sites (see Section 8.10.2). The NGS methods may include WGS or WES of tissue, plasma, and blood samples, but WGS or WES for germline analysis of blood samples will be performed only at participating sites.

Biomarker samples will be collected according to the schedule outlined in Section 1.3 (see Table 1 and Table 2). Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.10.3, biomarker samples will be destroyed no later than 5 years after the final CSR has been completed, with the following exceptions:

- Tissue samples that undergo WGS or WES will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/Ethics Committee–approved Informed Consent Form and applicable laws (e.g., health authority requirements)

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

8.8 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will not be performed in this study.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

Health economics and medical resource utilization assessments will not be performed in this study.

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.10.1 Use of Screen-Fail Samples (Participants at Participating Sites)

At participating sites, tumor tissue samples collected from participants who do not enroll in the study (screen-fail samples) may be used for research related to the disease under study and the development of disease-related tests or tools.

If a site does not permit research on screen-fail samples, this section of the protocol (Section 8.10.1) will not be applicable at that site.

8.10.2 Blood Samples for Whole-Genome Sequencing or Whole-Exome Sequencing (Participants at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with

susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will include exploration of germline variants.

DNA extracted from blood and plasma may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/Ethics Committee and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 8.10.2) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/Ethics Committee-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Data generated from blood samples collected for WGS or WES will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants.

If permitted by local law, a participant may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the participant’s medical record. Samples may be stored and analyzed in the

future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Appendix 1).

8.10.3 Samples for Research Biosample Repository (Participants Providing Separate Consent at Participating Sites)

8.10.3.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides).
The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. The RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

8.10.3.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/Ethics Committee and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.10.3) will not be applicable at that site.

8.10.3.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to giredestrant, diseases, or drug safety:

- Leftover blood, serum, plasma, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites if requested) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole-genome sequencing and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Research Biosample Repository samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/Ethics Committee–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.10.3.4 Data Protection, Use, and Sharing

Research Biosample Repository samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual participant basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants. In addition, given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants, unless required by

law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following e-mail address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the participant's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

8.10.3.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period.
A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

8.10.3.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the participant. However, if RBR samples

have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following e-mail address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.10.3.7 Monitoring and Oversight

Research Biosample Repository samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/Ethics Committee review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

9. STATISTICAL CONSIDERATIONS

Efficacy analyses will consist of all enrolled participants who received any amount of study drug and had a histological assessment at baseline.

Safety analyses will include all enrolled participants who received any amount of study treatment.

9.1 STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested for this study.

9.1.1 Sample Size Determination

The purpose of this study is estimation and hypothesis generation regarding the effect of giredestrant monotherapy on 6-month regression rate. Approximately 45 participants will be enrolled in this study. For the signal-seeking nature of this study, it is important to detect scenarios where the underlying true 6-month regression rate is considerably greater than a historical benchmark. Of similar importance is to be able to rule out cases where the underlying true 6-month regression rate is noticeably less than this

benchmark. To this end, with 45 participants, the probability that an observed 40% CI excludes the historical benchmark of 6-month regression rate of 0.75 (Gunderson et al. 2012) is computed via simulation for the scenarios when the underlying rates are 0.65 and 0.75. Results are provided in Table 6.

Table 6 Exclusion of the Historical Benchmark of 6-Month Regression Rate of 0.75 by the Observed 40% Confidence Interval

	True Underlying 6-Month Regression Rate	
	0.65	**0.85**
Lower 40% CI limit ≥ 0.75	0.028	0.866
40% CI covers 0.75	0.173	0.122
Upper 40% CI limit < 0.75	0.799	0.012

Participants that do not have a histological assessment at a minimum of 6 months will be excluded from the analysis of the primary efficacy endpoint. Participants that have had a centrally determined pathological regression at any point before Month 6 will not be excluded from the analysis of the primary efficacy endpoint. A total of approximately 45 participants is projected to be enrolled to account for participants that will be excluded.

9.2 ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 7.

Table 7 Participant Analysis Sets

Participant Analysis Set	Description
FAS	All enrolled participants; participants will be included in the analyses according to the treatment to which they were assigned.
SE	All participants exposed to study treatment; participants will be analyzed according to the treatment that they actually received.
EE	All participants who received any amount of study drug and had a histological assessment at baseline, i.e., before the first exposure to any amount of study drug. Participants without any post-baseline assessments will be excluded.

EE = efficacy evaluable; FAS = full analysis set; SE = safety-evaluable.

9.3 STATISTICAL ANALYSES

The Statistical Analysis Plan will be finalized prior to the primary analysis and it will include a more technical and detailed description of the statistical analyses described in

this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.3.1 General Considerations

This study will evaluate the efficacy and safety of giredestrant in participants with Grade 1 endometrioid EC.

9.3.2 Efficacy Analysis

9.3.2.1 Primary Efficacy Analysis

The primary efficacy objective for this single-arm study is to evaluate the efficacy of giredestrant monotherapy on the basis of the regression rate by Month 6 assessment (Month 6 regression rate), which is defined as any regression observed by histological analysis by Month 6 after the first administration of any amount of study drug. Regression is defined as degeneration and atrophy of endometrial glands of residual lesion or absence of any cancerous portion. The Month 3 assessment is preferred to be taken at the Cycle 4 visit. The Month 6 assessment is preferred after the completion of the Cycle 6 visit.

The analysis set for this primary efficacy objective defined as Table 3.

For the clinical evaluation of regression rate by Month 6, participants will also need at least 1 post-baseline histological assessment.

- The primary analysis will be conducted after all participants in the analysis set for the primary efficacy objective have had an assessment for regression by Month 6 or discontinued the study beforehand. No formal statistical testing is planned.

9.3.2.2 Secondary Efficacy Analysis

The secondary efficacy analysis will be based on the following endpoints:

- Complete regression rate, defined as the participants who have an assessment of 100% of non-cancer/non-atypical hyperplasia by Month 6 assessment, as defined in Table 3

  The proportion of the complete regression rate will be calculated based on the efficacy evaluable population.

- Duration of regression, defined as the time from the first regression to time of the first worsening, as defined in Table 3

  Median of time to relapse will be calculated based on the participants who have regression.

- Time to regression, defined as the time from the first study treatment to the first observation of EC regression as in Table 3

  Median of time to regression will be calculated based on the efficacy evaluable population.

- Time to relapse or loss of clinical benefit per investigator, defined as the time from the first study treatment to relapse of the EC, or loss of clinical benefit per

investigator, whichever occurs first. Participants will be censored if they have surgery at Month 6 and no relapse or loss of clinical benefit occurs before surgery.

Median of time to relapse or loss of clinical benefit will be calculated based on the efficacy evaluable population.

9.3.2.3 Exploratory Efficacy Analysis

The exploratory efficacy analysis will be based on the following endpoints:

- Regression rate by Month 6, which is defined the same as the primary endpoint in Table 3. Proportion will be calculated for participants that received any amount of study drug and had a histological assessment at baseline. Participants who did not have any histological assessments will be considered non-responders. No formal statistical testing is planned.
- Regression rate by 9 months, which is defined as any regression observed by histological analysis by 9 months after the first administration of any amount of study drug. Estimands are defined as described in Table 3. The proportion of regression rate by 9 months will be calculated.
- Regression rate by 12 months, which is defined as any regression observed by histological analysis by 12 months after the first administration of any amount of study drug. Estimands are defined as described in Table 3. The proportion of regression rate by 12 months will be calculated.
- Durable regression, defined as participants who have at least two consecutive regressions, as defined in Table 3. The proportion of durable regression will be calculated based on the efficacy evaluable population.
- Regression, assessed per the pathologist by Month 6, as defined in Table 3. The proportion of regression as assessed per the pathologist by Month 6 will be calculated based on the efficacy evaluable population.

9.3.3 Safety Analysis

All safety analyses will be performed on the safety-evaluable population. Participants will be grouped by the treatment they actually received, where participants who received any amount of giredestrant are included in the giredestrant arm.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment–emergent adverse events) will be summarized

by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

9.3.4 Other Analyses

9.3.4.1 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized.

9.3.4.2 Summaries of Treatment Group Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age) will be summarized by treatment arm. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

9.3.4.3 Pharmacokinetic Analyses

The PK population will consist of all participants, who have at least 1 evaluable giredestrant plasma concentration. Individual plasma concentrations of giredestrant will be listed and summarized. Giredestrant PK data may be pooled and analyzed using the population PK analysis approach, as appropriate, and reported separately from the study report.

Additional PK analyses will be conducted as appropriate.

9.3.4.4 Biomarker Analyses

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies. Results may be presented in a separate report.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

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A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) or Ethics Committee by the investigator and reviewed and approved by the IRB/Ethics Committee before the study is initiated.

Any substantial amendments to the protocol will require IRB/Ethics Committee and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/Ethics Committee annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/Ethics Committee
- Notifying the IRB/Ethics Committee of serious adverse events or other significant safety findings, as required by IRB/Ethics Committee procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 Code of Federal Regulations (CFR, U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/Ethics Committee, Clinical Trial Directive (2001/20/EC) or Regulation (E.U.) No. 536/2014 (E.U. sites only), and all other applicable local regulations

A1–2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/Ethics Committee.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or the participant's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/Ethics Committee policy.

A copy of each Informed Consent Form must be provided to the participant or the participant’s legally authorized representative.

A1–4 DATA PROTECTION

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/Ethics Committee members, and by inspectors from health authorities.

A1–5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 20 sites globally will participate to enroll approximately 45 participants. Enrollment will occur through an interactive voice or Web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8 and Appendix 6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1–7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic Case Report Forms (eCRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/Ethics Committee review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/Ethics Committee or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/Ethics Committees, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results.
In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/Ethics Committee in accordance with established IRB/Ethics Committee policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local laboratory.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
• Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and lactate dehydrogenase
• Coagulation: INR, aPTT, and PT
• Thyroid function testing: thyroid-stimulating hormone, free T3 (or total T3 for sites where free T3 is not performed), and free T4
• HIV serology: HIV-1/2 antibody
• HBV serology: HBsAg, HBsAb, and total HBcAb for all individuals; HBV DNA for individuals with negative HBsAg and HBsAb tests and a positive total HBcAb test Individuals with a positive quantitative HBV DNA at screening (must be < 500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests as outlined in the schedule of activities (see Section 1.3).
• HCV serology: HCV antibody for all individuals; HCV RNA for individuals with a positive HCV antibody test
• Lipids (fasting): cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides
• Pregnancy test All female participants of childbearing potential will have a serum pregnancy test performed at screening, within 7 days prior to initiation of study treatment and an additional urine pregnancy test within 24 hours prior to initiation of study treatment. Urine pregnancy tests will be performed at specified subsequent visits, starting Day 1 of each cycle. A pregnancy test will be done immediately prior to any endometrial sampling. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Urine pregnancy tests will be performed until treatment completion/discontinuation visit.
• Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria). Urinalysis should be performed as clinically indicated during study treatment.
• FSH and Estradiol

HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus.

Investigators must document their review of each laboratory safety report.

Appendix 3
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

  Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section A3–3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale. The investigator will use the grading scale in Table A3-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table A3-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

Table A3-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, e-mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge

summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than

24 hours after the investigator becomes aware of the event), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 28 days after the final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 28 days after the final dose of study treatment), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and e-mailing the paper Clinical Trial Adverse Event/Special Situations Form, using the fax number or e-mail address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF.
Avoid colloquialisms and abbreviations. Only 1 adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by 1 adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A3–7.2 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all 3 events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A3–7.3 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–5 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.4 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected.
A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy

- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.3 for details on recording persistent adverse events).

A3–7.5 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.3 for details on recording persistent adverse events).

A3–7.6 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ ULN) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–7.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.7 DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1) that are attributed by the investigator solely to progression of endometrial cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should

be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section A3–6.

A3–7.8 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study.
When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A3–7.9 LACK OF EFFICACY OR WORSENING OF ENDOMETRIAL CARCINOMA

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of endometrial carcinoma on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of endometrial carcinoma"). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on histology and/or follow-up surveillance. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

A3–7.10 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section A3–2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.11 CASES OF OVERDOSE , MEDICATION ERROR, DRUG ABUSE, OR DRUG MISUSE

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the participant, drug misuse could involve the drug being administered to someone other than the participant.

Special situations and adverse events associated with special situations are to be reported separately on the Adverse Event eCRF, as outlined in the sections below.

A3–7.11.1 Reporting Special Situations

All special situations associated with giredestrant, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the participant: Enter the drug name and "participant supplied drug to third party" as the event term. Check the "Drug misuse" box.

A3–7.11.2 Reporting Adverse Events Associated with Special Situations

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria

or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). For giredestrant, adverse events associated with special situations should be recorded as described below for each situation:

- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

As an example, an accidental overdose that resulted in a headache would require 2 entries on the Adverse Event eCRF, 1 entry to report the accidental overdose (special situation) and 1 entry to report the adverse event (headache).
The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

A3–7.12 SAFETY BIOMARKER DATA

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

Appendix 4
Safety Plan: Management of Identified and Potential Risks

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A4–1 IDENTIFIED RISKS ASSOCIATED WITH GIREDESTRANT

Giredestrant is not approved, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with giredestrant in completed and ongoing studies. On the basis of clinical data available to date, the following identified (known) and potential (anticipated) risks for giredestrant are outlined below. Please refer to the Giredestrant Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of study participants.
Eligibility criteria have been designed to exclude individuals at higher risk for toxicities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. An independent Data Monitoring Committee will review safety data regularly throughout the study (see Section 4.1.1).
In addition, guidelines for managing adverse events (see Table A3-1), including criteria for treatment interruption or discontinuation, are provided below.

A4–1.1 GASTROINTESTINAL TOXICITIES

Gastrointestinal (GI) effects, such as diarrhea and nausea, were very common (≥ 10%) in participants treated with giredestrant, and vomiting was seen with common (≥ 1 to < 10%) frequency. These GI toxicities were generally mild to moderate, with the majority of cases being Grade 1 in maximum severity. The vast majority of cases resolved without intervention or interruption of study drug. Participants receiving treatment with giredestrant should be closely monitored for GI effects and any consequent effects such as changes in blood chemistry parameters or dehydration. Supportive care should be followed per institutional guidelines.

A4–1.2 ARTHRALGIA

Arthralgia was very common (≥10%) in participants treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum severity. The vast majority of cases resolved without intervention or interruption of study drug. Management of arthralgia should be according to local standard of care and institutional guidelines.

A4–1.3 MUSCULOSKELETAL PAIN

Musculoskeletal pain was very common (≥10%) in participants treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum severity. The vast majority of cases resolved without intervention or interruption of study drug. Management of musculoskeletal pain should be according to institutional guidelines.

A4–1.4 HOT FLUSH

Hot flush was common (≥1 to < 10%) in participants treated with giredestrant in line with giredestrant's anti-estrogenic pharmacologic activity. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum severity. Hot flush should be managed according to institutional guidelines.

Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) have both been shown to be safe and to reduce the severity of hot flushes in participants with breast cancer. Other pharmacological options for the treatment of hot flushes may include gabapentin, clorindine, or alternative herbal agents (Committee on Practice Bulletins-Gynecology 2012).

A4–1.5 DIZZINESS

Dizziness was common (≥1 to <10%) in participants treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum severity. The vast majority of cases resolved without intervention or interruption of study drug. Dizziness should be managed according to institutional guidelines.

A4–1.6 FATIGUE

Fatigue was very common (≥ 10%) in participants treated with giredestrant. The cases were generally mild to moderate, with the majority of cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug. Fatigue should be managed according to institutional guidelines.

A4–1.7 BRADYCARDIA

Bradycardia was commonly reported in patients treated with giredestrant. All cases were non-serious and mild to moderate, with most cases being Grade 1 in maximum intensity. The vast majority of cases resolved without intervention or interruption of study drug.

In participants with preexisting baseline conditions for which they are already receiving a stable dose of β-blockers or calcium-channel antagonists, investigators should carefully monitor participants for worsening of bradycardia following study treatment and follow the recommended management guidelines as noted in Table A4-1.

A4–1.8 HEPATOTOXICITY

Events of AST increased and/or ALT increased, were very commonly reported in patients treated with giredestrant (≥1 to <10%). Events of blood bilirubin increased were commonly reported. The majority of events were Grade 1 or Grade 2, with few

However, from across the entire development program (approximately N = 1260), a total of 3 serious cases were received. All 3 serious cases were assessed as related to giredestrant by the reporting investigator. Please refer to Giredestrant Investigator's Brochure, Version 6 for more information.

A4–1.9 HEADACHE

Headache was commonly reported in patients treated with giredestrant ($\geq$1 to $<$10%). Cases were non-serious and Grade 1 or Grade 2 in severity. Most headache events resolved without treatment.

A4–2 POTENTIAL RISKS ASSOCIATED WITH GIREDESTRANT

Information described below on potential risks is based on data from Phase I Study GO39932 as of the clinical cutoff date (CCOD) 17 September 2021 (per Giredestrant IB v6) with emphasis on the 30 mg giredestrant single agent cohort.

A4–2.1 VENOUS THROMBOEMBOLIC EVENTS (INCLUDING PULMONARY EMBOLISM)

In Study GO39932, there has been 1 serious Grade 3 case of pulmonary embolism occurring in a patient receiving giredestrant at the higher dose of 100 mg and a non-serious case of Grade 2 deep vein thrombosis occurring in a patient receiving 100 mg giredestrant in combination with palbociclib treatment. Both cases were assessed as unrelated to giredestrant. Please refer to Giredestrant IB v6 for more information. Participants should be closely monitored for signs and symptoms of thrombosis and instructed to immediately seek medical attention if thrombosis is suspected.

A4–2.2 RENAL TOXICITY OR INCREASED CREATININE

Dose-dependent effects on the kidneys were observed in repeat-dose studies in both rats and monkeys given giredestrant. No cases of acute kidney injury have been reported with single-agent giredestrant. In Study GO39932 adverse events that may be suggestive of renal toxicity have been reported. All adverse events were non-serious and Grade 1 in maximum severity, with the exception of 3 patients who experienced Grade 2 adverse events (occurring in the higher dose giredestrant cohort or in the palbociclib combination cohort). There have been no Grade 2 events in patients receiving 30 mg giredestrant as a single agent.

A4–2.3 CHANGES IN FEMALE REPRODUCTIVE ORGANS AND MENOPAUSAL SYMPTOMS

Based on the anti-estrogenic pharmacologic activity of giredestrant, the following effects are anticipated to occur: loss of muscle and bone, vaginal dryness or discharge,

irritation, mood swings, and decreased libido. These symptoms could potentially be more severe than those experienced by typical menopausal participants.

In Study GO39932, the following adverse events were reported with common frequency in patients receiving giredestrant 30 mg as a single agent: vulvovaginal dryness, vaginal discharge, dyspareunia, vulvovaginal pruritus, and atrophic vulvovaginitis. All events were non-serious and Grade 1 in maximum severity. No patient required any changes to dosing due to adverse events and the majority of patients did not receive treatment for the adverse events reported.

For management of vaginal dryness, non-hormonal vaginal lubricants and moisturizers are encouraged on a first instance (Committee on Practice Bulletins-Gynecology 2012).

A4–2.4 FEMALE AND MALE FERTILITY

The effects of giredestrant on fertility in humans have not been studied.

In nonclinical studies, perturbation and the arrest of the estrus cycle was observed microscopically in early development in both rats and monkeys. There was evidence of a return to estrus cycling following a 16-week recovery period.

In nonclinical studies no microscopic effects on male reproductive organs were attributed to administration of giredestrant in a 13-week study in male rats.

As these findings remains incompletely explained any participants with concerns for future fertility should be made aware of this potential issue prior to joining this study. Their concerns, including fertility preservation, should be discussed prior to enrolling in any study with giredestrant.

A4–2.5 EMBRYOFETAL TOXICITY

On the basis of the anti-estrogenic pharmacological activity of giredestrant, administration of giredestrant during pregnancy is expected to have an adverse effect and poses a risk to the human fetus, including birth defects and miscarriage.

A4–2.6 DRUG–DRUG INTERACTIONS

Giredestrant has a low potential for clinically relevant drug-drug interactions.

See Section 6.8 for further details on potential drug-drug interactions and recommendations regarding concomitant medications.

A4–2.7 RECURRENCE OF ENDOMETRIAL CANCER

Events that are clearly consistent with the expected pattern of disease recurrence should not be recorded as adverse events. These data will be captured as efficacy assessment data only. The expected pattern of disease recurrence will be based on determination by the investigator after an integrated assessment of radiographic data, biopsy sample results (if available), and clinical status. Every effort should be made to document disease recurrence with use of objective clinical, radiological, histological, or cytological evidence as per protocol (Section 8.1.1). If there is any uncertainty as to whether an event is due to disease recurrence, it should be reported as an adverse event.

Recurrence of disease should not be recorded as an adverse event or serious adverse event, since recurrence of disease will be captured as an efficacy endpoint. However, in situations in which there is no confirmation, the underlying symptoms should be captured as adverse events and assessed accordingly for seriousness, severity, and causality until a diagnosis or cause for such events is established or until confirmation of estrogen receptor-positive breast cancer recurrence. If the symptoms are later confirmed to be due to recurrence of disease, then symptoms reported as adverse events should be retracted. Data for disease recurrence will be captured as efficacy assessment data only.

A4–3 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A4–3.1 DOSE MODIFICATIONS

No dose reductions are permitted for giredestrant. See Section A4–3.3 for further details on management of adverse events associated with giredestrant.

A4–3.2 TREATMENT INTERRUPTION

Giredestrant may be temporarily suspended or delayed for up to 28 days in participants who experience toxicity considered to be related to study drug. Please note that the investigator should always exercise their clinical judgement based on the nature of adverse event, recovery status and benefit-risk to the participant when assessing the interruption time required (if needed). In case of frequent treatment interruptions, possible discontinuation of study treatment should be discussed with participants.

See Section A4–3.3 for further details on management of adverse events associated with giredestrant.

A4–3.3 MANAGEMENT GUIDELINES

Guidelines for management of specific adverse events are outlined in Table A4-1. Additional guidelines are provided in the subsections below.

Table A4-1 Guidelines for Management of Participants who Experience a Giredestrant-Related Toxicity

Event	Action to be Taken
Elevation of Hepatic Transaminases	
General guidance	• If participant presents with jaundice, coagulopathy, abdominal pain, or other symptoms suggestive of hepatic toxicity, perform liver function tests with additional evaluation per institutional guidelines • If hepatic enzymes are elevated with no obvious cause found, consult with hepatologist • Treat participant with hepatic enzyme elevation according to local standard of care
Grade 1 or 2	• Continue giredestrant • Rule out alternative etiologies (e.g., concomitant medications, or biliary obstruction) • Instigate more frequent monitoring with increased monitoring of liver function tests (at least fortnightly until resolved) • Treat participant according to local standard of care
Grade 3	• Withhold giredestrant • Consider consultation with hepatologist • Once event resolves Grade ≥ 1, resume giredestrant at full dose with increased monitoring until the event is assessed as resolved or stable
Grade 4 or meets criteria as defined by Hy's Law (see Section A3–7.6)	• Permanently discontinue giredestrant • Consult with hepatologist
Gastrointestinal Events (Nausea, Vomiting, Diarrhea)	
General guidance	• Monitor closely for gastrointestinal symptoms. If participant presents with nausea, vomiting, or diarrhea, manage according to local standard of care, including use of anti-diarrheal agents and supportive care, such as hydration and dietary modification, as appropriate. • Infectious or alternate etiologies should be ruled out
Grade 1	• Continue giredestrant
Grade 2	• Manage and treat according to local standard of care • If persistent despite appropriate medical therapy, withhold giredestrant until resolution to Grade 1 or better

Table A4-1 Guidelines for Management of Participants who Experience a Giredestrant-Related Toxicity

Event	Action to be Taken
Grade ≥ 3	• Withhold giredestrant until event resolves to Grade 1 or better • Manage and treat participant according to local standard of care • Consider consulting with gastroenterologist • Resume giredestrant at regular dose once the event resolves to Grade 1 or better
Venous Thromboembolic Events (Including Pulmonary Embolism)	
General guidance	• Advise participants to seek immediate medical attention if they become aware of any symptoms of pulmonary embolism or deep vein thrombosis, such as acute onset of chest pain, shortness of breath, or swelling in extremities
Grade 1	• Continue giredestrant
Grade ≥ 2	• Withhold giredestrant until participant is stable (any thrombolytic therapy and inpatient anticoagulation has been completed) • Manage and treat participant according to local standard of care • Resume giredestrant at full dose once the participant is stable • Permanently discontinue giredestrant for recurrent thromboembolic events
Bradycardia	
General guidance	• Monitor participant closely for symptomatic bradycardia
Grade 1	• Continue giredestrant • Continue to monitor participant per schedule of activities (Section 1.3) • If heart rate falls below 40 beats per minute, withhold giredestrant until heart rate returns to > 40 beats per minute if participant remains asymptomatic
Grade 2	• Withhold giredestrant and consult with cardiologist • Resume giredestrant at full dose once the event improves to Grade 1 or better and heart rate returns to > 40 beats per minute
Grade ≥ 3	• Permanently discontinue giredestrant and consult with cardiologist
Renal Toxicity or Increased Creatinine	
Grade 1 or 2	• Continue giredestrant • Manage participant according to local standard of care
Grade ≥ 3	• Permanently discontinue giredestrant • Manage participant according to local standard of care • Consult with nephrologist

Table A4-1 Guidelines for Management of Participants who Experience a Giredestrant-Related Toxicity

Event	Action to be Taken
Non-Hematologic Toxicity	
Grade 1 or 2	• Continue giredestrant • Rule out alternative etiologies
Grade 3	• Withhold giredestrant until symptoms resolve to Grade 1 or better, and then resume giredestrant at full dose
Grade 4	• Permanently discontinue giredestrant. Participants not thought to be at risk of further acute toxicity may be rechallenged with giredestrant following the investigator's assessment of the benefits and risks. The Medical Monitor is available to advise as needed.

Appendix 5
Collection of Pregnancy Information

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A5–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 10 days after the final dose of giredestrant (or the period of time specified in the local prescribing guidelines). A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event electronic Case Report Form (eCRF). The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A5–2 ABORTIONS

A spontaneous abortion in a female participant exposed to study treatment should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A5–3 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

Appendix 6
Genetics: Use and Analysis of DNA for Mandatory Samples

Genetic variation may impact a participant's response to study treatment and susceptibility to, and severity and progression of, disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and the Institutional Review Board or Ethics Committee allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to giredestrant/endometrial cancer and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to giredestrant and/or treatments of this drug class and endometrial cancer. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

DNA samples will be analyzed as described in Section 8.7. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to giredestrant or study treatments of this class to understand the study disease or related conditions.

The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on giredestrant continues but no longer than 5 years or other period as per local requirements.

Appendix 7 Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Product Name	IMP/NIMP Designation	Marketing Authorization Status in EEA and U.K.	Used within Marketing Authorization
Giredestrant (RO7197597)	IMP (test product)	Not approved	No

EEA = European Economic Area; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; U.K. = United Kingdom.

Appendix 8
Abbreviations

Abbreviation or Term	Definition
bpm	beats per minute
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
CT	computed tomography
ctDNA	circulating tumor DNA
D&C	dilation and curettage
EC	endometrial carcinoma
eCRF	electronic Case Report Form
EDC	electronic data capture
EH	endometrial hyperplasia
EIN	endometrial intraepithelial neoplasia
EMB	endometrial biopsy
ER	estrogen receptor
ESR1	estrogen receptor 1
HER2	human epidermal growth factor receptor 2
IHC	immunhistochemistry
IM	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IxRS	interactive voice or Web-based response system
Ki67	proliferative index
LBD	ligand binding domain
LHRH	leutinizing hormone-releasing hormone
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
PD	pharmacodynamic
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic
PO	orally
PR	progesterone receptor

Appendix 8: Abbreviations

Abbreviation or Term	Definition
Q12W	every 12 weeks
QD	once a day
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
ULN	upper limit of normal
WES	whole-exome sequencing
WGS	whole-genome sequencing

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