Clinical trial results:
A european, multicentre, phase II/III randomised double-blind, placebo controlled study evaluating lanreotide as maintenance therapy in patients with non-resectable duodeno-pancreatic neuroendocrine tumours after first-line treatment

Summary

EudraCT number	2013-004069-14
Trial protocol	DE BE IE GB
Global end of trial date	22 January 2020

Results information

Result version number	v1 (current)
This version publication date	31 March 2022
First version publication date	31 March 2022

Trial information

Trial identification

Sponsor protocol code	PRODIGE31

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02288377
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fédération Francophone de Cancérologie Digestive (FFCD)
Sponsor organisation address	7 Bd Jeanne d'Arc, Dijon, France, 21000
Public contact	Karine Le Malicot, Fédération Francophone de Cancérologie Digestive (FFCD), 33 380393479, karine.le-malicot@u-bourgogne.fr
Scientific contact	Karine Le Malicot, Fédération Francophone de Cancérologie Digestive (FFCD), 33 380393479, karine.le-malicot@u-bourgogne.fr

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	15 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 January 2020
Global end of trial reached?	Yes
Global end of trial date	22 January 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the rate of patients alive and progression free at 6 months, assessed by the investigator according to RECIST criteria, version 1.1.

Protection of trial subjects:

The study was done in accordance with the Declaration of Helsinki (amended 2000) and the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) Note for Guidance on Good Clinical Practice and approved by the appropriate Ethics Committees.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 50
Worldwide total number of subjects	53
EEA total number of subjects	51

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)	23

From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Fifty-three pts were randomised in 15 centres in 3 countries (France, Belgium and UK) between January 2015 and October 2018.

Pre-assignment

Screening details:

Before randomisation, standard examinations (biological, clinical, ECG) and quality of life evaluations (QLQ-C30 + GINET 21) as well as the EQ-5D questionnaire including the Spitzer scale were done. In terms of imaging, chest, abdomen and pelvis CT scan with early arterial timing, or abdominal and pelvic MRI with contrast + chest CT-scan with contr

Period 1

Period 1 title	Randomized Patients (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

In order to guarantee blinding of the investigator and all the staff, all injections were administered by a specifically trained and qualified person (for example, a nurse) otherwise not involved in the study procedures in the centre. Pts were given a randomisation/treatment arm number according to their order of entry into the study by an Interactive Web Response System (IWRS).

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Arm

Arm description:

The study treatment was initiated after randomisation, within the 6 weeks following the confirmation date of stable disease or objective response. Once the randomisation was performed, the patients received a single dose every 4 weeks (every 28 days).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Injection

Dosage and administration details:

The placebo injection consisted of a 0.9% saline solution provided as follows:
- A 2 mL ampoule containing 1 mL of NaCl at 0.9%
- An empty syringe of 0.5 ml with an automatic security system and a 20 mm needle of 1.2 mm external diameter and 1.0 mm internal diameter sealed in a laminate bag.

The placebo was stored at the recommended temperature: between +2°C and +8°C. The instructions regarding the subcutaneous product injection were provided in a leaflet accompanying each batch. Both products were provided by the logistics department of CMC&E, Beaufour IPSEN Industry, 20 rue Ethe Virton, 28100 Dreux (France), and delivered to the study sites.

Arm title	Lanreotide Arm

Arm description:

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Arm type	Active comparator

Investigational medicinal product name	SOMATULINE LP 120 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

This treatment was similar to the commercialised form available in France under the name SOMATULINE® LP 120 mg, apart from tertiary packaging and labelling.
Treatment was provided in a pre-filled syringe of 0.5 mL with a 20 mm needle of 1.2 mm external diameter, sealed in a laminated bag and in a cardboard box. Each pre-filled syringe hadan automatic security system.
Each 0.5 mL syringe contained a supersaturated acetate solution of lanreotide corresponding to 0.246 mg of lanreotide base/mg of solution, for subcutaneous injection of a 120 mg dose of lanreotide.
The lanreotide was stored at the recommended temperature: between +2°C and +8°C. The instructions regarding the product injection were provided in a leaflet accompanying each batch.

Number of subjects in period 1	Placebo Arm	Lanreotide Arm
Started	26	27
Treated Patients (mITT population)	25	27
Completed	25	27
Not completed	1	0
Not treated	1	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo Arm

Reporting group description:

The study treatment was initiated after randomisation, within the 6 weeks following the confirmation date of stable disease or objective response. Once the randomisation was performed, the patients received a single dose every 4 weeks (every 28 days).

Reporting group title	Lanreotide Arm

Reporting group description:

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Reporting group values	Placebo Arm	Lanreotide Arm	Total
Number of subjects	26	27	53
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)	14	9	23
From 65-84 years	12	18	30
85 years and over	0	0	0
Age continuous Units: years			
median	62.5	66	
inter-quartile range (Q1-Q3)	51 to 71	57 to 72	-
Gender categorical Units: Subjects			
Female	13	12	25
Male	13	15	28
Gender Units: Subjects			
Male	13	15	28
Female	13	12	25

Subject analysis sets

Subject analysis set title	Placebo Arm
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomised patients in the study who did not withdrew their consent before the randomisation. These patients were considered in the allocated group by randomisation, even if they receive a different treatment.
mITT population was considered as the primary population for efficacy analysis.

Subject analysis set title	Lanreotide Arm
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomised patients in the study who did not withdrew their consent before the randomisation. These patients were considered in the allocated group by randomisation, even if they receive a different treatment.
mITT population was considered as the primary population for efficacy analysis.

Reporting group values	Placebo Arm	Lanreotide Arm	
Number of subjects	25	27	
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	13	9	
From 65-84 years	12	18	
85 years and over	0	0	
Age continuous Units: years			
median			
inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female			
Male			
Gender Units: Subjects			
Male	12	15	
Female	13	12	

End points

End points reporting groups

Reporting group title	Placebo Arm

Reporting group description:

The study treatment was initiated after randomisation, within the 6 weeks following the confirmation date of stable disease or objective response. Once the randomisation was performed, the patients received a single dose every 4 weeks (every 28 days).

Reporting group title	Lanreotide Arm

Reporting group description:

T

Subject analysis set title	Placebo Arm
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomised patients in the study who did not withdrew their consent before the randomisation. These patients were considered in the allocated group by randomisation, even if they receive a different treatment.
mITT population was considered as the primary population for efficacy analysis.

Subject analysis set title	Lanreotide Arm
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomised patients in the study who did not withdrew their consent before the randomisation. These patients were considered in the allocated group by randomisation, even if they receive a different treatment.
mITT population was considered as the primary population for efficacy analysis.

Primary: Rate of patients alive without progression at 6 months

End point title	Rate of patients alive without progression at 6 months[1]

End point description:

The primary endpoint for phase II is the rate of patients alive and progression free at 6 months, evaluated according to the results of imaging assessment done 6 months after the randomisation. This evaluation is done by the investigator according to RECI

End point type	Primary

End point timeframe:

6 months after the randomisation

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: The study was a non-comparative study and was stopped prematurely at 53 patients. That's why no statistical analyses was done.

End point values	Placebo Arm	Lanreotide Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	27		
Units: patients				
Progression and/or death	11	7		
Alive without Progression	13	19		
Not evaluable	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

PFS was defined as the time between randomisation and the date of the first event (radiological or clinical progression or death). Pts who were alive and progression-free were censored at the time of the last news

End point type	Secondary

End point timeframe:

until the end of the follow-up or the apperance of progression or death

End point values	Placebo Arm	Lanreotide Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	27		
Units: Months				
median (inter-quartile range (Q1-Q3))	7.6 (3 to 9)	19.4 (7.6 to 32.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival considered all deaths, and time was calculated from randomisation to death.

End point type	Secondary

End point timeframe:

Until the end of the follow-up or death (Whatever the cause)

End point values	Placebo Arm	Lanreotide Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	27		
Units: patients				
Death	7	2		
Alive	18	25		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs (related and unrelated, expected and unexpected) occurring in the course of the study, from the signature of the informed consent form and until 30 days after the last dose of the study drug were reported by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo arm

Reporting group description:

All patients included in the mITT population having received at least one treatment injection. These patients were analysed in terms of the treatment received.

Reporting group title	Lanreotide Arm

Reporting group description:

All patients included in the mITT population having received at least one treatment injection. These patients were analysed in terms of the treatment received.

Serious adverse events	Placebo arm	Lanreotide Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 25 (12.00%)	5 / 27 (18.52%)	
number of deaths (all causes)	7	2	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Peritoneal Haemorraghe			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain upper			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 25 (0.00%)	2 / 27 (7.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant biliary obstruction			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholescystitis acute			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo arm	Lanreotide Arm	
Total subjects affected by non-serious adverse events subjects affected / exposed	22 / 25 (88.00%)	26 / 27 (96.30%)	
Vascular disorders Flushing subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	2 / 27 (7.41%) 2	
Hot flush subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	2 / 27 (7.41%) 2	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4	2 / 27 (7.41%) 2	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 27 (3.70%) 1	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 7	12 / 27 (44.44%) 12	
Fatigue subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 7	8 / 27 (29.63%) 8	
Injection site reaction subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	4 / 27 (14.81%) 4	
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	2 / 27 (7.41%) 2	

Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 25 (12.00%)	9 / 27 (33.33%)	
occurrences (all)	3	9	
Abdominal pain			
subjects affected / exposed	8 / 25 (32.00%)	14 / 27 (51.85%)	
occurrences (all)	8	14	
Constipation			
subjects affected / exposed	5 / 25 (20.00%)	4 / 27 (14.81%)	
occurrences (all)	5	4	
Diarrhoea			
subjects affected / exposed	7 / 25 (28.00%)	20 / 27 (74.07%)	
occurrences (all)	7	20	
Nausea			
subjects affected / exposed	4 / 25 (16.00%)	7 / 27 (25.93%)	
occurrences (all)	4	7	
Vomiting			
subjects affected / exposed	1 / 25 (4.00%)	4 / 27 (14.81%)	
occurrences (all)	1	4	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 25 (4.00%)	4 / 27 (14.81%)	
occurrences (all)	1	4	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 25 (4.00%)	3 / 27 (11.11%)	
occurrences (all)	1	3	
Pruritus			
subjects affected / exposed	0 / 25 (0.00%)	3 / 27 (11.11%)	
occurrences (all)	0	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 25 (8.00%)	3 / 27 (11.11%)	
occurrences (all)	2	3	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 25 (4.00%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Back Pain			
subjects affected / exposed	0 / 25 (0.00%)	6 / 27 (22.22%)	
occurrences (all)	0	6	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 25 (12.00%)	3 / 27 (11.11%)	
occurrences (all)	3	3	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	4 / 25 (16.00%)	5 / 27 (18.52%)	
occurrences (all)	4	5	
Hypoglycaemia			
subjects affected / exposed	2 / 25 (8.00%)	2 / 27 (7.41%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported