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Study Protocol

Developmental Clinical Studies - Reversing endometrial glucocorticoid deficiency in heavy menstrual bleeding

"**Dex**amethasone **F**or **E**xcessive **M**enstruation" **DexFEM**

Co-sponsors	University of Edinburgh & NHS Lothian ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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Note: There is no exact SPC since the capsules do not have a marketing authorisation, but equivalents are provided in APPENDIX 1

PROTOCOL APPROVAL

Developmental Clinical Studies - Reversing endometrial glucocorticoid deficiency in heavy menstrual bleeding

EudraCT number 2012-003405-98 (Sponsor's Protocol Code Number **dexFEMv1**)

Signatures

Professor Hilary Critchley Chief Investigator	Signature	22nd August 2017 Date
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Dr Raymond French Sponsor(s) Representative	Signature	23 AUG 2017 Date
Dr Pamela Warner Principal Co-Investigator	PE Warner Signature	22/8/2017 Date

list of abbreviations

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
AE	Adverse Event
AR	Adverse Reaction
bd	twice daily
CRF	Case Report Form
Dex	Dexamethasone
DexFEM	This study [**Dex**amethasone **F**or **E**xcessive **M**enstruation]
DMC	Data Monitoring Committee
EB	Endometrial Biopsy
ECTU	Edinburgh Clinical Trials Unit
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HMB	Heavy Menstrual Bleeding
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
LH	Luteinising Hormone
LH+8	8th day after LH surge
LHu+x	Day of menstrual cycle that is the xth after 'day of LH surge as detected in urine', measured by daily urine dip-sticks [ie day 0 = day of 1st colour change indicating LHu surge detected; so, day LHu+7 = 7th day after 1st LHu surge signal, and this will usually correspond to 'physiological' LH+8]
MBL	Menstrual Blood Loss measurement
MC	Menstrual Collection, of all used sanitary protection
MD	Menstrual Diary
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
RCT	Randomised Controlled Trial
Rx	'Treatment' cycle, either with Dexamethasone, or placebo
RIE	Royal Infirmary of Edinburgh
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TP	Tayside Pharmaceuticals
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

summary

Professional summary

Background Menstrual bleeding complaints affect quality of life and comprise a substantial societal burden, including major impact on health care use and costs. Current medical therapy for heavy menstrual bleeding (HMB) is often ineffective and/or associated with unacceptable side effects. There is unmet clinical need for targeted, effective, medical treatment strategies for HMB. Our findings from research into mechanisms in HMB has led to the conclusion that women with HMB have enhanced endometrial inactivation of cortisol by 11βHSD2 resulting in local endometrial glucocorticoid deficiency, changes in prostaglandin (PG) production, and altered structure and deficient vasoconstriction of the endometrial vasculature. We therefore anticipate that luteal phase "rescue" of endometrial glucocorticoid deficiency will provide a novel approach to therapy for women with HMB. The synthetic glucocorticoid dexamethasone (Dex) is a potent cortisol surrogate and glucocorticoid receptor (GR) agonist that resists 11βHSD2 inactivation. In a non-human primate study we have observed a striking reduction in menstrual blood loss after Dexamethasone administration.

Objectives We aim to show proof-of-concept that Dexamethasone administration in women with HMB will improve the capacity of endometrial vasculature for efficient vasoconstriction when menses commences, and hence reduce menstrual bleeding. Our proposal is a novel use of an existing, well-characterised medical treatment (Dex).

Methods We propose a parallel group randomised controlled trial in women with HMB (confirmed by objective menstrual blood loss (MBL) measurement over two cycles as 50mL or more on average), comparing Dexamethasone (over a range of potential doses) to placebo treatment. The trial design will be response-adaptive, whereby randomisation probabilities change across time to ensure that maximum information is obtained in the critical region of the underlying dose-response curve (that containing the 'optimum' dose). This has the added advantage that relatively more and more women are randomised to the doses emerging as most effective. Such a design is the most parsimonious way to enable both robust demonstration of the therapeutic effect of Dexamethasone on HMB, and reliable identification of the optimal dose to take forward for future further study in a Phase III trial.

Work Up Stage Adaptive designs such as this require a work up stage to enable the simulation modelling necessary to determine a robust final design specification with adequate power (here, the expected number of patients required lies in the range 100-108). In addition this work up stage will allow two clinical studies to be executed. Data collected in these will inform the modelling and simulation, but will also enhance mechanistic and pharmacodynamic understanding of observed Dexamethasone effect, and will be an invaluable preliminary check of safety of *this 'first-in-HMB' use of oral Dexamethasone.* These studies will involve treating in total 20 women with HMB with two cycles of Dexamethasone (1.5mg daily).

RCT The intervention will be oral Dexamethasone treatment randomised to one of a range of doses (between 0.4 and 1.8 mg daily), or placebo. The primary outcome is reduction in objectively measured menstrual blood loss (MBL). Treatment will be twice daily, continuing for 5 days, starting on day LH+8 of menstrual cycle (where LH is Luteinising Hormone, and 'LH+8' the 8th day after LH surge. This Rx start day will be determined as day **LHu+7** where LH**u** is first *detection* of 'LH surge', measured by daily urine dipsticks, or by estimation from recent cycle length data). The expected study size (dependent on simulations of work up stage) will be 108 at most.

Once completed the RCT proposed will provide proof of concept, together with dose/pharmacodynamic data, which will justify further investment in:

(a) A Phase III study of oral Dexamethasone versus current standard therapy;

(b) Development of local Dexamethasone delivery to enhance therapeutic index;

and/ or (c) development of alternative GR agonists for HMB.

Lay summary

Heavy periods are literally a monthly 'curse' for millions of women. Menstrual complaints have a broad negative impact on the lives of women - affecting their everyday activities, including work, family life and relationships. Menstrual problems can occur any time between 12 and 55 years of age, but heavy menstrual bleeding (HMB) is most common between 30 and 50 years of age, which is also the stage when women have numerous aspirations, roles and responsibilities, which would be severely curtailed by menstrual complaints. The regular impact of menstruation (about a quarter of a woman's life - 7 days out of 28) can lead to low mood, which can in turn impact further on quality of life and fulfillment of roles. For those in families with low income, the cost of sanitary protection for HMB can also be a recurring burden on the family budget.

A million women a year seek medical help for their condition, consuming considerable NHS resource, in terms of consultations with GPs (or attendances at hospital clinics) and tests and prescriptions. Unfortunately the treatments on offer are often ineffective and many women complain of unacceptable side effects. Although hysterectomy can solve the problem of heavy bleeding most women would rather avoid taking this 'irreversible' step which is not surprising as close to half of all babies born in the UK have mothers aged 30 or older. There is therefore an urgent requirement for development of novel, effective, medical treatments for heavy periods.

Our plan builds on previous research comparing the lining of the womb in women with and without heavy bleeding. This has provided compelling evidence that the activity of glucocorticoids in the endometrium of women with HMB is deficient. We believe this deficiency results in altered structure of the blood vessels of the womb, which could lead to increased menstrual bleeding. We hope to demonstrate that a glucocorticoid (dexamethasone; Dex), already in common use for other conditions, will reverse the observed endometrial glucocorticoid deficiency, and hence be beneficial in women requesting treatment for HMB.

Dexamethasone will be given to women in the second half of their menstrual cycle, in the week prior to their expected period (menses) and we expect Dexamethasone given over this time period will improve the ability of blood vessels in the endometrium to efficiently constrict when menses commences, and hence reduce menstrual bleeding. While this is a novel use of Dexamethasone, it is in wide-spread use eg .glucocorticoids are used to treat medical conditions in early pregnancy including asthma and rheumatoid arthritis. A lot is already known about the side-effects that can occur with Dexamethasone and that they are dependent on the duration of treatment as well as the dose. This leads us to expect that Dexamethasone will be unlikely to be cause problems during the short courses of treatment we plan to use in this study.

We anticipate that this new medical treatment will benefit women of reproductive age suffering from heavy bleeding by reducing their blood loss, thus improving their quality of life and avoiding time off work or interruption to their participation in family activities. Our beneficiaries will therefore be the women, their families and employers, and in terms of costs saved, society and the economy.

1 INTRODUCTION

1.1 BACKGROUND

Heavy menstrual bleeding

Heavy menstrual bleeding (HMB) is defined as excessive menstrual blood loss which interferes with a woman's physical, social, emotional and or material quality of life.[1] In the UK, 1 million women annually seek help for heavy menstrual bleeding.[1] In women aged between 30 and 40 years it will in many cases be fibroids which are causing HMB and disrupting everyday life.[2] In the US 10-15% of women aged 25-64 will require a hysterectomy for fibroids.[3] There is national recognition that menstrual complaints represent a clinical area of unmet need as evidenced by the first national HMB audit of current practice and patient-reported outcomes (2010-2014) commissioned by the Healthcare QIP.[4, 5]

The cause(s) of HMB are not fully understood, although in some cases it can be the result of pathology (endometrial polyps, fibroids or (pre) malignancy). These can be diagnosed by current clinical investigations (ultrasound, hysteroscopy) and histological evaluation by an expert pathologist using criteria first established in the 1950s. However, approximately 50% of cases of HMB occur in the absence of obvious pathology. In these circumstances HMB is likely to be a consequence of a disturbance in local molecular and cellular mechanisms regulated by sex steroids and their dynamic interplay with the endocrine, vascular and immune systems associated with tissue oedema and immune cell influx. Women with HMB may have (i) decreased vasoconstriction and increased blood flow, (ii) decreased vascular homeostasis, (iii) an excessive inflammatory response at menses, or (iv) defective repair of the post-menstrual endometrium. One or a combination of these peri-menstrual defects will lead to heavy and/or prolonged bleeding. Over-expression of COX-2, disturbed PG signalling, deficient vascular development and abnormal angiogenesis are reported in women with HMB.[6]

Current treatment options

Hysterectomy and endometrial ablation are common surgical treatments (both rendering the woman infertile and the former being major abdominal surgery). The commonly prescribed medical treatments for HMB are:

i. COX-inhibitors, which suppress biosynthesis of PGE2 by inhibition of COX enzyme activity, are a commonly-used first-line treatment during menses for women with HMB.[1, 7]
ii. Anti-fibrinolytic therapy
iii. The progestin-releasing intra-uterine system (LNG-IUS; “Mirena system”) which reduces menstrual bleeding.

End Users and Benefits: End users will be women of reproductive age requesting treatment for HMB, and who will benefit in terms of amelioration of HMB, improved quality of life, capacity to optimise their productivity in employment and to participate in family activities. Therefore, beneficiaries will be the women, their families and employers, and in terms of costs saved, society and the economy.

The trial will be conducted according to GCP. There will be close scrutiny of any adverse events according to protocol.

1.2 RATIONALE FOR STUDY

Current treatments and their limitations:

Treatment costs for HMB have been reported to exceed £65m; an estimated 3.5 million work-days are lost annually.[8] Work loss from HMB is estimated as $1692 annually per woman in US.[4] A recent systematic review conservatively estimated annual direct and indirect economic costs of menstrual bleeding complaint as in the order of $1 billion and $12 billion, respectively.[9] Current medical therapy for HMB (see also 1.1 Current treatment options), is either ineffective or associated with side effects that women find unacceptable (such as break-through bleeding on LNG-IUS). Up to one third of women will fail to respond to the main current medical approaches as follows:

i. COX-inhibitors are inadequate for many women. We suggest this is because they target only some of the downstream consequences of glucocorticoid deficiency, and not the components mediated by other GR targets, eg TSP-1.

ii. Despite increased fibrinolytic activity in women with HMB,[10] anti-fibrinolytic therapy provides only partial relief in some women.[11] In women with MBL > 80mL, tranexamic acid is found to reduce MBL,[12] particularly where baseline MBL is substantial (over 120ml), but despite this many will, continue to have MBL exceeding 80ml. The explanation might be that changes in vascular structure and/or tone play a role over and above any influence of haemostasis, the mechanism targeted by this therapy.

iii. LNG-IUS, a contraceptive, is unsuitable for women with HMB seeking to become pregnant, and in others is unacceptable in up to 1 in 5 users.[13] For some women use of this method results in amenorrhoea, which is not always acceptable, or ongoing and unpredictable unscheduled bleeding, intolerable to many women. Furthermore, although it has been envisaged that LNG- IUS would be a more cost-effective option than surgery, recent economic research concludes that hysterectomy remains the most cost-effective first-line intervention for HMB,[14] highlighting the unmet clinical need for a cost-effective medical alternative to hysterectomy. As many as 1 in 5 women discontinue use of progestin therapies for HMB (systemic and locally delivered) on account of unacceptable and unscheduled bleeding.[13]

In the US 10-15% of women aged 25-64 will require a hysterectomy for fibroids[3] costing the USA $3 billion annually.[15] Hysterectomy[16] is commonly the surgical solution even in the absence of large fibroids, but bears high costs and risks. The CMO identified £15 million could be saved per annum if the hysterectomy rate was reduced. Many women want to avoid having surgery and there are also concerns regarding fertility-ending surgical interventions in this age group (given half of all UK-born babies (47%) are to women aged 30 or older[17]).

In summary, there is an unmet need for sustainable and affordable long-term medical therapy – none to date exists. There is national recognition of current need to address women's menstrual complaints as evidenced by a (first) national audit of current practice in the management of HMB and patient-reported outcomes (2010-2014) commissioned by the Healthcare QIP.[5] Given the demographic trend to later child-bearing[17] there is a substantial unmet need world-wide for a medical treatment for HMB which preserves fertility.

Justification for study

Our proposal is founded upon data from MRC Programme and Project Grants; G0000066; G0500047; G0600048 where we have characterized disrupted glucocorticoid signalling in the endometrium of women with HMB **providing compelling evidence that glucocorticoid deficiency plays an important role mechanistically in modulating processes** that lead to altered structure and deficient vasoconstriction of the endometrial vasculature, and hence to increased menstrual bleeding, and we now also have crucial non-human primate data giving clear support for the proposed intervention.

In the normal cycle, blood vessel proliferation, differentiation and vasoconstriction in the endometrium are tightly regulated to ensure that a controlled and self-limited endometrial shedding occurs at menses. This is followed by a tightly regulated inflammatory response to endometrial injury to ensure successful healing with a return to normal architecture, prior to the next cycle of vascular proliferation.[18] Our recent data[19] have highlighted the importance of glucocorticoid metabolism within the endometrium in modulating local cortisol concentrations.

Endometrial glucocorticoid deficiency in HMB: Glucocorticoids are vasoconstricting and angiostatic steroids which modulate prostaglandin (PG) production.[20] Glucocorticoid deficiency may explain the increased PGE2: PGF2α ratio, reduced anti-angiogenic thrombospondin-1(TSP-1) and relative vasoconstrictor deficiency in endometrium from women with HMB.[21-23] We have shown that endometrium from women with HMB has: (i) increased 11βhydroxysteroid dehydrogenase type 2 (11βHSD2), an enzyme which inactivates cortisol – a finding consistent with local deficiency in endometrial cortisol (thus excess local inactivation of anti-inflammatory glucocorticoid (cortisol) by 11βHSD2;[19] and (ii) displays augmented endometrial COX-2 expression and biosynthesis of PGs[24] and a *higher* PGE2: PGF2α ratio than women with normal blood loss.[23]

Studies of kidney function[25], and of colon tumours[20], have shown that pharmacologic inhibition of 11βHSD2 activity suppresses COX-2 expression. Thus glucocorticoid deficiency links increased expression of 11βHSD2, in endometrium from women with HMB,[19] with over-expression of COX-2, disturbed PG signalling, deficient vascular development and abnormal angiogenesis.[21, 24, 26] Increasing glucocorticoid levels within the endometrium could offer a novel therapeutic approach for women with HMB by modulating vascular development and vasoconstriction at time of menses. There are several potential approaches including use of a GR agonist which is less susceptible than cortisol to 11βHSD2. Dexamethasone (Dex) has higher affinity for GR than cortisol, but lower affinity for 11βHSD2 ('bypasses' the effect of 11βHSD2).

Research hypothesis

Our proposed approach is novel use of synthetic glucocorticoid to "rescue" luteal phase deficiency of cortisol, and thus improve endometrial vasculature and hence vasoconstriction when menses commences, and thus reduce menstrual bleeding.

Description of proposed treatment

On the basis of the above hypothesis our proposed treatment is a new therapeutic use of an existing, well-characterised medical treatment - oral Dexamethasone, a synthetic glucocorticoid and a potent cortisol surrogate. The treatment regimen will be oral Dexamethasone treatment twice daily, continuing for 5 days, starting on day LH+8 of menstrual cycle. However, since timing of cycle is to be by serial urine dipstick-testing, commencing early in the follicular phase (exact day of cycle to start testing being determined according to usual cycle length), treatment start will be day **LHu+7** [where day 0, LHu, is the day of 'LH surge' as identified by dip-stick urine

testing – ie first colour change -, and day LHu+7 = 7 days after that]. In the adaptive trial, women who do not wish to carry out serial dipstick testing, will be permitted to participate. The treatment start date will be estimated from their recent cycle length data.

This will be a first use of any modality of glucocorticoid for treatment of HMB. Dexamethasone-eluting stents have been used following intra-vascular instrumentation to protect against neointimal proliferation while progestogen eluting IUS is well established; a similar strategy for local/ intra-uterine delivery is therefore feasible and innovative.

With regard to evidence that the proposed treatment will be effective, we have demonstrated (in a non-human primate model) that short-term systemic Dexamethasone administration substantially lowers menstrual blood loss (MBL) in female Macaques. The Dexamethasone dose used was equivalent to 1.5 mg daily in a woman of average weight. This dose reduced mean measured MBL by 21% after one treatment cycle, and by 31% after two, and the four animals with heaviest baseline MBL had the greatest reductions (26% to 47%).

***Safety**:* Dexamethasone is well characterised and widely used in clinical care. Glucocorticoids are used to treat medical conditions in pregnancy (in 1st trimester for asthma; rheumatoid arthritis; hyperemesis gravidarum). Side effects are well documented and known to be dependent on duration as well as dose and on the susceptibility of the recipient (eg to diabetes mellitus), so are unlikely to be limiting during short courses in younger women with doses that are 'peri-physiological', as proposed here. Note that typical equivalent doses in an acute exacerbation of obstructive airways disease, for example, would be >3 mg/d, or over 60% more than the maximum dose proposed here.

Further development: This study will provide proof-of-concept and hence will be a stepping-stone to more sophisticated/ targeted steroid treatment of HMB. Given the proposed treatment is an existing, well-characterized drug ‘drug development’ costs will be comparatively low. Demonstration of efficacy will justify both a Phase III trial of oral Dexamethasone treatment versus standard medical treatment, and development of a locally active preparation, eg a Dexamethasone-eluting intrauterine system (IUS). Proof-of-concept with systemic administration will provide evidence/data to fast-track development of local delivery systems.

Research question

Does treatment with short term Dexamethasone ameliorate HMB?

Incidence and diagnosis of HMB

A systematic review in developing countries has reported a prevalence of excessive menstrual bleeding in developing countries of 4 to 9%,[27] while other studies, utilising diverse means of classifying HMB, have reported prevalences of 11 to 52%.[1]

The Nice Guideline recommends that for clinical purposes, HMB should be defined as excessive menstrual blood loss which interferes with the woman’s physical, emotional, social and material quality of life, and which can occur alone or in combination with other symptoms.[1] However, for research purposes, objective confirmation of heavy menstrual blood loss is still employed. We will screen in terms of measured blood loss exceeding 50mL (MBL>=50), and assess treatment effect in terms of reduction in MBL, but will also assess subjective impact of periods before and on treatment.

What would be a worthwhile improvement in study outcomes?

In trials of medical treatments for HMB it is generally held that a 25% reduction in MBL would be a worthwhile improvement. However, it has also been recommended

that any interventions should aim also to improve quality of life measures.[1] We will also ascertain subjective assessment of treatment effect and 'satisfaction' with treatment effect on periods will be a secondary indicator of worthwhile improvement.

2 STUDY OBJECTIVES

Note that in sections 2 and 3 we have to provide details for our set of 3 clinical studies – the two small clinical studies in the work up stage, and the main adaptive RCT. In order to make this as clear as possible we will, where needed, separate out into **Work-up clinical studies** (grouped as a pair, but to be specified as Study 1 and Study 2) and **adaptive RCT** (study 3).

2.1 OBJECTIVES

2.1.1A Primary Objective for Workup studies

To gather preliminary safety and efficacy data from first-in-HMB use of oral dexamethasone (Dex), in women suffering from objectively verified HMB

2.1.2A Secondary Objectives Work up studies *(across both Workup studies, unless specified otherwise)*

i. To collect *additional* information (for example, establishing levels of within- and between-participant variability in laboratory-measured MBL) that could be fed into development of the adaptive RCT design
   - To assess effect of Dex on co-occurring period pain (which is a strong factor in treatment-seeking for HMB.[12, 14])
   - To explore effect of Dex according to baseline MBL, in particular the subgroup of patients with MBL 50 to 79mL, and subgroup with MBL 80mL or higher. This is because the majority of treatment trials have selected on MBL >80mL, but many women presenting with complaint of HMB have MBL<80mL.[7, 28] Therefore there is as yet no published evidence to guide treatment strategy for them.
   - To relate diary assessment of treatment effect against measured MBL.
   - To explore whether Dexamethasone has a carry-over effect.

ii. In mechanistic workup study *(Workup 1 only)*:
   - To establish whether endometrial biopsy is an indicator of MBL change and of Dexamethasone treatment effect
   - To determine MRI perfusion changes under Dexamethasone treatment
   - To assess predictive value of MRI for endometrial biopsy findings and ensuing MBL
   - To examine whether an assay can be developed for Dexamethasone concentration in endometrial biopsy

2.1.1B Primary Objective for adaptive RCT

To identify the optimal dose of oral dexamethasone (Dex) for amelioration of HMB in women with objectively verified HMB

2.1.2B Secondary Objectives adaptive RCT

i. To gather safety data for Dexamethasone in women with objectively verified HMB
ii. To collect information to enable development of local delivery system(s) for Dexamethasone
iii. To establish that an adaptive trial design is an efficient method of screening doses to identify which should be taken forward to a Phase III trial against standard treatment

2.2 ENDPOINTS

2.2.1A Primary Endpoint Work up studies

Study 1 (Mechanistic) Change in mean MBL between baseline and Dexamethasone treatment cycles

Study 2 Difference in mean MBL between placebo and Dexamethasone treatment cycles

2.2.2A Secondary Endpoints Work up studies

Menstrual diary score for volume of menstrual period
Satisfaction with treatment
Unacceptable side-effects
Period pain
Mechanistic (Study 1) examination of response to luteal phase administration of Dexamethasone, by comparing an un-treated and a treated cycle in terms of:

- Endometrial tissue ~ cellular markers of vessel differentiation
  ~ inflammatory markers
- Dexamethasone concentration in tissue & blood
- Blood flow ie MRI assessment of perfusion and permeability
  ~ ovarian function
  ~ mechanistic blood parameters eg glucose, lipid profile, full blood count

2.2.1B Primary Endpoint adaptive RCT

Change in mean MBL between baseline and cycles during randomised (Dexamethasone/placebo) treatment

2.2.2B Secondary Endpoints adaptive RCT

Menstrual diary score for volume of menstrual period
Satisfaction with treatment
Intolerable side-effects
Period pain

3 STUDY DESIGN

The main research proposed is a response-adaptive parallel group randomised trial comparing Dexamethasone (in a range of doses from 0.4 to 1.8 mg total dose per day) to *placebo* treatment.

A response-adaptive parallel group trial will:

- adapt the treatment allocation probabilities in response to the outcomes recorded on patients who have already completed the trial, in order to maximise the information gathered about the dose-response relationship;
- identify the optimal dose, with flexibility to handle a variety of potential shapes of underlying dose-response curves;
- ensure as few women as possible are randomised to ineffective (or less effective) doses;
- maximise the study power to estimate the effect of Dexamethasone versus placebo.

Development of this adaptive design requires a Bayesian approach and extensive preliminary simulation studies to explore empirically the performance of candidate designs under a range of assumptions. Reliable information is needed to determine which assumptions are relevant/ plausible, and, given that Dexamethasone has

never before been used for HMB, the 'first-in-HMB' work-up studies will also inform the modelling and simulation.

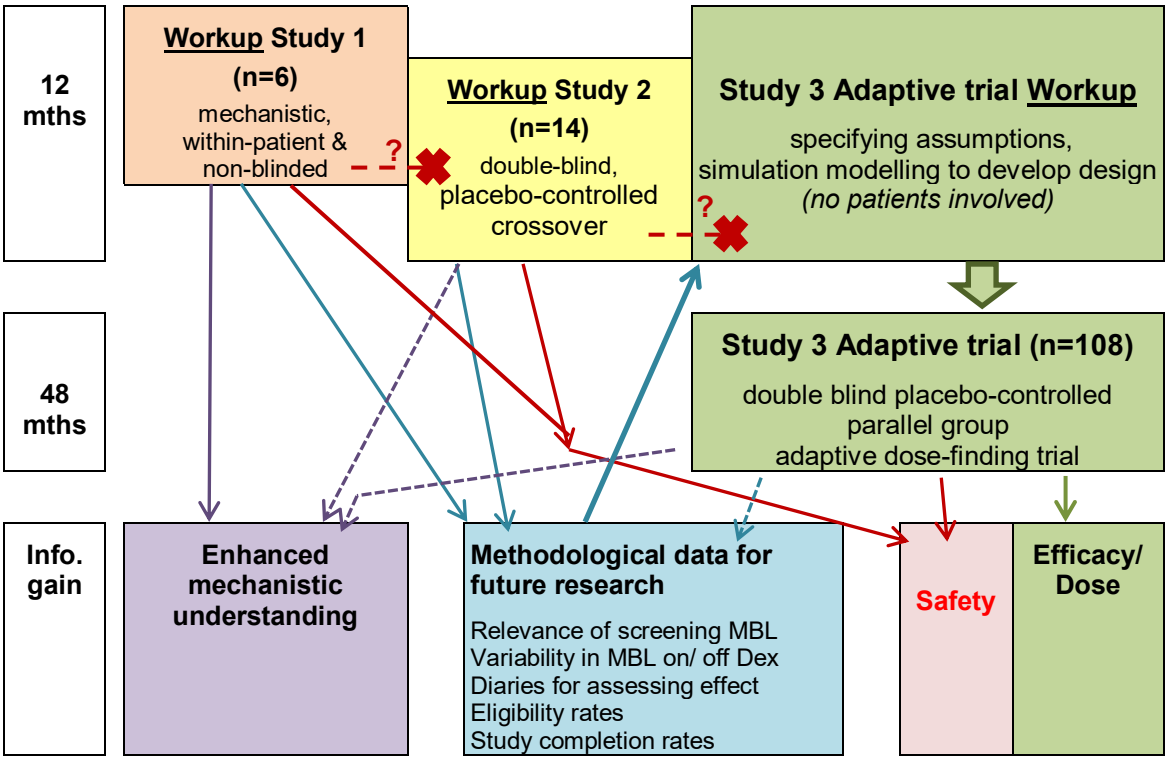
3.1 DESIGN

The research will proceed as:

- a **Workup** stage (comprising Simulation work and design development for the adaptive trial, plus 2 preliminary clinical studies), followed by
- execution of the main **Adaptive RCT**.

This is illustrated in the diagram below and described in more detail in the following sections.

Diagram 1 Mapping studies & information gain across Workup and Adaptive Trial phases (12 months & 54 months respectively ie not to scale)



This diagram shows (dashed red lines) that serious safety concerns at the end of Workup Study 1 could lead to stopping Study 2, or concerns arising from Study 1 and 2 combined could prevent study 3 from going ahead. It also shows that if all three studies go ahead, they will all contribute data regarding safety (solid red arrows). Study 1 will provide mechanistic understanding, and to an extent, indirectly, so will studies 2 and 3. Methodological data derived from Studies 1 and 2 feed into the Workup stage of study 3 (thick blue arrow), and if the adaptive trial goes ahead, it also will contribute to methodological knowledge.

i. **Work-up** (12 months) will consist of a series of simulation studies for the adaptive trial, to ensure the robustness of the adaptive trial design, plus two preliminary clinical studies to obtain methodological data that can contribute to the modelling, to enhance mechanistic understanding of observed Dexamethasone effect, and as a valuable first check of safety of oral Dexamethasone at 1.5mg per day.

   a. ***Adaptive design simulation studies***
   These will involve no patient recruitment/data collection, but parameters fed into the models might be altered in the light of data emerging from the

preliminary clinical studies. Preparatory simulation studies will confirm the robustness of the adaptive trial design. Simulations will be performed via fractional factorial design, covering a range of design options and model assumptions.
The design options to be considered will include:

1. Number of active doses;
2. The criterion by which the randomisation schedule will be adapted: options include minimising the variance of some relevant parameter such as ED_{95} (the minimum dose with near-maximal efficacy);
3. The length of the "run-in" period during which the initial randomisation schedule is fixed, until sufficient MBL outcomes are available to inform adaptation;
4. After 'run-in', the frequency with which the randomisation schedule should be adapted.

Assumptions to be assessed include:

5. The shape and parameters of the true dose-response curve for Dexamethasone on the primary outcome, MBL change from baseline.
6. The variance of the primary outcome, guided by the data gathered in the crossover work-up study 2.
7. The accrual rate of patients to the study.

Although a Bayesian approach will be used to permit effective adaptation within the design, the performance of the adaptive design will be assessed in terms of its frequentist properties (statistical power and significance level) across combinations of the above assumptions and design options. The final design selected will be one which performs well across a broad range of scenarios.

b. ***Clinical Workup study 1 - 'First-in-HMB' (mechanistic)*** (**Figure 1)**: In a non-blinded study, six patients will have luteal phase endometrial biopsy and MRI for each of: one non-treated cycle, and the second of two following cycles treated with Dexamethasone 1.5mg daily.

Figure 1 Design for Workup Study 1 ('First in HMB' study (n=6)

Screen	No Rx	Dex 1	Dex 2
M	M+	M	M+

Key: 1 column = 1 research 'cycle' ie from first non-period day to end of next period
D= diary only, **M**= MBL & diary, **M+** = M plus MRI & endometrial Biopsy

Women will have to complete one screening cycle, and only if MBL>=50mL will they proceed to participate in the study, involving one untreated cycle followed by two treated cycles. Participants will have MBL and diary assessment in all 4 of these cycles.

Total duration of participation is 4 cycles (including screening). The Dex-treated cycles should be consecutive. However, if necessary to enable participation (ie to accommodate holidays, absence from home etc, that might overlap with study urine testing/collection or a menstrual collection), a gap is permissible between uplift of screening period MBL collection and commencing participation in study 1, or between uplift of no treatment cycle MBL collection and the first Dex treatment cycle. A maximum of one menstrual period may be 'off-study' in this way, and participation would need to re-commence in time for the urine collection/dip-stick testing required leading up to the next menstrual period.

c. ***Clinical Workup study 2 - Methodological refinement***

We *will undertake a double-blind crossover trial of up to 14 women* – comprising one screening cycle, followed by 2 treatment blocks of two cycles each, where the treatment in a block will be placebo or Dexamethasone (1.5mg daily), randomised to order (**Figure 2**) ie either placebo then Dexamethasone, or the reverse. Women will have to complete one screening cycle, and only if MBL>=50mL will they proceed to participate in the study.

Figure 2 Design for Workup Study 2 – (Methodological study (n=14)

	1st Rx block		2nd Rx block	
Screen	**1st cycle**	**2nd cycle**	**1st cycle**	**2nd cycle**
M	D	M	D	M

Key: 1 column = 1 menstrual cycle
D= diary only, **M**= MBL & diary,

Total duration of participation is 5 cycles (including screening).There will be diary assessment in all periods, but MBL only in screening and in the second cycle of each 'treatment' block. (See section 7 Table 2 for further detail of assessments.) The pairs of cycles within a treatment (Rx) block should be consecutive. However, if necessary to enable participation (ie to accommodate holidays, absence from home etc, that might overlap with urine dip-stick testing/ menstrual collection), a gap is permissible, between uplift of screening period MBL and randomisation into study 2, or between uplift of MBL collection at the end of the first 2-cycle treatment block and the next 2-cycle treatment block. A maximum of one menstrual period may be 'off-study' in this way, and participation would need to re-commence in time for urine dip-stick testing required leading up to the Rx prior to the next menstrual period.

ii. **Adaptive RCT execution phase, Study 3** (54 months) – this will be the response-adaptive, double blind, parallel group, dose-finding randomised controlled trial informed by the workup stage. The design is shown in **Figure 3**.

Figure 3 Design for Study 3 (Adaptive RCT) (n=up to 108)

Screen		**Rx**		
M	M	D	M	M

Key: 1 column = 1 menstrual cycle
D= diary only, **M**= MBL & diary,
Rx = adaptively randomised to one of 6 Dexamethasone doses, or placebo, double blind

Total duration of participation is 5 study menstrual cycles. If necessary, to enable participation (ie to accommodate holidays, absence from home etc, that might overlap with urine dip-stick testing/a menstrual collection), an elective gap is permissible between uplift of second screening period MBL collection and randomisation to study 3. A maximum of one menstrual period may be 'off-study' in this elective way, and participation would need to re-commence in time for urine dip-stick testing required leading up to the Rx prior to the first Rx menstrual period.

Ideally, the three Rx cycles should be consecutive. In this study, administration of treatment each cycle is date-specified, by counting days after LH surge, or estimating this date from history of cycle lengths so far (see page 13/14). However, women's menstrual cycles can vary markedly in length, especially in the run up to menopause. Occasionally a very short cycle may occur, such that menstrual bleeding commences without an LH surge having been detected, and before the

last possible treatment start date that had been calculated from the cycle length history so far. Either way, such occurrence of a random very short period would mean no treatment at all could or would have been taken, and hence the cycle remains untreated. [The issue here is not 'accidentally' omitting to take treatment, but the natural vagaries of menstrual cycles making Rx administration an impossibility in some cycles.] For such occurrences the procedure will be that the very short cycle is *excluded* from the study cycles being considered for evaluation of treatment effect on MBL. The treatment supplied, and assessments of period, will be rolled forward to the *next* menstrual cycle. The aim of this approach is that each participant has three 'treatable' menstrual cycles (defined as cycles in which the menstrual period commences more than 7 days after the dip-stick detection of LH, or commences after the historically-calculated date for starting treatment). This approach means that, in the case of a few patients, if a very short cycle intervenes, her three treatment cycles will be non-consecutive.

Therefore, although participation comprises a maximum of 5 'study' cycles – two screening and three treatment - it is theoretically possible that the woman's participation might encompass more than 5 consecutive menstrual cycles – taking into account the possibility of an elective 'study break' (as described above, between screening and first treatment cycle) and the possibility of very short ('untreatable') cycles occurring during the treatment phase (albeit these likely to be uncommon).

The adaptive dose-finding trial will evaluate the effect of oral (systemic) Dexamethasone across a wide range of doses with the aim of identifying the minimum dose with near-maximal efficacy: that is, the optimal dose to be studied in a subsequent Phase III trial. Placebo plus 6 active doses will be studied i.e, total daily doses of 0.4, 0.8, 1.0, 1.2, 1.5 and 1.8 mg. [The dose set includes the 1.5mg total daily dose for which initial efficacy and safety data will already have been gathered in the workup studies.] For the entire study a fixed proportion of participants will be randomised to placebo (2/7). and the remainder randomised to one of the 6 Dexamethasone daily doses, For an initial period there will be equal allocation across the 6 Dexamethasone arms, but at intervals after this the randomisation probabilities for Dexamethasone doses will be adapted (i.e.after approximately 16, 32, 50, 66 and 84 patients have been randomised) with adaptation based on the MBL outcomes recorded in the trial to date. The updates to the randomisation probabilities will ensure that maximum information is obtained in the critical region of the underlying dose-response curve (that which contains the 'optimum' dose), which has the added advantage that as the trial progresses relatively more and more women will be randomised to the doses emerging as most effective The primary outcome, MBL, is well suited to the adaptive design context: MBL data are promptly available after treatment, giving the potential for rapid adaptation to the accumulating data.

3.2 STOPPING RULES

Appendix 4 presents a chart of the timing of screening, 'treatment' and final follow up for the two clinical studies in the Workup phase. This shows that recruitment and treatment for Study 2 will commence before Study 1 is completed.
There will be no stopping rules for non-blinded workup study 1 (n=6, who should all complete within two months of each other). However, study clinical staff will be in regular contact with all patients throughout their involvement. If patients report side-effects that trouble them or are of clinical concern then the Trial Steering Committee will consider discontinuation of the study in consultation with the Trial Management Group. For the crossover trial (study 2) and the adaptive RCT (study 3), no formal stopping rules will be implemented via interim analysis for futility or efficacy. An independent data monitoring committee DMC will be convened to review unblinded

data during study 2 to monitor the emerging safety data, and in study 3 to regularly review the safety and efficacy data including the proposed adaptations of the randomisation schedule. This DMC will be able to recommend termination of either study in the event of major safety concerns being identified. The independently-chaired Trial Steering Committee will guide the decision on whether to proceed to study 3 following studies 1 and 2.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

In the three studies the expected numbers of participants will be 6, up to 14 and up to 108. Greater numbers than this will need to be screened (approximately 12, 28 and 220 respectively).The recruitment periods are expected to be 3 months, 5 months and up to 48 months. The number of sites involved is 4 – all NHS Lothian. Patients may thus be seen at:

- community gynaecology clinic for HMB (Chalmers, Chalmers St), or
- hospital gynaecology clinics in NHS Lothian to which they have been referred (RIE, StJH, Roodlands).

The participant population will be women complaining of HMB who are referred to secondary care or the Chalmers clinic for management, plus any patients self-referring, as allowed, to Chalmers. Additionally:

(i) Through the auspices of the Scottish Primary Care Research (SPCRN), letters about the study will be sent to potentially eligible women on co-operating Lothian GP practice lists, specifically to women who have codes recorded on the GP system that are possibly suggestive of HMB. Letters will come from each woman's GP and enclosed with the letter will be a brief preliminary information leaflet about the research. (In addition, we will follow up with a reminder letter, but not to any who have replied.) Some of the GP practices might request study leaflets to have to hand in the surgery, in case a patient consults with HMB, who has not been selected by the list search as a 'possible' for HMB. The same preliminary leaflets will be made available to GPs to give to patients if they decide they wish to do so. The next step would be GP referral in the usual way, or the woman could contact the study directly via the telephone number on the leaflet, as for SPCRN mail-out.

(ii a) We will seek media coverage of the trial, including the use of social media such as Facebook, and invite any women with the complaint and possibly interested in the trial, to contact us for more information and/or telephone discussion (the same preliminary information leaflet as above could be posted out to enquirers, if they indicate they would like this).

(ii b) We have prepared a press advertisement and also a poster for placing in Lothian NHS clinical areas (GP practice surgeries and community and hospital gynaecological clinic areas). These invite any woman with the complaint and possibly interested in the trial, to contact us for more information and/or telephone discussion (in the same way as above, preliminary information leaflets could be posted out to enquirers, if wished).

(iii) We will collaborate with the NHS Research Scotland register (SHARE) to search for women living in Lothian, and nearby areas such as Borders and Fife, who may be potentially suitable to participate in DexFEM. The SHARE staff will search the register, contact women who might be suitable, and, may send the woman a preliminary information leaflet. With permission from individual women thus contacted, SHARE will pass contact details to the research team of women who have indicated they are interested in participating in DexFEM.

Any of these women (i, ii a and/or b, and iii above) who reply to the study team that they might be interested in participation in the research, will receive full information about the research (patient information sheet – PIS), and will be given appointments at RIE or Chalmers to discuss participation with the clinical research team prior to consent being taken.

4.2 INCLUSION CRITERIA

Women will be invited to participate in screening phase if they fulfil the following criteria:

- **Complaint of HMB**, including women with fibroids
- Pre-menopausal
- Age 18 years and over
- Describing menstrual cycles every 21- 42 days
- Provide written informed consent prior to any study related procedures and be able to comply with study related procedures

If the woman is considered at risk of pregnancy - that is, she has not been sterilised nor undergone bilateral salpingectomy, and is at any point in the study sexually active with any man who has neither been sterilised nor has confirmed azoospermia - then she is willing to use a non-hormonal method of contraception (condom, diaphragm) for that sexual relationship, until her participation in the study has ended. Women will proceed to participate in research study treatment phase only if they fulfil the additional screening criterion (based on the MBL volume) relevant to the study (i.e. Study 1 or 2 or 3) for which they are being screened:

- **Workup (**Study 1 or 2)– MBL for single screening period is >= 50mL
- **Adaptive RCT (**Study 3)– average MBL for two screening menstrual collections is >= 50mL

4.3 EXCLUSION CRITERIA

To be eligible for inclusion in this study women must **not** meet **any** of the following exclusion criteria:

- Planning a pregnancy during their period of study participation
- Currently breast-feeding
- History or current uterus, cervix, ovarian or breast cancer
- Known severe coagulation disorder
- Needing to, or intending to, continue taking any of the **prohibited medications** listed hereunder (see page 28 section **6.7.3** for more details):
  - ~ Warfarin
  - ~ Glucocorticoid treatment with systemic, or inhaled, or 'potent' topical, or 'very potent' topical preparations
  - ~ Sex steroid administration by any route
  - ~ GnRH agonist or antagonist
  - ~ Acetylsalicylic acid
  - ~ Mefenamic acid or antifibrinolytic drugs such as tranexamic acid

  *For all these prohibited medications, a patient who has been taking such medication may be included in the study **subject to an adequate wash-out period** prior to screening MBL collection – see table at end of this list (overleaf)*
- Renal or liver dysfunction
- Has active Graves' disease

- Ongoing thyroid dysfunction and who have abnormal TFTs in the 3 months prior to the screening visit
- Diabetes mellitus
- Pharmocologically-treated moderate/severe hypertension
- Psychotic depressive illness
- Hereditary galactose intolerance, lactase deficiency or glucose galactose malabsorption (due to lactose content of trial medication)
- Has a problem with alcohol or drug abuse
- Has a mental condition rendering her unable to understand the nature and scope of the study
- Participation in treatment phase in any earlier DexFEM study (1 or 2)
- Is currently enrolled in an investigational drug or device study or participated in such a study within the previous 30 days and is still in exclusion period
- For the first workup study (Study 1), only, there will be an additional exclusion criterion of any contra-indication to MRI (eg claustrophobic feelings)

For Table of wash-out times please see overleaf.

Wash-out times required prior to (first) screening menstrual collection		
Prohibited medication		**Wash-out**
GnRH agonist/ antagonist:	3 to 6 month sustained-release preparation	52 wks
	Immediate or monthly sustained-release preparation	26 wks
Glucocorticoid -	systemic, inhaled, or potent/very potent topical*	4 wks
Sex steroid:	Progestins (systemic/ progestin-releasing intra-uterine system)	4 wks
	Oral contraceptive,	4 wks
Acetylsalicylic acid,		1 wk
Mefenamic acid or antifibrinolytic drugs such as tranexamic acid		1 wk
Warfarin		1 wk

* *See list of **potent/very potent topical** glucocorticoid preparations in section 6.7.3 (box) page 28*

4.4 CO-ENROLMENT

Women participating in DexFEM cannot be co-enrolled into another investigational drug or device study or participated in such a study within the previous 30 days.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

We will recruit women **with complaint of HMB**, referred to gynaecological services in NHS Lothian. NHS Lothian operates a centralised clinic appointment booking system.

The research nurse and CRF will attend relevant gynaecology clinics across NHS Lothian (Royal Infirmary Edinburgh which receives approx. 400 referrals with menstrual problems per quarter, as per a 4-week audit in 2009/2010; St John's Hospital; Roodlands). We will also have access to women self-referring, or referred with HMB to the medical gynaecology clinic at Chalmers Hospital (Edinburgh Community Health Partnership; Sexual & Reproductive Health Services; collaborator, Dr AE Gebbie). Women attending these NHS clinics with a complaint of HMB will be approached by clinical research nurses, clinical research fellows (who are all part of the direct care team) and medical staff providing care to women with gynaecological complaints in NHS Lothian.

Given the large throughput of referrals to routine menstrual dysfunction clinics, and the limited number of clinicians/research nurses with detailed knowledge of the DexFEM study, there is a risk that some women referred to the clinics with HMB, who might welcome participation in the DexFEM study, might not have the DexFEM research mentioned to them when attending their clinic appointment. Therefore women awaiting appointments at the menstrual dysfunction clinics at RIE will be sent a study preliminary information leaflet and covering letter from the PI, who is a member of their direct care team. This will allow patients who are possibly interested in the DexFEM study to contact the research team directly, and discuss further what taking part in DexFEM would involve. This will reduce the chance of women referred with HMB missing the opportunity to participate in DexFEM.

In addition (see also 4.1 page 21):

(i) We will collaborate with the Scottish Primary Care Research Network (SPCRN) who will set up a process to write to potentially eligible women who have a complaint of HMB recorded in the record system of SPCRN-collaborating GPs. Women will be contacted via their GP and asked to contact the research team directly if they may be interested in taking part in the study. Follow up reminder letters can also be sent, to those who have not replied.

(ii) We will advertise the trial in the media (local press, radio etc), and using social media such as Facebook, and also place posters in NHS Lothian clinical areas (GP surgeries, community and hospital gynae clinic areas) giving a contact number for any women interested to participate in the trial.

(iii) We will collaborate with SHARE to search the SHARE register for potentially suitable women with HMB who might be interested in participating in DexFEM.

5.2 CONSENTING PARTICIPANTS

Women referred to NHS gynaecology clinics, responding to SPRCN letter, media coverage, or an invite via the SHARE research register, who have expressed interest in participation in DexFEM, will be given the study Patient Information Sheet and allowed ample time to read the information and consider whether they wish to participate in the study. Those taking consent will be the CI, the clinical research fellow(s) appointed for the study, and other medical staff assisting with support for the study.

5.3 SCREENING FOR ELIGIBILITY

Screening for work-up will require one baseline MBL measurement >= 50ml. Entry into adaptive RCT will require baseline MBL >= 50ml averaged over 2 periods.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

They will be offered routine NHS gynaecological care.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

The first workup study (Study 1) is an open study which is not randomised. For studies 2 and 3, randomisation will be carried out by an authorised research team member (CI, clinical research fellow, other medical staff assisting with the study, study research nurses) via the web-based randomisation service to be managed centrally by ECTU. This randomisation service will be available 24 hours a day, 7 days a week.

Study 2 The second workup crossover trial (Study 2), randomisation will determine which of the two possible orders of treatment will occur (placebo then Dexamethasone, or vice versa; double blind, n=14). Random permuted blocks will be applied in random sequence to enable approximately equal allocation of 7 participants to each ordering of treatments.

Adaptive RCT Study 3 The adaptive RCT (Study 3), randomisation will be double blind and proceed in six phases. Across the entire study a fixed proportion of patients (2/7) will be allocated to placebo, in order to protect the interpretability of the trial results from any drift in participant characteristics during the course of the RCT. . During phase one (approximately the first 16 patients enrolled) the remainder of patients will be assigned to one of the active Dexamethasone daily doses with equal allocation across Dexamethasone groups. At the end of the first and next 4 phases – that is, after approximately 16, 32, 50, 66 and 84 patients have been enrolled -, adaptive randomisation will be implemented. In the later phases, the probability of a patient

being assigned to any of the active Dexamethasone doses will change according to the cumulative MBL outcomes of patients already enrolled in the RCT by the end of the preceding phase. The NDLM (Normal Dynamic Linear Model) analysis (see section 9.2) will be run at regular intervals to allow the randomisation schedule to be adapted in the light of the accumulating MBL primary outcome data. (The intervals between adaptations to randomisation have been determined from the results of the modelling and simulations performed during the workup stage.) The allocation probability for each active Dexamethasone dose will depend on the amount of new information that it would be expected to provide about the underlying dose-response relationship, based on the results so far. Specifically, this utility measure would be the variance of some relevant parameter such as ED_{95} (the minimum dose with near-maximal efficacy).

The independent DMC will monitor the progression of the adaptive randomisation to ensure that the randomisation schedule is being adapted appropriately in response to the MBL data accumulating in the trial and in the light of the safety data being gathered.

5.5.2 Treatment Allocation

For studies 1 and 2, ECTU will supply treatment package numbers (study 1) or randomisation numbers (study 2) to Tayside Pharmaceuticals to be included in the labelling of the treatment capsule bottles.

For study 3 ECTU will supply randomisation numbers to RIE Pharmacy to be included in the treatment capsule bottle labelling. RIE Pharmacy will dispense treatment on receipt of a valid prescription in accordance with the treatment allocation list and dosing schedule.

Study IMP/Placebo capsules will be uplifted from Tayside Pharmaceuticals by TPS Medical (a pharmaceutical wholesaler) and delivered to RIE Pharmacy, marked for the attention of Hazel Milligan. For ‘dispensing’ to each patient, a clinical member of the study team will collect the relevant study medication (for studies 2 and 3, according to randomisation code) from pharmacy, and the medication will either be handed over to the patient at a clinic visit, if timing of visit is suitable, or will be delivered to the patient’s home by one of the study research nurses (no more than two bottles at one time).

5.5.3 Emergency Unblinding Procedures

In the double blind studies (workup crossover study 2 and adaptive RCT study 3), neither the patient nor the Investigator will know which treatment has been allocated. Breaking of the study blind should only be performed where knowledge of the treatment is essential for further management of the patient. Unless there is such a clinical requirement, the blind will not be broken until after data entry is complete, the validity of the data is checked, all queries resolved and the patient populations agreed. Unblinding of the treatment allocation for a patient can only be performed by contacting the Edinburgh Clinical Trials Unit (ECTU). The relevant contact names, telephone and fax number will be provided by the ECTU to the trial site and Sponsor in a working practice document.

5.5.4 Withdrawal of Study Participants

In all studies, if a patient is unable to tolerate the trial medication or develops a significant adverse event, or falls pregnant (see section 11), trial medication will be discontinued. The patient will be followed up for safety and efficacy outcomes. An early termination visit would be conducted and would include a check of safety bloods. Participants can withdraw at any time, or the investigator or care-providing clinician may withdraw the patient if it is deemed medically necessary. The reasons for withdrawal/ discontinuation and any adverse events will be recorded. A clear distinction will be made as to whether the patient is withdrawing from trial treatments/procedures

whilst allowing further follow-up, or whether the patient is also refusing further follow-up.

6 INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

6.1.1 Study Drug Identification

The test drug is oral Dexamethasone. The proposed study drug will be taken orally in capsule form, so no delivery technology (e.g. proprietary materials) will be required.

6.1.2 Study Drug Manufacturer

Tayside Pharmaceuticals* (TP) (MIA(IMP) 14076) will be responsible for the manufacture of Dexamethasone Capsules using Dexamethasone Micronised Powder Ph Eur, Lactose Ph Eur and hard gelatin capsules. Full details of the manufacture will be included in the Abbreviated IMP Dossier for submission to the MHRA. All manufactured batches of IMP will be released by a TP Qualified Person.
* *Tayside Pharmaceuticals* | *Ninewells Hospital* | *Dundee* | *DD1 9SY*

6.1.3 Marketing Authorisation Holder

The capsules to be used do not have a Marketing Authorisation.

6.1.4 Labelling and Packaging

Work-up Study 1 (Study 1; unblinded)

TP will manufacture Dexamethasone 0.75mg capsules and will provide two bottles containing 10 capsules for each patient. The bottles will be labelled “One capsule to be taken twice a day” and the bottles will be identified as Cycle 1 and Cycle 2. All labelling requirements of Annex 13 of EU Guidelines to GMP will be included on the bottles.

Work-up Study 2 (Study 2; blinded cross-over)

TP will manufacture Dexamethasone 0.75mg Capsules and matching Placebo Capsules. Each patient will receive two bottles of 10 Dexamethasone Capsules and two bottles of 10 Placebo Capsules The bottles will be labelled “One capsule to be taken twice a day” and will be identified as Cycle 1, Cycle 2, Cycle 3 and Cycle 4 according to the randomisation schedule. All labelling requirements of Annex 13 of EU Guidelines to GMP will be included on the bottles.

Adaptive trial (Study 3)

TP will manufacture bulk supplies of active and placebo capsules for all arms of the trial (6 strengths of Dexamethasone 0.2, 0.4, 0.5, 0.6, 0.75 and 0.9 mg capsules plus matched Placebo) and the bulk containers will be labelled to identify the strength of the capsules.

These will be held by Pharmacy, Royal Infirmary of Edinburgh and will be dispensed on receipt of a valid prescription in accordance with the treatment allocation list and dosing schedule and labelled from the bulk supplies by the Pharmacy, Royal Infirmary of Edinburgh. Each patient will receive treatment for 2 cycles, 2 bottles of 10 capsules of either placebo or one of the doses prepared (for treatment bd over 5 days), followed by 1 bottle (for 3rd cycle treatment) of 10 capsules (for treatment bd over 5 days). The bottles will be labelled “One capsule to be taken twice a day”. All labelling requirements of Annex 13 of EU Guidelines to GMP will be included on the bottles.

6.1.5 Storage

The active and placebo capsules manufactured by TP must be stored at 15 to 25 °C.

6.1.6 Summary of Product Characteristics or Investigators Brochure

The Summary of Product Characteristics (SmPC) is given in Appendix 1.

Since the active and placebo capsules used in this trial are manufactured from Dexamethasone Powder Ph Eur and/or Lactose Powder Ph Eur, they do not have a Marketing Authorisation and therefore there is no SmPC or Investigator's Brochure. An Abbreviated IMP Dossier will be produced for submission to the MHRA along with the CTA Application.

The SmPC for Dexamethasone Tablets BP 2.0mg (Aspen) is included as Appendix 1a and this lists the range of contra-indications, precautions, warnings and side effects associated with Dexamethasone therapy. The same information will apply to the Dexamethasone Capsules to be used in this study.

No SmPC exists for Lactose Ph Eur. No side effects are attributable to Lactose Ph Eur and the only known warnings and precautions for use are patients with rare hereditary galactose intolerance, lactase deficiency or glucose galactose malabsorption. Patients with the conditions should not be included in the trial. (Appendix 1b – SmPC for German licensed Placebo Tablets – MA 6927122.00.00)

6.2 PLACEBO

Tayside Pharmaceuticals will manufacture Placebo Capsules (Lactose Ph Eur in a hard gelatin capsule) to match active Dexamethasone Capsules.

6.3 DOSING REGIME

Oral Dexamethasone treatment twice daily, dose not taking weight into account, fixed in workup studies (1.5mg in total per day, bd), randomised in RCT (0.4 to 1.8 mg in total per day, bd). Treatment will continue for 5 days, starting on day LH+8 of menstrual cycle, which will be identified as day **LHu+7**, where LHu is the day of 1st colour-change on serial dip-stick-testing of urine.

In case a study participant does not detect an LH surge by means of dip-stick testing, we will, for each treatment cycle, specify a latest day in the cycle to commence treatment, to avoid missed treatment. For each individual woman her 'fall-back' treatment start date will be calculated 'pro rata' on the basis of her cycle length documented in previous cycles eg screening. For example, for a woman with a standard 28 day cycle, the day of LHu surge (detected in urine) would be expected to be day 13, and hence treatment would commence on days 20 to 24, ending 4 days before start of her next period. Such a woman will be instructed to start treatment on day 20 if she fails to detect a LH**u** surge before that.

6.4 DOSE CHANGES

None anticipated

6.5 PARTICIPANT COMPLIANCE

Women will be asked to keep a Testing &Treatment Record (diary) to record study medication intake. Women will be asked to bring study medication to each visit or at end of each treated cycle – so medications may be counted for compliance. They will be asked to return all unused medications (tablets in a bottle). These will be recorded in the CRF and destroyed by Pharmacy.

6.6 OVERDOSE

If overdose occurs, no specific antidote or treatment is required. The maximum supply of drug any woman will have at any time is as below:

Study 1 of work up: women have 2 bottles of medication at a time in their possession (0.75mg capsules to be taken twice daily for 5 days)

Study 2 of work up: women have 2 bottles of medication at a time in their possession (0.75mg capsules to be taken twice daily for 5 days)
Study 3 (adaptive trial): women have in their possession no more than 2 bottles of medication at doses 0.4-1.8mg daily for 5 days

6.7 OTHER MEDICATIONS

6.7.1 Non-Investigational Medicinal Products

In the first workup study (Study 1) women will be administered Gadolinium for the purposes of MRI (two MRIs scans per woman).

Gadolinium is used routinely in the context of MRI. The standard dose which we will be using is 0.2mg/kg. In a very small percentage of cases people may experience hypersensitivity or an allergic reaction to gadolinium. Side effects are very rare but can include mild headache, light -headedness, urticaria, wheezing, nausea and vomiting and local pain.

If eGFR is normal at screening then it is unlikely that there will be any change to renal function after two doses of the gadolinium contrast.

In order to minimise artefact from bowel movement, and thereby improve image quality, Buscopan (hyoscine butylbromide) 20mg will be given IV immediately prior to MRI scan to temporarily reduce bowel movement. This is frequently used in abdomino-pelvic research MRI protocols and is well tolerated.

6.7.2 Permitted Medications

Any medications other than those excluded by the protocol, which are considered necessary for the subjects' welfare and/or which will not interfere with the study medication, may be given at the discretion of the Investigator.

The Investigator will record in the appropriate section of the Case Report Form (CRF) all concomitant medications taken by the subject during the study from the date of signature of informed consent and for the duration of the study.

6.7.3 Prohibited Medications

All drugs listed below are prohibited medications for the entire study. However, if a patient has ***discontinued*** use she may be considered for inclusion in the study (provided eligible in all other respects), but **only after a sufficient wash-out period has elapsed**. Required wash-out times are shown in a table in section **4.3** (page 23).

Warfarin

Sex steroid administration by any route

Mefenamic acid

Antifibrinolytic drugs such as tranexamic acid

GnRH agonist and antagonist:

Immediate release or monthly sustained release depot preparation

3 or 6 months sustained release depot preparation.

Glucocorticoid treatment as specified hereunder:

Any systemic or inhaled treatment

Any 'potent' topical, or 'very potent' topical preparation (see list in box below).

TOPICAL GLUCOCORTICOIDS (BNF 65)

Potent Topical Glucocorticoids (BNF 65)

Beclometasone dipropionate 0.025%;

Betamethasone valerate 0.1% *(Betacap, Betesil, Bettamousse, Betnovate, Cutivate, Diprosone, Elocon)*

Hydrocortisone butyrate *(Locoid, Crelo, Metosyn)*

Mometasone furoate *0.1% (Nerisone, Synalar)*

With antimicrobials – (*Aureocort)*

Betamethasone and clioquinol,

Betamethasone and meomycin *(Fucibet, Lotriderm, Synalar C, Synalar N)*

With salicylic acid - *(Diprosalic)*

Very Potent Topical Glucocorticoids (BNF 65)

Clarelux, Dermovate, Etrivex, Nerisone Forte

With antimicrobials –

Clobetaol with neomycin and nystatin

7 STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

Toxicity will be monitored by blood pressure and **safety bloods** (plasma glucose, HbA1c, LFT and urea and electrolytes) at recruitment and at the end of treatment phase (each treatment phase in the case of cross-over Workup study 2). Data on any side-effects reported (and AEs, ARs, and UARs) will be collected across all three studies for 30 days after last study tablet.

Any woman at risk of pregnancy in a treatment cycle will be asked to carry out a pregnancy test as a precaution prior to starting study treatment. The only other specific safety assessment required prior to administration of the study treatment is a check, via the initial safety blood at recruitment, of plasma glucose and HbA1c.

7.2 STUDY ASSESSMENTS

Assessments common to both stages:

i. **Patient Clinical History –** recording key features e.g. parity, treatments, full blood count, serum ferritin etc
ii. **Questionnaires** based on those used in previous studies[29, 30]
(a) **At recruitment** – Recruitment Questionnaire detailing HMB problem including duration, associated menstrual symptoms, impact of daily life;
b) **At end of treatment –** Treatment Questionnaire eliciting subjective assessment of effect of treatment, by asking about most recent (treated) menstrual period, including comparison of 'heaviness' compared to before entering study.
iii. **Study cycle diary** - a combination of two measures:
    a) **Testing & Treatment record–** to record in all 'treatment' cycles, date to start LH-testing using dip-sticks, day of dip-stick colour change (LHu

surge), day to start treatment, study capsules taken, day of start of next period.

b) Menstrual diary – as used previously(29, 30) to enable in all cycles an estimate of volume of MBL, via recording prospectively sanitary product usage during period (to enable estimation of MBL), and to elicit, at the end of each period, subjective assessment of 'heaviness', menstrual symptoms, and unexpected symptoms (ie possible AEs).

iv. **MBL** objective laboratory measurement of collected used sanitary protection by modified alkaline haematin method (validated in our laboratory)[30]. For 'treatment' periods the menstrual collection (MC) will be for the complete period, however long its duration. However for the single screening periods of studies 1 and 2 and the 2nd screening period of study 3, uplift of the menstrual collection will be timed to be as soon as possible after the first 7 days of the period/menstrual collection (or sooner, of course, if the period ends sooner). This 'by-day-7' uplift is in order to ensure that participants who are eligible in terms of objective MBL, progress from screening to treatment phase without having to miss a cycle. The limit is needed to allow enough time after uplift to assay the screening menstrual collection required to confirm eligibility in terms of MBL and then, if eligible, deliver the allocated 'treatment' bottle to the woman in time for treatment to start. The following points have been taken into consideration in making this decision: (i) A minority of women have periods extending beyond 7 days, and where blood loss day-by-day across a period has been ascertained, the vast majority occurs in the first 5 days; (ii) Our threshold for eligibility for study entry is lower than the conventional threshold of 80mL, by more than 37%. (iii) All screening menstrual diaries will be completed for entire periods, so these data will be available to support/inform later analysis of treatment effect.

v. **Day of LH peak** will be monitored by means of commercially available urine dip-sticks in all treatment cycles (and, in Study 1, in the no treatment cycle) and recorded in study cycle diary.

vi. **Ovarian function** with Dexamethasone treatment will be assessed in both clinical workup studies in the 2nd treatment cycle by (twice weekly urine aliquot) assayed for E and P metabolites to provide mechanistic insight to action of Dex[31] , and in the 1st workup study in the 'no treatment' cycle as well. In the adaptive trial this ovarian function assessment will be in the 3rd treatment cycle. These assessments will enhance mechanistic understanding.

Tables 1, 2 and 3 below show an overview of timings of assessments in the two Workup clinical studies, and the adaptive trial. *More detailed timings are given in section 8.*

Table 1 Overview of assessments for Study 1- First in HMB (n=6):

	Recruit. visit	Screening period	No Rx	Rx Dex	
Cycle		**1**	**1**	**1st**	**2nd**
Recruitment Qu.	✓				
Menstrual Diary ('MBL')		✓	✓	✓	✓
Laboratory MBL		✓	✓	✓	✓
Testing & Treatment record				✓	✓
MRI			✓		✓
Endometrial biopsy			✓		✓
Ovarian Function			✓		✓
Safety bloods	✓				✓
Treatment Review Qu.					✓

Table 2 Overview of assessments for Study 2- Methodological (n=14):

	Recruit. visit	Screening period	Treatment 1		Treatment 2	
Cycle		**1**	**1**	**2**	**3**	**4**
Recruitment Qu.	✓					
Menstrual Diary ('MBL')		✓	✓	✓	✓	✓
Laboratory MBL		✓		✓		✓
Testing & Treatment record			✓	✓	✓	✓
Ovarian Function				✓		✓
Safety bloods	✓			✓		✓
Treatment Review Qu.				✓		✓

Table 3 Overview of assessments for adaptive trial Study 3 (n=108)

	Recruit. visit	Screening		Treatment		
Cycle		**1**	**2**	**1**	**2**	**3**
Clin.History & Recruitment Qu.	✓					
Laboratory MBL		✓	✓		✓	✓
Menstrual Diary ('MBL')		✓	✓			
Study Diary ('MBL'+ **Testing & Trt**.)				✓	✓	✓
Ovarian Function						✓
Safety bloods	✓					✓
Treatment Review Qu.						✓

Additional assessments in initial 'first in HMB' <u>workup study</u> Study 1 to advance mechanistic and pharmacodynamic understanding:

i. <u>Endometrial morphology in response to Dexamethasone and assay for Dex concentration</u>: *(see **endometrial biopsy** in **Table 1** page 27)*
It will be essential to determine the endometrial response to luteal phase administration of Dexamethasone. Six women will have "pipelle" endometrial biopsies in a treated and un-treated cycle. Samples will be timed to day LHu+13 (i.e. if treated cycle, last day of Dexamethasone administration). Endometrial tissue will be: (i) transported in medium for dexamethasone assay by LCMS/MS; (ii) fixed for histological assessment and immunohistochemistry (IHC); (iii) placed in RNA later/ snap frozen for extraction of mRNA (quantitative real-time PCR; qRT-PCR) or protein.

Endometrial samples will be histologically assessed to characterise vascular morphology and differentiation, and local inflammatory response. Evaluations will include:

(i) determination of vessel differentiation by expression of cellular markers CD31, myosin heavy chain (MHC), alpha smooth muscle actin (αSMA), collagen;

(ii) expression of inflammatory markers: COX-1, COX-2, PGDH, IL-8, VEGF, and TSP-1 (IHC and qRT-PCR). Endometrial and plasma samples collected at time of biopsy will be assayed for Dexamethasone concentration with a validated "in-house" Dex assay (Mass Spectrometry Core Lab; collaboration Dr Ruth Andrew) to evaluate Dexamethasone exposure in subjects by assessing Dex concentrations achieved systemically and in target tissue, i.e. endometrium.

Note: At the end of the study surplus samples of endometrium and blood will be stored (with patient's written consent) in our Female Reproductive Tract Tissue Resource.

ii. Uterine/endometrial perfusion and permeability will be assessed in the late-secretory phase (LHu+13) of a treated and control cycle with DCE-MRI (dynamic contrast-enhanced MR imaging) utilising our on-site dedicated research 3T Siemens Verio MR scanner, and images analysed using pharmacokinetic modelling techniques that permit us to monitor changes in uterine permeability kinetics and plasma volume fraction, as recently applied in the fibroid uterus.[32] *(see **MRI** in **Table 1** page 27)*

8 DATA COLLECTION

Data collection has already been well detailed in section 7.2 above, with timing shown in Tables 1, 2 and 3. In addition, Table 4 (below & overleaf) provides an inventory of all formal assessments, specifying the data source. and also notes whether a hospital visit is required. Table 5 lists other patient contacts,

Table 4. Inventory of assessments by source, study (1/2/3), timing & who collecting data

Time-points*	Source	Data
All studies Standard referral appt	Referral letter	Referral reason, age
	Clinical consultation	Referral complaint, heaviness of periods, cycle length/regularity, Other exclusion criteria
All studies Recr. visit = clinic appointment specifically for study	Discussion with patient	
	Consent	
	Electronic notes (TRAK)	*Safety blood values (see below) if results available in last 3 months
	Safety blood (base-line) - if not already available – see above *	HBa1c, glucose, liver function, urea and electrolytes
	Recruitment Qu – *could be completed at home and returned with 1st MC*	Patient details, health, about periods and impact on QoL
Screening – all studies: 1st mens. after recr.; &, **study 3** *only*,also 2nd after recr.	Menstrual collection (**MC**)	MBL ('average' for screening must be >= 50 mL to proceed)
	Menstrual diary	Days bleeding, protection used & soaking, overall heaviness, MBL volume score, associated menstrual symptoms, other symptoms

Table 4 *continued overleaf*

DATA COLLECTION Table 4 *continued*

Time-points*	Source	Data
Study 1 - No treatment cycle	**MRI**	**Pelvic blood flow**
	Endometrial biopsy	**Tissue characteristics**
	Menstrual collection	MBL
	Menstrual diary	As above
Study 1 - 1st Dex cycle	Menstrual collection	MBL
	Menstrual diary + Testing & Treatment Record	Diary as above for screening, plus Record of dip-stick testing, capsules taken
Study 1 – 2nd Dex cycle	**MRI**	**Pelvic blood flow**
	Endometrial biopsy	**Tissue characteristics**
	Menstrual collection	MBL
	Menstrual diary + Testing & Treatment Record	As above
	Ovarian function	Hormonal profile across cycle
All MC study cycles:	Blood-sample taken at each MC uplift	Haemoglobin level, for MBL assay
Study 2 & 3 all Rx cycles	Menstrual diary + Testing & Treatment Record	As above
Study 2 cycles 2 & 4	Menstrual collection	MBL
	Ovarian function	Hormonal profile across cycle
Study 3 cycles 2 & 3	Menstrual collection	MBL
Study 3 cycle 3	Ovarian function	Hormonal profile across cycle
All studies (post-last-Rx, at MC up-lift	Treatment Rev. Qu	Opinion of treatment
	Safety-blood	As above
Study 2 (also at end 1st Rx blk)	Treatment Rev. Qu Safety-blood	As above

Notes: All questionnaires and diaries are ***self-complete by patient***

Only the blue sections are formal clinic attendances

The red data are obtained via investigations that require a hospital attendance, if possible both for the same cycle will be organised for the same visit.

Table 5. Other contacts with study patients

Phone & person contacts with nurse			
Numerous eg every MC uplift and by phone at many points within cycle		No formal data collection, but any worrying informal info will be acted on – see #	
Additional clinic appts:			
Study 3 mid cycle 2 of Rx (optional)	Consultation with dr.	AEs	Doctor
All studies final follow-up appt. approx.30days post-last-Rx *	Consultation with dr.	Review of treatment. AEs	CRT
Study 2 *only* (f-up appt. also post-last-menses of 1st Rx block)	Consultation with dr.	As above	CRT

Notes: **Only the blue sections are formal clinic attendances**

#At every phone and face-to-face contact of nurse with patient there will be enquiry 'How are you?' and the opportunity to follow up on potential AEs. If mentioned then an AE report form will be completed by the nurse. In addition this will happen formally via the menstrual Diary that is completed every Rx cycle.

* final clinic appointment will be arranged wherever possible between 30 and 37 days post-last-treatment but, where this is not feasible, the visit can be between 20 and 45 days. If before 30 days there will be a subsequent phone call after the 30 day time-point to check on AEs up to that point. After the final visit the patient will return to normal clinical care.

Maximising completeness

The study nurses, in particular, and study doctors, will develop excellent rapport with patients to maximise completeness. Questionnaire completion will be maximised by reasonable follow-up phone-calls.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

Work-up clinical studies 1 and 2. The first study will comprise 6 women, which will provide essential first-in-HMB safety data alongside mechanistic data from MRI, endometrial biopsy and ovarian function. Study 2, the cross-over study, will aim to involve 14 women. In addition to providing an initial indication of efficacy, this will provide information on between- and within-individual variability in MBL from a relevant patient population to inform the adaptive RCT, Study 3. Study 2 will provide useful information even if fewer than 14 are recruited. Once the final simulation analyses for study 3 commence there can be no further benefit, to informing those analyses, from further recruitment to study 2, so recruitment to study 2 will cease at the end of phase 1. In studies 1 and 2, patients who withdraw will be replaced where feasible.

Adaptive RCT Study 3: An adaptive design with flexible modelling of the dose response curve using a normal dynamic linear model will lead to considerable efficiency gains, since the estimate of efficacy at a given dose will be informed by that at neighbouring doses. In terms of sample size required, efficiency gains are in the range 25%-40% for a broad spectrum of adaptive designs.[33] Precise benefits of the adaptive design in this context will be determined by the development simulation studies during the work-up stage. In addition there will be ethical advantages associated with the adaptive design since a greater proportion of women will be randomised to doses which have a higher chance of being efficacious. For reference, assuming a within-woman SD in MBL change of 18mL (based on measurements from two cycles at baseline and two during treatment,[34]) a conventional parallel group design exploring placebo and 3 active doses randomised in the ratio 2:1:1:1 would have, with 100 patients, 80% power to detect a mean difference of 16.4mL between each of the active treatments and placebo (equivalent to a clinically important 25% reduction for a baseline MBL of 65ml) at a 1.67% 2-sided significance level (analysis by two sample t-test, Bonferroni-corrected for multiple comparisons). Relative to the standard design, the adaptive design gives greater scope to make direct comparisons between doses, which is more relevant to our study objective of identifying the optimal dose to take forward to Phase III.

In the RCT, patients who withdraw from the study will be replaced. Based on experience of dropout rates from previous studies in this area, a maximum of 108 patients would require to be randomised to achieve 100 women completing the study. Given referrals to the study site gynaecology clinics and the new source of recruitment via media advertising, posters in NHS gynae clinical areas and SPCRN letters to women on GP practice lists (with indicators for HMB), it is expected that the required sample size will be achievable during the planned recruitment period.

9.2 PROPOSED ANALYSES

All analyses will be performed according to the intention to treat principle.
Hypothesis testing will be performed at the 5% significance level.

9.2.1 **Study 1**

9.2.1.1 Baseline characteristics

Summary data will be used to describe baseline characteristics: mean, standard deviation, median, minimum, maximum for continuous variables, and number (percentage) of individuals for categorical variables.

9.2.1.2 Primary endpoint

The change in MBL between baseline and Dexamethasone treatment cycles will be analysed using a paired t-test and 95% confidence interval.

9.2.1.3 Secondary endpoints

Summary data will be provided for continuous (menstrual diary score for menstrual period volume) and categorical (satisfaction with treatment, presence of unacceptable side effects, period pain) secondary outcomes as in section 9.2.1.1.

9.2.2 **Study 2**

9.2.2.1 Baseline characteristics

Summary data will be used to compare baseline characteristics between women randomised to Dexamethasone followed by Placebo, versus those randomised to Placebo followed by Dexamethasone: mean, standard deviation, median, minimum, maximum for continuous variables, and number (percentage) of individuals for categorical variables.

9.2.2.2 Primary endpoint

The difference in MBL between placebo and Dexamethasone treatment cycles will be analysed using a normal linear mixed model. A 95% confidence interval will be reported for the mean difference, Dexamethasone minus Placebo.

9.2.2.3 Secondary endpoints

The difference in menstrual diary score for menstrual period volume between placebo and Dexamethasone treatment cycles will be analysed using a normal linear mixed model. A 95% confidence interval will be reported for the mean difference, Dexamethasone minus Placebo.

Categorical secondary endpoints will be analysed using a generalised linear mixed model. A 95% confidence interval will be reported for the odds ratio, Dexamethasone versus Placebo.

9.2.3 **Study 3**

9.2.3.1 Baseline characteristics

Summary data will be used to compare baseline characteristics between women randomised to placebo and each of the Dexamethasone doses: mean, standard deviation, median, minimum, maximum for continuous variables, and number (percentage) of individuals for categorical variables.

9.2.3.2 Primary endpoint

The dose-response curve for change in MBL between baseline and cycles during randomised treatment will be analysed using a Normal Dynamic Linear Model (NDLM)[35] which is flexible and requires few assumptions about the shape of the underlying dose-response curve. The NDLM requires a Bayesian analysis framework, including the specification of prior distributions for all parameters. Suitable prior distributions will be confirmed by modelling and simulations during the work-up phase. The NDLM analysis will determine which of the doses studied is optimal to take forward for further study (in terms of posterior probability of efficacy, efficacy being defined as a 25% reduction in MBL versus baseline). For each Dexamethasone dose, a 95% credible interval will be calculated for the mean difference in MBL change versus placebo. Mean baseline MBL will be included as a covariate in the NDLM.

9.2.3.3 Secondary endpoints

The menstrual diary score for menstrual period volume will be analysed using the method given for the primary endpoint in section 9.2.3.2. Binary or ordinal secondary endpoints will be analysed using a generalised dynamic linear model. For each Dexamethasone dose, a 95% credible interval will be calculated for the odds ratio versus placebo.

A detailed statistical analysis plan for each of the three studies will be finalised prior to the locking of the study database and, in the case of the crossover trial study 2 and the adaptive RCT study 3, prior to unblinding of the treatment codes.

10 ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SmPC)/Investigator's Brochure (IB).

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after joining the trial must be reported in detail in the Case Report Form (CRF) or AE form. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgement. Participants with AEs present at the last visit must be followed up until resolution of the event.

10.1 DEFINITIONS

10.1.1 An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

10.1.2 An **adverse reaction** (AR) is any untoward or unintended response to an IMP which is related to any dose administered to that participant.

10.1.3 A **serious adverse event** (SAE), **serious adverse reaction** (SAR) or **suspected unexpected serious adverse reaction** (SUSAR) is any AE, AR or UAR that at any dose:

- results in death;
- is life threatening* (i.e. the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires in-patient hospitalisation**^** or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect.
- results in any other significant medical event not meeting the criteria above (e.g. may jeopardise the participant or may require intervention to prevent one of the other listed criteria).

***** Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^ Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria.

10.1.4 A **Suspected Unexpected Serious Adverse Reaction** (SUSAR) is any adverse reaction that is classed as serious and is suspected to be caused by the IMP that is **not** consistent with the information about the IMP in the SPC or IB.

10.2 DETECTING AEs AND SAEs

All AEs and SAEs will be recorded from the time a participant signs the consent form to take part in the study until **30 days after last Rx dose.**

Participants will complete a menstrual diary for every menstrual period during their participation. At the end of the period/diary, two questions ask about the period just finished, and a third asks if any unusual symptoms have occurred, since the end of the previous period up until now, with a free-text box for response. The diaries will be collected timeously and the study nurse will check anything written in this box, and follow up for further elaboration, and formal reporting if warranted.

Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified by support departments e.g. laboratories. .

10.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

Coughs, common colds, and other common minor ailments will not be recorded as AEs.

10.4 ASSESSMENT OF AEs AND SAEs

Seriousness, causality, severity and expectedness will be assessed as though the participant is taking active IMP. Cases that are considered serious, possibly, probably or definitely related to IMP and unexpected (i.e. SUSARs) will be unblinded.

The Investigator is responsible for assessing each AE.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

10.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.3.

10.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly related or unrelated) to the IMP will be considered as related to the IMP (ARs/SARs).

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR/SAR.

Unrelated: where an event is not considered to be related to the IMP.

Possibly Related: Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug.

Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

10.4.3 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the CRF or AE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

10.4.4 Assessment of Expectedness

If an event is judged to be an AR/SAR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SmPC/IB.

The event may be classed as either:

Expected: the AR is consistent with the toxicity of the IMP listed in the SmPC/IB.

Unexpected: the AR is not consistent with the toxicity in the SmPC/IB.

10.5 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.4, Assessment of Expectedness.

The SAE form will be transmitted via email to safety@accord.scot .Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be sent by fax to ACCORD on +44 (0)131 242 9447 or may be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will

contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

10.5.1 SAES/SARS/SUSARS NOT TO BE REPORTED

The following events are expected in this patient population and will not be reported to the ACCORD office within 24 hours, even in situations where these expected events fulfil the criteria of serious (as defined in section 10.1.3) of the trial protocol.

Nausea
Mild abdominal pain
Indigestion
Dizziness
Tiredness, feeling weak, skin changes
Mild headache
Mood change, sleep disturbance, irritability
Menstrual bleeding disturbance leading to anaemia

10.6 REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD will inform Investigators at participating sites of all SUSARs and any other arising safety information.

A Development Safety Update Report will be submitted to the regulatory competent authority and main REC annually, listing all SARs and SUSARs.

10.7 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator will follow each participant until resolution of the event or death of the participant. Follow up information on an SAE will be reported to the ACCORD office.

AEs still present in participants at the last study visit will be monitored until resolution of the event or until no longer medically indicated.

11. PREGNANCY

Pregnancy is not considered an AE or SAE; however, the Investigator will collect pregnancy information for any female participants or female partners of male participants who become pregnant while participating in the study. The Investigator will record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy.

All pregnant female participants and partners of male participants will be followed up until following the outcome of the pregnancy.

Should a patient become pregnant their treatment with Dexamethsone will be discontinued and the patient will be withdrawn from the study.

12 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), a Trial Manager and coordinating nurse.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

12.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trials. The composition of the TSC will be in accordance with the MRC Guidelines for Good Clinical Practice in Clinical Trials (1998)[1] and will include an independent chair, at least two other independent members and the Chief Investigator. The TSC membership and terms of reference will be agreed prior to the commencement of the trials and a copy of the terms of reference retained in the trial master file.

12.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The DMC will be composed of at least three independent members, including a gynaecologist, an endocrinologist and a statistician. The DMC membership and terms of reference will be agreed prior to commencement of the trials and a copy of the terms of reference stored in the trial master file .

12.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12.5 RISK ASSESSMENT

An independent risk assessment will be performed by an ACCORD Clinical Trials Monitor to determine if monitoring is required and if so, at what level. An independent risk assessment will also be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

[1] http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002416

12.6 STUDY MONITORING AND AUDIT

An ACCORD Clinical Trials Monitor or an appointed monitor will visit the Investigator site prior to the start of the study and during the course of the study if required, in accordance with the monitoring plan if required. Investigator sites will be risk assessed by the ACCORD QA Manager, or designee, in order to determine if audit by the ACCORD QA group is required.

13 GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favorable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

13.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, and any relevant amendments.

13.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

13.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes.

13.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

13.3.3 Data Recording

The Principle Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

13.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

The ACCORD Research Governance & QA Office will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF), where required, and that appropriate documentation is available in local ISFs.

13.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

13.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

14 STUDY CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of a urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

14.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Investigators will not implement any deviation from the protocol without agreement from the Chief Investigator and appropriate REC, Regulatory Authority and R&D approval except where necessary to eliminate an immediate hazard to trial participants.

In the event that an Investigator needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.Deviation logs / violation forms will be transmitted via email to QA@accord.scot Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be sent by fax to ACCORD on **+44 (0)131 242 9447** or may be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

14.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and take the appropriate action.

Not every violation from the protocol needs to be reported to the regulatory authority as a serious breach. If the sponsor(s) deem the incident to be a violation that does not constitute a serious breach from the protocol when identified, corrective and preventative actions will be taken where appropriate and they will be recorded in file notes, held within the TMF and ISF.

14.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

14.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@ed.ac.uk.

In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study.

Upon completion of the study, the Investigator will upload clinical trial results onto the EudraCT database on behalf of the Sponsor.

The Investigator will submit a short confirmatory e-mail to the MHRA (CT.Submission@mhra.gsi.gov.uk) once the result-related information has been uploaded to EudraCT, with 'End of trial: result-related information: EudraCT XXXX-XXXXXX-XX' as the subject line. The Sponsor(s) will be copied in this e-mail (QA@accord.scot). It should be noted that you will not get an acknowledgment e-mail or letter from the MHRA.

14.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

There is not the option to continue the drug beyond the study period.

14.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's Nation Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

15 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

15.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

15.3 PEER REVIEW

Results from studies will be published in peer reviewed journals and will be presented at International conferences where there will be expert peer discussion and debate.

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APPENDIX 1: Summary of Product Characteristics

Appendix 1a. SPC for Dexamethsone 2mg tablets

Dexamethasone Tablet BP 2.0mg -(eMC) -

1 Dexamethasone Tablets

Summary of Product Characteristics Last Updated on eMC 07-Sep-2017 | Aspen

1. Name of the medicinal product

Dexamethasone Tablets BP 2.0mg

2. Qualitative and quantitative composition

Each tablet contains 2.0mg dexamethasone PhEur.

3. Pharmaceutical form

Tablet

White, round and flat tablets with bevelled edges and a diameter of 6 mm, coded XC above, and 8 below on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Indicated in a wide variety of disorders amenable to glucocorticoid therapy, as well as an adjunct in the control of cerebral oedema.

4.2 Posology and method of administration

In general, glucocorticoid dosage depends on the severity of the condition and response of the patient. Under certain circumstances, for instance in stress and changed clinical picture, extra dosage adjustments may be necessary. If no favourable response is noted within a couple of days, glucocorticoid therapy should be discontinued.

Adults

Usually, daily oral dosages of 0.5 - 10 mg are sufficient. In some patients higher dosages may be temporarily required to control the disease. Once the disease is under control the dosage should be reduced or tapered off to the lowest suitable level under continuous monitoring and observation of the patient. **(See Section 4.4)**

For a short dexamethasone suppression test, 1mg dexamethasone is given at 11 p.m. and plasma cortisol measured the next morning. Patients who do not show a decrease in cortisol can be exposed to a longer test: 500 micrograms dexamethasone is given at 6 hourly intervals for 48 hours followed by 2mg every 6 hours for a further 48 hours. 24 hour-urine collections are made before, during and at the end of the test for determination of 17-hydroxycorticosteroids.

Children

0.01-0.1mg/kg of body weight daily.

Dosage of glucocorticoids should be adjusted on the basis of the individual patient's response.

4.3 Contraindications

Systemic infection unless specific anti-infective therapy is employed.
Hypersensitivity to any ingredient.
Avoid live vaccines in patients receiving immuno suppressive doses (serum antibody response diminished).
In general no contraindications apply in conditions where the use of glucocorticoids may be life saving.

4.4 Special warnings and precautions for use

A patient information leaflet should be supplied with this product.
In post-marketing experience tumour lysis syndrome (TLS) has been reported in patients with haematological malignancies following the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.
Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 for pharmacokinetic interactions that can increase the risk of side effects), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.
Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.
The results of a randomised, placebo-controlled study suggest an increase in mortality if methylprednisolone therapy starts more than two weeks after the onset of Acute Respiratory Distress Syndrome (ARDS). Therefore, treatment of ARDS with corticosteroids should be initiated within the first two weeks of onset of ARDS (see also section 4.2.).
Preterm neonates:
Available evidence suggests long-term neurodevelopmental adverse events after early treatment (<96 hours) of premature infants with chronic lung disease at starting doses of 0.25 mg/kg twice daily.
Undesirable effects may be minimised by using the lowest effective dose for the minimum period, and by administering the daily requirement as a single morning dose or whenever possible as a single morning dose on alternative

days. Frequent patient review is required to appropriately titrate the dose against disease activity.

Dexamethasone withdrawal

Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment.

In patients who have received more than physiological doses of systemic corticosteroids (approximately 1mg dexamethasone) for greater than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids but there is uncertainty about HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 1mg dexamethasone is reached, dose reduction should be slower to allow the HPA-axis to recover.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses of up to 6mg daily of dexamethasone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be *considered* even after courses lasting 3 weeks or less:

• Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks.
• When a short course has been prescribed within one year of cessation of long-term therapy (months or years).
• Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
• Patients receiving doses of systemic corticosteroid greater than 6mg daily of dexamethasone.
• Patients repeatedly taking doses in the evening.

During prolonged therapy any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

Patients should carry 'Steroid treatment' cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.

Anti-inflammatory/Immunosuppressive effects and Infection

Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The clinical presentation may

often be atypical, and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised. Appropriate anti-microbial therapy should accompany glucocorticoid therapy when necessary e.g. in tuberculosis and viral and fungal infections of the eye. *Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients.* Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunisation with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

Measles. **Patients should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs; prophylaxis with intramuscular normal immunoglobulin may be needed.**

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary

a. Osteoporosis (post-menopausal females are particularly at risk)
b. Hypertension or congestive heart failure
c. Existing or previous history of severe affective disorders (especially previous steroid psychosis)
d. Diabetes mellitus (or a family history of diabetes)
e. History of tuberculosis
f. Glaucoma (or a family history of glaucoma)
g. Previous corticosteroid-induced myopathy
h. Liver failure
i. Renal insufficiency
j. Hypothyroidism
k. Epilepsy
l. Peptic ulceration
m. Migraine
n. Certain parasitic infestations in particular amoebiasis

o. Incomplete natural growth since glucocorticoids on prolonged administration may accelerate epiphyseal closure

Caution should be exercised when using corticosteroids in patients who have recently suffered myocardial infarction as myocardial rupture has been reported.

After administration of glucocorticoids serious anaphylactoid reactions such as glottis oedema, urticaria and bronchospasm have occasionally occurred particularly in patients with a history of allergy.

If such an anaphylactoid reaction occurs, the following measures are recommended: immediate slow intravenous injection of 0.1-0.5ml of adrenaline (solution of 1:1000: 0.1-0.5mg adrenaline dependent on body weight), intravenous administration of aminophylline and artificial respiration if necessary.

Dexamethasone Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in children

Corticosteroids cause dose-related growth retardation in infancy, childhood and adolescence, which may be irreversible.

Use in the Elderly

The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Rifampicin, rifabutin, carbamazepine, phenobartital, phenytoin, primidone, and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.

Dexamethasone is a moderate inducer of CYP 3A4. Co-administration of dexamethasone with other drugs that are metabolized by CYP 3A4 (e.g., indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentrations.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Ephedrine also accelerates the metabolism of dexamethasone.

The effects of anticholinesterases are antagonised by corticosteroids in myasthenia gravis.

The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids, and the

hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.
The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.
Oral contraceptives (oestrogens and progestogens) increase plasma concentration of corticosteroids. The antiviral drug ritonavir also increases the plasma concentration of dexamethasone.
Dexamethasone reduces the plasma concentration of the antiviral drugs indinavir and saquinavir.
The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication.
Patients taking NSAIDs should be monitored since the incidence and/or severity of gastro-intestinal ulceration may increase.
Patients taking methotrexate and dexamethasone have an increased risk of haematological toxicity.
Antacids, especially those containing magnesium trisilicate have been reported to impair the gastrointestinal absorption of glucocorticoid steroids. Therefore, doses of one agent should be spaced as far as possible from the other.

4.6 Fertility, pregnancy and lactation

The ability of corticosteroids to cross the placenta varies between individual drugs, however, dexamethasone readily crosses the placenta.
Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man (see also section 5.3). However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

Lactation

Corticosteroids may pass into breast milk, although no data are available for dexamethasone. Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The incidence of predictable undesirable effects, including hypothalamic-pituitary-adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see section 4.4).

Endocrine/metabolic

Suppression of the hypothalamic-pituitary-adrenal axis, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea, Cushiongoid faces, hirsutism, weight gain, premature epiphyseal closure, impaired carbohydrate tolerance with increased requirement for anti-diabetic therapy, negative protein and calcium balance, increased appetite

Anti-inflammatory and Immunosuppressive effects

Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (see section 4.4), decreased responsiveness to vaccination and skin tests

Musculoskeletal

Osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, proximal myopathy

Fluid and electrolyte disturbance

Sodium and water retention, hypertension, potassium loss, hypokalaemic alkalosis

Neuropsychiatric

A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown.

Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal. Aggravation of epilepsy.

Psychological dependence.

Ophthalmic

Increased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning, exacerbation of opthalmic viral or fungal diseases, chorioretinopathy

Eye disorders

Vision, blurred (see also section 4.4)

Gastrointestinal

Dyspepsia, peptic ulceration with perforation and haemorrhage, acute pancreatitis, oesophagael ulceration and candidiasis, abdominal distension and vomiting

Dermatological
Impaired healing, skin atrophy, bruising, telangiectasia, striae, acne
General
Hypersensitivity including anaphylaxis, has been reported. Leucocytosis, thromboembolism, myocardial rupture following recent myocardial infarction, nausea, malaise, hiccups
Withdrawal symptoms and signs
Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see section 4.4).
A 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

It is difficult to define an excessive dose of a corticosteroid as the therapeutic dose will vary according to indication and patient requirements. Exaggeration of corticosteroid related adverse effects may occur. Treatment should be asymptomatic and supportive as necessary.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Dexamethasone is a synthetic glucocorticoid whose anti-inflammatory potency is 7 times greater than prednisolone. Like other glucocorticoids, dexamethasone also has anti-allergic, antipyretic and immunosuppressive properties.
Dexamethasone has practically no water and salt-retaining properties, and is therefore particularly suitable for use in patients with cardiac failure or hypertension. Because of its long biological half-life (36-54 hours), dexamethasone is especially suitable in conditions where continuous glucocorticoid action is desired.

5.2 Pharmacokinetic properties

Corticosteroids, are, in general, readily absorbed from the gastro-intestinal tract. They are also well absorbed from sites of local application. Water-soluble forms of corticosteroids are given by intravenous injection for a rapid response; more prolonged effects are achieved using lipid-soluble forms of corticosteroids by intramuscular injection.
Corticosteroids are rapidly distributed to all body tissues. They cross the placenta and may be excreted in small amounts in breast milk.
Most corticosteroids in the circulation are extensively bound to plasma proteins, mainly to globulin and less so to albumin. The corticosteroid-binding

globulin has high affinity but low binding capacity, while the albumin has low affinity but large binding capacity. The synthetic corticosteroids are less extensively protein bound than hydrocortisone (cortisol). They also tend to have longer half-lives.
Corticosteroids are metabolised mainly in the liver but also in the kidney, and are excreted in the urine. The slower metabolism of the synthetic corticosteroids with their lower protein-binding affinity may account for their increased potency compared with the natural corticosteroids.

5.3 Preclinical safety data

In animal studies, cleft palate was observed in rats, mice, hamsters, rabbits, dogs and primates: not in horses and sheep. In some cases these divergences were combined with defects of the central nervous system and of the heart. In primates, effects in the brain were seen after exposure. Moreover, intra-uterine growth can be delayed. All these effects were seen at high dosages.

6. Pharmaceutical particulars

6.1 List of excipients

Potato starch PhEur, propylene glycol PhEur, magnesium stearate PhEur, and lactose PhEur.

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C protected from light.

6.5 Nature and contents of container

White, cylindrical wide mouth containers with screw caps made of high density polyethylene (HDPE) with a child resistant polypropylene screw cap, containing 50, 100 or 500 tablets.
Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder

Aspen Pharma Trading Limited, 3016 Lake Drive, Citywest Business Campus, Dublin 24, Ireland

8. Marketing authorisation number(s)

PL 39699/0056

9. Date of first authorisation/renewal of the authorisation

29/03/1990 / 17/06/2010

10. Date of revision of the text

02/08/2017

Appendix 1b SPC for Lactose powder for capsules

P0343A

Summary of Product Characteristics
P-Tablets white 8mm 'Lichtenstein'.

1. **NAME OF THE MEDICINAL PRODUCT**
P-Tablets white 8mm 'Lichtenstein'

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Contains lactose (see section 4.4)
For the full listing of excipients see section 6.1.

3. **DOSAGE FORM**
Tablets.

4. **CLINICAL SPECIFICATIONS**

4.1 **Therapeutic indications**
As advised by the doctor.

4.2 **Posology and method of administration**
To be taken in accordance with the doctor's prescription.

4.3 **Contraindications**
Hypersensitivity to any of the medicine's excipients.

4.4 **Special warnings and precautions for use**
Patients with rare hereditary galactose intolerance, lactase deficiency or glucose galactose malabsorption should not take P-Tablets white 8mm 'Lichtenstein'.

4.5 **Interaction with other medicinal products and other forms of interaction**
None known.

4.6 **Pregnancy and lactation**
No known risks to date.

4.7 **Side effects**
None known.

4.8 **Overdose**
Not applicable.

5. **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**
Pharmacotherapeutic group: Placebo
ATC code V03AX.

5.2 **Pharmacokinetic properties**
Not applicable.

5.3 **Preclinical safety data**
Not applicable.

6. **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
Cellulose powder, lactose monohydrate, magnesium stearate (Ph. Eur.), microcrystalline cellulose.

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
3 years.

6.4 **Special precautions for storage**
Do not store above 25°C.

6.5 **Nature and contents of container**
Packs of 50 (N2) and 100 (N3) tablets.

7. **MARKETING AUTHORISATION HOLDER**
Winthrop Arzneimittel GmbH
Ummitzer Strasse 5
56218 Mülheim-Kärlich
Tel.: 0180 / 20 20 010
Fax: 0180 / 20 20 011

8. **MARKETING AUTHORISATION NUMBER**
6927122.00.00

9. **DATE OF RENEWAL OF THE AUTHORISATION**
19th May, 2003

10. **DATE OF REVISION OF THE TEXT**
April 2009

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APPENDIX 2: Trial Steering Committee

TSC members as at 09/12/2013

Prof Maryann Lumsden, University of Glasgow – Chair
Dr Dharani Hapangama, University of Liverpool
Prof S Bhattacharya, University of Aberdeen
Prof Hilary Critchley – PI
Dr Pam Warner – Principal Co-Investigator
Dr Scott Semple - Co-Investigator
Prof Christopher Weir - Co-Investigator
Prof Brian Walker - Co-Investigator
Heather Charles – ACCORD (or representative)
Anne Douglas – Trial Manager
Gina Cranswick Edinburgh Clinical Trials Unit

APPENDIX 3: Data Monitoring Committee

DMEC – as at 30/01/2013
Mr T Justin Clark, Consultant Obstetrician and Gynaecologist, Birmingham Women's Hospital - CHAIR

Rebecca Reynolds, Centre for Cardiovascular Sciences, University of Edinburgh

Professor Adrian Mander, MRC Biostatistics Unit, Institute of Public Health, Cambridge

Dr Ertan Saridogan, University College Hospital, London

APPENDIX 4: Chart showing timing across workup phase for recruitment, screening, 'treatment' phase and final follow up visit.

			Dec-12	Jan-13	Feb-13	Mar-13	Apr-13	May-13	Jun-13	Jul-13	Aug-13	Sep-13	Oct-13	Nov-13	
Month :			1	2	3	4	5	6	7	8	9	10	11	12	
n MBL-screened	n to Rx														
4	2			M+	* M+	M+	* M+	FV							
8	4				M+	* M+	M+	* M+	FV						
8	4					M+	M	M+	M	M+	FV				
8	4						M+	M	M+	M	M+	FV			
8	4							M+	M	M+	M	M+	FV		
4	2								M+	M	M+	M	M+	FV	
Total	40	**20**													
Number agreeing to MBL screening this month			**2**	**6**	**8**	**8**	**8**	**6**	**2**						
Number MBL eligible and entering study proper this month					**2**	**4**	**4**	**4**	**4**	**2**					
Number finished study and Final Visit this month								**2**	**4**	**0**	**4**	**4**	**4**	**2**	Total=20
CUMULATIVE number so far MBL-screened & entering studies 1 and 2					**2**	**6**	**10**	**14**	**18**	**20**					
CUMULATIVE number complete d 2 months Dex up to menstrual diary							**2**	**6**	**6**	**10**	**14**	**18**	**20**		
CUMULATIVE number completed 2 months Dex, and FV re AEs								**2**	**6**	**6**	**10**	**14**	**18**	**20**	

By this point only 2 would have completed Study 1 30 day visit to ask about AEs (although all 6 would have completed up to last MD), but another 12 have entered study 2 Rx phase!*

By this point all 6 in study 1 should have completed final AE check, but another 12 are already started/starting Rx* in study 2! *(18-6=12)*

** NB Rx in study 2 is approx 50% placebo in first 2 months, 50% Dex.*

KEY

Both studies		Screening MBL of menstrual period (only, ***no*** data for cycle outside period)
Both studies	M	Menstrual diary only (for period at ***end*** of this data 'cycle') — *M is shown at right-hand end of cell to remind that it is the period at end of 'data cycle'*
Both studies	**M+**	M Diary + Menstrual Collection — *ditto*
Both studies	FV	Final Visit between 20 to 45 days after last Rx capsule
Study 1 *(NT and 2nd Rx)*	*	MRI and EB assessments
Study 1 *NT*		No treatment 'cycle' *('cycle' running up to and **including** menstrual period)*
Study 1 *Rx*		Dex 'cycle' (unblind) *('cycle' running up to and **including** menstrual period)*
Study 2 *Rx*		Blind Dex/placebo ***1st*** Rx block *(each 'cycle' running up to and **including** menstrual period)*
Study 2 *Rx*		Blind Dex/placebo ***2nd*** Rx block *(each 'cycle' running up to and **including** menstrual period)*
		Analysis & reporting