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

Summary

EudraCT number	2012-003405-98
Trial protocol	GB
Global end of trial date	29 March 2018

Results information

Result version number	v1 (current)
This version publication date	01 January 2020
First version publication date	01 January 2020

Trial information

Trial identification

Sponsor protocol code	dexFEMv2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01769820
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ACCORD University of Edinburgh & NHS Lothian
Sponsor organisation address	QMRI 49 Little France Cres, Edinburgh, United Kingdom, EH16 4TJ
Public contact	ACCORD enquiries, Research Governance & QA Office, +44 01312426226, enquiries@accord.scot
Scientific contact	Ray French, Research Governance & QA Office, +44 01312426226, resgov@accord.scot
Sponsor organisation name	ACCORD NHS Lothian
Sponsor organisation address	QMRI, 49 LIttle France Cres, Edinburgh, United Kingdom,
Public contact	Enquiries, ACCORD, NHS Lothian, +44 1312423328, enquiries@accord.scot
Scientific contact	Fiona McArdle, ACCORD, NHS Lothian, +44 1312423328, enquiries@accord.scot

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2018
Global end of trial reached?	Yes
Global end of trial date	29 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Work-up studies (Studies 1&2): To gather preliminary safety and efficacy data from first-in-Heavy Menstrual Bleeding use of oral dexamethasone, in women suffering from objectively verified Heavy Menstrual Bleeding (HMB) Adaptive RCT (Study 3): To identify the optimal dose of oral dexamethasone for reduction of Heavy Menstrual Bleeding in women with objectively verified HMB.

Protection of trial subjects:

Trial was carried out under Medicines for Human Use (Clinical Trials) Regulations and ICH GCP. Trial participants were supported throughout the trial by experienced research nurses and clinical researchers.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 107
Worldwide total number of subjects	107
EEA total number of subjects	107

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	107

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment to the adaptive randomised trial took place between 2014 and 2018. First patient was consented for screening on 29/01/2014, first patient randomised on 01/07/2014 and the last visit for last patient was on 29/03/2018.

Pre-assignment

Screening details:

Recruitment in Lothian (Scotland) via gynaecology outpatient clinics; family medicine; media advertising.

Women aged 18 years or over; reporting regular 28-42 day menstrual cycles; complaining of Heavy Menstrual Bleeding; with measured volume of menstrual blood loss (MBL) across two screening cycles (menstrual periods) averaging ≥ 50mL.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Computer-generated pseudo-random numbers were used to generate the randomised allocation sequence. A web-based randomisation system ensured the allocation sequence was concealed from researchers, clinical staff and participants. To maintain concealment, bulk supplies of placebo and Dexamethasone were held by hospital pharmacy who dispensed trial medication in bottles labelled with a unique randomisation number from the list provided by the Edinburgh clinical trials unit.

Arms

Are arms mutually exclusive?	Yes
Arm title	placebo

Arm description:

placebo capsule taken orally, twice daily over 5 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

PLacebo capsule, Lactose Ph Eur, taken twice daily over 5 days

Arm title	Dexamethasone 0.4mg

Arm description:

Dexamethasone taken orally twice daily over 5 days. Total daily dose is 0.4mg

Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

twice daily Dexamethasone 0.2mg over 5 days ; total dose 0.4mg

Arm title	Dexamethasone 0.8mg
Arm description:	
Dexamethasone taken orally twice daily over 5 days. Total daily dose is 0.8mg	
Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
twice daily oral Dexamethasone 0.4mg; total daily dose 0.8mg	
Arm title	Dexamethasone 1.0mg
Arm description:	
Dexamethasone taken orally twice daily over 5 days: total daily dose is 1.0mg	
Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
Dexamethasone 0.5mg taken orally twice daily over 5 days;total dose 1.0mg	
Arm title	Dexamethasone 1.2mg
Arm description:	
Dexamethasone taken orally twice daily over 5 days. Total daily dose 1.2mg	
Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
Dexamethasone 0.6mg taken orally twice daily;total dose 1.2mg	
Arm title	Dexamethasone 1.5mg
Arm description:	
Dexamethasone taken orally twice daily over 5 days. Total daily dose 1.5mg	
Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
Dexamethasone 0.75mg taken orally twice daily;total dose 1.5mg	
Arm title	Dexamethasone 1.8mg
Arm description:	
Dexamethasone taken orally twice daily over 5 days. Total daily dose 1.8mg	
Arm type	Experimental

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Dexamethasone 0.9mg taken orally twice daily;total dose 1.8mg

Number of subjects in period 1	placebo	Dexamethasone 0.4mg	Dexamethasone 0.8mg
Started	27	6	9
Completed	23	5	9
Not completed	4	1	0
Consent withdrawn by subject	2	-	-
Physician decision	2	1	-
Lost to follow-up	-	-	-

Number of subjects in period 1	Dexamethasone 1.0mg	Dexamethasone 1.2mg	Dexamethasone 1.5mg
Started	23	9	15
Completed	21	8	14
Not completed	2	1	1
Consent withdrawn by subject	1	-	1
Physician decision	1	-	-
Lost to follow-up	-	1	-

Number of subjects in period 1	Dexamethasone 1.8mg
Started	18
Completed	16
Not completed	2
Consent withdrawn by subject	2
Physician decision	-
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	placebo
Reporting group description:	
placebo capsule taken orally, twice daily over 5 days.	
Reporting group title	Dexamethasone 0.4mg
Reporting group description:	
Dexamethasone taken orally twice daily over 5 days. Total daily dose is 0.4mg	
Reporting group title	Dexamethasone 0.8mg
Reporting group description:	
Dexamethasone taken orally twice daily over 5 days. Total daily dose is 0.8mg	
Reporting group title	Dexamethasone 1.0mg
Reporting group description:	
Dexamethasone taken orally twice daily over 5 days: total daily dose is 1.0mg	
Reporting group title	Dexamethasone 1.2mg
Reporting group description:	
Dexamethasone taken orally twice daily over 5 days. Total daily dose 1.2mg	
Reporting group title	Dexamethasone 1.5mg
Reporting group description:	
Dexamethasone taken orally twice daily over 5 days. Total daily dose 1.5mg	
Reporting group title	Dexamethasone 1.8mg
Reporting group description:	
Dexamethasone taken orally twice daily over 5 days. Total daily dose 1.8mg	

Reporting group values	placebo	Dexamethasone 0.4mg	Dexamethasone 0.8mg
Number of subjects	27	6	9
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	27	6	9
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Mean age at baseline			
Units: years			
arithmetic mean	40.6	42.2	38.3
standard deviation	± 9.1	± 11.6	± 8.5
Gender categorical			
gender - all female			
Units: Subjects			
Female	27	6	9

Male	0	0	0

Ethnicity			
ethnic group			
Units: Subjects			
White	26	6	9
Mixed	0	0	0
Asian	0	0	0
African	1	0	0
caribbean	0	0	0
Not disclosed	0	0	0
Smoking history Units: Subjects			
Current	6	3	1
Previous	3	1	1
never	18	2	7
No. of births (if applicable) Units: Subjects			
None	10	1	2
one	3	1	2
two	9	3	3
three	4	1	2
four	0	0	0
five	0	0	0
six	1	0	0
Patient has painful periods Units: Subjects			
yes	21	5	4
no	6	1	5
no. years HMB has been a problem Units: years			
arithmetic mean	8	4.4	9.2
standard deviation	± 7.1	± 4.1	± 5.9
Minimum duration menses over past 3 mnths Units: days			
arithmetic mean	6.1	7.2	4.7
standard deviation	± 2.8	± 4	± 1.1
Maximum duration menses over past 3 mnths Units: days			
arithmetic mean	7.7	8.2	5.6
standard deviation	± 3.7	± 3.4	± 1
Mean screening menstrual blood loss Units: mL			
arithmetic mean	158.3	161.9	111
standard deviation	± 134.4	± 88.2	± 45.5
No. years since last pregnancy Units: Years			
arithmetic mean	8.3	13.5	8.9
standard deviation	± 5.3	± 7.3	± 6.5

Reporting group values	Dexamethasone 1.0mg	Dexamethasone 1.2mg	Dexamethasone 1.5mg
Number of subjects	23	9	15
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	23	9	15
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Mean age at baseline			
Units: years			
arithmetic mean	39.9	44.4	40
standard deviation	± 6.9	± 3.5	± 9.3
Gender categorical			
gender - all female			
Units: Subjects			
Female	23	9	15
Male	0	0	0
Ethnicity			
ethnic group			
Units: Subjects			
White	22	7	13
Mixed	0	1	0
Asian	1	1	1
African	0	0	0
caribbean	0	0	0
Not disclosed	0	0	1
Smoking history Units: Subjects			
Current	0	0	1
Previous	7	3	4
never	16	6	10
No. of births (if applicable) Units: Subjects			
None	8	5	4
one	5	1	5
two	5	0	5
three	3	2	1
four	2	1	0
five	0	0	0
six	0	0	0
Patient has painful periods Units: Subjects			
yes	18	6	14

no	5	3	1

no. years HMB has been a problem			
Units: years			
arithmetic mean	9.2	12.2	11.5
standard deviation	± 9.1	± 12.4	± 11.6
Minimum duration menses over past 3 mnths			
Units: days			
arithmetic mean	6.1	5.3	5.4
standard deviation	± 2.6	± 0.9	± 1.7
Maximum duration menses over past 3 mnths			
Units: days			
arithmetic mean	7.3	6.1	8.1
standard deviation	± 2.3	± 0.9	± 3.5
Mean screening menstrual blood loss			
Units: mL			
arithmetic mean	162.1	104.5	162.1
standard deviation	± 83.3	± 35.6	± 125
No. years since last pregnancy			
Units: Years			
arithmetic mean	8.6	15.2	12.1
standard deviation	± 7.4	± 6.1	± 5.2

Reporting group values	Dexamethasone 1.8mg	Total	
Number of subjects	18	107	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	18	107	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Mean age at baseline			
Units: years			
arithmetic mean	42.6		
standard deviation	± 8.3	-	
Gender categorical			
gender - all female			
Units: Subjects			
Female	18	107	
Male	0	0	

Ethnicity			
ethnic group			
Units: Subjects			
White	16	99	
Mixed	0	1	
Asian	0	3	
African	1	2	
caribbean	1	1	
Not disclosed	0	1	
Smoking history			
Units: Subjects			
Current	3	14	
Previous	3	22	
never	12	71	
No. of births (if applicable)			
Units: Subjects			
None	5	35	
one	2	19	
two	6	31	
three	4	17	
four	1	4	
five	0	0	
six	0	1	
Patient has painful periods			
Units: Subjects			
yes	11	79	
no	7	28	
no. years HMB has been a problem			
Units: years			
arithmetic mean	7.1		
standard deviation	± 8.9	-	
Minimum duration menses over past 3 mnths			
Units: days			
arithmetic mean	5.2		
standard deviation	± 1.2	-	
Maximum duration menses over past 3 mnths			
Units: days			
arithmetic mean	6.8		
standard deviation	± 2.8	-	
Mean screening menstrual blood loss			
Units: mL			
arithmetic mean	159.8		
standard deviation	± 71.7	-	
No. years since last pregnancy			
Units: Years			
arithmetic mean	14		
standard deviation	± 8.4	-	

