



Clinical trial results:

Open label extension study of lanreotide Autogel 120 mg in patients with non functioning entero-pancreatic endocrine tumour

Summary

EudraCT number	2008-004019-36
Trial protocol	FR CZ SK BE ES PL GB SE IT
Global end of trial date	04 December 2015

Results information

Result version number	v1 (current)
This version publication date	28 December 2017
First version publication date	28 December 2017

Trial information

Trial identification

Sponsor protocol code	2-55-52030-729
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00842348
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma SAS
Sponsor organisation address	65 quai Georges Gorse, Boulogne Billancourt, Cedex, France, 92650
Public contact	Medical Director, Oncology, Ipsen Pharma SAS, clinical.trials@ipsen.com
Scientific contact	Medical Director, Oncology, Ipsen Pharma SAS, 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	04 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 December 2015
Global end of trial reached?	Yes
Global end of trial date	04 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Study 2-55-52030-729 (hereafter referred to as extension Study 729) assessed the long term safety of administration of lanreotide Autogel 120 milligrams (mg) every 28 days in patients with non functioning entero-pancreatic neuroendocrine tumour (NET). Study 729 is the extension to the original study protocol, 2-55-52030-726 (hereafter referred to as core Study 726) which was a randomised, double-blind, placebo-controlled, parallel group study in patients with metastatic or locally advanced non functioning entero-pancreatic NET. Eligible patients from core Study 726 could be enrolled in the open label extension Study 729 but enrolment was not mandatory. In extension Study 729, all patients received the same treatment (lanreotide Autogel 120 mg) but certain results analyses were performed using patients as randomised in the core Study 726. As such, overall enrolment for the trial (enrolled per country and per age group) is presented for the core Study 726.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice. This study also adhered to all local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 February 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	Belgium: 4
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	India: 4
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	United States: 30
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Germany: 14

Worldwide total number of subjects	204
EEA total number of subjects	170

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)	111
From 65 to 84 years	91
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

In core Study 726, patients were enrolled at 48 sites across 14 countries (204 randomised to receive study treatment). In extension Study 729, patients were enrolled at 24 sites across 10 countries (89 enrolled to receive open label study treatment). The study was initiated in February 2009 and completed in December 2015

Pre-assignment

Screening details:

Patients treated in core Study 726 were eligible for entry into this extension study if they met either of the following criteria:

1. Stable disease after 96 weeks of treatment, irrespective of treatment received during Study 726, or
2. Disease progression (PD) during course of Study 726 and the code break showed the patient had received placebo.

Period 1

Period 1 title	Start core Study 726 to start Study 729
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

In core Study 726, 2 sets of individual sealed code break envelopes were prepared by an Ipsen Randomisation Manager to enable code break procedures of individual subjects without compromising the blind of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	LA:LA (Study 726:Study 729)

Arm description:

Patients who received lanreotide Autogel 120 mg in core Study 726 and who continued to receive open label lanreotide Autogel 120 mg in extension Study 729. Note, all patients in extension Study 729 received the same dose of lanreotide Autogel (120 mg) once every 28 days. This arm is referred to as LA:LA to designate randomised treatment in core Study 726:open label treatment in extension Study 729.

Arm type	Experimental
Investigational medicinal product name	Lanreotide Autogel
Investigational medicinal product code	Lanreotide Autogel 120 mg
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Lanreotide Autogel 120 mg was administered every 28 days via deep subcutaneous (s.c.) injections (in the superior external quadrant of the buttock).

Arm title	PB:LA (Study 726:Study 729)
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Arm description:

Patients who received placebo in core Study 726 and who received open label lanreotide Autogel 120 mg in extension Study 729. Note, all patients in extension Study 729 received the same dose of lanreotide Autogel (120 mg) once every 28 days. This arm is referred to as PB:LA to designate randomised treatment in core Study 726:open label treatment in extension Study 729.

Arm type	Experimental
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Saline solution 0.9% administered via deep s.c. injection every 28 days.

Number of subjects in period 1	LA:LA (Study 726:Study 729)	PB:LA (Study 726:Study 729)
Started	101	103
Completed	42	47
Not completed	59	56
Did not enter Study 729	59	56

Period 2

Period 2 title	Study 729
Is this the baseline period?	Yes ^[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LA:LA (Study 726:Study 729)

Arm description:

Patients who received lanreotide Autogel 120 mg in core Study 726 and who continued to receive open label lanreotide Autogel 120 mg in extension Study 729. Note, all patients in extension Study 729 received the same dose of lanreotide Autogel (120 mg) once every 28 days. This arm is referred to as LA:LA to designate randomised treatment in core Study 726:open label treatment in extension Study 729.

Arm type	Experimental
Investigational medicinal product name	Lanreotide Autogel
Investigational medicinal product code	Lanreotide Autogel 120 mg
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Lanreotide Autogel 120 mg was administered every 28 days via deep subcutaneous (s.c.) injections (in the superior external quadrant of the buttock).

Arm title	PB:LA (Study 726:Study 729)
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Arm description:

Patients who received placebo in core Study 726 and who received open label lanreotide Autogel 120 mg in extension Study 729. Note, all patients in extension Study 729 received the same dose of lanreotide Autogel (120 mg) once every 28 days. This arm is referred to as PB:LA to designate randomised treatment in core Study 726:open label treatment in extension Study 729.

Arm type	Experimental
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Investigational medicinal product name	Lanreotide Autogel
Investigational medicinal product code	Lanreotide Autogel 120 mg
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Lanreotide Autogel 120 mg was administered every 28 days via deep subcutaneous (s.c.) injections (in the superior external quadrant of the buttock).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Since certain efficacy data is reported for the intention-to-treat (ITT) population which comprised all patients randomised in core Study 726, it was necessary for Subject Disposition to represent those enrolled in this preceding study. Thus, Period 1 presents data for patients enrolled in core Study 726 until the start of extension Study 729, and Period 2 presents data for patients enrolled in extension Study 729. Period 2 is therefore the baseline period for this extension study.

Number of subjects in period 2^[2]	LA:LA (Study 726:Study 729)	PB:LA (Study 726:Study 729)
Started	42	47
Completed	16	9
Not completed	26	38
Adverse event, serious fatal	1	2
Sponsor's decision	1	-
Consent withdrawn by subject	2	4
Due to non-availability of investigational product	-	1
Adverse event, non-fatal	1	1
Due to Sponsor stopping the study	1	1
PD (including deaths due to PD)	18	28
Surgical resection	1	-
Protocol deviation	1	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number enrolled worldwide corresponds to all patients randomised in core Study 726 (n=204). This was necessary due to the presentation of certain efficacy data for this patient population (i.e. ITT population). Baseline characteristics are presented for the safety population which comprised all patients who received at least one dose of lanreotide Autogel in extension Study 729 (n=89).

Baseline characteristics

Reporting groups

Reporting group title	LA:LA (Study 726:Study 729)
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Reporting group description:

Patients who received lanreotide Autogel 120 mg in core Study 726 and who continued to receive open label lanreotide Autogel 120 mg in extension Study 729. Note, all patients in extension Study 729 received the same dose of lanreotide Autogel (120 mg) once every 28 days. This arm is referred to as LA:LA to designate randomised treatment in core Study 726:open label treatment in extension Study 729.

Reporting group title	PB:LA (Study 726:Study 729)
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Reporting group description:

Patients who received placebo in core Study 726 and who received open label lanreotide Autogel 120 mg in extension Study 729. Note, all patients in extension Study 729 received the same dose of lanreotide Autogel (120 mg) once every 28 days. This arm is referred to as PB:LA to designate randomised treatment in core Study 726:open label treatment in extension Study 729.

Reporting group values	LA:LA (Study 726:Study 729)	PB:LA (Study 726:Study 729)	Total
Number of subjects	42	47	89
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	64.8 ± 10.8	61.3 ± 10.2	-
Gender categorical Units: Subjects			
Female	23	22	45
Male	19	25	44
Race Units: Subjects			
Asian	0	3	3
Black or African American	1	0	1
Caucasian/White	41	44	85

End points

End points reporting groups

Reporting group title	LA:LA (Study 726:Study 729)
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Reporting group description:

Patients who received lanreotide Autogel 120 mg in core Study 726 and who continued to receive open label lanreotide Autogel 120 mg in extension Study 729. Note, all patients in extension Study 729 received the same dose of lanreotide Autogel (120 mg) once every 28 days. This arm is referred to as LA:LA to designate randomised treatment in core Study 726:open label treatment in extension Study 729.

Reporting group title	PB:LA (Study 726:Study 729)
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Reporting group description:

Patients who received placebo in core Study 726 and who received open label lanreotide Autogel 120 mg in extension Study 729. Note, all patients in extension Study 729 received the same dose of lanreotide Autogel (120 mg) once every 28 days. This arm is referred to as PB:LA to designate randomised treatment in core Study 726:open label treatment in extension Study 729.

Reporting group title	LA:LA (Study 726:Study 729)
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Reporting group description:

Patients who received lanreotide Autogel 120 mg in core Study 726 and who continued to receive open label lanreotide Autogel 120 mg in extension Study 729. Note, all patients in extension Study 729 received the same dose of lanreotide Autogel (120 mg) once every 28 days. This arm is referred to as LA:LA to designate randomised treatment in core Study 726:open label treatment in extension Study 729.

Reporting group title	PB:LA (Study 726:Study 729)
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Reporting group description:

Patients who received placebo in core Study 726 and who received open label lanreotide Autogel 120 mg in extension Study 729. Note, all patients in extension Study 729 received the same dose of lanreotide Autogel (120 mg) once every 28 days. This arm is referred to as PB:LA to designate randomised treatment in core Study 726:open label treatment in extension Study 729.

Subject analysis set title	Total LA (Study 729)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All patients treated with open label lanreotide Autogel 120 mg (LA) in extension Study 729.

Subject analysis set title	Lanreotide Autogel - Randomised Treatment in Study 726
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All patients randomised to lanreotide Autogel 120 mg in core Study 726. Patients continuing into extension Study 729 received open label lanreotide Autogel 120 mg once every 28 days.

Subject analysis set title	Placebo - Randomised Treatment in Study 726
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All patients randomised to placebo in core Study 726. Patients continuing into extension Study 729 received open label lanreotide Autogel 120 mg once every 28 days.

Primary: Number of Patients with Treatment Emergent Adverse Events (TEAEs) during extension Study 729

End point title	Number of Patients with Treatment Emergent Adverse Events (TEAEs) during extension Study 729 ^[1]
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End point description:

Adverse events (AEs) that were ongoing from core Study 726 at the time of entry into extension Study 729 were transcribed into the case report form (CRF) for Study 729 with a start date corresponding to the original report of this AE in Study 726. All new AEs that started after the last visit in core Study 726 (i.e. irrespective of whether the AE had onset before or after giving informed consent for extension Study 729) were recorded in the CRF for Study 729.

An AE was considered as a treatment emergent adverse event (TEAE) for Study 729 if:

- It was not present prior to receiving the first dose of study treatment in Study 729; or,
- It was present prior to receiving the first dose of study treatment in Study 729 but the intensity increased after the first dose of study treatment in Study 729.

Analysis was performed on the the safety population which comprised all patients who received at least one dose of open label lanreotide Autogel in extension Study 729.

End point type	Primary
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End point timeframe:

Throughout the study until the completion/early discontinuation visit.

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: Only descriptive analysis was planned and performed for the primary end point.

End point values	LA:LA (Study 726:Study 729)	PB:LA (Study 726:Study 729)	Total LA (Study 729)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	42	47	89	
Units: Participants	40	46	86	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS): Kaplan-Meier Estimate

End point title	Progression Free Survival (PFS): Kaplan-Meier Estimate
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End point description:

The time from randomisation in core Study 726 to the first occurrence of either PD (measured using Response Evaluation Criteria In Solid Tumours criteria) or death in Study 726 or in extension Study 729, or equivalently, the PFS time. Tumour assessments for the placebo group after switching to open label lanreotide Autogel in extension Study 729 were excluded for the purpose of this analysis. Estimation of the median was based on the Kaplan-Meier method.

Analysis was performed on the ITT population which comprised all patients randomised in core Study 726 (regardless of whether they continued into extension Study 729). The ITT population was analysed using patients as randomised in core Study 726 (i.e. to either lanreotide Autogel or placebo).

End point type	Secondary
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End point timeframe:

Throughout the study (every 24 weeks and at completion/withdrawal visit)

End point values	Lanreotide Autogel - Randomised Treatment in Study 726	Placebo - Randomised Treatment in Study 726		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	101	103		
Units: weeks				
median (confidence interval 95%)	154.14 (123.57 to 237.43)	72.00 (48.43 to 84.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Subsequent Disease Progression or Death

End point title	Time to Subsequent Disease Progression or Death
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End point description:

The time to subsequent PD or death, defined as time from PD in core Study 726 (while receiving placebo treatment) to subsequent PD or death, in extension Study 729 (while receiving open label lanreotide Autogel treatment).

Analysis was performed on the ITT population for the subgroup of patients with PD during placebo treatment in core Study 726 who continued into extension Study 729 (n=32).

End point type	Secondary
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End point timeframe:

Throughout the study (every 24 weeks and at completion/withdrawal visit)

End point values	Placebo - Randomised Treatment in Study 726			
Subject group type	Subject analysis set			
Number of subjects analysed	32			
Units: weeks				
median (confidence interval 95%)	76.14 (40.29 to 106.86)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were monitored from the time that the patient withdrew or completed core Study 726 until withdrawal in extension Study 729 (up to maximum duration of 6.2 years during Study 729).

Adverse event reporting additional description:

Data reported as TEAEs, defined as any AE that:

- Was not present prior to receiving the first dose of study treatment in Study 729; or,
- Was present prior to receiving the first dose of study treatment in Study 729 but the intensity increased after the first dose of study treatment in Study 729.

Analysis was performed on the safety population.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	LA:LA (Study 726:Study 729)
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Reporting group description:

Patients who received lanreotide Autogel 120 mg in core Study 726 and who continued to receive open label lanreotide Autogel 120 mg in extension Study 729. Note, all patients in extension Study 729 received the same dose of lanreotide Autogel (120 mg) once every 28 days. This arm is referred to as LA:LA to designate randomised treatment in core Study 726:open label treatment in extension Study 729.

Reporting group title	Total LA (Study 729)
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Reporting group description:

All patients treated with open label lanreotide Autogel 120 mg (LA) in extension Study 729.

Reporting group title	PB:LA (Study 726:Study 729)
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Reporting group description:

Patients who received placebo in core Study 726 and who received open label lanreotide Autogel 120 mg in extension Study 729. Note, all patients in extension Study 729 received the same dose of lanreotide Autogel (120 mg) once every 28 days. This arm is referred to as PB:LA to designate randomised treatment in core Study 726:open label treatment in extension Study 729.

Serious adverse events	LA:LA (Study 726:Study 729)	Total LA (Study 729)	PB:LA (Study 726:Study 729)
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 42 (26.19%)	25 / 89 (28.09%)	14 / 47 (29.79%)
number of deaths (all causes)	2	5	3
number of deaths resulting from adverse events	1	3	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Pain			
subjects affected / exposed	1 / 42 (2.38%)	1 / 89 (1.12%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Cancer			

subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour Necrosis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 42 (2.38%)	1 / 89 (1.12%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 42 (2.38%)	1 / 89 (1.12%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face Oedema			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema Peripheral			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden Death			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Reproductive system and breast disorders			
Ovarian Cyst			

subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural Effusion			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anastomotic Stenosis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Incisional Hernia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Procedural Haematoma			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Compression Fracture			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial Fibrillation			

subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Restrictive Cardiomyopathy			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral Infarction			
subjects affected / exposed	1 / 42 (2.38%)	1 / 89 (1.12%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stroke In Evolution			
subjects affected / exposed	1 / 42 (2.38%)	1 / 89 (1.12%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Eye disorders			
Retinal Vein Occlusion			
subjects affected / exposed	1 / 42 (2.38%)	1 / 89 (1.12%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual Impairment			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Adhesions			
subjects affected / exposed	1 / 42 (2.38%)	1 / 89 (1.12%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 89 (1.12%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ileus			
subjects affected / exposed	1 / 42 (2.38%)	1 / 89 (1.12%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 42 (2.38%)	1 / 89 (1.12%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	0 / 42 (0.00%)	4 / 89 (4.49%)	4 / 47 (8.51%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Upper			
subjects affected / exposed	0 / 42 (0.00%)	2 / 89 (2.25%)	2 / 47 (4.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Obstruction			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Obstruction			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 42 (4.76%)	2 / 89 (2.25%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Prerenal Failure			
subjects affected / exposed	1 / 42 (2.38%)	1 / 89 (1.12%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Hepatitis Viral			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative Wound Infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased Appetite			

subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte Imbalance			
subjects affected / exposed	0 / 42 (0.00%)	1 / 89 (1.12%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	LA:LA (Study 726:Study 729)	Total LA (Study 729)	PB:LA (Study 726:Study 729)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 42 (76.19%)	69 / 89 (77.53%)	37 / 47 (78.72%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 42 (2.38%)	4 / 89 (4.49%)	3 / 47 (6.38%)
occurrences (all)	1	6	5
Hypertension			
subjects affected / exposed	4 / 42 (9.52%)	9 / 89 (10.11%)	5 / 47 (10.64%)
occurrences (all)	4	9	5
General disorders and administration site conditions			
Injection Site Pain			
subjects affected / exposed	1 / 42 (2.38%)	4 / 89 (4.49%)	3 / 47 (6.38%)
occurrences (all)	1	4	3
Asthenia			
subjects affected / exposed	0 / 42 (0.00%)	4 / 89 (4.49%)	4 / 47 (8.51%)
occurrences (all)	0	4	4
Pyrexia			
subjects affected / exposed	0 / 42 (0.00%)	3 / 89 (3.37%)	3 / 47 (6.38%)
occurrences (all)	0	5	5
Injection Site Nodule			
subjects affected / exposed	0 / 42 (0.00%)	3 / 89 (3.37%)	3 / 47 (6.38%)
occurrences (all)	0	3	3
Fatigue			

subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 6	9 / 89 (10.11%) 12	4 / 47 (8.51%) 6
Oedema Peripheral subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 4	4 / 89 (4.49%) 5	1 / 47 (2.13%) 1
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	6 / 89 (6.74%) 9	3 / 47 (6.38%) 6
Oropharyngeal Pain subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	5 / 89 (5.62%) 6	2 / 47 (4.26%) 3
Dyspnoea subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	3 / 89 (3.37%) 3	3 / 47 (6.38%) 3
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5	4 / 89 (4.49%) 5	0 / 47 (0.00%) 0
Investigations			
Weight Decreased subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	4 / 89 (4.49%) 6	3 / 47 (6.38%) 5
Injury, poisoning and procedural complications			
Procedural Pain subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	4 / 89 (4.49%) 7	3 / 47 (6.38%) 6
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 6	6 / 89 (6.74%) 8	2 / 47 (4.26%) 2
Headache subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2	6 / 89 (6.74%) 6	4 / 47 (8.51%) 4
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	6 / 89 (6.74%) 7	3 / 47 (6.38%) 4
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	8 / 42 (19.05%) 28	23 / 89 (25.84%) 53	15 / 47 (31.91%) 25
Nausea subjects affected / exposed occurrences (all)	7 / 42 (16.67%) 15	13 / 89 (14.61%) 26	6 / 47 (12.77%) 11
Constipation subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 8	9 / 89 (10.11%) 14	4 / 47 (8.51%) 6
Abdominal Discomfort subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 5	5 / 89 (5.62%) 8	2 / 47 (4.26%) 3
Dyspepsia subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 5	7 / 89 (7.87%) 9	2 / 47 (4.26%) 4
Abdominal Distension subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	7 / 89 (7.87%) 10	4 / 47 (8.51%) 7
Haemorrhoids subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	3 / 89 (3.37%) 3	3 / 47 (6.38%) 3
Steatorrhoea subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2	7 / 89 (7.87%) 7	5 / 47 (10.64%) 5
Rectal Haemorrhage subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	4 / 89 (4.49%) 4	4 / 47 (8.51%) 4
Abdominal Pain subjects affected / exposed occurrences (all)	7 / 42 (16.67%) 7	14 / 89 (15.73%) 16	7 / 47 (14.89%) 9
Vomiting			

subjects affected / exposed occurrences (all)	7 / 42 (16.67%) 8	12 / 89 (13.48%) 19	5 / 47 (10.64%) 11
Abdominal Pain Upper subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 4	12 / 89 (13.48%) 13	9 / 47 (19.15%) 9
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	7 / 42 (16.67%) 10	14 / 89 (15.73%) 19	7 / 47 (14.89%) 9
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 6	7 / 89 (7.87%) 9	2 / 47 (4.26%) 3
Dry Skin subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 5	5 / 89 (5.62%) 7	2 / 47 (4.26%) 2
Pruritus subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	4 / 89 (4.49%) 6	3 / 47 (6.38%) 5
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	3 / 89 (3.37%) 3	0 / 47 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 6	10 / 89 (11.24%) 18	6 / 47 (12.77%) 12
Neck Pain subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	4 / 89 (4.49%) 4	1 / 47 (2.13%) 1
Myalgia subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	3 / 89 (3.37%) 4	3 / 47 (6.38%) 4
Osteoporosis subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	3 / 89 (3.37%) 3	3 / 47 (6.38%) 3

Back Pain subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	9 / 89 (10.11%) 13	6 / 47 (12.77%) 10
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 6	10 / 89 (11.24%) 13	7 / 47 (14.89%) 7
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 6	5 / 89 (5.62%) 7	1 / 47 (2.13%) 1
Viral Infection subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5	6 / 89 (6.74%) 7	2 / 47 (4.26%) 2
Sinusitis subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	3 / 89 (3.37%) 3	0 / 47 (0.00%) 0
Urinary Tract Infection subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2	7 / 89 (7.87%) 8	5 / 47 (10.64%) 6
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	5 / 89 (5.62%) 10	4 / 47 (8.51%) 9
Metabolism and nutrition disorders			
Hyperglycaemia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	4 / 89 (4.49%) 4	1 / 47 (2.13%) 1
Diabetes Mellitus subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2	6 / 89 (6.74%) 6	4 / 47 (8.51%) 4
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	4 / 89 (4.49%) 5	4 / 47 (8.51%) 5
Decreased Appetite subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5	8 / 89 (8.99%) 10	4 / 47 (8.51%) 5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 March 2012	• To confirm that an interim analysis was to be performed when all patients completed core Study 726 and that some statistical tests of efficacy were to be performed.
22 October 2013	• To increase the maximum expected duration of the study to approximately 8 years. • To confirm that a second interim analysis was to be performed in order to be able to provide a safety update report during the review procedure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26743120>