



Clinical trial results:

An open, 3-cohort, phase II trial testing oral administration of lucitanib in patients with FGFR1-amplified or non-amplified estrogen receptor positive metastatic breast cancer.

Summary

EudraCT number	2013-000288-10
Trial protocol	BE GB IT DE ES HU FR
Global end of trial date	05 April 2017

Results information

Result version number	v1 (current)
This version publication date	13 April 2018
First version publication date	13 April 2018

Trial information

Trial identification

Sponsor protocol code	CL2-80881-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02053636
WHO universal trial number (UTN)	-
Other trial identifiers	BIG: BIG 2-13

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.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	05 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 April 2017
Global end of trial reached?	Yes
Global end of trial date	05 April 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the objective response rate (ORR) of single agent lucitanib in metastatic breast cancer patients with FGFR1-amplified, FGFR1-non-amplified with 11q amplification, or FGFR1-non-amplified without 11q amplification.

Protection of trial subjects:

The study was performed in accordance with the ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2013
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	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Canada: 4
Worldwide total number of subjects	76
EEA total number of subjects	60

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)	60
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients with metastatic breast cancer ER+/HER2-, in disease progression, who received at least first line anticancer therapy in the metastatic setting and no more than 2 lines of chemotherapy with or without targeted therapy. There was no limit of lines of endocrine therapy and targeted therapy.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding implementation details.

Allocation details:

Patients were allocated based on their FGFR1 and 11q amplification status into one of the three Cohorts.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Patients with FGFR1 amplified, irrespective of 11q amplification status.

Arm type	Experimental
Investigational medicinal product name	S 80881
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Lucitanib was administered orally, once daily, on a continuous administration schedule in fasting conditions (at least 2 hours prior to and 2 hours after a meal), until unacceptable toxicity according to the investigator, disease progression or withdrawal of consent. The starting dose of lucitanib had been reduced from 15 mg to 10 mg per protocol Amendment No. 5. Patients enrolled prior to the protocol Amendment No. 5 who had already started on the 15 mg daily dose were permitted to continue receiving lucitanib at their current dose if the investigator deemed appropriate. Otherwise, the dose of lucitanib was to be reduced to 10 mg daily when starting the following cycle. Patients enrolled from protocol amendment No. 5 were not allowed to receive doses >10 mg daily.

Arm title	Cohort 2
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Arm description:

Patients with FGFR1-non-amplified and 11q amplification.

Arm type	Experimental
Investigational medicinal product name	S 80881
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Lucitanib was administered orally, once daily, on a continuous administration schedule in fasting conditions (at least 2 hours prior to and 2 hours after a meal), until unacceptable toxicity according to the investigator, disease progression or withdrawal of consent.

The starting dose of lucitanib had been reduced from 15 mg to 10 mg per protocol Amendment No. 5. Patients enrolled prior to the protocol Amendment No. 5 who had already started on the 15 mg daily dose were permitted to continue receiving lucitanib at their current dose if the investigator deemed appropriate. Otherwise, the dose of lucitanib was to be reduced to 10 mg daily when starting the following cycle. Patients enrolled from protocol amendment No. 5 were not allowed to receive doses >10 mg daily.

Arm title	Cohort 3
Arm description: Patients with FGFR1 and 11q non-amplified.	
Arm type	Experimental
Investigational medicinal product name	S 80881
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Lucitanib was administered orally, once daily, on a continuous administration schedule in fasting conditions (at least 2 hours prior to and 2 hours after a meal), until unacceptable toxicity according to the investigator, disease progression or withdrawal of consent.

The starting dose of lucitanib had been reduced from 15 mg to 10 mg per protocol Amendment No. 5. Patients enrolled prior to the protocol Amendment No. 5 who had already started on the 15 mg daily dose were permitted to continue receiving lucitanib at their current dose if the investigator deemed appropriate. Otherwise, the dose of lucitanib was to be reduced to 10 mg daily when starting the following cycle. Patients enrolled from protocol amendment No. 5 were not allowed to receive doses >10 mg daily.

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	32	18	26
Completed	32	18	26

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1
Reporting group description: Patients with FGFR1 amplified, irrespective of 11q amplification status.	
Reporting group title	Cohort 2
Reporting group description: Patients with FGFR1-non-amplified and 11q amplification.	
Reporting group title	Cohort 3
Reporting group description: Patients with FGFR1 and 11q non-amplified.	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	32	18	26
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)	28	14	18
From 65-84 years	4	4	8
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	32	18	26
Male	0	0	0

Reporting group values	Total		
Number of subjects	76		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	60		
From 65-84 years	16		
85 years and over	0		

Gender categorical			
Units: Subjects			
Female	76		
Male	0		

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
Patients with FGFR1 amplified, irrespective of 11q amplification status.	
Reporting group title	Cohort 2
Reporting group description:	
Patients with FGFR1-non-amplified and 11q amplification.	
Reporting group title	Cohort 3
Reporting group description:	
Patients with FGFR1 and 11q non-amplified.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Defined as all included patients who had taken at least one dose of study treatment.	

Primary: Objective Response Rate

End point title	Objective Response Rate ^[1]
End point description:	
Objective Response Rate was defined as the proportion of patients for whom a confirmed complete response, or confirmed partial response as best overall response was observed during treatment, according to RECIST version 1.1 criteria, evaluated by the investigator. A partial or complete response as best response warranted confirmation at least 4 weeks after first documentation.	
End point type	Primary
End point timeframe:	
Objective Response Rate was evaluated every 8 weeks +/- 5 days after the start of the investigational product and until the end of treatment.	

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: No formal comparisons were intended or carried out between cohorts (i.e. Cohort 1 vs Cohort 2 vs Cohort 3) or between dosing regimens (i.e. 15 mg vs 10 mg).

End point values	Cohort 1	Cohort 2	Cohort 3	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	32	18	26	76
Units: Patients	6	0	4	10

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Emergent adverse events on treatment (EAEs) were defined as adverse events occurring or worsening (in terms of severity) or becoming serious between the first study drug intake date (included) and the last study drug intake date + 28 days (included).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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Reporting groups

Reporting group title	All patients
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Reporting group description:

All patients who had taken at least one dose of study treatment.

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 76 (50.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences causally related to treatment / all	18 / 18		
deaths causally related to treatment / all	0 / 0		
Lymphoedema			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			

subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General physical health deterioration			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Ejection fraction decreased			

subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cholangitis			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatocellular injury			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Hydrocholecystitis			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Jaundice cholestatic			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver injury			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Portal vein thrombosis			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Nephrotic syndrome			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infected skin ulcer			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events subjects affected / exposed	75 / 76 (98.68%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	62 / 76 (81.58%) 194		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Mucosal inflammation subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	21 / 76 (27.63%) 39 26 / 76 (34.21%) 41 4 / 76 (5.26%) 4 10 / 76 (13.16%) 12 5 / 76 (6.58%) 9		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Oropharyngeal pain	11 / 76 (14.47%) 12 6 / 76 (7.89%) 6 4 / 76 (5.26%) 4		

subjects affected / exposed occurrences (all)	7 / 76 (9.21%) 7		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 6		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	17 / 76 (22.37%) 35		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	19 / 76 (25.00%) 36		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	9 / 76 (11.84%) 13		
Blood bilirubin increased subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 5		
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	17 / 76 (22.37%) 42		
Lipase increased subjects affected / exposed occurrences (all)	5 / 76 (6.58%) 8		
Platelet count decreased subjects affected / exposed occurrences (all)	6 / 76 (7.89%) 12		
Transaminases increased subjects affected / exposed occurrences (all)	5 / 76 (6.58%) 10		
Weight decreased subjects affected / exposed occurrences (all)	10 / 76 (13.16%) 11		
Nervous system disorders			

Dizziness			
subjects affected / exposed	11 / 76 (14.47%)		
occurrences (all)	13		
Headache			
subjects affected / exposed	26 / 76 (34.21%)		
occurrences (all)	47		
Lethargy			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	19		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	7		
Neutropenia			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	14		
Thrombocytopenia			
subjects affected / exposed	13 / 76 (17.11%)		
occurrences (all)	20		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	14 / 76 (18.42%)		
occurrences (all)	17		
Abdominal pain upper			
subjects affected / exposed	13 / 76 (17.11%)		
occurrences (all)	24		
Ascites			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	13 / 76 (17.11%)		
occurrences (all)	17		
Diarrhoea			

subjects affected / exposed	28 / 76 (36.84%)		
occurrences (all)	69		
Dry mouth			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	7		
Dyspepsia			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	7		
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	6		
nausea			
subjects affected / exposed	36 / 76 (47.37%)		
occurrences (all)	54		
Stomatitis			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	25 / 76 (32.89%)		
occurrences (all)	41		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Erythema			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	6		
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	11		
Pruritus			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Renal and urinary disorders			

Haematuria subjects affected / exposed occurrences (all)	5 / 76 (6.58%) 5		
Proteinuria subjects affected / exposed occurrences (all)	25 / 76 (32.89%) 88		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	36 / 76 (47.37%) 45		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	12 / 76 (15.79%) 17		
Back pain subjects affected / exposed occurrences (all)	10 / 76 (13.16%) 12		
Bone pain subjects affected / exposed occurrences (all)	6 / 76 (7.89%) 8		
Muscle spasms subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 6		
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	5 / 76 (6.58%) 7		
Myalgia subjects affected / exposed occurrences (all)	8 / 76 (10.53%) 14		
Infections and infestations Sinusitis subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 4		
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed	20 / 76 (26.32%)		
occurrences (all)	25		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2013	<p>The amendment concerned mainly:</p> <ul style="list-style-type: none">-Modifications in inclusion/exclusion criteria: restriction for normal serum potassium level at entry and normal creatinine clearance (> 60 ml/min).-Addition of clinical management rules in case of QTcF prolongation > 500 msec and LVEF decrease.-Addition of ECG and LVEF evaluation time points at C1D1 (pre-dose and tmax) and Day 28 respectively.
16 December 2013	<p>The amendment aimed to, principally:</p> <ul style="list-style-type: none">-Implement an Independent Data Monitoring Committee, to provide the Steering Committee with independent recommendations regarding the continuation, modification or interruption of the trial based on benefice/risk ratio analysis.-Modify inclusion criteria: only one archived tumour sample mandatory at screening and ability to give consent.-Modify exclusion criteria: history of thromboembolic events and hereditary risk factors added.-Remove the serum blood sample for soluble growth factor analysis at the end of treatment visit.-Add a 10mL plasma blood sample at C1D1.-Collect archived primary tumour tissue, if available, to perform comparative assays with metastatic tissue samples.-Add optional new biopsies collection at baseline for cohort 1 and 2.-Add optional new biopsy collection between C1D14-C1D28, and at EOT for cohort 3.-Add Hungary to the study countries.-Clarify sample nature (free circulating DNA, circulating growth factors).-Prohibit radiotherapy during the study.-Postpone the study initiation date to November 2013.
11 June 2014	<p>The main purpose of this amendment was to increase the level of safety management, following the temporary interruption of the study due to the incidence of hypertensive events observed. Main changes were:</p> <ul style="list-style-type: none">-Addition of a C1D4 visit to monitor early toxicities especially early increase in blood pressure.-Modification and strengthening of the management of hypertension, QTc prolongation, LVEF decreases and liver toxicities. A paragraph was added for nausea and vomiting management. The toxicity managements included also the possibility to reduce the daily dose to 10 mg, 7.5 mg and 5 mg.-Patients were to measure blood pressure daily at home on the 1st cycle and at least twice a week afterwards and at screening.-Update of the background information section: platelet count decrease and anorexia have been added as expected adverse events.-Inclusion criteria update (any prior first-line of anticancer therapy in the metastatic setting, AST/ALT ≤ 3 ULN irrespective of the presence of liver metastases).-Exclusion criteria update (history of clinically significant or uncontrolled cardiac disease, hypertension criterion, history of thrombotic disorders criterion, history of renal diseases, involvement in another clinical trial except for observational trials, uncontrolled diabetes mellitus).-Prohibition of any oral anticoagulant as concomitant treatment and prohibition of aspirin if taken concomitantly with oral anti-platelet agents.-Mention that patients with evidence of liver disease or injury should avoid drugs known to be hepatotoxic, ie paracetamol/acetaminophen.-Possibility to use tumours imagery anterior to ICF for baseline assessment if performed within the 28 day screening period prior to the 1st drug intake.-Implementation of time windows for scheduled visits and LVEF examination.-Possibility to send 20 slides of the screening tumour samples to ICR instead of the whole tumour block.

25 February 2015	<p>It concerned mainly the update of prohibited, contraindicated and not recommended medications in association with lucitanib:</p> <ul style="list-style-type: none"> -Exclusion criteria update and clarification: patients receiving administration of strong inhibitors of CYP2C8 and/or CYP3A4 or strong inducers of CYP3A4 added, mutation of Factor V of Leiden as an example of thromboembolism hereditary risk factors removed, serum potassium below LLN at screening. -Clarifications about coagulation test, time window to perform laboratory tests, ER/PR and HER2 testing, troponin test to be evaluated, liver toxicity management, decrease LVEF management and hypothyroidism management. -Implementation of recommendations in case of missed or incomplete intake of drug dose. -Update on permitted medication: LHRH analogue provided that the treatment was initiated prior to the initiation of study drug with documented disease progression. -Update on prohibited drugs: strong inhibitors of CYP3A4 or CYP2C8, strong dual inhibitors of CYP3A4 and CYP2C8 and strong inducers of CYP3A4 to be prohibited. Moderate inhibitors of CYP3A4 or CYP2C8 and moderate dual inhibitor of CYP3A4 and CYP2C8 not recommended. Herbal supplement strongly not recommended. Verapamil and diltiazem deleted from prohibited drugs.
27 August 2015	<p>The amendment concerned mainly the reduction of the starting dose of lucitanib from 15 mg to 10 mg daily. Patients who were already on the 15 mg daily dose were permitted to continue at their current dose based on the investigator's decision (if well controlled hypertension and others toxicities at 15mg and patients benefited from this dose). Otherwise, lucitanib dose was to be reduced to 10 mg at the start of following cycle. Other changes included:</p> <ul style="list-style-type: none"> -Introduction of the new formulation of lucitanib (tablets). -Clarification and updates on management of hypertension, minor clarification of general and renal toxicities management. -Possibility to send 20 representative and serial slides for the optional biopsies instead of tumour block in case of strict internal policy of the site. -Addition of 10 ml of blood collected at each time point (C1D1, C1D14, EOT) for circulating tumour DNA analysis. -Removal of optional on-treatment biopsy. -Clarification of adverse events definition .
02 February 2016	<p>Following the report of a case of Posterior Reversible Encephalopathy Syndrome (PRES), this amendment was designed to add precautionary measures in case a patient experienced symptoms suggestive of PRES. It included:</p> <ul style="list-style-type: none"> -An update of the background information section: information about a case of PRES with lucitanib observed within the context of FINESSE. -The addition of a paragraph for the management of symptoms suggestive of PRES and confirmed PRES. -Clarification of the exclusion criteria relative to treatment withdrawal window in case a patient received another IMP before the first dose of lucitanib.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 May 2014	<p>In May 2014, upon IDMC recommendation, the study Steering Committee and the Sponsor decided to temporarily interrupt patients' enrolment due to the incidence of hypertension events. A protocol amendment (Amendment No. 3), including strict measures to follow and manage hypertension, was issued in June 2014. After approval of Amendment No. 3, the recruitment had been resumed with a restricted number of sites and controlled recruitment before the full activation of all sites.</p>	11 September 2014

31 May 2016	Halt on recruitment on 31-May-2016 by IDMC until the next IDMC meeting (90 days later). This was to allow more time for a consideration of efficacy in patients currently on treatment at 10mg, recognising that the lucitanib exposure in the 10 mg group at this time was very low (mean 22 days at the time of data lock).	-
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Notes:

Limitations and caveats

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

On 4-August-2016, it was decided to prematurely and definitively halt the recruitment of patients: a data analysis from the lucitanib breast cancer clinical development program showed that lucitanib was not likely to be superior than standard of care

Notes: