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SUPPLEMENTARY DATA

Supplementary Table SI Trial information regarding the Phase III trials comparing ulipristal with long-term treatment (Euctr, 2014; Middelkoop *et al.*, 2021).

UCON-trial	Ulipristal acetate versus conventional management of heavy menstrual bleeding (HMB; including uterine fibroids): a randomized controlled trial and exploration of mechanism of action
Study website	http://www.isrctn.com/ISRCTN20426843
EudraCT number	2014-003408-65
Recruitment start date	01 April 2015
Funding	National Institute for Health Research (UK)
Study design	A multicentre, randomized controlled trial
Study aim	Determine if ulipristal acetate (UPA) is more effective at reducing the burden of Heavy Menstrual Bleeding (HMB) symptoms than Levonorgestrel intrauterine system (LNG-IUS) after 12 months of treatment.
Patient population	Women who present to primary and secondary care with HMB (age $\geq$ 18 years). Participants will be recruited from the gynaecological, out-patient clinics of participating centres, fitting around their current service provision.
Intervention	Ulipristal acetate; up to three repeated courses alternated with 2 months medication free intervals
Comparison	LNG-IUS
Treatment duration	12 months
Follow-up	12-month questionnaire. Gynaecology clinic appointment (UPA group receive 12-month ultrasound, blood sample, endometrial biopsy. LNG-IUS group receive 12-month ultrasound and blood sample).
Outcomes measures	**Primary outcome measure** The condition-specific Menorrhagia Multi-Attribute Scale (MMAS) designed and validated to capture the impact of HMB on women's day-to-day life. **Secondary outcome measures:** (1) Menstrual bleeding will be captured by validated Pictorial Blood Loss Assessment Chart (PBAC). The standard PBAC is a validated and well used assessment of menstrual blood loss in women. The PBAC will be supplemented by visual analogue scales for menstruation duration, regularity and pelvic pain (2) Uterine Fibroid Symptom and Quality of Life (UFS-QoL) instrument, which contains a health related quality of life (HRQoL) domain and a symptom domain. This instrument will be only given to women diagnosed with fibroids (3) Sexual Activity Questionnaire, a measure of sexual functioning, used in other HMB trials. The sexual activity questionnaire is a valid, reliable and acceptable measure for describing the sexual functioning of women in terms of pleasure and discomfort. It is quick and easy to administer and has good face validity delineating between the sexual functioning of pre and post-menopausal women (4) Satisfaction with treatment outcome measured on a 5-point Likert scale. Specific statements about the experience and the acceptability of the treatment and the beliefs about the value of the treatment will be elicited from the participants (5) Adherence to trial treatments, as reported by the participant (6) Serious adverse events and reactions reported by participants, principally those that are serious and detailed in the respective Summary of Product Characteristics (SmPC) and those that are unexpected (7) Clinical measurements to assess safety and efficacy will include serum haemoglobin as appropriate, oestradiol, pelvic ultrasound (endometrial appearance; fibroid volume) and endometrial biopsies (reported according to pre-agreed criteria by independent pathologists blinded to treatment allocations) (8) Impact on endometrial tissue architecture including regulation of the vascular compartment (9) Impact on endometrial steroid responsiveness, proliferation, survival and inflammatory processes (10) Expression of genes implicated in pre-malignant change including tumour suppressors (11) Effects on uterine/fibroid structure and vascularity as determined by MRI-DCE and high-resolution structural MRI
Intended inclusions	Initial sample size: 220, which needed to be inflated after the first trial suspension in November 2017. This meant that all randomized women who had not completed their full 12-month UPA treatment course needed to be replaced. *Recalculated sample size after first trial suspension:* **302**
Temporary on hold	First trial suspension: 30 November 2017 as per order EMA. Trial recommenced September 2017. Second trial suspension: 12 March 2020 as per EM
Recruitment end date	Trial closed October 2020
Included patients	236
Overall trial end date	31 May 2021

(continued)

Protocol adaptations	**Current secondary outcome measures as of 21 May 2020:** (1) Menstrual bleeding will be captured by validated PBAC (2) Cycle regularity and duration (3) Visual analogue scales (0–10) for pelvic pain during periods, intercourse and at other times. (4) Sexual Activity Questionnaire, a measure of sexual functioning, used in other HMB trials (5) General quality of life (EuroQoL—EQ-5D-5L) and ICECAP-A (6) Satisfaction with treatment on a 5-point Likert scale (7) Participant rating of effect of treatment on HMB over 12 months measured on a 4-point Likert scale (8) Whether participant is willing to recommend the treatment to a friend (9) Surgical intervention (hysterectomy, endometrial ablation and other gynaecological surgery) (10) Adherence to trial treatments and reasons for changing treatment, as reported by the participant (11) Serious adverse events and reactions reported by participants, principally those that are serious and detailed in the respective SmPC and those that are unexpected (12) Clinical measurements via pelvic ultrasound: uterine volume, evidence of adenomyosis, presence of fibroids, largest fibroid volume, endometrial thickness, endometrial appearance (regular/irregular), evidence of ovarian cysts (13) Clinical measurement via endometrial biopsy: primary diagnosis (normal/benign/hyperplasia/malignant) and further sub-diagnoses if non-normal (14) Clinical measurement via blood samples: liver function (including alanine transaminase (ALT) and aspartate aminotransferase (AST) and other tests according to local protocols) serum haemoglobin and oestradiol levels (15) Functional outcomes (16) Impact on endometrial tissue architecture including regulation of the vascular compartment (17) Impact on endometrial steroid responsiveness, proliferation, survival and inflammatory processes (18) Expression of genes implicated in pre-malignant change including tumour suppressors (19) Effects on uterine/fibroid structure and vascularity as determined by MRI-DCE and high resolution structural MRI
Other	Results expected 2022
MYOMEX-2 Trial	Ulipristal versus standard surgical treatment in symptomatic uterine fibroids
Study website	https://zorgevaluatienederland.nl/evaluations/myomex-2 (Dutch only)
EudraCT number	2017-005120-16
Recruitment start date	13 December 2018
Funding	NWO (Nederlands Organisatie voor Wetenschappelijk Onderzoek) ZonMW NWO: Dutch Organization for Scientific Research; ZonMw is a Public Benefit Organization
Study design	A multicentre, randomized controlled trial
Study aim	To investigate the (cost-) effectiveness of ulipristal acetate (UPA) long-term administration in comparison to 'standard' surgical treatment in patients with moderate to severe complaints due to uterine fibroids.
Patient population	Pre-menopausal women (age $\geq$ 18 years) with one or multiple symptomatic fibroids requiring surgical treatment.
Intervention	Ulipristal acetate; up to four repeated courses alternated with 2 months medication free intervals
Comparison	Surgical treatment, can be either uterine artery embolization (UAE), myomectomy or hysterectomy. All mode of surgery apply (laparoscopic and laparotomy and in case of hysterectomy: vaginal approach is also included)
Treatment duration (UPA)	Up to four intermittent courses. Patients will be 'on medication' for a total duration of 13 (3 courses) to 18 months (4 courses), including 2 or 3 medication free intervals of 2 months.
Follow-up	24 months after start ulipristal or surgery
Outcomes measures	**Primary outcome measures with regard to patient:** Fibroid-specific quality of life, measured by the Symptom Severity Score (SSS) as a part of the Uterine Fibroid Symptom Quality of Life (UFS-QOL) questionnaire outcome at 24 months after randomization. **Primary outcome measures with regard to costs (using internet medical consumption questionnaires; iMCQ):** (1) Direct healthcare costs (2) Costs due to loss of productivity (absenteeism from work) (3) Patient costs (informal care, other care services paid for by patients themselves) **Secondary outcome measures with regard to patient:** (1) What is the effect of the intervention on quality of life parameters, such as pain, societal participation and sexual functioning? (2) What is the effect of the intervention on fibroid specific complaints such as volume reduction (UPA group); amount of menstrual bleeding (PBAC-score) and haemoglobin level. (3) What is the re-intervention rate in both treatment groups and how many patients choose for an intervention after treatment with UPA? (4) What is the effect on patient preference and satisfaction? (5) Which complications/side-effects occur? (6) What is the effect of UPA-usage on the blood results, regarding liver function? (7) Which sub-groups benefit most within the study group (subgroup-analysis)

(continued)

Intended inclusions	179 Patients are randomly assigned in a 2:1 ratio to two groups. Intervention group: 119; Comparison group: 60
Temporary on hold	Currently on hold from 18 March 2020. Reason: PRAC Article 31 Referral procedure • PRAC recommendation date: 04 September 2020. Recommendation: Revoke marketing authorization of ulipristal acetate for uterine fibroids • CHMP recommendation date: 13 November 2020. Recommendation: Restricting use of ulipristal acetate for uterine fibroids
Recruitment end date	–
Included patients	38
Overall trial end date	–
Protocol adaptations	–
Other	Currently still on hold, awaiting European Commission Final decision