Clinical trial results:
A phase I, single center, open-label parallel group trial to compare the pharmacokinetics of NOMAC between healthy female adolescents (aged 14-17 years) and healthy female adults (aged 18-50 years) after single dose administration of NOMAC-E2 tablets

Summary

EudraCT number	2008-002142-38
Trial protocol	GB
Global end of trial date	18 May 2009

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	24 June 2015

Trial information

Trial identification

Sponsor protocol code	P05873

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Registration: MK-8175A-009

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000250-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 May 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2009
Global end of trial reached?	Yes
Global end of trial date	18 May 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To compare the pharmacokinetics of NOMAC (nomegestrol acetate) between female adolescents (aged 14-17 years) and female adults (aged 18-50 years) after single dose administration of NOMAC- E2 (17beta-estradiol).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 March 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	15
Adults (18-64 years)	15
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study enrolled healthy female participants with a normal menstrual cycle. Other inclusion and exclusion criteria applied.

Pre-assignment

Screening details:

A total of 52 participants were screened and 30 participants were enrolled in the study.

Pre-assignment period milestones

Number of subjects started	30
Number of subjects completed	30

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	NOMAC-E2 Ages 14-17

Arm description:

Healthy female participants, ages 14 to 17 years, with normal menstrual cycles, received a single oral dose of NOMAC-E2, consisting of 2.5 mg NOMAC and 1.5 E2.

Arm type	Experimental
Investigational medicinal product name	NOMAC-E2
Investigational medicinal product code	
Other name	SCH 900121, MK-8175A
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single oral dose of NOMAC-E2, consisting of 2.5 mg NOMAC and 1.5 mg E2.

Arm title	NOMAC-E2 Ages 18-50

Arm description:

Healthy female participants, ages 18 to 50 years, with normal menstrual cycles, received a single oral dose of NOMAC-E2, consisting of 2.5 mg NOMAC and 1.5 E2.

Arm type	Control
Investigational medicinal product name	NOMAC-E2
Investigational medicinal product code	
Other name	SCH 900121, MK-8175A
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single oral dose of NOMAC-E2, consisting of 2.5 mg NOMAC and 1.5 mg E2.

Number of subjects in period 1	NOMAC-E2 Ages 14-17	NOMAC-E2 Ages 18-50
Started	15	15
Completed	15	15

Baseline characteristics

Reporting groups	
Reporting group title	NOMAC-E2 Ages 14-17
Reporting group description:	
Healthy female participants, ages 14 to 17 years, with normal menstrual cycles, received a single oral dose of NOMAC-E2, consisting of 2.5 mg NOMAC and 1.5 E2.	
Reporting group title	NOMAC-E2 Ages 18-50
Reporting group description:	
Healthy female participants, ages 18 to 50 years, with normal menstrual cycles, received a single oral dose of NOMAC-E2, consisting of 2.5 mg NOMAC and 1.5 E2.	

Reporting group values	NOMAC-E2 Ages 14-17	NOMAC-E2 Ages 18-50	Total
Number of subjects	15	15	30
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)	15	0	15
Adults (18-64 years)	0	15	15
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	15.5	33.3	
standard deviation	± 1	± 9	-
Gender categorical			
Units: Subjects			
Female	15	15	30
Male	0	0	0

End points

End points reporting groups

Reporting group title	NOMAC-E2 Ages 14-17
Reporting group description:	
Healthy female participants, ages 14 to 17 years, with normal menstrual cycles, received a single oral dose of NOMAC-E2, consisting of 2.5 mg NOMAC and 1.5 E2.	
Reporting group title	NOMAC-E2 Ages 18-50
Reporting group description:	
Healthy female participants, ages 18 to 50 years, with normal menstrual cycles, received a single oral dose of NOMAC-E2, consisting of 2.5 mg NOMAC and 1.5 E2.	

Primary: Time to maximum concentration (Tmax) of NOMAC 2.5 mg

End point title	Time to maximum concentration (Tmax) of NOMAC 2.5 mg[1]
End point description:	
Blood samples were collected for determination of NOMAC levels predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours after dosing. NOMAC in plasma was determined using validated liquid chromatographic assays with mass spectrometric detection.	
End point type	Primary
End point timeframe:	
Predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours postdose	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Justification: No statistical analysis was performed for the primary end point Time to Maximum
Concentration (Tmax) of NOMAC 2.5 mg.

End point values	NOMAC-E2 Ages 14-17	NOMAC-E2 Ages 18-50		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: hours				
median (full range (min-max))	2.52 (1 to 6)	3.03 (2 to 4.07)		

Statistical analyses

No statistical analyses for this end point

Primary: Maximum concentration (Cmax) of NOMAC 2.5 mg

End point title	Maximum concentration (Cmax) of NOMAC 2.5 mg
End point description:	
Blood samples were collected for determination of NOMAC levels predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours after dosing. NOMAC in plasma was determined using validated liquid chromatographic assays with mass spectrometric detection.	
End point type	Primary
End point timeframe:	
Predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours postdose	

End point values	NOMAC-E2 Ages 14-17	NOMAC-E2 Ages 18-50		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	6.92 (± 30.8)	6.56 (± 32.8)		

Statistical analyses

Statistical analysis title	Cmax Geometric Mean Ratio
Comparison groups	NOMAC-E2 Ages 14-17 v NOMAC-E2 Ages 18-50
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.33

Primary: Area under the concentration-time curve from time 0 to last determination (0-tlast) of NOMAC 2.5 mg

End point title	Area under the concentration-time curve from time 0 to last determination (0-tlast) of NOMAC 2.5 mg

End point description:

Blood samples were collected for determination of NOMAC levels predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours after dosing. NOMAC in plasma was determined using validated liquid chromatographic assays with mass spectrometric detection.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours postdose

End point values	NOMAC-E2 Ages 14-17	NOMAC-E2 Ages 18-50		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: ng·h/mL				
geometric mean (geometric coefficient of variation)	86.9 (± 25.9)	91.5 (± 23.6)		

Statistical analyses

Statistical analysis title	AUC 0-tlast Geometric Mean Ratio
Comparison groups	NOMAC-E2 Ages 14-17 v NOMAC-E2 Ages 18-50
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.14

Primary: Area under the concentration-time curve from time 0 to infinity (AUC0-∞) of NOMAC 2.5 mg

End point title	Area under the concentration-time curve from time 0 to infinity (AUC0-∞) of NOMAC 2.5 mg

End point description:

Blood samples were collected for determination of NOMAC levels predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours after dosing. NOMAC in plasma was determined using validated liquid chromatographic assays with mass spectrometric detection.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours postdose

End point values	NOMAC-E2 Ages 14-17	NOMAC-E2 Ages 18-50		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: ng·h/mL				
geometric mean (geometric coefficient of variation)	95.6 (± 26.3)	106 (± 35.3)		

Statistical analyses

Statistical analysis title	AUC0-∞ Geometric Mean Ratio
Comparison groups	NOMAC-E2 Ages 14-17 v NOMAC-E2 Ages 18-50

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.13

Primary: Weight-normalized apparent clearance (wn-CL/f) of NOMAC 2.5 mg

End point title	Weight-normalized apparent clearance (wn-CL/f) of NOMAC 2.5 mg

End point description:

Blood samples were collected for determination of NOMAC levels predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours after dosing. NOMAC in plasma was determined using validated liquid chromatographic assays with mass spectrometric detection.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours after dosing

End point values	NOMAC-E2 Ages 14-17	NOMAC-E2 Ages 18-50		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: L/h/kg				
geometric mean (geometric coefficient of variation)	0.441 (± 27.3)	0.36 (± 36)		

Statistical analyses

Statistical analysis title	wn-CL/f Geometric Mean Ratio
Comparison groups	NOMAC-E2 Ages 14-17 v NOMAC-E2 Ages 18-50
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.54

Primary: Weight-normalized apparent volume of distribution (wn-Vd/f) of NOMAC 2.5 mg

End point title	Weight-normalized apparent volume of distribution (wn-Vd/f) of NOMAC 2.5 mg

End point description:

Blood samples were collected for determination of NOMAC levels predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours after dosing. NOMAC in plasma was determined using validated liquid chromatographic assays with mass spectrometric detection.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours postdose

End point values	NOMAC-E2 Ages 14-17	NOMAC-E2 Ages 18-50		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: L/kg				
geometric mean (geometric coefficient of variation)	25 (± 40.9)	25 (± 30.1)		

Statistical analyses

Statistical analysis title	wn-Vd/f Geometric Mean Ratio
Comparison groups	NOMAC-E2 Ages 14-17 v NOMAC-E2 Ages 18-50
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.29

Primary: Apparent terminal half-life (t1/2) of NOMAC 2.5 mg

End point title	Apparent terminal half-life (t1/2) of NOMAC 2.5 mg

End point description:

Blood samples were collected for determination of NOMAC levels predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours after dosing. NOMAC in plasma was determined using validated liquid chromatographic assays with mass spectrometric detection.

End point type	Primary

End point timeframe:

Predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 33, 57, 81, 105, and 129 hours postdose

End point values	NOMAC-E2 Ages 14-17	NOMAC-E2 Ages 18-50		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: hours				
geometric mean (geometric coefficient of variation)	39.3 (± 45.4)	48.1 (± 45.9)		

Statistical analyses

Statistical analysis title	t1/2 Geometric Mean Ratio
Comparison groups	NOMAC-E2 Ages 14-17 v NOMAC-E2 Ages 18-50
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.13

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From screening up to 6 days after study drug administration	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	NOMAC-E2 Ages 14-17
Reporting group description:	
Healthy female participants, ages 14 to 17 years, with normal menstrual cycles, received a single oral dose of NOMAC-E2, consisting of 2.5 mg NOMAC and 1.5 E2.	
Reporting group title	NOMAC-E2 Ages 18-50
Reporting group description:	
Healthy female participants, ages 18 to 50 years, with normal menstrual cycles, received a single oral dose of NOMAC-E2, consisting of 2.5 mg NOMAC and 1.5 E2.	

Serious adverse events	NOMAC-E2 Ages 14-17	NOMAC-E2 Ages 18-50	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	NOMAC-E2 Ages 14-17	NOMAC-E2 Ages 18-50	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 15 (33.33%)	3 / 15 (20.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
occurrences (all)	3	0	
Hemicephalalgia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Abdominal Pain Lower			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Vaginal discharge			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Vaginal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Varicella			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2009	Amendment 1: As a result of requests from the Institute of Child Health/Great Ormond Street Hospital Research Ethics Committee (30 Guilford Street, London, WC1N 1 EH), serology testing (HIV and hepatitis) was removed from the younger age group and revised for the adult population only.
17 February 2009	For Amendment 2, there were 2 requests of the Institute of Child Health/Great Ormond Street Hospital Research Ethics Committee (REC), 30 Guilford Street, London, WC1N 1 EH: 1. Serology testing (HIV, hepatitis etc.), which had been removed from the younger age group, also be removed for the adult population. 2. REC noted from evidence given that the average age of menarche is 12.8 years and that contraception could be prescribed from the time when girls had a regular periods for 6 months: this would be around the age of 13.5. Although the REC understood the pressure to prescribe for the younger age group, it was of the view that the case was not clearly made for the drug to be tested in the 12-14 years olds. The REC however felt that they could approve the research for 14+s. The 12 and 13 year old age group should therefore be removed from the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported