A PHASE 3, PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, MULTI-CENTER, STUDY OF THE EFFICACY AND SAFETY OF LANREOTIDE AUTOGEL/ DEPOT 120 MG PLUS BSC VS. PLACEBO PLUS BSC FOR TUMOR CONTROL IN SUBJECTS WITH WELL DIFFERENTIATED, METASTATIC AND/OR UNRESECTABLE TYPICAL OR ATYPICAL LUNG NEUROENDOCRINE TUMORS

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Primary Objective* To describe the antitumour efficacy of LAN monotherapy plus BSC every 28 days, in terms of progression-free survival (PFS), measured by central review using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria,...

Ethical review	Approved WMO
Status	Completed
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON49581

Source
ToetsingOnline

Brief title
SPINET

Condition

- Respiratory tract neoplasms

Synonym
Lung neuroendocrine tumours

Research involving
Human

Sponsors and support

Primary sponsor: Ipsen Pharmaceuticals
Source(s) of monetary or material Support: Industry-funded

Intervention

Keyword: Lanreotide, Lung neuroendocrine tumours

Outcome measures

Primary outcome

Primary Endpoint

Progression-free survival (PFS) for subjects randomized in LAN group, assessed by central review using RECIST v1.1 criteria every 12 weeks, defined as the time from randomization to disease progression or death from any causes in either the double blind phase, or in the open label period.

Secondary outcome

Secondary Efficacy Endpoints

* Progression-free survival (PFS), assessed by central review using RECIST v1.1 criteria every 12 weeks, defined as the time from randomization to disease progression or death from any causes during the double-blind phase,

* Progression-free survival (PFS), assessed by local review using RECIST v1.1

criteria every 12 weeks, defined as the time from randomization to disease progression or death from any causes during the double-blind phase,

* ORR: objective response rate of CR or PR measured by RECIST v1.1 criteria every 12 weeks until the Post Treatment/Early Withdrawal Visit during the double- blind phase,

* Time to treatment failure during the double-blind phase, defined as the time from randomization to disease progression [defined as the minimum (time to event according to central review, time to event according to local review)] using RECIST v1.1, death, consent withdrawn, an AE, protocol deviations, lost to follow-up, the appearance of carcinoid syndrome or other hormone related syndrome necessitating the initiation of SSAs (rescue octreotide and/or LAR SSA), or initiation of anticancer treatment,

* Mean changes from Baseline in biomarker CgA at Week 8, Week 12 and every 12 weeks thereafter until the Post DB and in the OL treatment phases,

* Proportion of subjects with decrease in CgA *30% at Week 8, in the population of subjects with an elevated CgA (*2 x ULN) at Baseline during the double-blind and the OL treatment phases,

* Change in QoL, as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) questionnaire from Baseline to Week 12, every 12 weeks and at the Post

Treatment /Early Withdrawal Visit and in OL Extension Treatment and Follow-up Phases, * Time to QoL deterioration, defined by a decrease from baseline in EORTC QLQ-C30 score of at least10 points during the double-blind, the OL treatment and during the follow-up phases,

* Mean changes from Baseline in urinary 5-HIAA levels at Week 8, and every 12 weeks thereafter, and at the Post Treatment/Early Withdrawal Visit and in OL Extension Treatment in subjects with elevated urinary 5-HIAA (*2 x ULN) at Baseline.

Secondary Safety Endpoints

Safety and tolerability assessments throughout the study:

* Adverse Events (AEs) grouped by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term, and graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03,

* Clinical evaluations (medical and surgical history and physical evaluations, including biochemistry/hematology, ECG, anti-Lanreotide antibodies),

* Gallbladder echography, if biological and/or clinical inflammatory symptoms appear during the course of the study.

Exploratory Endpoints

* CBR: best overall response of CR, PR or SD measured by RECIST v1.1 criteria every 12 weeks until the Post Treatment/Early Withdrawal Visit,

* Variation of the TGR within 12 months prior to Baseline, Baseline to Week 12,

every 12 weeks and at the Post Treatment/Early Withdrawal Visit. The TGR is calculated from tumour size (sum of the longest diameters of target lesions as per RECIST v1.1 criteria and tumour volume. Tumour size will be measured from MRI (optimal) or CT scans collected within 12 months prior to first lanreotide Autogel® 120 mg administration and then every 28 days during treatment period (i.e. the scans used for disease progression evaluation), and using the same imaging technique (CT scan or MRI) every 12 weeks during the treatment period.

* Lanreotide serum concentrations.

Biobanking programme:

For subjects participating in the optional research biobanking programme, serum and whole blood samples will be taken for further potential analyses aimed at:

* Exploring the association of biomarkers with drug activity (clinical benefit and mechanisms of action),
* Exploring the association of biomarkers with AEs, or other effects associated with LAN treatment.
* Exploring biomarkers of diagnostic assays and establishing the performance characteristics of these assays.

Study description

Background summary

Neuroendocrine tumours (NETs) comprise a heterogeneous group of neoplasms originating from neural crest cells, endocrine glands, endocrine islets or the diffuse endocrine system. The majority of NETs are sporadic and little is known about their risk factors. In some cases NETs form part of heritable tumour

syndromes such as multiple endocrine neoplasia type 1 or tuberous sclerosis.

Although considered rare malignancies, recent data suggest an increase in NETs incidence over the past 30 years, with 5.2 cases per 100,000 population per year. NETs of pancreatic, intestinal and bronchopulmonary origin are the most common, with the incidence of bronchopulmonary or bronchial NETs at 1.35 per 100,000; this is seemingly a drastic increase from the annual incidence of 0.3 per 100,000 of 1973 [Yao 2008]. Bronchial NETs account for approximately 1 to 2 percent of all lung malignancies in adults and roughly 20 to 30 percent of all NETs. NETs of thorax include lung and thymus NETs.

There are 4 types of lung neuroendocrine cancers - typical carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma (NECs), and small-cell lung cancer (SCLC). Like neuroendocrine tumours at other body sites, bronchial NETs are thought to derive from peptide- and amine-producing neuroendocrine cells that have migrated from the embryologic neural crest.

While surgery remains the treatment of choice for patients with resectable tumours, there are limited options for those with advanced or metastatic disease with unresectable tumours. The primary goal in the treatment of unresectable, advanced NETs is to prevent tumour progression and reduce the symptoms related to carcinoid syndrome when present. Typical and atypical carcinoid metastatic lung NETs are associated with poor prognosis; with median survival averaging 17 months and the 5-year survival rate approximately at 27%. However, recent studies dedicated to stage IV lung NETs suggest better median OS of 5 to 10 years for atypical and typical carcinoids. There is a clear unmet need in patients with advanced lung NETs.

Limited data are available regarding treatment for advanced lung NETs due to the rarity of the disease. In most cases, treatment guidelines are extrapolated from the clinical experience with the more common gastrointestinal (GI) NETs or mixed retrospective studies. Recently recommendations issued from the European Neuroendocrine Tumour Society for best practice for typical and atypical pulmonary carcinoid have been published. To date, available data on the application of Somatostatin analogs (SSAs) or other systemic intervention in lung NETs come from two prospective studies conducted in lung NETs progressive patients:
- In RADIANT 2 study, the median PFS (measured by local and central review in the lung NET subgroup), was 2.8 and 5.6 months, respectively, in the octreotide group (n=11) versus 8.8 and 13.6 months, respectively, in the everolimus plus octreotide group (n=33).
- In RADIANT 4 study, conducted in patients with well-differentiated (G1/G2), advanced, progressive, non-functional NET of lung or GI origin, a reduction of 52% in the relative risk of progression or death with everolimus versus placebo (Hazard ratio = 0.48 (95% CI, 0.35-0.67); p<0.00001) was demonstrated in the overall population.
There are also some data reported from retrospective single centre study

involving 61 patients with lung NET treated with SSAs, the estimated median PFS was 17.4 months (12.8 months in the AC subgroup and 24.8 months in the TC subgroup). In another study where nine patients were treated with octreotide and 13 patients were treated with lanreotide, a median PFS of 18.1 months was reported for 22 patients (32% of whom had AC). In a further study, a median PFS of 16.5 months was reported in 22 patients treated with SSAs.

Recently, the CLARINET study demonstrated that first-line treatment with Lanreotide Autogel/Depot 120 mg, a somatostatin analogue (SSA), significantly prolonged progression free survival among subjects with metastatic grade 1 or 2 enteropancreatic NETs of (Ki 67 <10%) [Caplin 2014]. This is the first and only registration study of an SSA (Lanreotide Autogel/Depot 120 mg) demonstrating a cancer treatment benefit in this gastrointestinal and pancreatic NET population. While, subjects with bronchial neuroendocrine tumours (B-NETs) were not included in CLARINET, there is a well-established basis for the use of SSAs like Lanreotide Autogel/Depot 120 mg in the management of lung NETs * the high expression of the somatostatin receptors SSTR2A and SSTR3

Besides their role in imaging for NETs (somatostatin receptor scintigraphy (SRS) or octreotide scan), SSAs are also therapeutically used mainly to control hormone related symptoms, which occur in up to 40% of cases of hypersecretion in patients with advanced lung NET tumours.

Recent updates of NCCN & ENETs guidelines recommend SSA in first line for the treatment of locoregional unresectable or metastatic lung NETs as an option beyond *observation* [21, 22]. Consequently, it was decided to prematurely stop the recruitment in the SPINET study and to transition subjects still treated in the double-blind phase to the OL treatment phase.

The new aim of this Phase 3, multicenter, prospective, randomized placebo controlled clinical study is to describe the antitumour efficacy and safety of Lanreotide Autogel/Depot 120 mg (LAN) plus Best Supportive Care (BSC) in subjects with well differentiated, metastatic and/or unresectable, typical or atypical, lung NETs. Placebo plus BSC/best supportive care was chosen as the control arm because there are no definitive, well-controlled studies demonstrating the efficacy and safety of SSAs in this setting. Current 2015 NCCN recommendations for Lung NET include observation for asymptomatic low-bulk typical pulmonary carcinoids. 2015 European Neuroendocrine Tumor Society (ENETS) guidance includes observation for asymptomatic pulmonary carcinoids of low proliferative index [9].

Further details can be found in the Investigator Brochure (IB).

Study objective

Primary Objective
* To describe the antitumour efficacy of LAN monotherapy plus BSC every 28

days, in terms of progression-free survival (PFS), measured by central review using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria, every 12 weeks, in subjects with unresectable and/or metastatic well differentiated, typical or atypical lung neuroendocrine tumoursin either the double blind phase, or in the OL period

Secondary Efficacy Objectives
* To describe the antitumour efficacy during the double-blind phase of LAN monotherapy plus BSC every 28 days and placebo plus BSC, in terms of progression free survival (PFS), measured by central review using RECIST v1.1 criteria, every 12 weeks, in subjects with unresectable and/or metastatic well differentiated, typical or atypical lung NETs.
* To describe the antitumour efficacy during the double-blind phase of LAN monotherapy plus BSC every 28 days and placebo plus BSC, in terms of progression free survival (PFS), measured by local review using RECIST v1.1 criteria, every 12 weeks, in subjects with unresectable and/or metastatic well differentiated, typical or atypical lung NETs.
* To describe the objective response rate (ORR) of LAN monotherapy plus BSC every 28 days and placebo plus BSC, as assessed by RECIST v 1.1criteria (proportion of subjects with an objective response of partial response (PR) or complete response (CR)) in the double blind phase,
* To describe time to treatment failure (Kaplan Meier estimates) of LAN monotherapy plus BSC every 28 days and placebo plus BSC in the double blind phase,
* To describe the changes from Baseline in the biomarker chromogranin A (CgA) during the double-blind and the OL treatment phases,
* To describe the proportion of subjects with a decrease of CgA *30% at week 8 in the population of subjects with an elevated CgA (*2 x ULN) at Baseline during the double- blind and the OL treatment phases,
* To describe the change in Quality of Life (QoL) from baseline, as assessed by the EORTC QLQ-C30 questionnaire during the double-blind, the OL treatment and the follow-up phases,
* To describe the time to deterioration of QoL (using EORTC QLQ-C30) during the double-blind, the OL treatment and the follow-up phases,
* To describe the changes in urinary 5-hydroxyindoleacetic acid (5-HIAA) in subjects with elevated urinary 5-HIAA (*2 x ULN) at Baseline during the double-blind and the OL treatment phases.

Secondary Safety Objective
* To evaluate the clinical and biological safety profile.

Exploratory Objectives
* To describe the clinical benefit rate (CBR) of LAN monotherapy plus BSC every 28 days and placebo plus BSC, as assessed by RECIST v 1.1 criteria (proportion of subjects with a best overall response of PR, CR or stable disease (SD)),
* To evaluate the effect on tumour growth rate (TGR), as assessed by

central review prior to and during administration,
* To monitor lanreotide serum concentration in subjects with advanced lung NET.

Study design

This is a Phase 3, prospective, multi-center, randomized, double-blind study describing the efficacy and safety of LAN plus BSC and placebo plus BSC for the treatment of well-differentiated typical or atypical, metastatic and/or unresectable lung NETs. The study will be conducted at approximately 80 centers in the United States, Canada and Europe. At time of protocol Amendment #5, a total of 38 centers have actively recruited at least one subject (active recruitment is defined by at least one informed consent signed).

As planned initially, a total of 216 eligible subjects with well-differentiated typical or atypical, metastatic and/or unresectable lung NETs, and a positive somatostatin receptor imaging (SRI) (Octreoscan® * grade 2 Krenning scale; Ga-PET scan: uptake greater than liver background), had to be randomized 2:1 to either LAN plus BSC (120mg/28 days) or placebo plus BSC following the stratification of 1) typical versus atypical and 2) prior chemotherapy versus no prior chemotherapy*. Due to the premature stop of the recruitment (as per Protocol Amendment #5), 77 subjects are enrolled. All subjects still treated in the DB Phase will enter into the OL Extension Period (either for follow-up or for OL treatment). The transition to the OL treatment period, will be done by country and per subject, at the next planned scheduled visit (i.e. approximately 28 days from the last injection). Subjects enrolled into the study will stay on LAN therapy (i.e. OL Treatment Period) until evidence of disease progression (assessed locally and confirmed centrally), development of unacceptable toxicity, or premature withdrawal for any reason or up to 18 months after the last subject randomised. After disease progression subjects will be followed for survival, QoL and all subsequent anticancer treatments up to the end of the study.
* cytotoxic chemotherapy or molecular targeted therapy or interferon.

The study contains two phases: the DB Phase, and the OL Extension Phase. The DB Phase included: Screening, Baseline and Treatment periods and the OL Extension Phase consists of two periods: Treatment Period and Follow-Up Period.
* The DB Phase included a Screening Period to establish protocol eligibility and disease characteristics. The Baseline Visit confirmed eligibility prior to randomization and treatment. The DB Phase of the study will end with Protocol Amendment #5 and will be followed by the OL Treatment Period.

If a subject progresses during the DB phase, the subject will be proposed to enter the OL Extension phase:
* If the subject was on placebo and progressed during the DB phase, the subject will be offered the opportunity to enter the treatment period of the OL extension phase and to receive LAN every 28 days.

* If the subject was on LAN and progressed during the DB phase, the subject will enter the follow-up period of the OL extension phase and be followed for QoL/survival and all subsequent anticancer treatments received will be recorded.
The OL Treatment Period will stop once all subjects will have centrally progressed or 18 months after the last subject randomised (i.e. end of study).

After approval of Protocol Amendment #5: * All ongoing subjects in the DB Phase, who have no yet progressed, will enter the OL Treatment Period. The subjects in the OL Treatment Period will be followed up to disease progression (assessed locally and confirmed centrally), development of unacceptable toxicity, or withdrawal from the study treatment for any other reason or up to 18 months after the last subject randomised.
* if a subject progresses during the DB phase, the subject will enter the OL follow-up period
* If a subject progresses during the OL Treatment Period, the subject will enter the OL follow-up period.
* The follow-up period of the OL extension phase will stop at the same time as the OL Treatment Phase (ie, end of study * up to 18 months after the last subject randomised).

At the end of the OL Extension Treatment period, if subjects are still benefiting from treatment (i.e. not progressing) and there is sufficient evidence of the safety and efficacy of it, the subjects will have the option, to continue to receive lanreotide 120 mg every 28 days up to disease progression or unacceptable toxicity. In such a situation, as permitted by local regulations, lanreotide 120 mg will be provided free of charge by the sponsor to the sites under its commercial packaging. During this period, the physician will report immediately to Ipsen Pharmacovigilance Contact any safety concerns arising from the use of the product.

Intervention

N/A

Study burden and risks

The investigation of Lanreotide in this patient population is justified, based upon the clinical and nonclinical safety profile, the inadequacy of alternative treatments available to patients, the limited life expectancy due to malignant disease, and the strength of the scientific hypothesis under evaluation. Thus the benefit/risk assessment for this Phase III study supports the administration of LAN to patients with well differentiated, metastatic and/or resectable typical or atypical lung neuroendocrine tumours.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria
(1) Provision of written informed consent prior to any study related procedures,
(2) Subjects aged * 18 years,
(3) Have metastatic and/or unresectable pathologically confirmed well-differentiated, typical or atypical neuroendocrine tumour of the lung,
(4) Histologic evidence of well differentiated NETs of the lung
(typical and atypical according to the WHO criteria evaluated locally),
(5) Has a mitotic index <2 mitoses/2 mm2 for typical carcinoid (TC) and *10 mitoses/2 mm2 and/or foci of necrosis for atypical carcinoid (AC),
(6) At least one measurable lesion of the disease on imaging (CT or MRI; RECIST v1.1),
(7) Positive somatostatin receptor imaging (SRI) (Octreoscan® * grade 2 Krenning scale; Ga-PET scan: uptake greater than liver background),

(8) ECOG performance status 0-1,
(9) Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to randomization. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required,
(10) Female subjects who are at risk of becoming pregnant must agree to use an effective method of contraception such as double barrier contraception, an injectable, combined oral contraceptive
or an intra-uterine device (IUD). The subject must agree to use the contraception during the whole period of the study and for eight months after the last study drug administration. Non childbearing potential is defined as being postmenopausal for at least 1 year, or permanently sterilized at least 3 months before study entry,
(11) Male subjects must agree that, if their partner is at risk of becoming pregnant, they will use an effective method of contraception (see above). The subject must agree to use the contraception during the whole period of the study and for eight months after the last study drug administration,
(12) Signed HIPAA authorization where required,
(13) Subjects must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period and willing to return to the study site for the follow-up evaluation as specified in the protocol.

Exclusion criteria

Exclusion criteria
(1) Poorly differentiated or high grade carcinoma, or neuroendocrine tumours not of lung origin,
(2) Subjects with multiple endocrine neoplasia type 1 (MEN 1),
(3) Has been treated with an SSA at any time prior to randomization, except if that treatment was for less than 15 days (e.g. peri-operatively) of short acting SSA or one dose of long acting SSA and the treatment was received more than 6 weeks prior to randomization,
(4) Has been treated with Peptide receptor radionuclide therapy (PRRT) at any time prior to randomization,
(5) Has been treated for lung NET with chemotherapy* within 4 weeks of randomization (whatever the number of cycles),
(6) Has been treated with more than two lines of chemotherapy * for lung NET,
(* cytotoxic chemotherapy or molecular targeted therapy or interferon)
(7) Treated with surgery within 6 weeks prior to randomization,
(8) Previous local therapy (e.g. chemo-embolization, bland, or radio-embolization) is allowed if completed > 6 weeks prior to randomization. For subjects who received local therapy prior to randomization, there must be documented growth of measurable disease within the embolization field prior to study,
(9) Symptomatic subjects requiring SSA for symptom management (please also note the exclusion criteria No. 3),
(10) Subjects with known ectopic production of adrenocorticotropic hormone (ACTH) or other hormonal secreting subjects allowed * ONLY if symptoms adequately controlled without SSAs,
(11) Subjects on concomitant Growth Hormone (GH) antagonist, cyclosporine or

bromocriptine
(12) Inadequate bone marrow function as per investigator*s judgement,
(13) Severe renal insufficiency as defined by a calculated creatinine clearance <30 mL/min,
(14) Total bilirubin >2 x ULN, AST, ALT or Alk Ph >5xULN, lipase, amylase >2xULN,
(15) Serum albumin <3.0 g/dL unless prothrombin time is within the normal range,
(16) Known hypersensitivity to the study drug,
(17) Present cholecystitis,
(18) Uncontrolled congestive heart failure
(19) Glycosylated hemoglobin (HbA1c) > 8.5%,
(20) Abnormal findings, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, would compromise the subject*s safety or the outcome of the study,
(21) Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and proven no evidence of recurrence for 5 years,
(22) Pregnant or lactating women or those of childbearing potential age and not practicing a medically acceptable method for birth control,
(23) Subjects who have participated in any therapeutic clinical study/received any investigational agent within 30 days of randomization.
(24) Clinically significant cardiac arrhythmia, bradycardia, tachycardia that would compromise patient safety or the outcome of the study
(25) Uncontrolled hypothyroidism

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	30-01-2018

Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Somatuline® Autogel® 120mg
Generic name:	LANREOTIDE ACETATE
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-01-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-06-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-09-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	12-04-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-10-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-10-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-004992-62-NL
ClinicalTrials.gov	NCT02683941
CCMO	NL60202.031.16

Study results

Date completed:	29-05-2020

Results posted: 13-10-2021

First publication
27-08-2021