International Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of the Efficacy and Safety of KIACTA* in Preventing Renal Function Decline in Patients With AA Amyloidosis

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Primary ObjectiveThe primary objective of this double-blind, randomized, placebo-controlled, Phase 3 study is to assess the efficacy and safety of treatment with Kiacta in adult patients with AA amyloidosis. Efficacy will be assessed by the time...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nephropathies
Study type	Interventional

Summary

ID

NL-OMON39822

Source
ToetsingOnline

Brief title
Celtic KIACTA*

Condition

- Nephropathies

Synonym
AA amyloidosis, renal function disorder

Research involving
Human

Sponsors and support

Primary sponsor: Celtic Therapeutics Development Switzerland SARL
Source(s) of monetary or material Support: C.T. Development Switzerland SARL;Chemin de Pacottaz 1;Legier-Chiesaz is the sponsor' s addresss in Europe

Intervention

Keyword: AA amyloidosis, eprodisate disodium, KIACTA□, renal function

Outcome measures

Primary outcome

The primary efficacy endpoint will be the time from Baseline to the earliest of

a persistent decrease in CrCl of 40% or more, a persistent increase in SCr of

80% or more, or progression to ESRD.

Secondary outcome

The secondary efficacy endpoint will be the rate of change (slope) in CrCl over

time.

The exploratory efficacy endpoints will be the following:

* Time from Baseline to a persistent decrease in CrCl of 40% or more, a

persistent increase in SCr of 80% or more, progression to ESRD, or all-cause

mortality;

* Time from Baseline to a decrease in CrCl of 50% or more, an increase in SCr

of 100% or more, progression to ESRD, or all-cause mortality;

* Times from Baseline to a persistent decrease in CrCl of 40% or more, a

persistent increase in SCr of 80% or more, a decrease in CrCl of 50% or more,

an increase in SCr of 100% or more, progression to ESRD, and all-cause

mortality (each component of the previously mentioned exploratory endpoints);

* Rates of change (slope) in 1/SCr, eGFR (as calculated with the modification of diet in renal disease formula), and serum cystatin C over time; and

* Absolute changes from Baseline in CrCl, SCr, eGFR, proteinuria, urinary protein/creatinine ratio, serum cystatin C, and serum amyloid A at each study visit.

Study description

Background summary

In the first Phase 2/3 study (CL-503004), Kiacta showed a consistent, clinically meaningful, and statistically significant effect in the preservation of kidney function in patients with AA amyloidosis. In this new study, doses will be the same as the ones used in the previous studies (CL-503004 and OLE CL-503009) as Kiacta is safe and was well tolerated following chronic administration for up to 6 years. The rationale for conducting this second Phase 3 study is to provide additional evidence for the efficacy and safety of Kiacta in patients with AA amyloidosis and to confirm the findings of the CL-503004 study. (zie section 5.2 protocol version 1.1 dd 05 aug10)

Study objective

Primary Objective
The primary objective of this double-blind, randomized, placebo-controlled, Phase 3 study is to assess the efficacy and safety of treatment with Kiacta in adult patients with AA amyloidosis. Efficacy will be assessed by the time from Baseline to the primary endpoint. This primary efficacy endpoint will be the time from Baseline to the earliest of a persistent decrease in creatinine clearance (CrCl) of 40% or more, a persistent increase in serum creatinine (SCr) of 80% or more, or progression to end-stage renal disease (ESRD). Safety will be assessed by the incidence of nonserious adverse events (AEs) and serious AEs (SAEs). Neither progression to ESRD nor a clinically significant change in CrCl or SCr will be considered an AE or SAE.

Secondary Objectives
The secondary objective will be to assess the effect of treatment with Kiacta on the slope of CrCl over time

Exploratory Objectives
The exploratory objectives will be to assess the effects of treatment with

Kiacta on the time from Baseline to a persistent decrease in CrCl of 40% or more, a persistent increase in SCr of 80% or more, progression to ESRD, or all-cause mortality. Assessments will also be made of the effect on time from Baseline to a decrease in CrCl of 50% or more, an increase in SCr of 100% or more, progression to ESRD, or all cause mortality. Additionally, time from Baseline to each component of the previously mentioned exploratory endpoints will be assessed individually. Other exploratory objectives will include the slopes of 1/SCr, estimated glomerular filtration rate (eGFR), and serum cystatin C over time. Absolute changes from Baseline in CrCl, SCr, eGFR, proteinuria, urinary protein/creatinine ratio, serum cystatin C, and serum amyloid A will be measured every 3 months throughout the duration of the study, including the last study visit as applicable.

Study design

This will be a multicenter, international, randomized, double-blind, placebo-controlled study with 1 unblinded interim analysis (IA). Patients diagnosed with AA amyloidosis will be randomly assigned at a 1:1 ratio to receive either Kiacta or placebo. Randomization will be stratified by averaged screening proteinuria (<3 or *3 g/day) and averaged screening eGFR (<60 or *60 mL/min/1.73 m2). Patients will be assessed as follows:
* Twice during the screening period (Month *3 to Week *1);
* At Baseline;
* Every 3 months until one of the following has occurred:
o ESRD has been confirmed by adjudication,
o The CrCl or SCr component of the primary endpoint has been reached and a minimum of 24 months of treatment has been completed,
o The end of the study is reached;
* At an early-termination, treatment-completion, or end-of-study (EOS) visit, as applicable.

Patients who experience a persistent decrease in CrCl or persistent increase in SCr and who have not completed a minimum of 24 months of treatment will remain in the study Investigational product for a total treatment period of 24 months, until they reach ESRD, or until the end of the study. Patients who do not experience a persistent decrease in CrCl or persistent increase in SCr within 24 months will remain on the study and on treatment until they reach ESRD or until the end of the study.

Patients will discontinue treatment when they reach ESRD but will remain in the study until ESRD is adjudicated by the clinical endpoint committee (CEC). If the CEC adjudicates the ESRD as absent, the patient will have the option to resume treatment. If the CEC adjudicates the ESRD as present, the patient will undergo an early-termination visit. All efforts will be made to ensure that patients who discontinue the study prior to adjudicated ESRD attend an early-termination visit.

Patient who discontinue treatment prematurely, will be asked to participate in a long-term follow-up study. These patients will be contacted by phone monthly and every 12 weeks a blood sample will be drawn. The follow-up study is conducted in parallel with the main study, meaning that the follow-up study will also end when the main study is ended. It is expected that both studies will be ongoing untl March 2014.
The patients can participate in the follow-up study until their kidney function decreases to end stage kidney disease, until the start of permanent renal replacement therapy or kidney transplant or until the end of the main study.

All patients who remain on treatment at the end of the study will attend an end-of-study visit. Telephone or e-mail contact will be made monthly from Baseline until the end of the study, and survival and renal function status (ESRD or not) of all patients will be assessed at the end of the study.

The study will end when approximately 104 adjudicated events are reached. The number of events and enrollment target for the study will be refined at the IA. Following the IA, the protocol will be amended to reflect the exact number of events required. At the end-of-study visit, patients who complete the study will be offered the option to continue treatment in an expanded access program or follow-up study.
Safety data from this study will be reviewed by an independent data monitoring committee. A CEC will be appointed to adjudicate potential endpoint events on an ongoing basis throughout the study.

Intervention

Study Drug Administration
Patients will receive either Kiacta or placebo, administered orally as 1 to 3 capsules (Kiacta 400 mg or placebo) twice a day from Baseline, depending on the CrCl. Eligible patients must have a CrCl of 25 mL/min/1.73 m2 or more during the screening period.

The dosage will be based on CrCl as determined with no correction for body surface area (in order to maintain consistency with previous studies) and the mean value of the 2 screening CrCl measurements. The dosage will be as follows:

Creatinine (mL/min) Kiacta(400 mg capsules twice daily) Placebo(twice daily)
>80 3 capsules (1200 mg) 3
capsules
30 to 80 2 capsules (800
mg) 2 capsules
<30 1 capsule (400 mg)
1 capsule

If the CrCl level increases or decreases to the next range level at a given

visit, the dose regimen has to be adjusted as per the above table.

Study burden and risks

See section 'Which side-effects can you expect' and 'Risks of the Biopsy Procedures' from the PIF mentioned below..
The most common and expected side effects and discomforts reported for KIACTA are diarrhea, headache, nausea and vomiting.
Other events less frequently described with this medication were: sore nose (like the common cold), cough, sore joints, back pain, dizziness, high blood pressure, fluid retention, sore stomach, itching, and indigestion.
When, despite every precaution, you or your partner becomes pregnant during the study this may have effects for your unborn child.
In addition, you might feel uncomfortable during some of the tests and may also have risks, such as:
Blood draws: Possible side effects of blood draws are pain, bruising, bleeding or infection at the site of the needle puncture. Blood draws may also cause temporary headache, nausea, and lightheadedness.
ECG: Skin irritation is rare but could occur during an ECG from the electrodes or gel that is used.
If a biopsy has to be performed to diagnose AA Amyloidosis, you may experience some additional side effects. You might feel uncomfortable during some of the tests and may also have risks, such as:
Abdominal wall fat pad biopsy: Although your health care provider may have numbed the skin, there can be some mild discomfort or pressure during the needle insertion. Afterward, the area may feel tender or bruised for several days.
Kidney biopsy: The amount of pain during and after the procedure depends on the patient. Because a local anesthetic is used, discomfort during the procedure is usually minimal. The anesthetic may burn or sting when first injected. After the procedure, the area may feel tender or sore for a few days. You may see bright, red blood in the urine the first 24 hours after the test. If the bleeding lasts longer, tell your health care provider.
Gum biopsy: The topical anesthetic should numb the area during the procedure, although some tugging or pressure may be felt. If there is bleeding, the blood vessels may be sealed off with an electric current or laser. This is called electrocauterization. After the numbness wears off, the area may be sore for a few days.
Rectal biopsy: There will be some discomfort during the procedure, and you may feel an urge to have a bowel movement. Cramping sometimes occurs as the instrument is placed into the rectal area.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

*Patients must be at least 18 years of age and no more than 80 years of age.
*Patients are males or nonpregnant, nonlactating females.
* Women must be of nonchildbearing potential (ie, more than 1 year postmenopausal or use effective contraception for at least 2 months prior to the baseline visit and through 30 days after the last dose of study medication
* Patients must have a confirmed diagnosis of AA amyloidosis during the screening period.
* Patients must have persistent proteinuria defined as urinary protein excretion *1 g/24 h at 2 distinct 24-hour urine collections at least 1 week apart during the screening period.
* Patients must have CrCl *25 mL/min/1.73 m² at 2 distinct 24-hour urine collections at least 1 week apart during the screening period.

Exclusion criteria

*Evidence or suspicion of chronic kidney disease secondary to a disease process other than

renal AA amyloidosis (eg, diabetes, long-standing uncontrolled hypertension, polycystic kidney disease, recurring polynephritis, or systemic lupus erythematosus).
*History of kidney transplantation.
*Evidence or suspicion of a cause of potentially reversible acute renal failure, such as uncontrolled hypertension, urinary tract infection, or drug nephrotoxicity within 3 months prior to the baseline visit.
*Presence of concomitant diseases or concomitant medication that could interfere with the interpretation of study results or compromise patient safety.
*Presence of conditions that could reduce life expectancy to less than 2 years.
*Presence of type 1 or type 2 diabetes mellitus.
*Presence of significant hepatic enzyme elevation or cirrhosis.
*Presence of unstable angina, myocardial infarction, coronary artery bypass graft surgery, or percutaneous transluminal coronary angioplasty within 6 months prior to the baseline visit.
*Presence of, or history of, stroke or transient ischemic attack within 6 months prior to the baseline visit.
*Presence of New York Heart Association class III or IV heart failure (Section 1).
*Use of any investigational drug within 30 days prior to the first screening visit.
*Initiation of, or any changes in, angiotensin converting enzyme inhibitor, angiotensin II receptor antagonist therapy, or renin inhibitor within 3 months prior to the baseline visit.
* Initiation of, or any changes in, cytotoxic agents, anti-tumor necrosis factor agents, anti-interleukin-1 or anti-interleukin-6 agents, or colchicine therapy within 3 months prior to the baseline visit.
*History of malignancy within 5 years prior to study entry, except for cervical carcinoma in situ, nonmelanomatous carcinoma of the skin, or ductal carcinoma in situ of the breast that has been surgically cured.

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:	Recruitment stopped
Start date (anticipated):	08-02-2012
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KIACTA
Generic name:	eprodisate disodium

Ethics review

Approved WMO Date:	30-12-2010
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-05-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-07-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-12-2011
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	15-12-2011
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)

Approved WMO Date:	23-01-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	02-04-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-05-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-10-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-10-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-07-2014
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-01-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-11-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-12-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2010-022313-25-NL
ClinicalTrials.gov	NCT01215747
CCMO	NL33777.068.10