End points

End points reporting groups

Reporting group title	placebo
Reporting group description: placebo capsule taken orally, twice daily over 5 days.	
Reporting group title	Dexamethasone 0.4mg
Reporting group description: Dexamethasone taken orally twice daily over 5 days. Total daily dose is 0.4mg	
Reporting group title	Dexamethasone 0.8mg
Reporting group description: Dexamethasone taken orally twice daily over 5 days. Total daily dose is 0.8mg	
Reporting group title	Dexamethasone 1.0mg
Reporting group description: Dexamethasone taken orally twice daily over 5 days: total daily dose is 1.0mg	
Reporting group title	Dexamethasone 1.2mg
Reporting group description: Dexamethasone taken orally twice daily over 5 days. Total daily dose 1.2mg	
Reporting group title	Dexamethasone 1.5mg
Reporting group description: Dexamethasone taken orally twice daily over 5 days. Total daily dose 1.5mg	
Reporting group title	Dexamethasone 1.8mg
Reporting group description: Dexamethasone taken orally twice daily over 5 days. Total daily dose 1.8mg	

Primary: Bayesian analysis of change in mean MBL: Dex 0.4mg

End point title	Bayesian analysis of change in mean MBL: Dex 0.4mg[1]
End point description: Note: The comparison groups are each of the Dexamethasone doses versus placebo. So we report an endpoint for the comparison of each Dexamethasone dose versus placebo.	
End point type	Primary
End point timeframe: Change in MBL between screening (mean of screening cycles 1 and 2) and mean of treatment cycles 2 and 3 (of 3) : average time period was 5 months	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The design used is a response-adaptive, double blind, parallel group, dose finding randomised controlled trial. A Bayesian approach was used to compare 6 doses of Dexamethasone to placebo. In order to fit our analyses with the EudraCT reporting system options we have to create endpoints for each comparison (eg 0.4mg Dexamethasone to placebo) and therefore cannot include all treatment arms within a single endpoint entry.

End point values	placebo	Dexamethasone 0.4mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	5		
Units: mL				
arithmetic mean (standard deviation)	-6.0 (± 51.3)	-7.8 (± 54.3)		

Statistical analyses

Statistical analysis title	Bayesian analysis of change in mean MBL: Dex 0.4mg

Statistical analysis description:

The dose-response curve for the primary outcome was analysed using a Bayesian second order normal dynamic linear model (NDLM), which is flexible and requires few assumptions about the shape of the underlying dose-response curve. The model adjusted for the screening MBL measurements of each woman. For each Dexamethasone dose, a 95% credible interval was then calculated for the mean difference in MBL change (Dexamethasone minus placebo).

Comparison groups	Dexamethasone 0.4mg v placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority[2]
Parameter estimate	Treatment contrast
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28
upper limit	23
Variability estimate	Standard deviation
Dispersion value	12.11

Notes:

[2] - As we used Bayesian analysis the precision/dispersion type is actually 95% 'Credible Intervals' - and not Confidence intervals.

Primary: Bayesian analysis of change in mean MBL: Dex 0.8mg

End point title	Bayesian analysis of change in mean MBL: Dex 0.8mg[3]

End point description:

Note: The comparison groups are each of the Dexamethasone doses versus placebo. So we report an endpoint for the comparison of each Dexamethasone dose versus placebo.

End point type	Primary

End point timeframe:

Change in MBL between screening (mean of screening cycles 1 and 2) and mean of treatment cycles 2 and 3 (of 3) : average time period was 5 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The design used is a response-adaptive, double blind, parallel group, dose finding randomised controlled trial. A Bayesian approach was used to compare 6 doses of Dexamethasone to placebo. In order to fit our analyses with the EudraCT reporting system options we have to create endpoints for each comparison (eg 0.4mg Dexamethasone to placebo) and therefore cannot include all treatment arms within a single endpoint entry.

End point values	placebo	Dexamethasone 0.8mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: mL				
arithmetic mean (standard deviation)	-6.0 (± 51.3)	-23.8 (± 41.7)		

Statistical analyses

Statistical analysis title	Bayesian analysis of change in mean MBL: Dex 0.4mg

Statistical analysis description:

The dose-response curve for the primary outcome was analysed using a Bayesian second order normal dynamic linear model (NDLM), which is flexible and requires few assumptions about the shape of the underlying dose-response curve. The model adjusted for the screening MBL measurements of each woman. For each Dexamethasone dose, a 95% credible interval was then calculated for the mean difference in MBL change (Dexamethasone minus placebo).

Comparison groups	placebo v Dexamethasone 0.8mg
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority[4]
Parameter estimate	Treatment contrast
Point estimate	-12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41
upper limit	9
Variability estimate	Standard deviation
Dispersion value	12.75

Notes:

[4] - As we used Bayesian analysis the precision/dispersion type is actually 95% 'Credible Intervals' - and not Confidence intervals.

Primary: Bayesian analysis of change in mean MBL: Dex 1.0mg

End point title	Bayesian analysis of change in mean MBL: Dex 1.0mg[5]

End point description:

The comparison groups are each of the Dexamethasone doses versus placebo. So we report an endpoint for the comparison of each Dexamethasone dose versus placebo.

End point type	Primary

End point timeframe:

Change in MBL between screening (mean of screening cycles 1 and 2) and mean of treatment cycles 2 and 3 (of 3) : average time period was 5 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The design used is a response-adaptive, double blind, parallel group, dose finding randomised controlled trial. A Bayesian approach was used to compare 6 doses of Dexamethasone to placebo. In order to fit our analyses with the EudraCT reporting system options we have to create endpoints for each comparison (eg 0.4mg Dexamethasone to placebo) and therefore cannot include all treatment arms within a single endpoint entry.

End point values	placebo	Dexamethasone 1.0mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	21		
Units: mL				
arithmetic mean (standard deviation)	-6.0 (± 51.3)	-18.5 (± 37.8)		

Statistical analyses

Statistical analysis title	Bayesian analysis of change in mean MBL: Dex 1.0mg

Statistical analysis description:

The dose-response curve for the primary outcome was analysed using a Bayesian second order normal dynamic linear model (NDLM), which is flexible and requires few assumptions about the shape of the underlying dose-response curve. The model adjusted for the screening MBL measurements of each woman. For each Dexamethasone dose, a 95% credible interval was then calculated for the mean difference in MBL change (Dexamethasone minus placebo).

Comparison groups	placebo v Dexamethasone 1.0mg
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority[6]
Parameter estimate	Treatment contrast
Point estimate	-8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29
upper limit	13
Variability estimate	Standard deviation
Dispersion value	10.43

Notes:

[6] - As we used Bayesian analysis the precision/dispersion type is actually 95% 'Credible Intervals' - and not Confidence intervals.

Primary: Bayesian analysis of change in mean MBL: Dex 1.2mg

End point title	Bayesian analysis of change in mean MBL: Dex 1.2mg[7]

End point description:

The comparison groups are each of the Dexamethasone doses versus placebo. So we report an endpoint for the comparison of each Dexamethasone dose versus placebo.

End point type	Primary

End point timeframe:

Change in MBL between screening (mean of screening cycles 1 and 2) and mean of treatment cycles 2 and 3 (of 3) : average time period was 5 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The design used is a response-adaptive, double blind, parallel group, dose finding randomised controlled trial. A Bayesian approach was used to compare 6 doses of Dexamethasone to placebo. In order to fit our analyses with the EudraCT reporting system options we have to create endpoints for each comparison (eg 0.4mg Dexamethasone to placebo) and therefore cannot include all treatment arms within a single endpoint entry.

End point values	placebo	Dexamethasone 1.2mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	8		
Units: mL				
arithmetic mean (standard deviation)	-6.0 (± 51.3)	5.8 (± 50.6)		

Statistical analyses

Statistical analysis title	Bayesian analysis of change in mean MBL: Dex 1.2mg

Statistical analysis description:

The dose-response curve for the primary outcome was analysed using a Bayesian second order normal dynamic linear model (NDLM), which is flexible and requires few assumptions about the shape of the underlying dose-response curve. The model adjusted for the screening MBL measurements of each woman. For each Dexamethasone dose, a 95% credible interval was then calculated for the mean difference in MBL change (Dexamethasone minus placebo).

Comparison groups	placebo v Dexamethasone 1.2mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority[8]
Parameter estimate	Treatment contrast
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28
upper limit	24
Variability estimate	Standard deviation
Dispersion value	13.19

Notes:

[8] - As we used Bayesian analysis the precision/dispersion type is actually 95% 'Credible Intervals' - and not Confidence intervals.

Primary: Bayesian analysis of change in mean MBL: Dex 1.5mg

End point title	Bayesian analysis of change in mean MBL: Dex 1.5mg[9]

End point description:

The comparison groups are each of the Dexamethasone doses versus placebo. So we report an endpoint for the comparison of each Dexamethasone dose versus placebo.

End point type	Primary

End point timeframe:

Change in MBL between screening (mean of screening cycles 1 and 2) and mean of treatment cycles 2 and 3 (of 3) : average time period was 5 months

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The design used is a response-adaptive, double blind, parallel group, dose finding randomised controlled trial. A Bayesian approach was used to compare 6 doses of Dexamethasone to placebo. In order to fit our analyses with the EudraCT reporting system options we have to create endpoints for each comparison (eg 0.4mg Dexamethasone to placebo) and therefore cannot include all treatment arms within a single endpoint entry.

End point values	placebo	Dexamethasone 1.5mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	14		
Units: mL				
arithmetic mean (standard deviation)	-6.0 (± 51.3)	-24.5 (± 31.5)		

Statistical analyses

Statistical analysis title	Bayesian analysis of change in mean MBL: Dex 0.4mg

Statistical analysis description:

The dose-response curve for the primary outcome was analysed using a Bayesian second order normal dynamic linear model (NDLM), which is flexible and requires few assumptions about the shape of the underlying dose-response curve. The model adjusted for the screening MBL measurements of each woman. For each Dexamethasone dose, a 95% credible interval was then calculated for the mean difference in MBL change (Dexamethasone minus placebo).

Comparison groups	placebo v Dexamethasone 1.5mg
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[10]
Parameter estimate	Treatment contrast
Point estimate	-15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37
upper limit	8
Variability estimate	Standard deviation
Dispersion value	11.53

Notes:

[10] - As we used Bayesian analysis the precision/dispersion type is actually 95% 'Credible Intervals' - and not Confidence intervals.

Primary: Bayesian analysis of change in mean MBL: Dex 1.8mg

End point title	Bayesian analysis of change in mean MBL: Dex 1.8mg[11]

End point description:

The comparison groups are each of the Dexamethasone doses versus placebo. So we report an endpoint for the comparison of each Dexamethasone dose versus placebo.

