TIGER-3: A Phase 3, Open-label, Multicenter, Randomized Study of Oral Rociletinib (CO-1686) Monotherapy Versus Single-agent Cytotoxic Chemotherapy in Patients with Mutant EGFR Non-small Cell Lung Cancer (NSCLC) After Failure of at Least 1 Previous EGFR-directed Tyrosine Kinase Inhibitor (TKI) and Platinum-doublet Chemotherapy

Published: 26-01-2015
Last updated: 14-04-2024

Primary Objective• To compare the anti-tumor efficacy of oral single-agent rociletinib, as measured by investigator assessment of the progression-free survival (PFS), with that of single-agent cytotoxic chemotherapy in patients with EGFR mutated,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Interventional

Summary

ID

NL-OMON43590

Source
ToetsingOnline

Brief title
Tiger-3

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
Non-small cell lungcancer; lungcancer

Research involving
Human

Sponsors and support

Primary sponsor: Clovis Oncology, Inc.
Source(s) of monetary or material Support: Clovis Oncology Inc

Intervention

Keyword: Non-Small Cell Lung Cancer, Oral CO-1686, single agent chemotherapy

Outcome measures

Primary outcome

Primary Endpoint:

• PFS according to RECIST Version 1.1 as determined by investigator assessment

(invPFS)

Secondary outcome

Secondary Endpoints:

• ORR and DR according to RECIST Version 1.1 as determined by investigator

assessment

• OS

• Treatment-emergent adverse events (AEs), laboratory abnormalities, and

electrocardiogram (ECG) abnormalities

• Plasma PK parameters for rociletinib based on sparse sampling

Exploratory Endpoints

• DCR according to RECIST version 1.1 as determined by investigator assessment

• Time-to-treatment failure

• OS, ORR, PFS, DR, and DCR in patients who cross over to receive rociletinib and in patients who continue to receive rociletinib beyond progression

• Change from baseline in PROs using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ C30), the EORTC Quality of Life Questionnaire Lung Cancer module (EORTC QLQ LC13) and in the EQ-5D

• Change from baseline in mutant EGFR levels in ctDNA obtained from plasma and urine

• OS, ORR, PFS, DR, and DCR based on plasma and urine EGFR mutation test results

• Positive and negative percent agreement between blood, urine and tissue results for T790M

• Identify biomarkers associated with response or resistance to rociletinib

Study description

Background summary

Rociletinib (CO 1686) is a novel, potent, small molecule irreversible TKI that selectively targets mutant forms of the epidermal growth factor receptor (EGFR) while sparing wild-type (WT) EGFR. Clovis Oncology, Inc. (Clovis) is developing rociletinib as a therapeutic agent to be administered orally to patients with mutant EGFR NSCLC.
Activating EGFR mutations are key drivers of NSCLC in 10% to 15% of patients of European descent and approximately 30% of patients of East Asian descent. Patients with the most common EGFR mutations, exon 21 L858R and deletions in exon 19, typically have good responses to therapy with first generation EGFR inhibitors such as erlotinib or gefitinib, and also with the second generation

inhibitor afatinib. Toxicity associated with erlotinib, gefitinib, and afatinib includes skin rash and diarrhea related to inhibition of the WT EGFR in skin and intestine, respectively.
Despite an impressive initial response to treatment, progression generally occurs after 9-14 months of erlotinib, gefitinib, or afatinib therapy, driven in approximately 60% of cases by a second site EGFR mutation in exon 20 called T790M (the *gatekeeper* mutation) which mediates resistance to first and second generation EGFR inhibitors. There are no approved therapies that target T790M specifically, and standard of care remains cytotoxic chemotherapy. Yu et al reported that T790M positive (T790M+) disease is fatal, with a median overall survival (OS) of less than 2 years.
Nonclinical data demonstrate that rociletinib inhibits T790M as well as the common activating mutations (L858R, del19) and has minimal inhibitory activity towards WT EGFR at therapeutic doses. It is anticipated that rociletinib will promote cell death in tumor cells with the T790M mutation, thus driving objective tumor responses and providing therapeutic benefit in patients who have acquired T790M mediated resistance to first generation EGFR inhibitors.
In the first in human study, CO 1686 008, in patients with advanced EGFR mutation positive NSCLC and previous treatment with an EGFR inhibitor, no maximum tolerated dose (MTD) was observed and 3 doses levels, 500 mg twice daily (BID), 625 mg BID, and 750 mg BID, were selected for further clinical evaluation of safety, tolerability and efficacy in the expansion cohorts.
Maturing data from this study suggest that patients treated with rociletinib at 500 mg BID and 625 mg BID experience responses that are comparable in frequency, depth, and duration, with an overall acceptable safety profile for this advanced cancer patient population. This current study will describe the risk/benefit profile of the rociletinib 500 mg BID and 625 mg BID doses.
As expected, due to its selectivity for mutant EGFR, events typical of WT EGFR inhibition (the combination of rash and chronic diarrhea) have not been observed with rociletinib. Furthermore, heavily pretreated patients have experienced durable Response Evaluation Criteria In Solid Tumors (RECIST) responses. The majority of these responders had most recently been treated with an EGFR TKI. Moreover, initial clinical data suggest that rociletinib may provide clinical benefits to patients who test negative with respect to the T790M mutation and the study has been designed to specifically investigate the effectiveness of rociletinib in this group of patients.
The goals of the current study (Protocol CO 1686-020) are to compare the anti tumor efficacy and safety of oral single-agent rociletinib with that of single-agent cytotoxic chemotherapy in patients with EGFR mutated, advanced/metastatic NSCLC after failure of at least 1 previous EGFR-directed TKI and 1 line of platinum containing doublet chemotherapy. An additional goal will be to determine the effectiveness of rociletinib in patients who test negative with respect to the T790M mutation.
Rociletinib is being developed with a companion diagnostic (Qiagen, United Kingdom) to identify patients whose tumors express activating EGFR mutations as well as the T790M resistance mutation.

Study objective

Primary Objective
• To compare the anti-tumor efficacy of oral single-agent rociletinib, as measured by investigator assessment of the progression-free survival (PFS), with that of single-agent cytotoxic chemotherapy in patients with EGFR mutated, advanced/metastatic NSCLC after failure of at least 1 previous EGFR-directed TKI and at least 1 line of platinum-containing doublet chemotherapy
Secondary Objectives
• To compare secondary measures of clinical efficacy (duration of response [DR], objective response rate [ORR], and OS) between patients randomized to rociletinib or single-agent cytotoxic chemotherapy
• To compare the safety and tolerability of rociletinib with that of single agent cytotoxic chemotherapy
• To determine pharmacokinetics (PK) of rociletinib using population PK (POPPK) methods and explore correlations between PK, exposure, response, and/or safety findings in patients randomized to rociletinib
Exploratory Objectives
• To evaluate clinical benefit of continued rociletinib treatment following disease progression in patients randomized to the rociletinib arm
• To evaluate clinical benefit of rociletinib treatment following disease progression in patients randomized to the comparator arm who cross over to receive rociletinib
• To compare quality of life (QoL) by patient-reported outcomes (PRO) between patients randomized to rociletinib or single-agent cytotoxic chemotherapy
• To evaluate concordance of mutant EGFR detection between tissue, urine, and plasma and assess rociletinib mediated alterations in mutant EGFR levels over time using circulating tumor deoxyribonucleic acid (ctDNA) obtained from plasma; analyze clinical endpoints based on plasma and urine EGFR mutation test results and compare findings from rociletinib treated patients with those treated with single-agent cytotoxic chemotherapy
• To explore tissue, urine, and blood-based biomarkers that may be predictive of response or primary resistance to rociletinib and investigate mechanisms of acquired resistance in the tissue, urine, and blood of patients who experience clinical progression during treatment with rociletinib and compare findings from rociletinib treated patients with those treated with single agent cytotoxic chemotherapy

Study design

This is a Phase 3, randomized, open-label, multicenter study evaluating the safety and efficacy of oral rociletinib compared with that of single-agent cytotoxic chemotherapy, in patients with previously treated mutant EGFR NSCLC. Eligible patients are those with mutant EGFR NSCLC previously treated with at least 1 EGFR inhibitor and at least 1 line of platinum containing chemotherapy doublet for advanced/metastatic NSCLC.

After providing informed consent to participate and screening to confirm eligibility, patients will be randomized 1:1:1 to receive rociletinib 500 mg BID, rociletinib 625 mg BID, or single-agent cytotoxic chemotherapy (investigator choice of pemetrexed, gemcitabine, docetaxel, or paclitaxel; choice of chemotherapy agent must be specified before randomization).
Randomization will be stratified according to:
1. History of brain metastases versus no history of brain metastases,
2. Eastern Cooperative Oncology Group (ECOG) performance status 0 versus ECOG performance status 1,
3. Territory of residence at time of randomization (East Asian versus non-East Asian).
All patients will provide a tumor biopsy during screening for central determination of T790M mutation status; tissue must be sent to the central laboratory before randomization. Switching therapy after biopsy sampling is not permitted as this may impact on the T790M mutation status. However, dose reduction of the therapy adopted at that time is permitted.
The treatment cycle length will be 21 days for all treatments. Treatment will continue, with tumor assessment every 6 ± 1 weeks, irrespective of regimen, until disease progression or until other withdrawal criteria are met (including completion of a single-agent chemotherapy regimen). If clinical progression is diagnosed then confirmation of disease progression with a computed tomography (CT) scan (per RECIST Version 1.1) will be required. Tumor scan at the End-of-Treatment Visit is not required if patient had radiographic evidence of disease progression on study, or it has been < 2 weeks since last on-study scan. In addition, a magnetic resonance imaging (MRI) may be used in place of a CT at end-of-treatment scan if required per local authorities.
Patients may opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR TKIs if: a) the patient provides additional consent, b) the investigator feels it is in the patient*s best interest, and c) the sponsor provides approval. In general, eligible patients may include those with asymptomatic systemic progression or locally symptomatic progression, such as brain metastases amenable to local treatment, with concomitant asymptomatic systemic progression or continued systemic disease control.
Patients randomized to the comparator chemotherapy arm may choose to cross over to receive rociletinib upon radiological progression. As with all patients, if clinical progression is diagnosed then confirmation of disease progression with a CT/MRI scan (per RECIST 1.1) will be required along with sponsor approval before crossing over to treatment with rociletinib. For patients who cross over, the starting dose of rociletinib (500 mg BID vs. 625 mg BID) will be the choice of the investigator.
When protocol specified therapy is discontinued, and the patient has yet to progress, patients will continue to undergo scheduled tumor assessments for monitoring of PFS. All patients will also be followed for survival status, and subsequent NSCLC cancer therapy.
Dosing may be delayed or reduced according to protocol-specified toxicity

criteria.
Patients will undergo serial assessments for anti-tumor efficacy, drug safety, and PROs. Sparse blood sampling for POPPK analyses will be conducted in all patients treated with rociletinib. A central laboratory will confirm presence or absence of the T790M mutation in formalin-fixed paraffin embedded (FFPE) tumor tissue. While results of the testing are not required prior to randomization, the tissue sample must be submitted to the central laboratory prior to randomization. Local laboratories will be used for hematology and chemistry. ECGs will be performed and interpreted locally for patient care decisions; however, tracings will be collected centrally for independent evaluation. Tumor scans will be acquired by the investigative site and evaluated locally for patient treatment decisions. Scans will also be collected and stored with a central vendor and quality control performed; central reading of scans will not be done unless requested by the sponsor. Following disease progression, patients who provide additional consent will undergo tumor biopsy before subsequent-line therapy is initiated.
AEs will be collected from the time the first dose of study drug is administered through to 28 days after the last protocol-specified treatment administration. Study procedure related AEs that occur after signing of the Informed Consent Form (ICF) but before administration of study drug will also be captured.
An Independent Data Monitoring Committee (IDMC) will review safety and efficacy data on a periodic basis to ensure an acceptable overall risk and benefit for patients participating in the study; however no formal analysis for futility or efficacy is planned. The IDMC will also monitor on an ongoing basis the proportion of T790M positive and T790M negative patients enrolled into the study, in order to ensure adequate enrollment of T790M positive patients. If an imbalance in enrollment by T790M status is observed, further enrollment may be restricted to T790M positive patients only.

Intervention

Patients will be randomized 1:1:1 to receive either rociletinib 500 mg BID, rociletinib 625 mg BID, or single-agent cytotoxic chemotherapy (investigator choice of pemetrexed, gemcitabine, docetaxel, or paclitaxel; choice of chemotherapy agent must be specified before randomization).
Rociletinib
Daily oral rociletinib at either 500 mg BID or 625 mg BID with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Treatment with rociletinib is continuous and each cycle will comprise of 21 days.
Pemetrexed
500 mg/m2 pemetrexed given intravenously on Day 1 of each 21-day cycle.
Gemcitabine
1250 mg/m2 gemcitabine given intravenously on Days 1 and 8 of each 21-day cycle.
Docetaxel
75 mg/m2 docetaxel (60 mg/m2 for patients residing in East-Asian territories) given intravenously on Day 1 of each 21-day cycle, or 35 mg/m2 docetaxel given

intravenously on a weekly basis as part of a continuous 21 day cycle; ie, dosing will be on Days 1, 8, and 15 of each 21 day cycle.
Paclitaxel
80 mg/m2 paclitaxel given intravenously as a 1 hour infusion, on a weekly basis as part of a continuous 21 day cycle; ie, dosing will be on Days 1, 8, and 15 of each 21-day cycle.

Study burden and risks

To date, approximately 472 patients with NSCLC have received at least one dose of rociletinib. Commonly reported side effects in these patients, which may have been due to taking the study drug, are listed below. However, since rociletinib is an experimental drug, not all side effects are known, and there is a risk that rare or previously unknown side effects may occur. It is important that you tell the study doctor or study staff about any side effects you are experiencing, even if you do not think they are due to taking the study drug

Common (>=20% of patients)
• Nausea
• Hyperglycemia (high blood glucose which is the same as high levels of sugar in the blood): High blood glucose can cause symptoms such as nausea, vomiting and feeling tired. You must tell your doctor if you notice any of these symptoms as it could be a sign your blood glucose is increasing. You may be asked to take another medicine to control high blood glucose levels.
• Feeling tired (fatigue)
• Loose stools (diarrhea)
• Changes in your ECG (electrocardiogram - tracing of your heart rhythm). Some patients experienced a lengthening of the waves in their ECG tracings, called increase in QT. In severe cases, this can cause changes to the rhythm of your heart; in rare instances, could result in death. You will be carefully monitored in the study for any changes to your ECG

Less common (5-19% of patients)
• Decrease in appetite
• Muscle spasms
• Vomiting
• Weight Loss
• Joint or muscle pain
• Dizziness
• Changes in blood tests that measure how well your kidney and liver are functioning
• Low blood counts (red blood cells, white blood cells and platelets)
• A low red blood cell count may make you feel tired or dizzy
• A low white blood cell count puts you at higher risk for infection
• A low platelet count affects the ability of your blood to clot and could lead to bleeding events

Rare (<5% of patients)
• Constipation
• Headache
• Rash
• Change in sense of taste
• Insomnia (difficulty sleeping)
• Lung inflammation (pneumonitis). Patients taking rociletinib who developed pneumonitis have recovered, but this event could be very serious and could result in death in rare cases
• Pancreatitis (inflammation of your pancreas, which in one patient resulted in death)
• Cataract (Clouding of the lens of the eye)

Contacts

Public
Clovis Oncology, Inc.

5500 Flatiron Parkway Suite 100
Boulder 80301 CO
US
Scientific
Clovis Oncology, Inc.

5500 Flatiron Parkway Suite 100
Boulder 80301 CO
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

All patients must meet all of the following inclusion criteria:
1. Histologically or cytologically confirmed metastatic or unresectable locally advanced NSCLC with radiological progression on the most recent therapy received
2. Documented evidence of a tumor with 1 or more EGFR activating mutations excluding exon 20 insertion
3. Disease progression confirmed by radiological assessment while receiving treatment with single-agent EGFR-TKI (eg, erlotinib, gefitinib, afatinib, or dacomitinib) or EGFR TKI in combination with other targeted therapy (eg, bevacizumab, immunotherpay). The washout period for the single agent EGFR-TKI and combination targeted therapy is a minimum of 3 days or 5 half lives, whichever is more applicable, prior to start of treatment.
4. Multiple lines of prior treatment are permitted and there is no specified order of treatment, but in the course of their treatment history, patients must have received and have radiologically documented disease progression following:
- At least 1 line of prior treatment with a single-agent EGFR TKI (eg, erlotinib, gefitinib, afatinib, or dacomitinib) or EGFR TKI in combination with other targeted therapy (eg, bevacizumab, immunotherapy)
o If EGFR-TKI is a component of the most recent treatment line, the washout period for the EGFR-TKI is a minimum of 3 days before the start of study drug treatment
AND
- A platinum-containing doublet chemotherapy (either progressed during therapy or completed at least 4 cycles without progression with subsequent progression after a treatment-free interval or after a maintenance treatment).
o If cytotoxic chemotherapy is a component of the most recent treatment line, treatment with chemotherapy should have been completed at least 14 days prior to start of study treatment. When an EGFR TKI is given in combination with platinum-containing doublet chemotherapy, treatment with the EGFR TKI may continue until at least 3 days before start of treatment.
5. Have undergone a biopsy of either primary or metastatic tumor tissue within 60 days prior to start of treatment and have tissue sent to the central laboratory prior to randomization
6. Measureable disease according to RECIST Version 1.1
7. Life expectancy of at least 3 months
8. ECOG performance status of 0 to 1
9. Age >= 18 years (in certain territories, the minimum age requirement may be higher eg, age >= 20 years in Japan and Taiwan, age >= 21 years in Singapore)
10. Patients should have recovered to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade <= 1 from any significant chemotherapy-related toxicities
11. Adequate hematological and biological function, confirmed by the following local laboratory values:
Bone marrow function
a. Absolute neutrophil count (ANC) >= 1.5 × 109/L
b. Platelets > 100.0 × 109/L
c. Hemoglobin >= 9 g/dL (or 5.6 mmol/L)
Hepatic function

d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 3 × upper limit of normal (ULN); if liver metastases, <= 5 × ULN
e. Bilirubin <= 2 × ULN
* Patients with documented Gilbert*s syndrome and conjugated bilirubin within the normal range may be allowed into the study. In this event, it will be documented that the patient was eligible based on conjugated bilirubin levels
Renal function
f. Creatinine clearance >= 45 mL/min
Electrolytes
g. Potassium and magnesium within normal range. Patients may receive supplements to meet this requirement.
Glucose
h. Fasting serum glucose <= 160 mg/dL (8.9 mmol/L)
i. Glycosylated hemoglobin (HgbA1C) < 8%
12. Written consent on an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved ICF before any study specific evaluation

Exclusion criteria

Any of the following criteria will exclude patients from study participation:
1. Any other malignancy associated with a high mortality risk within the next 5 years and for which the patients may be (but not necessarily) currently receiving treatment
* Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/or bone marrow transplant > 2 years prior
2. Known pre-existing interstitial lung disease
3. Tumor small cell transformation by local assessment, irrespective of presence of T790M-positive component
4. Patients with leptomeningeal carcinomatosis are excluded. Other central nervous system (CNS) metastases are only permitted if treated, asymptomatic, and stable (not requiring steroids for at least 2 weeks prior to randomization and the patient is neurologically stable; ie, free from new symptoms of brain metastases). If a patient has had brain metastasis treated within the previous 8 weeks, a follow-up scan must have been performed to confirm that treated metastasis remain controlled without evidence of new lesions.
5. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval and that treatment cannot be either discontinued or switched to a different medication (known to have no effect on QT) before starting protocol specified treatment (see http://crediblemeds.org/ for a list of QT-prolonging medications)
6. Prior treatment with rociletinib, or other drugs that target T790M-positive mutant EGFR with sparing of WT EGFR including but not limited to osimertinib, HM61713, and TAS-121
7. Any contraindications for therapy with pemetrexed, paclitaxel, gemcitabine or docetaxel unless a contraindication with respect to one of these drugs will not affect the use of any of the others as a comparator to rociletinib
8. Any of the following cardiac abnormalities or history:
a. Clinically significant abnormal 12-lead ECG, QT interval corrected using Fridericia*s method

(QTCF) > 450 msec
b. Inability to measure QT interval on ECG
c. Personal or family history of long QT syndrome
d. Implantable pacemaker or implantable cardioverter defibrillator
e. Resting bradycardia < 55 beats/min
9. Non-study related surgical procedures <= 7 days prior to randomization. In all cases, the patient must be sufficiently recovered and stable before treatment administration.
10. Females who are pregnant or breastfeeding
11. Refusal to use adequate contraception for fertile patients (females and males) while on treatment and for 6 months after the last dose of study treatment (rociletinib and chemotherapy irrespective of single cytotoxic agent used)
12. Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study, e.g., substance abuse, uncontrolled intercurrent illness including:
• uncontrolled diabetes
• active infection
• arterial thrombosis, and
• symptomatic pulmonary embolism
13. Any other reason the investigator considers the patient should not participate in the study
14. Treatment with live vaccines initiated less than 4 weeks prior to randomization

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-05-2015
Enrollment:	27
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Docetaxel
Generic name:	Docetaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gemcitabine
Generic name:	Gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	n/a
Generic name:	Rociletinib
Product type:	Medicine
Brand name:	Paclitaxel
Generic name:	Paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Pemetrexed
Generic name:	Pemetrexed
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-01-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-06-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-07-2015
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-09-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-11-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2014-003437-26-NL
ClinicalTrials.gov	NCT02322281
CCMO	NL52061.042.15