



Clinical trial results:

A phase II international multicentre randomised open label study of oral steroid sulphatase inhibitor BN83495 versus megestrol acetate (MA) in women with advanced or recurrent endometrial cancer.

Summary

EudraCT number	2009-010613-68
Trial protocol	BE GB FR ES CZ HU PL LT LV
Global end of trial date	10 July 2013

Results information

Result version number	v2 (current)
This version publication date	12 March 2016
First version publication date	01 August 2015
Version creation reason	• Correction of full data set Review and correction.

Trial information

Trial identification

Sponsor protocol code	X-55-58064-004
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00910091
WHO universal trial number (UTN)	U2009-0106-1368

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma
Sponsor organisation address	Z.I. de Courtaboeuf 5, Avenue du Canada, Les Ulis, France, 91940
Public contact	VP Clinical Sciences, Ipsen Pharma, clinical.trials@ipsen.com
Scientific contact	VP Clinical Sciences, Ipsen Pharma, clinical.trials@ipsen.com

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	10 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 July 2013
Global end of trial reached?	Yes
Global end of trial date	10 July 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the antitumour efficacy of BN83495 measured by percentage of women with advanced or recurrent endometrial cancer who have neither progressed nor died after 6 months of treatment.

Response and progression have been evaluated by the investigator (local review) in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumours (RECIST) committee version 1.0.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator:

Megestrol Acetate (MA)

Actual start date of recruitment	12 November 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Moldova, Republic of: 1
Country: Number of subjects enrolled	Ukraine: 4
Worldwide total number of subjects	73
EEA total number of subjects	54

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)	28
From 65 to 84 years	43
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 40 patients were to be recruited in each treatment group. However, due to the early recruitment termination, only 36 patients were enrolled in the irosustat arm and 37 patients in the MA arm

Period 1

Period 1 title	Randomised
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: BN83495 40 mg

Arm description:

BN83495 (Irosustat) 40 mg tablet by mouth once daily

Arm type	Experimental
Investigational medicinal product name	BN83495
Investigational medicinal product code	
Other name	Irosustat
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg tablet by mouth once daily

Arm title	Arm B: Megestrol Acetate 160 mg
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Arm description:

Megestrol Acetate (MA) 160 mg tablet by mouth once daily

Arm type	Active comparator
Investigational medicinal product name	Megestrol Acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

160 mg tablet by mouth once daily

Number of subjects in period 1	Arm A: BN83495 40 mg	Arm B: Megestrol Acetate 160 mg
Started	36	37
Completed	36	35
Not completed	0	2
Consent withdrawn by subject	-	2

Period 2	
Period 2 title	Treatment and Survival
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Arm A: BN83495 40 mg
Arm description: BN83495 (Irosustat) 40 mg tablet by mouth once daily	
Arm type	Experimental
Investigational medicinal product name	Arm A: BN83495 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: BN83495 (Irosustat) 40 mg tablet by mouth once daily	
Arm title	Arm B: MA 160 mg
Arm description: Megestrol Acetate (MA) 160 mg tablet by mouth once daily	
Arm type	Active comparator
Investigational medicinal product name	Arm B: MA 160 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: MA 160 mg tablet by mouth once daily	

Number of subjects in period 2	Arm A: BN83495 40 mg	Arm B: MA 160 mg
Started	36	35
Completed	32	31
Not completed	4	4
Consent withdrawn by subject	3	4
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups

Reporting group title	Arm A: BN83495 40 mg
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Reporting group description:

BN83495 (Irosustat) 40 mg tablet by mouth once daily

Reporting group title	Arm B: Megestrol Acetate 160 mg
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Reporting group description:

Megestrol Acetate (MA) 160 mg tablet by mouth once daily

Reporting group values	Arm A: BN83495 40 mg	Arm B: Megestrol Acetate 160 mg	Total
Number of subjects	36	37	73
Age categorical			
Units: Subjects			
<=18 years	12	16	28
Between 18 and 65 years	13	15	28
>=65 years	11	6	17
Age continuous			
Age continuous for Total population: Arithmetic mean (Standard Deviation) = 67.7 (\pm 10.0) years			
Units: years			
arithmetic mean	68.1	67.4	
standard deviation	\pm 11.4	\pm 8.6	-
Gender categorical			
Units: Subjects			
Female	36	37	73
BMI			
Units: Subjects			
<18.5	1	0	1
18.5 - 25	10	10	20
>25 - 30	10	8	18
>30	12	17	29
MISSING	3	2	5
Race			
Units: Subjects			
BLACK / AFRICAN AMERICAN	0	1	1
CAUCASIAN / WHITE	36	36	72
Eastern Cooperative Oncology Group(ECOG) Performance Status Score			
ECOG score ranges from 0 to 5, where 0: Asymptomatic, 1: Symptomatic but completely ambulatory, 2: Symptomatic (<50% in bed during the day - ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours), 3: Symptomatic (>50% in bed, but not bedbound - capable of only limited self-care, confined to bed or chair 50% or more of waking hours), 4: Bedbound (Completely disabled- cannot carry on any self-care) and 5: Death.			
Units: units on a scale			
arithmetic mean	0.8	0.7	
standard deviation	\pm 0.6	\pm 0.7	-

End points

End points reporting groups

Reporting group title	Arm A: BN83495 40 mg
Reporting group description: BN83495 (Irosustat) 40 mg tablet by mouth once daily	
Reporting group title	Arm B: Megestrol Acetate 160 mg
Reporting group description: Megestrol Acetate (MA) 160 mg tablet by mouth once daily	
Reporting group title	Arm A: BN83495 40 mg
Reporting group description: BN83495 (Irosustat) 40 mg tablet by mouth once daily	
Reporting group title	Arm B: MA 160 mg
Reporting group description: Megestrol Acetate (MA) 160 mg tablet by mouth once daily	

Primary: Percentage of Women With Advanced or Recurrent Endometrial Cancer Who Have Neither Progressed Nor Died at 6 months

End point title	Percentage of Women With Advanced or Recurrent Endometrial Cancer Who Have Neither Progressed Nor Died at 6 months ^[1]
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End point description:

Subject continuation in the study and Response Evaluation Criteria in Solid Tumours (RECIST) assessment has been based on investigator assessment and not on central review. The 6 month timepoint is defined as the treatment start date +183 days (26 weeks).

Intent-to-treat (ITT) population includes all randomized subjects who received at least one dose of study medication.

End point type	Primary
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End point timeframe:

Up to 6 months

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: Statistical analyses is not performed

End point values	Arm A: BN83495 40 mg	Arm B: Megestrol Acetate 160 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Percentage of subjects				
number (confidence interval 90%)	36.1 (24.3 to 49.8)	54.1 (40.8 to 66.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Event (AE)

End point title	Percentage of Participants With Adverse Event (AE)
End point description:	
Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: Life threatening/disabling and Grade 5: Death	
Assessment of AEs include type, incidence and severity graded by NCI-CTCAE version 3.0	
Safety Population: All randomised subjects who received at least one dose of study medication.	
End point type	Secondary
End point timeframe:	
Up to Day 28 follow-up	

End point values	Arm A: BN83495 40 mg	Arm B: Megestrol Acetate 160 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	35		
Units: Percentage of subjects				
number (not applicable)				
Any AEs	88.9	82.9		
Any TEAEs	88.9	82.9		
Intensity of TEAEs - Grade 5	2.8	2.9		
Intensity of TEAEs - Grade 4	5.6	0		
Intensity of TEAEs - Grade 3	22.2	25.7		
Intensity of TEAEs - Grade 2	63.9	45.7		
Intensity of TEAEs - Grade 1	80.6	74.3		
Intensity of TEAEs - Missing	5.6	0		
Causality of TEAEs - Related	55.6	37.1		
Causality of TEAEs - Not related	77.8	77.1		
TEAEs Leading to Withdrawal	8.3	2.9		
TEAEs Leading to Death	2.8	2.9		
SAEs	25	17.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability of BN83495 Based on Length of Exposure

End point title	Tolerability of BN83495 Based on Length of Exposure
End point description:	
Safety Population	
Length of exposure includes interruptions.	

End point type	Secondary
End point timeframe:	
Up to 2 years	

End point values	Arm A: BN83495 40 mg	Arm B: Megestrol Acetate 160 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	35		
Units: Week				
arithmetic mean (standard deviation)	34.94 (± 38.85)	55.2 (± 49.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability of BN83495 Based on Cumulative Dose Administered

End point title	Tolerability of BN83495 Based on Cumulative Dose Administered
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End point description:

Cumulative dose (CD) is the actual total dose administered.

Safety Population

Missing number of subjects = 2

End point type	Secondary
End point timeframe:	
Up to 2 years	

End point values	Arm A: BN83495 40 mg	Arm B: Megestrol Acetate 160 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	33		
Units: mg				
arithmetic mean (standard deviation)	9452.22 (± 10799.16)	60703.03 (± 51726.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability of BN83495 Based on Dose Interruptions and Reason for Interruptions

End point title	Tolerability of BN83495 Based on Dose Interruptions and Reason for Interruptions
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End point description:

Safety Population

Percentage of participants who had dose interruptions and reason for interruptions as AE, study treatment forgotten, and other reasons.

End point type	Secondary
End point timeframe:	
Up to 2 years	

End point values	Arm A: BN83495 40 mg	Arm B: Megestrol Acetate 160 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	35		
Units: Percentage of Participants				
number (not applicable)				
Dose Interruptions	27.8	34.5		
Reason for Interruptions (AE)	16.7	8.6		
Reason for Interruptions (Treatment forgotten)	0	8.6		
Reason for Interruptions (Other)	13.9	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants >65 Years of Age With No Change or Deterioration, Improvement of <10%, or Improvement of ≥10% on the EuroQoL Score

End point title	Percentage of Participants >65 Years of Age With No Change or Deterioration, Improvement of <10%, or Improvement of ≥10% on the EuroQoL Score
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End point description:

ITT population

EuroQoL (Quality of Life)-5 Dimensions (EQ-5D) is a participant answered questionnaire scoring 5 dimensions:

Mobility, self-care, usual activities, pain/discomfort and anxiety/depression. EQ-5D score ranges from 1 to 3 (1 = no problems, 2 = some problems, 3 = Severe problems).

The respondent is asked to indicate their health state by choosing the most appropriate statement in each of the 5 dimensions.

Three subjects withdrawn the consent from MA 160 mg group and did not have EuroQoL score up to week 32.

End point type	Secondary
End point timeframe:	
Up to week 32	

End point values	Arm A: BN83495 40 mg	Arm B: Megestrol Acetate 160 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	18		
Units: Percentage of Participants				
number (not applicable)				
No Change or Deterioration at week 2	54.2	50		
No Change or Deterioration at week 4	54.2	61.1		
No Change or Deterioration at week 8	25	50		
No Change or Deterioration at week 16	25	50		
No Change or Deterioration at week 24	16.7	33.3		
No Change or Deterioration at week 32	16.7	22.2		
Improvement of <10% at week 2	0	5.6		
Improvement of <10% at week 4	4.2	5.6		
Improvement of <10% at week 8	4.2	5.6		
Improvement of <10% at week 16	0	0		
Improvement of <10% at week 24	0	5.6		
Improvement of <10% at week 32	8.3	5.6		
Improvement of ≥10% at week 2	20.8	5.6		
Improvement of ≥10% at week 4	16.7	16.7		
Improvement of ≥10% at week 8	16.7	16.7		
Improvement of ≥10% at week 16	12.5	5.6		
Improvement of ≥10% at week 24	12.5	5.6		
Improvement of ≥10% at week 32	0	5.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Benefit [Including Completed Response (CR), Partial Response (PR), and Stable Disease (SD)] ≥12 Weeks

End point title	Percentage of Participants With Clinical Benefit [Including Completed Response (CR), Partial Response (PR), and Stable Disease (SD)] ≥12 Weeks
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End point description:

CR: Disappearance of all known disease & no new sites / disease related symptoms confirmed at least 12 weeks after

initial documentation. Disappearance of all non-target lesions. Normalization of tumor marker level confirmed at least 12

wks after initial documentation.

PR: Minimum 30% decrease in sum of the longest diameters of target lesions, taking as a reference the baseline

sum of the longest diameters confirmed at least 12 wks after initial documentation. PR is also recorded when all

measurable disease has completely disappeared, but a non-measurable component (i.e., ascites) is still present but not progressing. As well as persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above normal limits.
 RECIST defines SD for target lesions as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, no occurrence of progression disease for non-target lesions and no new lesion

End point type	Secondary
End point timeframe:	
Up to 2 years	

End point values	Arm A: BN83495 40 mg	Arm B: Megestrol Acetate 160 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Percentage of Participants				
number (not applicable)	36.1	51.4		

Statistical analyses

Statistical analysis title	Arm A: BN83495 40 mg, Arm B: MA 160 mg
Comparison groups	Arm A: BN83495 40 mg v Arm B: Megestrol Acetate 160 mg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1895
Method	Chi-squared

Secondary: Percentage of Participants With Overall Response (OR) Including CR and PR

End point title	Percentage of Participants With Overall Response (OR) Including CR and PR
End point description: ITT population.	
End point type	Secondary
End point timeframe:	
Up to 2 years	

End point values	Arm A: BN83495 40 mg	Arm B: Megestrol Acetate 160 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Percentage of subjects				
number (not applicable)	8.3	29.7		

Statistical analyses

Statistical analysis title	Arm A: BN83495 40 mg, Arm B: MA 160 mg
Comparison groups	Arm A: BN83495 40 mg v Arm B: Megestrol Acetate 160 mg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0203
Method	Chi-squared

Secondary: Percentage of Participants With First Documentation of Objective Tumour Progression From Randomisation

End point title	Percentage of Participants With First Documentation of Objective Tumour Progression From Randomisation
End point description:	
ITT population.	
End point type	Secondary
End point timeframe:	
Up to 2 years	

End point values	Arm A: BN83495 40 mg	Arm B: Megestrol Acetate 160 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Percentage of subjects				
number (not applicable)	83.3	64.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR) in Responders

End point title	Duration of Response (DR) in Responders ^[2]
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End point description:

ITT population.

DR is defined as period from the time that measurement criteria are first met for CR or PR until first date of documented Progressive Disease (PD) or death. DR was assessed in participants with a best overall response of CR or PR.

Arm A: BN83495 40 mg: Median (90% Confidence Interval) = Not Calculable (23.14, Not Calculable)

Arm B: Megestrol Acetate 160 mg: Median (90% Confidence Interval) = 105.14 (47.71, Not Calculable)

End point type	Secondary
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End point timeframe:

At 2 years

Notes:

[2] - 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: Arm A values are not entered due to system limitation. The details are updated in the Description field.

End point values	Arm B: Megestrol Acetate 160 mg			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Weeks				
number (not applicable)	105.14			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS) ^[3]
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End point description:

ITT population.

OS is defined as the time from the date of enrollment to the date of death due to any cause.

Arm B: Megestrol Acetate 160 mg: Subjects analysed is 37, median (90% Confidence Interval) = not calculable (56.14, not calculable)

End point type	Secondary
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End point timeframe:

At 2 years

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: Arm B values are not entered due to system limitation. The details are updated in the Description field.

End point values	Arm A: BN83495 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: weeks				
median (confidence interval 90%)	63.43 (37.57 to 100.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS): Time From Randomisation Until Objective Tumour Progression or Death From Any Cause

End point title	Progression Free Survival (PFS): Time From Randomisation Until Objective Tumour Progression or Death From Any Cause
End point description:	
End point type	Secondary
End point timeframe:	
Up to 2 years	

End point values	Arm A: BN83495 40 mg	Arm B: Megestrol Acetate 160 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Weeks				
median (confidence interval 90%)	16.14 (9 to 31.43)	40.14 (16.29 to 64)		

Statistical analyses

Statistical analysis title	Arm A: BN83495 40 mg
Comparison groups	Arm A: BN83495 40 mg v Arm B: Megestrol Acetate 160 mg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0484
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to day 28 follow-up

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Arm B: MA 160 mg
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Reporting group description: -

Reporting group title	Arm A: BN83495 40 mg
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Reporting group description: -

Serious adverse events	Arm B: MA 160 mg	Arm A: BN83495 40 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 35 (17.14%)	9 / 36 (25.00%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung Neoplasm Malignant			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour Haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 35 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 35 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 35 (2.86%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Acute			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Lower Respiratory Tract Infection subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased Appetite subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus Inadequate Control subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm B: MA 160 mg	Arm A: BN83495 40 mg	
Total subjects affected by non-serious adverse events subjects affected / exposed	29 / 35 (82.86%)	32 / 36 (88.89%)	
Vascular disorders			
Hot Flush subjects affected / exposed	3 / 35 (8.57%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Hypertension subjects affected / exposed	4 / 35 (11.43%)	2 / 36 (5.56%)	
occurrences (all)	4	2	
General disorders and administration site conditions			
Asthenia subjects affected / exposed	2 / 35 (5.71%)	6 / 36 (16.67%)	
occurrences (all)	2	6	
Fatigue			

subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	6 / 36 (16.67%) 6	
Oedema Peripheral subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Spinal Pain subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 36 (5.56%) 2	
Immune system disorders Contrast Media Allergy subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Reproductive system and breast disorders Pelvic Pain subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Vaginal Haemorrhage subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 36 (5.56%) 2	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	2 / 36 (5.56%) 2	
Dyspnoea subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 5	3 / 36 (8.33%) 3	
Pulmonary Embolism subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	1 / 36 (2.78%) 1	
Investigations Blood Creatinine Increased			

subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	3 / 36 (8.33%) 3	
Blood Lactate Dehydrogenase Increased subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Blood Urea Increased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 36 (5.56%) 2	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	1 / 36 (2.78%) 1	
Headache subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	3 / 36 (8.33%) 3	
Lethargy subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	1 / 36 (2.78%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	4 / 36 (11.11%) 4	
Gastrointestinal disorders Abdominal Pain subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	2 / 36 (5.56%) 2	
Abdominal Pain Upper subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	1 / 36 (2.78%) 1	
Constipation subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	5 / 36 (13.89%) 5	

Diarrhoea subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 6	5 / 36 (13.89%) 5	
Dry Mouth subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	1 / 36 (2.78%) 1	
Dyspepsia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	1 / 36 (2.78%) 1	
Nausea subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	7 / 36 (19.44%) 7	
Vomiting subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	6 / 36 (16.67%) 6	
Skin and subcutaneous tissue disorders			
Dry Skin subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 5	14 / 36 (38.89%) 14	
Rash subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	1 / 36 (2.78%) 1	
Skin Fissures subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Urticaria subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	1 / 36 (2.78%) 1	
Urinary Incontinence subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Urinary Retention			

subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 35 (5.71%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
Back Pain			
subjects affected / exposed	2 / 35 (5.71%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Muscle Spasms			
subjects affected / exposed	0 / 35 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 35 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Musculoskeletal Pain			
subjects affected / exposed	1 / 35 (2.86%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Osteoarthritis			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Cystitis			
subjects affected / exposed	2 / 35 (5.71%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 35 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Urinary Tract Infection			
subjects affected / exposed	6 / 35 (17.14%)	1 / 36 (2.78%)	
occurrences (all)	6	1	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 35 (2.86%)	3 / 36 (8.33%)	
occurrences (all)	1	3	
Dehydration			

subjects affected / exposed	0 / 35 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Hypercholesterolaemia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Hyperglycaemia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Hypocalcaemia			
subjects affected / exposed	1 / 35 (2.86%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Hypokalaemia			
subjects affected / exposed	2 / 35 (5.71%)	2 / 36 (5.56%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2009	The protocol was amended to clarify the conditions under which previous chemotherapy is acceptable in order to reflect recent changes in the standard Good Clinical Practice (GCP) and the use of chemotherapy in adjuvant setting. This amendment was to facilitate recruitment of patients into the study as most women with advanced or recurrent endometrial cancer had previously received chemotherapy in the adjuvant setting. The amendment also added an evaluation of AR status as an exploratory objective and made provisions for the assessment of skin dryness. Other non-substantial typographical, consistency errors and points of detail were corrected.
17 March 2010	The protocol was amended following discussions with external experts and the primary analysis of the study was modified from a comparison between the two treatment groups with 80% power to a comparison of the PFS rate at 6 months with a predefined threshold rate (one stage Fleming's design) and 90% power, thus reducing the risk of a false negative result and allowing for a clearer decision rule at the completion of the study.
04 November 2010	The protocol was amended to modify and clarify some inclusion and exclusion criteria as the previous protocol was deemed too stringent by the Investigators. Concomitant medications that should be avoided were updated, to include drugs metabolised by CYP1A2, which may be inhibited by irosustat metabolite.
16 January 2012	The protocol was amended for administrative reasons; to notify the change of the Sponsor's Medically Responsible Person and the job title mentioned on the signature page.
30 August 2012	The protocol was amended to simplify the following protocol planned assessments: the quality of life, oncogeriatric assessments, pharmacodynamics, pharmacokinetics, safety and exploratory analyses due to the discontinuation of the development of irosustat as monotherapy. This was considered to have no safety impact on the patients. The study design was also amended to clarify the anticipated end of study and clarification on the review of tumour response data was done.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

On 06 June 2011, the Sponsor (Ipsen) decided to discontinue the development of irosustat as monotherapy. This decision was based on the futility analysis from this current study and on the Phase I clinical study results obtained in locally advanced.

Notes: