Clinical trial results:
Phase II, open, adaptive, dose escalating, multicentre titration study to assess the efficacy and safety of repeated subcutaneous administration of different doses of BIM 23A760 in patients with carcinoid syndrome

Summary

EudraCT number	2009-013222-16
Trial protocol	SE NL LV CZ FI IE ES BE AT FR DE IT SK GB
Global end of trial date	15 December 2010

Results information

Result version number	v2 (current)
This version publication date	27 February 2016
First version publication date	12 August 2015
Version creation reason	• Correction of full data set Review and correction.

Trial information

Trial identification

Sponsor protocol code	8-55-52060-004

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma
Sponsor organisation address	65 quai Georges Gorse, Boulogne-Billancourt, France, 92100
Public contact	Ipsen Pharma, Ipsen Pharma, 33.(0).1 1.58.33.50.00, clinical.trials@ipsen.com
Scientific contact	Ipsen Pharma, Ipsen Pharma, 33.(0).1 1.58.33.50.00, 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	31 October 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2010
Global end of trial reached?	Yes
Global end of trial date	15 December 2010
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of repeated s.c. injections at different doses of BIM 23A760 on patient's overall satisfaction in terms of symptom relief (diarrhoea and/or flushes) in patients with carcinoid syndrome after 24 weeks of treatment.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 February 2010
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	Russian Federation: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Ireland: 1
Worldwide total number of subjects	8
EEA total number of subjects	7

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)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was terminated prematurely. Only 8 patients were treated in part A and no patients participated in part B.

Pre-assignment

Screening details:

Patients screened were 15 and not treated were 7 (2 subjects were not included due to early termination of study by sponsor and 5 subjects failed to meet inclusion criteria).

Period 1

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

Arms

Arm title	BIM 23A760

Arm description:

This dose adaptive study is planned to treat up to 20 patients in each starting dose cohort, with a maximum of three starting dose cohorts. The doses planned to be assessed are 1, 2, 4, 6 and 8 mg, however, the maximum starting dose will be 4 mg. The starting dose of the first cohort will be 1 mg; the first cohort will include at least five patients. After the first fifteen patients have been treated for 4 weeks, the results will be reviewed by a Data Review Committee. An extension phase (Part B) is planned for those subjects completing the initial study and fulfilling specific eligibility criteria (symptoms control, willingness to participate, safety and tolerability).

BIM 23A760: BIM 23A760 is a solution at a concentration of 5 mg/mL ready for subcutaneous injection. BIM 23A760 dose of 1, 2, 4, 6 and 8 mg can be given to the patient according to a dose escalation and titration process. Patients will receive 24 weekly injections of BIM 23A760 during the treatment period.

Arm type	Experimental
Investigational medicinal product name	BIM 23A760
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 mg, 2 mg, 4 mg

Number of subjects in period 1	BIM 23A760
Started	8
BIM 23A760 1 mg	3
BIM 23A760 2 mg	2
BIM 23A760 4 mg	3
Completed	0
Not completed	8
Consent withdrawn by subject	1
Adverse event, non-fatal	2

Study termination by sponsor	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description:

This dose adaptive study is planned to treat up to 20 patients in each starting dose cohort, with a maximum of three starting dose cohorts. The doses planned to be assessed are 1, 2, 4, 6 and 8 mg, however, the maximum starting dose will be 4 mg. The starting dose of the first cohort will be 1 mg; the first cohort will include at least five patients. After the first fifteen patients have been treated for 4 weeks, the results will be reviewed by a Data Review Committee. An extension phase (Part B) is planned for those subjects completing the initial study and fulfilling specific eligibility criteria (symptoms control, willingness to participate, safety and tolerability).

BIM 23A760: BIM 23A760 is a solution at a concentration of 5 mg/mL ready for subcutaneous injection. BIM 23A760 dose of 1, 2, 4, 6 and 8 mg can be given to the patient according to a dose escalation and titration process. Patients will receive 24 weekly injections of BIM 23A760 during the treatment period.

Reporting group values	Overall Trial	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
Adults (18-64 years)	8	8	
Age continuous Units: years			
arithmetic mean	62.1		
standard deviation	± 6.88	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	2	2	
Race/Ethnicity Units: Subjects			
Caucasian/ White	8	8	
Diabetic status Units: Subjects			
Diabetic	0	0	
Nondiabetic	8	8	
Post-menopausal status Units: Subjects			
Yes	6	6	
No	0	0	
N/A - Not applicable	2	2	

End points

End points reporting groups

Reporting group title	BIM 23A760

Reporting group description:

This dose adaptive study is planned to treat up to 20 patients in each starting dose cohort, with a maximum of three starting dose cohorts. The doses planned to be assessed are 1, 2, 4, 6 and 8 mg, however, the maximum starting dose will be 4 mg. The starting dose of the first cohort will be 1 mg; the first cohort will include at least five patients. After the first fifteen patients have been treated for 4 weeks, the results will be reviewed by a Data Review Committee. An extension phase (Part B) is planned for those subjects completing the initial study and fulfilling specific eligibility criteria (symptoms control, willingness to participate, safety and tolerability).

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Primary: Percentage of Patients With a Positive Overall Satisfactory Relief of Symptoms (Diarrhoea and/or Flushes) on the Likert Scale

End point title	Percentage of Patients With a Positive Overall Satisfactory Relief of Symptoms (Diarrhoea and/or Flushes) on the Likert Scale[1]

End point description:

Patient satisfaction based on a Likert scale from 0-5 (0 being not satisfied and 5 being completely satisfied)

Study was prematurely terminated and no data was collected/analyzed for this outcome measure.

End point type	Primary

End point timeframe:

Week 24

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: Due to premature termination of the study, no data was collected/analyzed and no patient participated in Part B.

End point values	BIM 23A760			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: Perceentage of participants				

Notes:

[2] - Study was prematurely terminated and no data was collected/analyzed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With Improvement in Symptoms (Diarrhoea and/or Flushes)

End point title	Percentage of Patients With Improvement in Symptoms (Diarrhoea and/or Flushes)

End point description:

Study was prematurely terminated and no data was collected/analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Up to week 24

End point values	BIM 23A760			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: Percentage of participants				

Notes:

[3] - Study was prematurely terminated and no data was collected/analyzed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Quality of Life (QoL) Assessment

End point title	Change in the Quality of Life (QoL) Assessment

End point description:

Study was prematurely terminated and no data was collected/analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Week 24

End point values	BIM 23A760			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: Percentage of participants				

Notes:

[4] - Study was prematurely terminated and no data was collected/analyzed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in 5 Hydroxyindoleacetic Acid (5 HIAA) and Chromogranin A

End point title	Change in 5 Hydroxyindoleacetic Acid (5 HIAA) and Chromogranin A

End point description:

Study was prematurely terminated and no data was collected/analyzed for this outcome measure.

End point type	Secondary

End point timeframe:
Week 24

End point values	BIM 23A760			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: Percentage of participants				

Notes:
[5] - Study was prematurely terminated and no data was collected/analyzed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reported Adverse Events, Including Any Findings From an Examination of the Injection Site(s)

End point title	Number of Subjects Reported Adverse Events, Including Any Findings From an Examination of the Injection Site(s)

End point description:

Analysis Population Description:
Both ITT (Intent-To-Treat) and safety populations were the same analysis group. Treatment emergent adverse events (TEAE) reported by 2 or more patients (safety population) by primary system organ class.

End point type	Secondary

End point timeframe:
Up to week 26

End point values	BIM 23A760			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Participants				
General Disorders & Administration Site Condition	5			
Gastrointestinal Disorder	4			
Nervous System Disorders	3			
Infections and Infestations	2			
Metabolism and Nutritional Disorders	2			
Neoplasms Benign, Malignant and unspecified	2			
Reproductive System and Breast Disorders	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Concentration (Cmin) BIM 23A760 Plasma Levels

End point title	Minimum Concentration (Cmin) BIM 23A760 Plasma Levels

End point description:

Study was prematurely terminated and no data was collected/analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

At 9 timepoints up to 1 week after 24th administration in week 24

End point values	BIM 23A760			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: Percentage of participants				

Notes:

[6] - Study was prematurely terminated and no data was collected/analyzed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration at 2 Hours Postdose (C2 Hours) BIM 23A760 Plasma LevelsStudy was prematurely terminated and no data was collected/analyzed for this outcome measure.

End point title	Concentration at 2 Hours Postdose (C2 Hours) BIM 23A760 Plasma LevelsStudy was prematurely terminated and no data was collected/analyzed for this outcome measure.

End point description:

Study was prematurely terminated and no data was collected/analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

At 8 timepoints up to week 24

End point values	BIM 23A760			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: Percentage of participants				

Notes:

[7] - Study was prematurely terminated and no data was collected/analyzed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to week 26

Adverse event reporting additional description:

Dose received prior to to AE onset

Two SAEs 'Confusional State' and 'Nausea' were not included as they occurred during screening phase, before starting study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	BIM 23A760

Reporting group description:

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BIM 23A760 was a solution at a concentration of 5 mg/mL ready for subcutaneous injection. BIM 23A760 doses of 1, 2, 4, 6 and 8 mg were to be given to the patient according to a dose escalation and titration process. Patients would have received 24 weekly injections of BIM 23A760 during the treatment period.

Serious adverse events	BIM 23A760		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BIM 23A760		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to liver			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Metastases to peripheral vascular system			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Injection site inflammation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	3		
Injection site pruritus			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Injection site reaction			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Oedema			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pelvic floor muscle weakness			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vulvovaginal dryness			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Eye disorders			

Vision blurred subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 3		
Abdominal pain subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Constipation subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Vomiting subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 3		
Abdominal distension subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Dyspepsia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Mucous stools subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Erythema subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Night sweats			

subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Musculoskeletal and connective tissue disorders Groin pain subjects affected / exposed occurrences (all) Systemic lupus erythematosus subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypoalbuminaemia subjects affected / exposed occurrences (all)	 2 / 8 (25.00%) 3 1 / 8 (12.50%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2010	Amendment 1 • The initial cohort to be treated at 1 mg was expanded to include a minimum of 15 patients and a maximum of 40 patients. • The scope of the DRC review was expanded to include pharmacokinetic data. • The exclusion criteria were amended so that patients who had received a radiolabelled SRL for reasons other than carcinoid syndrome treatment could be included in the study. • The exclusion criteria were reworded in line with the Phase II BIM 23A760 study in patients with acromegaly (Study 2-55-52060-003), to exclude patients with a known hypersensitivity to any compounds related to the test materials and/or any known contraindications to MRI/CT. • Changes relating to the withdrawal criteria which were requested by the German Competent Authorities for Study 2-55-52060-003 were also implemented for this study, to provide more comprehensive guidance on when and how to withdraw patients. • Two exclusion criteria, one regarding impaired creatinine clearance and one regarding fibrosis, were added at the request of the Competent Authority in Ireland. • For clarification of the tumour localisation, the exclusion criteria were reworded to specifically exclude patients with tumours of foregut or hindgut origin; only patients with tumours of midgut origin were eligible for the study. • Visit 1 hospitalisation was made optional because no study drug was administered at this visit and all assessments could be conducted without hospitalisation. • Other minor corrections and amendments were made to clarify certain procedures and to remove inconsistencies.
30 April 2010	Protocol amendment 2 • An extension phase was added to allow patients to continue treatment with BIM 23A760 in the study after completing 6 months of treatment, and to assess long term safety and efficacy of BIM 23A760 in patients with carcinoid syndrome. • The inclusion criterion regarding contraception was reworded to meet regulatory guidance for clinical trials where the potential interactions between the IMP and hormonal contraceptives were not yet known (CPMP/ICH/286/95). • The procedure to be followed in the event of a pregnancy was clarified; i.e. the IMP was to be discontinued and the patient had to be withdrawn from the study.

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.

Due to premature termination of the study, no data was collected/analyzed and no patient participated in Part B.

Notes: