# 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 |
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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:

T

| | |
|---|---|
| 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:

T

| Reporting group values | Placebo Arm | Lanreotide Arm | Total |
|---|---|---|---|
| Number of subjects | 26 | 27 | 53 |
| Age categorical<br>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<br>Units: years | | | |
| median | 62.5 | 66 | |
| inter-quartile range (Q1-Q3) | 51 to 71 | 57 to 72 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 13 | 12 | 25 |
| Male | 13 | 15 | 28 |
| Gender<br>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<br>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<br>Units: years | | | |
| median | | | |
| inter-quartile range (Q1-Q3) | | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | | | |
| Male | | | |
| Gender<br>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 | 1 / 25 (4.00%) | 2 / 27 (7.41%) | |
| occurrences (all) | 1 | 2 | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 2 / 27 (7.41%) | |
| occurrences (all) | 1 | 2 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | 2 / 27 (7.41%) | |
| occurrences (all) | 4 | 2 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 27 (3.70%) | |
| occurrences (all) | 2 | 1 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 7 / 25 (28.00%) | 12 / 27 (44.44%) | |
| occurrences (all) | 7 | 12 | |
| Fatigue | | | |
| subjects affected / exposed | 7 / 25 (28.00%) | 8 / 27 (29.63%) | |
| occurrences (all) | 7 | 8 | |
| Injection site reaction | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 4 / 27 (14.81%) | |
| occurrences (all) | 1 | 4 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 2 / 27 (7.41%) | |
| occurrences (all) | 1 | 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