

Rationale and design of ASTEROID 2, a randomized, placebo- and active comparator-controlled study to assess the efficacy and safety of vilaprisan in patients with uterine fibroids



Christian Seitz^{a,*}, Žana Bumbuliene^b, Ana Rosa Costa^c, Oskari Heikinheimo^d, Andrea Heweker^e, Robert Hudeček^f, Yves Jacquemyn^g, Gian Benedetto Melis^h, Pooja Parasharⁱ, Tomasz Rechberger^j, Antonio Cano Sánchez^k, Bart van Aken^l, János Zatik^m, Kristina Gemzell-Danielssonⁿ

^a Bayer AG, Development, Gynecologic Therapies, 13342 Berlin, Germany

^b Vilnius University Faculty of Medicine, Clinic of Obstetrics and Gynaecology, Santariskiu str. 2, Vilnius LT-08406, Lithuania

^c Serviço de Ginecologia e Obstetrícia, Hospital de São João, 4200-319 Porto, Portugal

^d Department of Obstetrics and Gynaecology, University of Helsinki and Helsinki University Hospital, PL 610, 00029 HUS, Finland

^e Praxis für Gynäkologie und Geburtshilfe, Steinstrasse 6a, D-06406 Bernburg, Germany

^f Department of Obstetrics and Gynecology, Faculty of Medicine, Masaryk University and University Hospital Brno, Obilní trh 11, 602 00 Brno, Czech Republic

^g Department of Obstetrics and Gynaecology, UZA Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium

^h Dipartimento di Scienze Chirurgiche, Clinica Ostetrica e Ginecologica, Università di Cagliari, SS 554, Bivio Sestu, 09042 Monserrato, Cagliari, Italy

ⁱ Nesttun Spesialistpraksis, Østre Nesttunveien 14, 5221 Nesttun, Bergen, Norway

^j Second Chair and Department of Gynaecology, Medical University of Lublin, ul. K. Jazewskiego 8, 20-090 Lublin, Poland

^k Hospital Clínico Universitario de Valencia, Av. de Blasco Ibáñez 15, 46010 València, Spain

^l Flevoziekenhuis, Hospitaalweg 1, 1315 RA Almere, Netherlands

^m Szent Anna Szuleszeti, Nogyogyaszati es Ultrahang Magan Rendelo, 48 Szent Anna utca, Debrecen, Hungary

ⁿ Department of Women's and Children's Health (KBH), K6, Karolinska Universitetssjukhuset Solna, H2:00, 17176 Stockholm, Sweden

ARTICLE INFO

Article history:

Received 5 September 2016

Received in revised form 2 February 2017

Accepted 4 February 2017

Available online 6 February 2017

Keywords:

Vilaprisan

Progesterone receptor modulator

Uterine fibroids

Ulipristal acetate

Amenorrhoea

ABSTRACT

Background: Uterine fibroids (UFs) may be treated with progesterone receptor modulators (PRMs), which have been shown to reduce heavy menstrual bleeding and the size of UFs. To date, one PRM (ulipristal acetate) has received regulatory approval for the treatment of UFs; therapy comprises intermittent treatment courses of up to 3 months each, followed by a break to allow two menstruations to occur. We report the design of ASTEROID (Assess Safety and efficacy of vilaprisan in patients with uTERine fibrOIDS) 2, a phase 2 study examining the efficacy and safety of a novel PRM, vilaprisan, in women with UFs.

Methods/design: In this randomized multi-arm study, vilaprisan (2 mg daily) will be administered in different regimens: continuous treatment for 12 or 24 weeks, or two 12-week treatment periods separated by a break to allow one menstruation to occur. Efficacy and safety will be compared with that of ulipristal acetate (5 mg daily) and placebo. Patients randomized to receive placebo for 12 weeks will also be given active treatment for 12 weeks. The primary measure of efficacy will be amenorrhoea rate; secondary measures include time to normalized menstrual bleeding and percentage change in UF volume. Endometrial changes will be monitored throughout the study.

Discussion: The placebo- and active comparator-controlled trial ASTEROID 2 is the first study to evaluate systematically the efficacy and safety of different treatment regimens of PRMs in women with UFs. The findings of this study will direct the planning of future clinical trials of vilaprisan.

© 2017 Bayer AG. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Abbreviations: AE, Adverse event; ASTEROID, Assess Safety and efficacy of vilaprisan in patients with uTERine fibrOIDS; HMB, Heavy menstrual bleeding; MP, Menstrual pictogram; MRI, Magnetic resonance imaging; PAEC, Progesterone receptor modulator associated endometrial change; PBAC, Pictorial blood loss assessment chart; PD, Pharmacodynamic; PGI, Patient Global Impression; PK, Pharmacokinetic; PRM, Progesterone receptor modulator; PRO, Patient-reported outcome; TVU, Transvaginal ultrasound; UF, Uterine fibroid; UF-DSD, Uterine Fibroid Daily Symptom Diary; UFIS, Uterine Fibroid Impact Scale; UFS-QoL, Uterine Fibroid Symptom and Quality of Life questionnaire; UPA, Ulipristal acetate; VPR, Vilaprisan.

* Corresponding author.

E-mail addresses: christian.seitz@bayer.com (C. Seitz), zana.bumbuliene@santa.lt (Ž. Bumbuliene), anacosta.md@gmail.com (A.R. Costa), oskari.heikinheimo@helsinki.fi (O. Heikinheimo), a.heweker@t-online.de (A. Heweker), rhudecek@fnbrno.cz (R. Hudeček), yves.jacquemyn@uza.be (Y. Jacquemyn), gineca.gmelis@tiscali.it (G.B. Melis), ipooja1329@gmail.com (P. Parashar), rechberger@yahoo.com (T. Rechberger), antonio.cano@uv.es (A.C. Sánchez), BvAken@Flevoziekenhuis.nl (B. van Aken), jzatic@yahoo.com (J. Zatik), kristina.gemzell@ki.se (K. Gemzell-Danielsson).

1. Introduction

Uterine fibroids (UFs) are the most common benign tumours in women. Findings from ultrasound screening of more than 1000 randomly selected members of an urban health plan suggest that 70–80% of women will develop UFs during their lifetime [1]. Although many women will remain asymptomatic, the presence of UFs can cause symptoms including heavy menstrual bleeding (HMB), pelvic pressure and pain [2], which have a significant impact on women's quality of life [3]. Many women undergo invasive procedures, including hysterectomy, to treat the symptoms of UFs [4]. In a study of medical records from a UK primary care database, nearly a quarter of women underwent hysterectomy or invasive procedures such as myomectomy or uterine artery embolization within 1 year of diagnosis of UFs [5]. Medical therapy for the long-term treatment of UFs would reduce the need for invasive procedures, which are associated with significant morbidity [6].

Progesterone receptor modulators (PRMs) act directly on progesterone receptors in the smooth muscle of UFs, resulting in inhibition of cell proliferation and stimulation of apoptosis [7,8]. In women with UFs, treatment with PRMs such as mifepristone, asoprisnil and ulipristal acetate (UPA) has been shown to induce amenorrhoea [9–13]; furthermore, UPA has been shown to reduce UF size to a similar extent as uterine artery embolization [14]. UPA (5 mg daily) is approved in the European Union for the intermittent treatment of moderate to severe symptoms of UFs in adult women of reproductive age [15]. Treatment with PRMs is known to induce benign histological changes of the endometrium known as progesterone receptor modulator associated endometrial changes (PAECs) [16]. In phase 3 clinical trials of UPA in women with UFs, the duration of treatment was initially limited to 3 months [10,11]. Recently, the efficacy and safety of up to four 3-month treatment courses of UPA have been evaluated in women with UFs; each treatment period was separated by a break to allow two menstruations to occur [17–19]. However, patients reported some return of symptoms (HMB and pain) and a corresponding reduction in quality of life during the treatment breaks [17,18]. The efficacy and safety of alternative UPA treatment regimens (for example, continuous treatment for 6 months) have not been evaluated.

Vilaprisan (VPR) is a novel PRM with a fivefold higher anti-progestagenic potency than UPA [20]. In a phase 1 study [21], treatment with VPR resulted in a dose-dependent reduction of menstrual bleeding in healthy volunteers. Observed non-bleeding rates (self-assessed intensity of menstrual bleeding as 'none' or 'spotting') reached more than 90% among women taking a 2 mg daily dose of VPR for 3 months [21]. Here, we report the design of ASTEROID (Assess Safety and efficacy of vilaprisan in patients with uTERine fibrOIDS) 2 (ClinicalTrials.gov identifier NCT02465814; EudraCT number 2014-004221-41). This phase 2 study is the first to evaluate systematically the efficacy and safety of different treatment regimens of PRMs in patients with UFs.

2. Methods/design

2.1. Study objectives

The primary objective of ASTEROID 2 is to assess the efficacy of VPR (12 and 24 weeks of treatment) compared with placebo (12 weeks) in patients with UFs. The safety of VPR and the efficacy of different VPR treatment regimens in comparison with UPA will be evaluated as secondary objectives. Further aims are to supplement data on the population pharmacokinetic (PK)/pharmacodynamic (PD) relationship for VPR in patients with UFs.

2.2. Study design

ASTEROID 2 is a multi-arm, randomized, parallel-group, phase 2 study of female patients with UFs, which is being carried out at approximately 70 centres in 16 European countries. The study comprises three main treatment groups (A, B and C) with a total of seven treatment arms (Fig. 1). All three groups of patients will take part in two 12-week treatment periods during the study. Patients randomized to groups A and B will receive VPR (2 mg once daily) or daily placebo tablets followed by VPR (2 mg once daily). Those in group C will receive the active comparator UPA (5 mg once daily), placebo followed by UPA, or UPA followed by placebo. Treatment period 1 will commence within 3 days of the start of the first menstruation following randomization.

For patients in group A, treatment periods 1 and 2 will run continuously without a break. Women will receive VPR for 24 weeks (treatment arm A1) or placebo for 12 weeks followed by VPR for 12 weeks (treatment arm A2). Women in group B will receive two 12-week courses of VPR (treatment arm B1) or placebo followed by VPR (treatment arm B2). For this group of patients, there will be a break at the end of treatment period 1 until menstruation occurs. Treatment period 2 will commence within 3 days of the start of menstruation. Women in group C will receive two 12-week courses of UPA (treatment arm C1), placebo followed by UPA (treatment arm C2) or UPA followed by placebo (treatment arm C3). All patients in group C will have a break at the end of treatment period 1 that will be long enough to allow two menstruations to occur. Treatment period 2 will commence within 3 days of the start of the second menstruation that occurs during the treatment break. This reflects the approved treatment regimen for UPA. For all groups A, B and C, a 12-week follow-up phase will commence at the end of treatment period 2.

All aspects of the study design and protocol have been approved and reviewed by the Institutional Review Board of each participating centre. The study will be conducted in compliance with the principles detailed in the Declaration of Helsinki and in accordance with Good Clinical Practice guidelines. Written informed consent will have been provided by all participants.

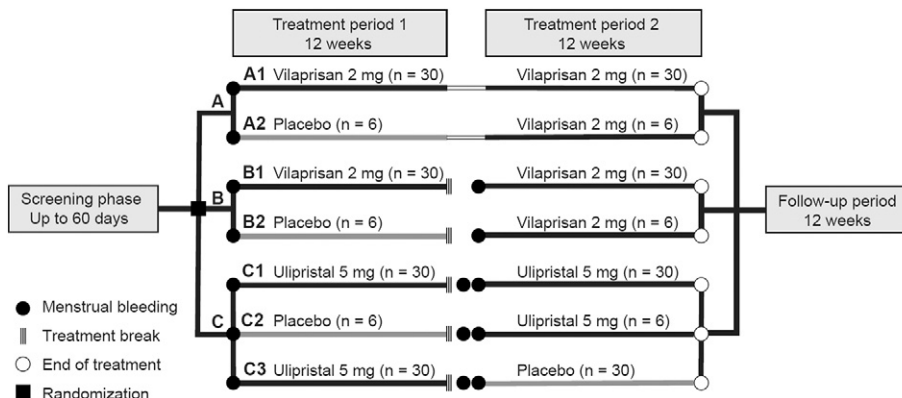


Fig. 1. Design of the ASTEROID 2 (Assess Safety and efficacy of vilaprisan in patients with uTERine fibrOIDS 2) study.

2.3. Patients

Patient eligibility for ASTEROID 2 will be confirmed during the screening period that will last for up to 60 days prior to randomization. Key inclusion and exclusion criteria are shown in Table 1. Women aged 18–50 years must have a diagnosis of UFs, documented by abdominal or transvaginal ultrasound (TVU). Eligible patients must have at least one UF with a largest diameter of ≥ 3 cm, and must experience HMB, defined as more than 80 mL of blood loss per menstrual cycle (measured by menstrual pictogram [MP]), that must occur within 10 days during the screening period. The MP employs a visual scoring system to document and assess menstrual fluid loss for each sanitary product (towels and/or tampons) that a patient uses [22,23].

2.4. Randomization and blinding

Eligible patients will be randomized in a blockwise manner, without stratification, to one of seven treatment arms as shown in Fig. 1. Owing to differences in the treatment regimens it will not be possible to achieve blinding between groups A, B and C. However, double blinding will be established between treatment arms A1 and A2, B1 and B2, and C1, C2 and C3. Therefore, patients and study investigators will be aware of the treatment group assignment, but will have no knowledge of the treatment arm allocation. To maintain blinding, VPR or UPA and their respective placebo tablets will be identical in appearance. Patients and investigators will be unblinded in the event of a suspected, unexpected serious adverse reaction.

Table 1
Key inclusion and exclusion criteria for the ASTEROID 2 study.

Key inclusion criteria
<ul style="list-style-type: none"> • Women aged 18–50 years at screening • Diagnosis of uterine fibroids documented by transvaginal or abdominal ultrasound at screening, with at least one uterine fibroid with a largest diameter ≥ 3 cm • HMB (>80 mL within 10 consecutive days) during the screening period as measured by menstrual pictogram • Normal or clinically insignificant findings in cervical smear (Pap test) • No significant endometrial pathology as determined by endometrial biopsy during the screening period • Use of non-hormonal (barrier) contraceptive for the duration of the study
Key exclusion criteria
<ul style="list-style-type: none"> • Pregnancy or lactation less than 3 months before the start of treatment <ul style="list-style-type: none"> • Uterine fibroid with a largest diameter > 10 cm • Haemoglobin levels ≤ 60 g/L or any condition requiring blood transfusion • Any condition or medication that may interfere with the conduct of the study or interpretation of the results, including: <ul style="list-style-type: none"> o severe coagulation disorders or anaemia unrelated to HMB o history of or current gynaecological cancer (including any ovarian tumours or pelvic masses of unclear aetiology that require further investigation) o endometrial ablation or uterine artery embolization < 6 months prior to screening o one or more ovarian cysts ≥ 3 cm in diameter, as measured by ultrasound o known or suspected uterine polyp > 1.5 cm o prior use of short-acting hormonal contraceptives (oral, vaginal or transdermal), contraceptive devices with or without hormone release (implant, intra-uterine device), tranexamic acid or other treatments for HMB, if not stopped or removed before the start of the menstrual cycle following screening visit 1 o prior use of injectable hormonal contraceptives, if last application was performed less than one application interval before the start of the menstrual cycle following screening visit 1 o prior use of gonadotropin-releasing hormone agonists, if not stopped at least one application interval before the start of the screening period; o previous use of ulipristal acetate without satisfactory treatment response o anticoagulants taken within the last 2 weeks prior to first study drug intake and during the treatment period • Undiagnosed abnormal genital bleeding

ASTEROID, Assess Safety and efficacy of vilaprisan in patients with uTERine fibrOIDS; HMB, heavy menstrual bleeding.

2.5. Efficacy measures

The primary efficacy variable is amenorrhoea, which is defined as no menstrual bleeding or spotting from the end of the last menstrual bleed (at the start of the respective treatment period) throughout the remainder of the treatment period (Table 2). If an endometrial biopsy was conducted during the treatment period, any bleeding on the day of biopsy or during the 3 days thereafter will not be considered in this evaluation. Other measures of efficacy that will be evaluated as secondary endpoints are outlined in Table 2.

2.6. Study procedures

The procedures to be carried out during study visits are outlined in Table 3. To assess HMB, patients will be asked to rate any menstrual bleeding within the past 24 h on a daily basis using the following categories: no bleeding, spotting, mild, moderate, severe and very severe. These data will be recorded electronically using the Uterine Fibroid Daily Symptom Diary (UF-DSD) [24]. A bleeding episode constitutes any days on which bleeding is recorded as mild, moderate, severe or very severe that are preceded and followed by at least 2 bleed-free days.

To measure the volume of UFs and of the uterus, pelvic magnetic resonance imaging (MRI) will be performed within 7 days of the time points outlined in Table 3. Images of diagnostic quality will be acquired using high-resolution MRI (1.5 Tesla or higher) without contrast agents. Volume measurements will be performed by two independent radiologists who will be blinded to treatment allocation. TVU or abdominal ultrasound (depending on UF location) will be performed to measure the transverse, longitudinal and antero-posterior diameters of the three largest UFs at the time points outlined in Table 3. The type of examination, the machine to be used and the investigator performing each examination will be consistent for each patient throughout the study.

Patient-reported outcomes (PROs) and treatment administration will be recorded using an electronic diary (eDiary) and tablet computer-based questionnaires. The PRO measures to be included in the eDiary

Table 2
Key efficacy endpoints for the ASTEROID 2 study.

Primary efficacy endpoint
<ul style="list-style-type: none"> • Amenorrhoea (yes/no), defined as no menstrual bleeding or spotting for the duration of the TP (except for the menstrual bleed at the start of the respective TP and any bleeding on the day of endometrial biopsy or within the 3 days thereafter)
Secondary efficacy endpoints
<ul style="list-style-type: none"> • Number of bleeding days per 28 days, from day 1 of the first TP until the day before the next TP would start <ul style="list-style-type: none"> • Time to onset of normalized bleeding, defined as the first day for which the menstrual blood loss (assessed by MP) for all subsequent 28-day cycles up to the end of the TP is less than 80 mL • Change in volume (%) of largest uterine fibroid compared with baseline, measured by MRI
Further efficacy endpoints
<ul style="list-style-type: none"> • Volume of menstrual blood loss per 28 days (assessed by MP) and during the first, second and third menstrual cycles after the end of treatment visit • Proportion of patients with 50% reduction in menstrual bleeding per 28 days (assessed by MP) compared with baseline • Time to onset of amenorrhoea, defined as the first day for which the menstrual blood loss is less than 2 mL for all subsequent 28-day cycles up to the end of the TP, as measured by MP • Time to start of bleeding after last study drug/placebo intake. If bleeding has to be induced, the patient's data will be censored at the time of induction • Change in volume of the largest uterine fibroid and of the uterus (% change compared with baseline), measured by both ultrasound and MRI • Proportion of patients undergoing surgical treatment • Change in patient-reported outcome and ClinRO questionnaire scores and assessments compared with baseline

ASTEROID, Assess Safety and efficacy of vilaprisan in patients with uTERine fibrOIDS; ClinRO, clinician reported outcome; MP, menstrual pictogram; MRI, magnetic resonance imaging; TP, treatment period.

Table 3
Schedule of procedures for the ASTEROID 2 study.

Period Visit	Screening			TP1			B	TP2			Follow-up 10
	1	2	3	4	5	6		7	8	9	
Timing (weeks following start of TP1 or TP2)				+4	+8	+12		+4	+8	+12	8–12 weeks after EOT
Informed consent	X										
Inclusion/exclusion criteria	X	(X)	X								
Demographics, smoking status, alcohol consumption, medical history	X										
Physical examination	X					X			X		X
Vital signs, body weight, height	X		X			X			X		X
Gynaecological examination including breast palpation	X					X			X		
Urine pregnancy test	X	X	X	X	X	X		X	X	X	X
Cervical smear	X								X		
Ultrasound examination	X	X	X	X	X	X		X	X	X	X
Endometrial biopsy		X								X	X
MRI			X			X				X	X
Safety, laboratory and urinalysis	X		X	X		X		X	X	X	
Additional laboratory parameters			X	X		X				X	
Blood sample for PK				X		X		X		X	
PROs (eDiary)											
UF-DSD including bleeding diary	→	→	→	→	→	→		→	→	→	→
Menstrual pictogram	→	→	→	→	→	→		→	→	→	→
UFIS	→	→	→	→	→	→		→	→	→	→
PROs (tablet computer)											
UFS-QoL	X		X			X				X	X
SF-36v2	X		X			X				X	X
PGI-S	X		X	X	X	X		X	X	X	X
PGI-C						X				X	
ClinRO (RAVE)											
CGI-S	X		X	X	X	X		X	X	X	X
CGI-C						X				X	

Ongoing data collection (daily questionnaire); (X), check of eDiary entries via the web. ASTEROID, Assess Safety and efficacy of vilaprisan in patients with uTERine fibrOIDS; B, treatment break; CGI-C, Clinician Global Impression of Change; CGI-S, Clinician Global Impression of Severity; ClinRO, clinician-reported outcome; EOT, end of treatment; MRI, magnetic resonance imaging; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetics; PROs, patient-reported outcomes; RAVE, electronic data capturing system; SF-36v2, 36-item Short-Form Health Survey Version 2; TP, treatment period; UF-DSD, Uterine Fibroid Daily Symptom Diary; UFIS, Uterine Fibroid Impact Scale; UFS-QoL, Uterine Fibroid Symptom and Quality of Life questionnaire.

are the UF-DSD, the MP and the Uterine Fibroid Impact Scale (UFIS). The UF-DSD will be used to document the severity of UF symptoms such as pain, swelling and bloating. The impact of these symptoms on daily activities, for example the ability to carry, lift, walk and stand, will be documented using the UFIS. The severity of vaginal bleeding will be assessed using the daily bleeding diary and the MP. The tablet computer-based questionnaires include the Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QoL), the 36-item Short-Form Health Survey Version 2, the Patient Global Impression (PGI) of Change and the PGI of Severity. These will be used to assess the impact of symptoms on various aspects of quality of life such as mood, self-consciousness, sexual function, and mental and emotional health.

2.7. Pharmacokinetics/pharmacodynamics

Plasma VPR and UPA concentrations will be determined using a validated liquid chromatography–mass spectrometry/mass spectrometry method. For analysing plasma VPR concentrations, blood samples will be taken at the time points outlined in Table 3. At the end of the study, the PK of VPR will be analysed using non-linear mixed effect models to describe the relationship between dose, time and plasma drug concentration. A population PK/PD model will be developed to describe the relationship between exposure and PD effects such as bleeding intensity. Plasma UPA concentrations will be compared with published data in order to assess treatment compliance.

2.8. Safety

Frequent visits to the study site are planned for safety monitoring (Table 3). Endometrial safety assessments will include monthly TVU investigations, analysis of bleeding patterns and endometrial biopsies. During TVU investigations, endometrial thickness will be measured and the ovaries will be evaluated. If follicle-like structures greater than

3 cm in diameter are observed, further TVU examinations will be carried out to monitor outcomes.

Patients will undergo three scheduled endometrial biopsies during the study. The first biopsy will be performed during the screening period, followed by a second biopsy after the end of treatment period 2 and a third during the follow-up phase (approximately 8 weeks after the end of treatment period 2). All biopsies will be performed on day 9 ± 2 of the menstrual cycle that occurs at the specified time point. If the endometrial thickness is found to be greater than 18 mm, or if a patient has been experiencing suspicious bleeding patterns, an unscheduled endometrial biopsy will be performed. If hyperplasia is detected, the study treatment will be stopped immediately and diagnostic sampling of the endometrium (such as curettage) may be considered. In the absence of these findings, patients will continue to take study medication and will undergo additional monitoring of endometrial thickness and bleeding patterns.

If amenorrhoea persists for up to 10 weeks after treatment cessation (either at the end of treatment period 1 or at the end of the study), patients will undergo additional unscheduled TVU and endometrial biopsy to check for endometrial changes. Menstruation will be induced by use of a progestin such as oral norethisterone acetate 2.5–10 mg daily for 10 days. Any patient who requires a progestin after treatment period 1 will not be entered into treatment period 2.

Laboratory safety tests include the measurement of hormones (such as follicle-stimulating hormone, progesterone, cortisol and thyroxine-binding globulin) and bone markers, serum chemistry, urinalysis, coagulation status and haematology profile. For patients with haemoglobin levels of 109 g/L or below, iron supplementation will be offered in a standard regimen. The occurrence of adverse events (AEs) will also be monitored.

A non-hormonal contraceptive method must be used from the beginning of treatment period 1 (i.e. at the start of menstruation following the screening visit) until the end of the study. However, regular

pregnancy testing will be performed throughout the study and unintended pregnancies will be closely monitored. Any pregnancy that occurs during the treatment or follow-up periods will be monitored in terms of outcomes for both mother and fetus/child, and, in the case of live births, until the child's first birthday. Any abnormal outcomes for mother or child will be reported as serious AEs.

2.9. Statistical analysis

The study populations that will be used for analysis of efficacy are the full analysis set, which will include all randomized patients who took at least one dose of study drug or placebo, and the per protocol set, which will include all patients in the full analysis set without any major protocol deviations. Protocol deviations include treatment, time schedule and procedure deviations, randomization errors and withdrawal criteria, and will be defined and assessed as major or minor before data are unblinded.

For primary efficacy analysis, the amenorrhoea rates with VPR (12 weeks of treatment and 24 weeks of treatment) and placebo (12 weeks) will be compared (Table 4). The null hypothesis that the proportion of patients with amenorrhoea in the vilaprisan group is equal to the proportion of patients with amenorrhoea in the placebo group, against the alternative hypothesis that they are not equal, will be tested at two time points (12 weeks and 24 weeks). Two hypotheses (Supplementary Table 1) will therefore be tested sequentially using a hierarchical (fixed sequence) testing procedure on a significance level of 5% (two-sided Fisher's exact test). The application of the fixed sequence testing approach means that an adjustment for multiplicity is not necessary. Missing data in the patient eDiaries will be imputed: the bleeding intensity for the missed day(s) will be assumed to be equivalent to the maximum intensity recorded on the day before or day after the missing day(s).

The secondary efficacy variables (Table 2) will be analysed descriptively; no hypothesis testing will be performed. To compare the efficacy of VPR with that of UPA, the amenorrhoea rate and number of bleeding days (both with two-sided 95% confidence intervals) will be compared. The treatment arms to be included in each analysis are outlined in Table 4.

Safety analyses will be performed on the safety analysis set, which will include all patients who took at least one dose of study drug or placebo. Each AE will be assigned to treatment with VPR, UPA or placebo. If the AE occurs when a patient is taking placebo after a treatment period with an active drug, the AE will be assigned to the active drug. The incidence of treatment-emergent AEs and drug-related AEs will be summarized using the Medical Dictionary for Regulatory Activities preferred terms.

Statistical analyses will be performed using Statistical Analysis Software (SAS Institute Inc., Cary, NC, USA). Data will be presented using descriptive statistics such as frequency or mean and standard deviation.

Table 4

Findings from different treatment arms of ASTEROID 2 that will be pooled to conduct the primary and secondary efficacy analyses.

Primary efficacy analysis (amenorrhoea rate):
• VPR at 12 weeks (treatment arm A1, n = 30) vs placebo at 12 weeks (treatment arms A2, B2 and C2 pooled, n = 18)
• VPR at 24 weeks (treatment arm A1, n = 30) vs placebo at 12 weeks (treatment arms A2, B2 and C2 pooled, n = 18)
Secondary efficacy analysis (amenorrhoea rate and number of bleeding days):
• VPR at 12 weeks (treatment arms A1 and B1 pooled, n = 60)
• UPA at 12 weeks (treatment arms C1 and C3 pooled, n = 60)
• VPR at 24 weeks with no treatment break (treatment arm A1, n = 30)
• VPR at 24 weeks including treatment break (treatment arm B1, n = 30)
• UPA at 24 weeks including treatment break (treatment arm C1, n = 30)

ASTEROID, Assess Safety and efficacy of vilaprisan in patients with utERine fibrOIDs; UPA, ulipristal acetate; VPR, vilaprisan.

Individual changes from baseline to the end of treatment will be analysed if appropriate.

2.10. Determination of sample size

Sample size calculations are based on the primary endpoint, amenorrhoea rate with VPR compared with placebo, and were performed using Power Analysis and Sample Size (PASS) 11 software (NCSS Statistical Software, Kaysville, UT, USA). An allocation ratio of 5:1 for each active treatment arm to its respective placebo arm was applied. Data from previous studies [11,21] were used to estimate the anticipated size of effect. Details of the calculations used for the primary and secondary efficacy analyses are shown in Supplementary Tables 2 and 3, respectively. Based on an expected amenorrhoea rate of 80% with VPR and 5% with placebo at a two-sided 5% significance level, 25 patients in the VPR arm and 5 in each of the three placebo arms would result in a power of at least 95%. Patients will not switch treatment arm and any patients who drop out of the study will not be replaced: an overall dropout rate of 17% is anticipated and is a conservative estimate based on previous experience in studies with similar populations and complexity (unpublished data). Therefore, 138 patients in total will be recruited – 30 in each active treatment arm and 6 in each placebo arm. Data from patients randomized to receive placebo for treatment period 1 will be pooled for the primary efficacy analysis (Table 4).

Secondary efficacy analyses will be reported in terms of descriptive statistics with two-sided 95% confidence intervals, calculated using the Clopper–Pearson method, as outlined in Supplementary Table 3. The inclusion of treatment arm C3 will allow at least 50 patients taking UPA (25 each from treatment arms C1 and C3), in addition to the 50 patients taking VPR (treatment arms A1 and B1), to be included in the secondary efficacy analysis (Supplementary Table 3).

3. Discussion

ASTEROID 2 is a randomized, placebo- and active comparator-controlled study with multiple treatment arms that is designed to evaluate the efficacy and safety of different treatment regimens of VPR, a novel PRM. Different regimens of VPR (2 mg daily) will be compared: continuous treatment for 12 or 24 weeks, and 12-week treatment periods separated by a break to allow one menstruation to occur. The active comparator UPA will be administered in the regimen that has received regulatory approval for the treatment of UFs: 12-week treatment periods separated by a break to allow two menstruations to occur [15]. PRMs can display effects ranging from antagonist to mixed antagonist/agonist actions at the progesterone receptor and pharmacological activity can be difficult to predict from *in vitro* data alone [25]. The most appropriate regimen for the treatment of UFs should be investigated for each PRM, and may not necessarily be the same for all members of this class of agents. ASTEROID 2 is the first study to assess systematically the effects of different treatment regimens of PRMs in women with UFs.

The use of PRMs is associated with the development of benign histological changes of the endometrium, termed PAECs [16], which are reversible upon treatment cessation and menstruation [10,11,17–19,26]. In the PEARL (PGL4001 Efficacy Assessment in Reduction of symptoms due to uterine Leiomyomata) phase 3 clinical studies of UPA, 62% of women taking UPA 5 mg daily for 12 weeks developed PAECs, compared with 6% of those taking placebo [10]. In a study of the contraceptive effects of UPA delivered continuously via an intravaginal ring for 24 weeks, the proportion of healthy volunteers found to have PAECs was 78.8% [26]. In contrast, PAECs were observed in 38.5% of patients with UFs who received the PRM mifepristone (5 mg daily) for 9 months [9]. Taken together, these data suggest that endometrial findings may differ depending on the PRM being studied, as well as the duration of treatment [16], and highlight the importance of establishing agent-specific treatment regimens for patients with UFs.

The frequency, duration and intensity of menstrual bleeding are subject to variability in response to factors such as physical and emotional stress, which can result in amenorrhoea [27]. The comparison of VPR with placebo in ASTEROID 2 is therefore required in order to distinguish treatment effects from the natural variability of menstruation and the influence of factors unrelated to treatment. Furthermore, there has only been one previous study comparing the active comparator, UPA, with placebo [10]. In the absence of established assay sensitivity, a comparison of VPR with UPA alone would be associated with a risk of overestimating the treatment effect of VPR [28]. The inclusion of placebo in ASTEROID 2 will establish assay sensitivity and internal validity of the trial [28]. However, from an ethical perspective, it is important that the number of patients treated with placebo is minimized because alternative options for the treatment of UFs already exist; if left untreated, the symptoms of UFs can have a considerable negative impact on patients' quality of life. Therefore, an imbalanced randomization approach (5:1 active:placebo) has been incorporated into the design of ASTEROID 2, and data from the placebo treatment arms will be pooled to enhance statistical power. Moreover, all patients who are randomized to receive placebo will then also be given active treatment for at least 12 weeks in treatment period 2. The comparison of VPR with UPA will provide further validation of the study findings, a recognized benefit of a multi-arm clinical trial design [29]. Furthermore, findings from treatment arm C3 (UPA 5 mg daily for 12 weeks followed by daily placebo tablets) will be compared with those from patients receiving VPR (2 mg daily for 12 weeks) in ASTEROID 1 (ClinicalTrials.gov identifier NCT02131662), which is assessing the efficacy and safety of different doses of VPR in women with UFs for 12 weeks.

In the PEARL phase 3 studies, once daily dosing of UPA 5 mg for 12 weeks resulted in amenorrhoea in 73–75% of patients [10,11]. The definition of amenorrhoea was a score of 2 or less on the 28-day pictorial blood loss assessment chart (PBAC). However, this measure has limitations because the PBAC method [30] was developed and validated for use with sanitary products that were no longer available at the time of the PEARL studies. In ASTEROID 1 and 2, HMB will be assessed using the MP, which has been validated for use with modern sanitary wear [22,23].

The findings of several studies suggest that the prevalence of UFs may be higher in women of African origin than in Caucasian women [1,31]. However, no women of African origin were recruited in PEARL I, and this population made up less than 10% of the patients in PEARL II [32]. ASTEROID 2 is being carried out at over 70 centres in Europe, where the active comparator, UPA, is currently approved for the intermittent treatment of UFs [15]. The ethnic diversity of the European population is likely to be reflected in the study population enrolled into ASTEROID 2. In addition, the population to be studied in ASTEROID 1 will include women from the USA and Japan. Taken together, the results of these studies are expected to provide further insight into the efficacy of VPR in women of diverse ethnic backgrounds, including those of African descent.

In summary, ASTEROID 2 is a multi-arm, placebo and active-comparator study that will assess the efficacy and safety of VPR. This is the first study to assess systematically the efficacy and safety of different treatment regimens of PRMs. Data are expected to be available in 2017. The findings of ASTEROID 2 will direct the planning of future studies of VPR in women with UFs.

Funding source

This study was funded by Bayer AG (BAY 1002670/17541), Berlin, Germany.

Authors' roles

All authors contributed to the study concept, design and implementation. All authors were involved in revising the manuscript for

important intellectual content, and approved the final version of the manuscript.

Conflicts of interest

ARC has served on medical advisory boards for Gedeon Richter, HRA Pharma and MSD, and has been an invited speaker at scientific meetings for Bayer AG, Gedeon Richter, MSD, OM Pharma and Tecnimed. Her institution has received grants for conducting the ASTEROID clinical trials. KG-D occasionally serves on advisory boards and has been an invited speaker at scientific meetings for Bayer AG, Exelgyn, HRA Pharma, Gedeon Richter Actavis and MSD/Merck on an *ad hoc* basis. Her institution has received grants for conducting the ASTEROID 1 and 2 clinical trials. OH has served on advisory boards for Bayer AG, Gedeon Richter and MSD Finland (part of Merck & Co., Inc.), and has designed and lectured at educational events for these companies. TR has been an invited speaker for Gedeon Richter at scientific meetings. YJ has been an invited speaker at scientific meetings for Bayer AG and Gedeon Richter, and has served on advisory boards for Gedeon Richter. All authors and/or their institutions received funding for their work on ASTEROID 2 with the exception of CS, who is an employee of Bayer AG.

Acknowledgements

Medical writing support was provided by Emma Bolton DPhil and William Gattrell PhD of Oxford PharmaGenesis, Oxford, UK, with funding from Bayer AG.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.cct.2017.02.002>.

References

- [1] D.D. Baird, D.B. Dunson, M.C. Hill, D. Cousins, J.M. Schectman, High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence, *Am. J. Obstet. Gynecol.* 188 (1) (2003) 100–107.
- [2] S. Gupta, J. Jose, I. Manyonda, Clinical presentation of fibroids, *Best Pract. Res. Clin. Obstet. Gynaecol.* 22 (4) (2008) 615–626.
- [3] E. Downes, V. Sikirica, J. Gilabert-Estelles, S.C. Bolge, S.L. Dodd, C. Maroulis, D. Subramanian, The burden of uterine fibroids in five European countries, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 152 (1) (2010) 96–102.
- [4] S.M. Elahi, F. Odejinmi, Overview of current surgical management of fibroids: 'Organ-preserving modalities', *J. Obstet. Gynaecol.* 28 (1) (2008) 28–31.
- [5] E. Martín-Merino, L.A.G. Rodríguez, M.-A. Wallander, S. Andersson, M. Soriano-Gabarró, The incidence of hysterectomy, uterus-preserving procedures and recurrent treatment in the management of uterine fibroids, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 194 (2015) 147–152.
- [6] S.M. Lyon, K. Cavanagh, Uterine artery embolisation - a treatment alternative for women with fibroids, *Aust. Fam. Physician* 35 (5) (2006) 300–303.
- [7] W. Chen, N. Ohara, J. Wang, Q. Xu, J. Liu, A. Morikawa, H. Sasaki, S. Yoshida, D.A. Demanno, K. Chwalisz, T. Maruo, A novel selective progesterone receptor modulator asoprisnil (J867) inhibits proliferation and induces apoptosis in cultured human uterine leiomyoma cells in the absence of comparable effects on myometrial cells, *J. Clin. Endocrinol. Metab.* 91 (4) (2006) 1296–1304.
- [8] P. Horak, M. Mara, P. Dunder, K. Kubinova, D. Kuzel, R. Hudecek, R. Chmel, Effect of a selective progesterone receptor modulator on induction of apoptosis in uterine fibroids in vivo, *Int. J. Endocrinol.* 2012 (2012) 436174, <http://dx.doi.org/10.1155/2012/436174>.
- [9] J.L. Carbonell, R. Acosta, Y. Perez, A.G. Marrero, E. Trellez, C. Sanchez, G. Tomasi, Safety and effectiveness of different dosage of mifepristone for the treatment of uterine fibroids: a double-blind randomized clinical trial, *Int. J. Womens Health* 5 (2013) 115–124.
- [10] J. Donnez, T.F. Tatarchuk, P. Bouchard, L. Puscasiu, N.F. Zakharenko, T. Ivanova, G. Ugocsai, M. Mara, M.P. Jilla, E. Bestel, P. Terrill, I. Osterloh, E. Loumaye, Ulipristal acetate versus placebo for fibroid treatment before surgery, *N. Engl. J. Med.* 366 (5) (2012) 409–420.
- [11] J. Donnez, J. Tomaszewski, F. Vazquez, P. Bouchard, B. Lemieszczuk, F. Baro, K. Nouri, L. Selvaggi, K. Sadowski, E. Bestel, P. Terrill, I. Osterloh, E. Loumaye, Ulipristal acetate versus leuprolide acetate for uterine fibroids, *N. Engl. J. Med.* 366 (5) (2012) 421–432.
- [12] S.H. Eisinger, T. Bonfiglio, K. Fiscella, S. Meldrum, D.S. Guzick, Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas, *J. Minim. Invasive Gynecol.* 12 (3) (2005) 227–233.

- [13] A.R.W. Williams, H.O.D. Critchley, J. Osei, S. Ingamells, I.T. Cameron, C. Han, K. Chwalisz, The effects of the selective progesterone receptor modulator asoprisnil on the morphology of uterine tissues after 3 months treatment in patients with symptomatic uterine leiomyomata, *Hum. Reprod.* 22 (6) (2007) 1696–1704.
- [14] P. Czuczwar, S. Wozniak, P. Szkodziak, P. Milart, E. Wozniakowska, W. Wrona, T. Paszkowski, Influence of ulipristal acetate therapy compared with uterine artery embolization on fibroid volume and vascularity indices assessed by three-dimensional ultrasound: prospective observational study, *Ultrasound Obstet. Gynecol.* 45 (6) (2015) 744–750.
- [15] Esmya Summary of Product Characteristics Available from: <http://www.medicines.org.uk/emc/medicine/26068> 2015 (Accessed 20 January 2017).
- [16] G.L. Mutter, C. Bergeron, L. Deligdisch, A. Ferenczy, M. Glant, M. Merino, A.R. Williams, D.L. Blihe, The spectrum of endometrial pathology induced by progesterone receptor modulators, *Mod. Pathol.* 21 (5) (2008) 591–598.
- [17] J. Donnez, O. Donnez, D. Matule, H.J. Ahrendt, R. Hudecek, J. Zatik, Z. Kasilovskiene, M.C. Dumitrascu, H. Fernandez, D.H. Barlow, P. Bouchard, B.C. Fauser, E. Bestel, E. Loumaye, Long-term medical management of uterine fibroids with ulipristal acetate, *Fertil. Steril.* 105 (1) (2016) 165–173 (e4).
- [18] J. Donnez, R. Hudecek, O. Donnez, D. Matule, H.J. Arhendt, J. Zatik, Z. Kasilovskiene, M.C. Dumitrascu, H. Fernandez, D.H. Barlow, P. Bouchard, B.C. Fauser, E. Bestel, P. Terrill, I. Osterloh, E. Loumaye, Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids, *Fertil. Steril.* 103 (2) (2015) 519–527.
- [19] J. Donnez, F. Vazquez, J. Tomaszewski, K. Nouri, P. Bouchard, B.C. Fauser, D.H. Barlow, S. Palacios, O. Donnez, E. Bestel, I. Osterloh, E. Loumaye, Long-term treatment of uterine fibroids with ulipristal acetate, *Fertil. Steril.* 101 (6) (2014) 1565–1573.
- [20] A. Wagenfeld, W. Bone, W. Schwede, M. Fritsch, O.M. Fischer, C. Moeller, BAY 1002670: a novel, highly potent and selective progesterone receptor modulator for gynaecological therapies, *Hum. Reprod.* 28 (8) (2013) 2253–2264.
- [21] B. Rohde, C. Seitz, A. Kaiser, M. Schultze-Mosgau, B. Schütt, Pharmacodynamic effects and safety of the novel selective progesterone receptor modulator vilaprisan. Available from: http://seud-congress.com/files/107/COMM_2015/SAMED1/H/05...Beate_Rohde.pdf (Accessed 20 January 2017). Presented at the 1st SEUD Congress, Paris, France, 2015.
- [22] J.L. Magnay, T.M. Nevatte, C. Seitz, S. O'Brien, A new menstrual pictogram for use with feminine products that contain superabsorbent polymers, *Fertil. Steril.* 100 (6) (2013) 1715–1721.
- [23] J.L. Magnay, T.M. Nevatte, S. O'Brien, C. Gerlinger, C. Seitz, Validation of a new menstrual pictogram (superabsorbent polymer-c version) for use with ultraslim towels that contain superabsorbent polymers, *Fertil. Steril.* 101 (2) (2014) 515–522.
- [24] K. Wichmann, M.S. Mattera, A. Filonenko, C. Seitz, M. Schaefer, J. Goldstein, C. Gerlinger, I. Wiklund, Assessing the patient-reported symptoms and impacts of uterine fibroids: development of Uterine Fibroid Daily Symptom Scale (UF-DSD) and Uterine Fibroid Impact Scale (UFIS). Available from: <http://seud.org/wp-content/uploads/2016/05/10-Wichmann.pdf> (Accessed 20 January 2017). Presented at the 2nd SEUD Congress, Barcelona, Spain, 2016.
- [25] W. Afhuppe, A. Sommer, J. Muller, W. Schwede, U. Fuhrmann, C. Moller, Global gene expression profiling of progesterone receptor modulators in T47D cells provides a new classification system, *J. Steroid Biochem. Mol. Biol.* 113 (1–2) (2009) 105–115.
- [26] Y. Huang, J.T. Jensen, V. Brache, L. Cochon, A. Williams, M.-J. Miranda, H. Croxatto, N. Kumar, H. Sussman, E. Hoskin, M. Plagianos, K. Roberts, R. Merkatz, D. Blithe, R. Sitruk-Ware, A randomized study on pharmacodynamic effects of vaginal rings delivering the progesterone receptor modulator ulipristal acetate: research for a novel estrogen-free, method of contraception, *Contraception* 90 (6) (2014) 565–574.
- [27] L.T. Fourman, P.K. Fazeli, Neuroendocrine causes of amenorrhea—an update, *J. Clin. Endocrinol. Metab.* 100 (3) (2015) 812–824.
- [28] ICH Harmonised Tripartite Guideline, Choice of Control Group and Related Issues in Clinical Trials Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline.pdf (Accessed 20 January 2017).
- [29] B. Freidlin, E.L. Korn, R. Gray, A. Martin, Multi-arm clinical trials of new agents: some design considerations, *Clin. Cancer Res.* 14 (14) (2008) 4368–4371.
- [30] J.M. Higham, P.M. O'Brien, R.W. Shaw, Assessment of menstrual blood loss using a pictorial chart, *Br. J. Obstet. Gynaecol.* 97 (8) (1990) 734–739.
- [31] L.M. Marshall, D. Spiegelman, R.L. Barbieri, M.B. Goldman, J.E. Manson, G.A. Colditz, W.C. Willett, D.J. Hunter, Variation in the incidence of uterine leiomyoma among premenopausal women by age and race, *Obstet. Gynecol.* 90 (6) (1997) 967–973.
- [32] CADTH Common Drug Reviews, Ulipristal Acetate (Fibristal) (5 mg Tablets): Treatment of Moderate to Severe Signs and Symptoms of Uterine Fibroids in Adult Women of Reproductive Age Who are Eligible for Surgery. The Duration of Treatment is Limited to Three Months, Canadian Agency for Drugs and Technologies in Health, Ottawa (ON), 2013.