End point type	Primary

End point timeframe:

Change in MBL between screening (mean of screening cycles 1 and 2) and mean of treatment cycles 2 and 3 (of 3) : average time period was 5 months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The design used is a response-adaptive, double blind, parallel group, dose finding randomised controlled trial. A Bayesian approach was used to compare 6 doses of Dexamethasone to placebo. In order to fit our analyses with the EudraCT reporting system options we have to create endpoints for each comparison (eg 0.4mg Dexamethasone to placebo) and therefore cannot include all treatment arms within a single endpoint entry.

End point values	placebo	Dexamethasone 1.8mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	16		
Units: mL				
arithmetic mean (standard deviation)	-6.0 (± 51.3)	-36.7 (± 53.8)		

Statistical analyses

Statistical analysis title	Bayesian analysis of change in mean MBL: Dex 1.8mg

Statistical analysis description:

The dose-response curve for the primary outcome was analysed using a Bayesian second order normal dynamic linear model (NDLM), which is flexible and requires few assumptions about the shape of the underlying dose-response curve. The model adjusted for the screening MBL measurements of each woman. For each Dexamethasone dose, a 95% credible interval was then calculated for the mean difference in MBL change (Dexamethasone minus placebo).

Comparison groups	placebo v Dexamethasone 1.8mg
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority[12]
Parameter estimate	Treatment contrast
Point estimate	-25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49
upper limit	-1
Variability estimate	Standard deviation
Dispersion value	12.21

Notes:

[12] - As we used Bayesian analysis the precision/dispersion type is actually 95% 'Credible Intervals' - and not Confidence intervals.

Secondary: Change from screening in diary-assessed volume of MBL:Dex 0.4mg

End point title	Change from screening in diary-assessed volume of MBL:Dex 0.4mg[13]

End point description:

The menstrual diary score (MDS) was calculated based on the method of scoring shown in Wyatt et al. (2001) using the patient responses to the menstrual chart in the patient study diary. The derived scores were calculated for each period day and then summed across all period days for each screening/treatment cycle. The difference in mean MDS between the treatment and screening phases was then calculated. The MDS is used to estimate the difference in menstrual period volume.
The comparison groups are each of the Dexamethasone doses versus placebo. So we report an endpoint for the comparison of each Dexamethasone dose versus placebo.

End point type	Secondary

End point timeframe:

Two screening menstrual cycles to 3 treatment cycles: average time period was 5 months

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The design used is a response-adaptive, double blind, parallel group, dose finding randomised controlled trial. A Bayesian approach was used to compare 6 doses of Dexamethasone to placebo. In order to fit our analyses with the EudraCT reporting system options we have to create endpoints for each comparison (eg 0.4mg Dexamethasone to placebo) and therefore cannot include all

treatment arms within a single endpoint entry.

End point values	placebo	Dexamethasone 0.4mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	5		
Units: mL				
arithmetic mean (standard deviation)	6.9 (± 102.0)	-13.1 (± 58.6)		

Statistical analyses

Statistical analysis title	Bayesian analysis:change in mean MBL- diary score

Statistical analysis description:

Bayesian analysis: A normal dynamic linear model was used to calculate the posterior median difference between each Dexamethasone dose and placebo according to the mean change from screening in diary-assessed volume of menstrual blood loss.
The analysis calculates median difference and 95% 'Credible intervals' - so not Confidence intervals

Comparison groups	Dexamethasone 0.4mg v placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[14]
Parameter estimate	Treatment contrast
Point estimate	-15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-59
upper limit	23
Variability estimate	Standard deviation
Dispersion value	20.51

Notes:

[14] - As we used Bayesian analysis the precision/dispersion is actually 95% 'Credible Intervals' - and not Confidence intervals.

Secondary: Change from screening in diary-assessed volume of MBL:Dex 0.8mg

End point title	Change from screening in diary-assessed volume of MBL:Dex 0.8mg[15]

End point description:

The menstrual diary score (MDS) was calculated based on the method of scoring shown in Wyatt et al. (2001) using the patient responses to the menstrual chart in the patient study diary. The derived scores were calculated for each period day and then summed across all period days for each screening/treatment cycle. The difference in mean MDS between the treatment and screening phases was then calculated. The MDS is used to estimate the difference in menstrual period volume.
The comparison groups are each of the Dexamethasone doses versus placebo. So we report an endpoint for the comparison of each Dexamethasone dose versus placebo.

End point type	Secondary

End point timeframe:

Two screening menstrual cycles to 3 treatment cycles - average time period is 5 months

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The design used is a response-adaptive, double blind, parallel group, dose finding randomised controlled trial. A Bayesian approach was used to compare 6 doses of Dexamethasone to placebo. In order to fit our analyses with the EudraCT reporting system options we have to create endpoints for each comparison (eg 0.4mg Dexamethasone to placebo) and therefore cannot include all treatment arms within a single endpoint entry.

End point values	placebo	Dexamethasone 0.8mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	9		
Units: mL				
arithmetic mean (standard deviation)	6.9 (± 102.0)	-40.5 (± 65.4)		

Statistical analyses

Statistical analysis title	Bayesian analysis:change in mean MBL- diary score

Statistical analysis description:

Bayesian analysis: A normal dynamic linear model was used to calculate the posterior median difference between each Dexamethasone dose and placebo according to the mean change from screening in diary-assessed volume of menstrual blood loss.
The analysis calculates median difference and 95% 'Credible intervals' - so not Confidence intervals

Comparison groups	placebo v Dexamethasone 0.8mg
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority[16]
Parameter estimate	Treatment contrast
Point estimate	-30
Confidence interval	
level	95 %
sides	2-sided
lower limit	-76
upper limit	7
Variability estimate	Standard deviation
Dispersion value	21.58

Notes:

[16] - The analysis calculates median difference and 95% 'Credible intervals' - so not Confidence intervals

Secondary: Change from screening in diary-assessed volume of MBL:Dex 1.0mg

End point title	Change from screening in diary-assessed volume of MBL:Dex 1.0mg[17]

End point description:

The menstrual diary score (MDS) was calculated based on the method of scoring shown in Wyatt et al. (2001) using the patient responses to the menstrual chart in the patient study diary. The derived scores were calculated for each period day and then summed across all period days for each screening/treatment cycle. The difference in mean MDS between the treatment and screening phases was then calculated. The MDS is used to estimate the difference in menstrual period volume.
The comparison groups are each of the Dexamethasone doses versus placebo. So we report an endpoint for the comparison of each Dexamethasone dose versus placebo.

End point type	Secondary

End point timeframe:

Two screening menstrual cycles to 3 treatment cycles - average time period is 5 months

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The design used is a response-adaptive, double blind, parallel group, dose finding randomised controlled trial. A Bayesian approach was used to compare 6 doses of Dexamethasone to placebo. In order to fit our analyses with the EudraCT reporting system options we have to create endpoints for each comparison (eg 0.4mg Dexamethasone to placebo) and therefore cannot include all treatment arms within a single endpoint entry.

End point values	placebo	Dexamethasone 1.0mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	21		
Units: mL				
arithmetic mean (standard deviation)	6.9 (± 102.0)	0.1 (± 55.4)		

Statistical analyses

Statistical analysis title	Bayesian analysis:change in mean MBL- diary score

Statistical analysis description:

Bayesian analysis: A normal dynamic linear model was used to calculate the posterior median difference between each Dexamethasone dose and placebo according to the mean change from screening in diary-assessed volume of menstrual blood loss.
The analysis calculates median difference and 95% 'Credible intervals' - so not Confidence intervals

Comparison groups	placebo v Dexamethasone 1.0mg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority[18]
Parameter estimate	Treatment contrast
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40
upper limit	24
Variability estimate	Standard deviation
Dispersion value	16.17

Notes:

[18] - The analysis calculates median difference and 95% 'Credible intervals' - so not Confidence intervals

Secondary: Change from screening in diary-assessed volume of MBL:Dex 1.2mg

End point title	Change from screening in diary-assessed volume of MBL:Dex 1.2mg[19]

End point description:

The menstrual diary score (MDS) was calculated based on the method of scoring shown in Wyatt et al. (2001) using the patient responses to the menstrual chart in the patient study diary. The derived scores were calculated for each period day and then summed across all period days for each screening/treatment cycle. The difference in mean MDS between the treatment and screening phases

was then calculated. The MDS is used to estimate the difference in menstrual period volume. The comparison groups are each of the Dexamethasone doses versus placebo. So we report an endpoint for the comparison of each Dexamethasone dose versus placebo.

End point type	Secondary

End point timeframe:

Two screening menstrual cycles to 3 treatment cycles - average time period is 5 months

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The design used is a response-adaptive, double blind, parallel group, dose finding randomised controlled trial. A Bayesian approach was used to compare 6 doses of Dexamethasone to placebo. In order to fit our analyses with the EudraCT reporting system options we have to create endpoints for each comparison (eg 0.4mg Dexamethasone to placebo) and therefore cannot include all treatment arms within a single endpoint entry.

End point values	placebo	Dexamethasone 1.2mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	8		
Units: mL				
arithmetic mean (standard deviation)	6.9 (± 102.0)	7.2 (± 23.3)		

Statistical analyses

Statistical analysis title	Bayesian analysis:change in mean MBL- diary score

Statistical analysis description:

Bayesian analysis: A normal dynamic linear model was used to calculate the posterior median difference between each Dexamethasone dose and placebo according to the mean change from screening in diary-assessed volume of menstrual blood loss.
The analysis calculates median difference and 95% 'Credible intervals' - so not Confidence intervals

Comparison groups	placebo v Dexamethasone 1.2mg
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority[20]
Parameter estimate	Treatment contrast
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41
upper limit	36
Variability estimate	Standard deviation
Dispersion value	19.85

Notes:

[20] - The analysis calculates median difference and 95% 'Credible intervals' - so not Confidence intervals

Secondary: Change from screening in diary-assessed volume of MBL:Dex 1.5mg

End point title	Change from screening in diary-assessed volume of MBL:Dex 1.5mg[21]

End point description:

The menstrual diary score (MDS) was calculated based on the method of scoring shown in Wyatt et al. (2001) using the patient responses to the menstrual chart in the patient study diary. The derived scores were calculated for each period day and then summed across all period days for each screening/treatment cycle. The difference in mean MDS between the treatment and screening phases was then calculated. The MDS is used to estimate the difference in menstrual period volume.
The comparison groups are each of the Dexamethasone doses versus placebo. So we report an endpoint for the comparison of each Dexamethasone dose versus placebo.

End point type	Secondary

End point timeframe:

Two screening menstrual cycles to 3 treatment cycles - average time period is 5 months

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The design used is a response-adaptive, double blind, parallel group, dose finding randomised controlled trial. A Bayesian approach was used to compare 6 doses of Dexamethasone to placebo. In order to fit our analyses with the EudraCT reporting system options we have to create endpoints for each comparison (eg 0.4mg Dexamethasone to placebo) and therefore cannot include all treatment arms within a single endpoint entry.

End point values	placebo	Dexamethasone 1.5mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	15		
Units: mL				
arithmetic mean (standard deviation)	6.9 (± 102.0)	-0.9 (± 51.9)		

Statistical analyses

Statistical analysis title	Bayesian analysis:change in mean MBL- diary score

Statistical analysis description:

Bayesian analysis: A normal dynamic linear model was used to calculate the posterior median difference between each Dexamethasone dose and placebo according to the mean change from screening in diary-assessed volume of menstrual blood loss.
The analysis calculates median difference and 95% 'Credible intervals' - so not Confidence intervals

Comparison groups	placebo v Dexamethasone 1.5mg
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority[22]
Parameter estimate	Treatment contrast
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44
upper limit	26
Variability estimate	Standard deviation
Dispersion value	17.4

Notes:

[22] - The analysis calculates median difference and 95% 'Credible intervals' - so not Confidence intervals

Secondary: Change from screening in diary-assessed volume of MBL:Dex 1.8mg

End point title	Change from screening in diary-assessed volume of MBL:Dex 1.8mg[23]

End point description:

The menstrual diary score (MDS) was calculated based on the method of scoring shown in Wyatt et al. (2001) using the patient responses to the menstrual chart in the patient study diary. The derived scores were calculated for each period day and then summed across all period days for each screening/treatment cycle. The difference in mean MDS between the treatment and screening phases was then calculated. The MDS is used to estimate the difference in menstrual period volume.
The comparison groups are each of the Dexamethasone doses versus placebo. So we report an endpoint for the comparison of each Dexamethasone dose versus placebo.

End point type	Secondary

End point timeframe:

Two screening menstrual cycles to 3 treatment cycles - average time period is 5 months

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The design used is a response-adaptive, double blind, parallel group, dose finding randomised controlled trial. A Bayesian approach was used to compare 6 doses of Dexamethasone to placebo. In order to fit our analyses with the EudraCT reporting system options we have to create endpoints for each comparison (eg 0.4mg Dexamethasone to placebo) and therefore cannot include all treatment arms within a single endpoint entry.

End point values	placebo	Dexamethasone 1.8mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	16		
Units: mL				
arithmetic mean (standard deviation)	6.9 (± 102.0)	-29.5 (± 59.5)		

Statistical analyses

Statistical analysis title	Bayesian analysis:change in mean MBL- diary score

Statistical analysis description:

Bayesian analysis: A normal dynamic linear model was used to calculate the posterior median difference between each Dexamethasone dose and placebo according to the mean change from screening in diary-assessed volume of menstrual blood loss.
The analysis calculates median difference and 95% 'Credible intervals' - so not Confidence intervals

Comparison groups	placebo v Dexamethasone 1.8mg
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority[24]
Parameter estimate	Treatment contrast
Point estimate	-32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-69
upper limit	4
Variability estimate	Standard deviation
Dispersion value	18.56

Notes:

[24] - The analysis calculates median difference and 95% 'Credible intervals' - so not Confidence intervals

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Consent to final follow-up visit (approx 30 days after day of last treatment)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	placebo
Reporting group description: placebo	
Reporting group title	Dexamethasone 0.4mg
Reporting group description: Dexamethasone taken orally twice daily over 5 days. Total dose is 0.4mg	
Reporting group title	Dexamethasone 0.8mg
Reporting group description: Dexamethasone taken orally twice daily over 5 days. Total dose is 0.8mg	
Reporting group title	Dexamethasone 1.0mg
Reporting group description: Dexamethasone taken orally twice daily total dose is 1.0mg	
Reporting group title	Dexamethasone 1.2mg
Reporting group description: Dexamethasone taken orally twice daily total dose 1.2mg	
Reporting group title	Dexamethasone 1.5mg
Reporting group description: Dexamethasone taken orally twice daily total dose 1.5mg	
Reporting group title	Dexamethasone 1.8mg
Reporting group description: Dexamethasone taken orally twice daily. Total dose 1.8mg	

Serious adverse events	placebo	Dexamethasone 0.4mg	Dexamethasone 0.8mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 26 (3.85%)	0 / 6 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
trapped sciatic nerve			
subjects affected / exposed	1 / 26 (3.85%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dexamethasone 1.0mg	Dexamethasone 1.2mg	Dexamethasone 1.5mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
trapped sciatic nerve			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dexamethasone 1.8mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
trapped sciatic nerve			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	placebo	Dexamethasone 0.4mg	Dexamethasone 0.8mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 26 (61.54%)	5 / 6 (83.33%)	6 / 9 (66.67%)
Vascular disorders			
vasomotor			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Surgery			
subjects affected / exposed	1 / 26 (3.85%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 26 (3.85%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	2
increased energy			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Menstrual discomfort			
subjects affected / exposed	5 / 26 (19.23%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	7	0	0
Vaginal discharge			
subjects affected / exposed	1 / 26 (3.85%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Respiratory symptom			
subjects affected / exposed	2 / 26 (7.69%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	1
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	2 / 26 (7.69%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	2	1	1
disturbed sleep			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Investigations			
Colposcopy			
subjects affected / exposed	1 / 26 (3.85%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Infected bite			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Fracture			

subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal injury			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 26 (3.85%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 26 (7.69%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Fatigue			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	2 / 26 (7.69%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	3	0	1
Sciatica			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
swollen neck glands			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
ear wax			

subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 26 (7.69%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	2	1	1
Abdominal distension			
subjects affected / exposed	1 / 26 (3.85%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	1
gastrointestinal disturbance			
subjects affected / exposed	1 / 26 (3.85%)	4 / 6 (66.67%)	1 / 9 (11.11%)
occurrences (all)	3	4	1
Skin and subcutaneous tissue disorders			
Dermatosis			
subjects affected / exposed	2 / 26 (7.69%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	2	2	1
vasomotor			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
urinary frequency			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal discomfort			
subjects affected / exposed	1 / 26 (3.85%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
joint fusion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Infection			
subjects affected / exposed	4 / 26 (15.38%)	2 / 6 (33.33%)	0 / 9 (0.00%)
occurrences (all)	5	2	0
Viral infection			

subjects affected / exposed	2 / 26 (7.69%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	1
Fungal infection			
subjects affected / exposed	2 / 26 (7.69%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Blood glucose fluctuation			
subjects affected / exposed	1 / 26 (3.85%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Increased appetite			
subjects affected / exposed	0 / 26 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	0

Non-serious adverse events	Dexamethasone 1.0mg	Dexamethasone 1.2mg	Dexamethasone 1.5mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 21 (80.95%)	6 / 9 (66.67%)	11 / 15 (73.33%)
Vascular disorders			
vasomotor			
subjects affected / exposed	1 / 21 (4.76%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Surgery			
subjects affected / exposed	1 / 21 (4.76%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	3
increased energy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Menstrual discomfort			
subjects affected / exposed	3 / 21 (14.29%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	4	1	1
Vaginal discharge			

subjects affected / exposed	2 / 21 (9.52%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	1
Infection			
subjects affected / exposed	1 / 21 (4.76%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Respiratory, thoracic and mediastinal disorders			
Respiratory symptom			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 21 (4.76%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	1	1	3
disturbed sleep			
subjects affected / exposed	1 / 21 (4.76%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Investigations			
Colposcopy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Infected bite			
subjects affected / exposed	1 / 21 (4.76%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Musculoskeletal injury			
subjects affected / exposed	2 / 21 (9.52%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	5 / 21 (23.81%)	2 / 9 (22.22%)	1 / 15 (6.67%)
occurrences (all)	6	2	1
Fatigue			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	3
Sciatica			
subjects affected / exposed	2 / 21 (9.52%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	1
Sleep disorder			
subjects affected / exposed	1 / 21 (4.76%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
swollen neck glands			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
ear wax			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	5 / 21 (23.81%)	1 / 9 (11.11%)	3 / 15 (20.00%)
occurrences (all)	6	2	4
Abdominal distension			
subjects affected / exposed	1 / 21 (4.76%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
gastrointestinal disturbance			

subjects affected / exposed	8 / 21 (38.10%)	2 / 9 (22.22%)	5 / 15 (33.33%)
occurrences (all)	10	3	7
Skin and subcutaneous tissue disorders			
Dermatosis			
subjects affected / exposed	1 / 21 (4.76%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	1	1	2
vasomotor			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Renal and urinary disorders			
urinary frequency			
subjects affected / exposed	1 / 21 (4.76%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal discomfort			
subjects affected / exposed	1 / 21 (4.76%)	0 / 9 (0.00%)	3 / 15 (20.00%)
occurrences (all)	2	0	3
joint fusion			
subjects affected / exposed	0 / 21 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Infection			
subjects affected / exposed	2 / 21 (9.52%)	2 / 9 (22.22%)	3 / 15 (20.00%)
occurrences (all)	4	3	6
Viral infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Fungal infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Blood glucose fluctuation			
subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Increased appetite			

subjects affected / exposed	0 / 21 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Dexamethasone 1.8mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 17 (76.47%)		
Vascular disorders			
vasomotor			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Surgery			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
increased energy			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Menstrual discomfort			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Vaginal discharge			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Respiratory symptom			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			

Mental status changes subjects affected / exposed occurrences (all) disturbed sleep subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 3 2 / 17 (11.76%) 4		
Investigations Colposcopy subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Injury, poisoning and procedural complications Infected bite subjects affected / exposed occurrences (all) Fracture subjects affected / exposed occurrences (all) Musculoskeletal injury subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 1 / 17 (5.88%) 1		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Sciatica	1 / 17 (5.88%) 1 0 / 17 (0.00%) 0 5 / 17 (29.41%) 9		

subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
swollen neck glands			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
ear wax			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Abdominal distension			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
gastrointestinal disturbance			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Dermatosis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
vasomotor			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Renal and urinary disorders			

urinary frequency subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Musculoskeletal and connective tissue disorders Musculoskeletal discomfort subjects affected / exposed occurrences (all) joint fusion subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1 0 / 17 (0.00%) 0		
Infections and infestations Infection subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all) Fungal infection subjects affected / exposed occurrences (all)	 5 / 17 (29.41%) 6 2 / 17 (11.76%) 2 0 / 17 (0.00%) 0		
Metabolism and nutrition disorders Blood glucose fluctuation subjects affected / exposed occurrences (all) Increased appetite subjects affected / exposed occurrences (all)	 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2013	Protocol wording clarification for workup studies: describe randomisation process, add NIMP for study 1, process for AE recording
22 October 2013	Protocol wording clarification for: Inclusion/exclusion criteria, study procedures
19 February 2014	Protocol wording clarification for adaptive trial; update processes for adaptive trial using experience from the completed work-up studies. Extension to recruitment period and approaches. New study materials.
18 December 2014	Protocol wording clarification; addition of new recruitment approach; New SmPC for Dexamethasone
23 May 2016	Extension to recruitment period; details for additional recruitment approach .
19 October 2017	Changes to RSI in SmPC for Dexamethasone.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported