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UK Heart and Renal Protection (UK HARP-III)

Submission date
11/12/2013

Recruitment status
No longer recruiting

Registration date
20/01/2014

Overall study status
Completed

Last Edited
16/07/2018

Condition category
Urological and Genital Diseases

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Chronic kidney disease affects about 1 in 10 adults. The illness can worsen over time. This means that some people eventually need to have dialysis or a kidney transplant. There are treatments that can slow the rate of decline of kidney function . However, despite such treatment some people still need transplantation or dialysis. The aim of the study is to investigate whether a new drug (LCZ696) has the potential to protect the kidneys better than the current standard treatment.

Who can participate?
Men and women aged 18 and over with chronic kidney disease who have increased levels of protein in their urine.

What does the study involve?
You will need to participate in the study for about 13 months. You will be asked to attend about seven hospital appointments, some of which may coincide with your routine renal outpatient appointments. In addition, we will measure your kidney function very precisely on two occasions during the study. At your first visit to the clinic a trained researcher (usually a nurse) will ask you about your medical history. The researcher will take your blood pressure and a sample of blood and urine. You will then be provided with a supply of the study tablets and asked to take two a day. This visit will take about 45 minutes. You may be asked to stop some of your current blood pressure treatment (because the study treatment will replace them). Over the course of the next few weeks you will have the chance to try out the study tablets. This will allow you and the study doctors and nurses to be sure the routine of taking these particular tablets agrees with you. Towards the end of this period you may be asked to collect your urine for 24 hours, but this is optional and you can still participate even if you dont want to do this. After at least 4 weeks of taking the study tablets you will be asked to attend a second appointment to see if you would like to continue. We will measure your kidney function and your blood pressure and we will ask for another blood and urine sample. Your height and weight will also be recorded at this visit. If you have had no problems with the study treatments during the first few weeks and are happy to continue, you will be asked to commit to the study for another 12 months. This visit will take about 30 minutes. Following this appointment you will take two different tablets once daily: an active tablet and a placebo (dummy) tablet. You will be randomly allocated to take either active LCZ696 and placebo irbesartan, or placebo LCZ696 and active irbesartan. Irbesartan is an angiotensin receptor blocker and is commonly used to treat kidney disease. At further visits you

will be asked to have a blood test after about two weeks to check your potassium level. This can be done at your GP surgery or your kidney clinic. The dose of your study treatment will then increase to the full dose (two tablets of active treatment and two tablets of placebo once daily). You will be asked to attend five further appointments (about 1, 3, 6, 9 and 12 months later) to see how you are getting on. Your blood pressure will be checked and a blood and urine sample will be taken at each visit. At the final visit you will have a second measurement of your kidney function. Each visit will last about 30 minutes.

What are the possible benefits and risks of participating?
You may be helping yourself, but you will most certainly be helping doctors and scientists improve treatment for people who have chronic kidney disease and who may be at risk of needing dialysis or a transplant. If successful, results from this study will help to design a larger trial of LCZ696 which could reliably show whether LCZ696 is better than current treatment in slowing the progression of chronic kidney disease. Most treatments have side effects which some people may experience and others do not. If you do experience any side effects while on the study they will be noted, so that scientists can learn from you. You can withdraw from the study if you wish. Irbesartan is generally very well-tolerated. It has been tested in thousands of people and is taken by hundreds of thousands of people worldwide. It lowers blood pressure so it can cause dizziness. Other side effects include nausea, muscle pain and fatigue. It can raise potassium levels in the blood and you will be monitored for this. Over 8,000 people have taken LCZ696 in other clinical trials and it is generally well-tolerated. It also lowers blood pressure so can cause dizziness and fatigue. Rarely it may cause swelling of the mouth and face. The treatment can raise potassium levels in the blood and you will be monitored for this. One patient who received LCZ696 had an allergic reaction which included abnormal liver function tests. At this stage, scientists cannot rule out the possibility of there being side effects (such as diarrhoea or muscle pains), or effects on other blood tests. Throughout the study you will be carefully monitored by our nursing team for possible side effects. At every visit, the study staff would discuss any new information about the drug with you. The study includes two measurements of your kidney function which involve an injection of a small amount of radioactive material. The dose of radioactivity is small (equivalent to one day of natural background radiation in the UK) and poses a negligible risk to health.

Where is the study run from?
The study is coordinated by the Clinical Trial Service Unit at the University of Oxford. There will be about 20 centres taking part around the UK.

When is the study starting and how long is it expected to run for?
The study will start in early 2014 and last for about one year. Participants will be recruited during the first 6 months and follow-up in the study is for 12 months.

Who is funding the study?
Novartis AG Pharma (UK)

Who is the main contact?
Dr Richard Haynes

Study website
http://www.harp3trial.org/

Contact information

Type(s)
Scientific

Contact name
Dr Richard Haynes

Contact details
Clinical Trial Service Unit
Richard Doll Building
Old Road Campus
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Oxford
United Kingdom
OX3 7LF

Additional identifiers

EudraCT/CTIS number
2013-004205-89

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
CTSUHARP3

Study information

Scientific Title
Randomized multicentre pilot study of LCZ696 versus irbesartan in patients with chronic kidney disease: UK Heart And Renal Protection (HARP)-III

Acronym
UK HARP-III

Study objectives
Current hypothesis as of 03/05/2016:
The primary aim is to assess the difference in the change in measured glomerular filtration rate from baseline to 12 months between participants allocated LCZ696 versus those allocated irbesartan control.

Previous hypothesis:
The primary aim is to assess the difference in the change in measured glomerular filtration rate from baseline to 6 months between participants allocated LCZ696 versus those allocated irbesartan control.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Nottinghamshire 2 REC, conditional approval received 05/12/2013, ref: 13/EM/0434

Study design
Multicentre double-blind randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Chronic kidney disease

Interventions
Current interventions as of 03/05/2016:
LCZ696: 200 mg orally once daily for 2 weeks then increased to 400 mg orally once daily for total duration 12 months.
Irbesartan: 150 mg orally once daily for 2 weeks then increased to 300 mg orally once daily for total duration 12 months.

Previous interventions:
LCZ696: 200 mg orally once daily for 2 weeks then increased to 400 mg orally once daily for total duration 6 months.
Irbesartan: 150 mg orally once daily for 2 weeks then increased to 300 mg orally once daily for total duration 6 months.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
LCZ696, irbesartan

Primary outcome measure
Current primary outcome measures as of 03/05/2016:
Change in measured glomerular filtration rate from baseline to 12 months

Previous primary outcome measures:
Change in measured glomerular filtration rate from baseline to 6 months

Secondary outcome measures
Current secondary outcome measures as of 03/05/2016:
1. Urine albumin:creatinine ratio will be measured from baseline to 12 months
2. Pharmacokinetics will be measured at 3 months

Previous secondary outcome measures:
1. Urine albumin:creatinine ratio will be measured from baseline to 6 months
2. Pharmacokinetics will be measured at 3 months

Overall study start date
01/11/2014

Completion date
01/03/2017

Eligibility

Key inclusion criteria
Current inclusion criteria as of 03/05/2016:
1. Men or women aged ≥18 years (at screening)
2. Established proteinuric chronic kidney disease i.e. on measurements in the last 3 months:
2.1. An estimated glomerular filtration rate ≥20 <45 mL/min/1.73m2 (estimated with Modification of Diet in Renal Disease [MDRD] or Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) OR
2.2. An estimated glomerular filtration rate ≥45 <60 mL/min/1.73m2 and albumin:creatinine ratio >20 mg/mmol (or protein:creatinine ratio >30 mg/mmol)

Previous inclusion criteria:
1. Men or women aged ≥18 years (at screening)
2. Established proteinuric chronic kidney disease i.e. on measurements in the last 3 months:
2.1. Estimated glomerular filtration rate (eGFR) ≥20 <60 mL/min/1.73m2 (estimated with Modification of Diet in Renal Disease [MDRD] or Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) AND
2.2. Urine albumin:creatinine ratio ≥30 mg/mmol

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants

400

Key exclusion criteria
1. Angiotensin receptor blocker (ARB) therapy contraindicated e.g. bilateral renal artery stenosis
2. Known intolerance of ARB
3. Current treatment with aliskiren
4. Mean systolic blood pressure >180 mmHg at screening visit (or investigator unwilling to withdraw angiotensin-converting enzyme inhibitors [ACEi], ARB or DRI for another reason)
5. Serum potassium >5.5 mmol/L (updated 03/05/2016; previously >5.2 mmol/L)
6. Presence of nephrotic syndrome (i.e. urine protein:creatinine ratio >350 mg/mmol [or albumin: creatinine ratio >300 mg/mmol] AND serum albumin <30 g/L) or currently receiving immunosuppression for nephrotic syndrome
7. Functioning renal transplant
8. Acute coronary syndrome, stroke or transient ischaemic attack in 3 months prior to Screening
9. Known chronic liver disease or alanine aminotransferase/aspartate aminotransferase (ALT /AST) >2x upper limit normal (ULN) at screening
10. History of angioedema (drug-related or otherwise)
11. Use of unlicensed investigational medicinal product in previous month
12. Pregnancy or women with child-bearing potential (refusing a reliable method of contraception3)
13. Medical history that might limit the patients ability to take study treatments for the duration of the study (e.g. severe respiratory disease, or recent history of alcohol or substance misuse or history of cancer or evidence of spread in last 5 years other than non-melanoma skin cancer)

Date of first enrolment
01/11/2014

Date of final enrolment
31/01/2016

Locations

Countries of recruitment
United Kingdom

Study participating centre
Oxford University Hospitals
United Kingdom
-

Study participating centre
Royal Free London
United Kingdom
-

Study participating centre
Royal Derby Hospital
United Kingdom
-

Study participating centre
Queen Elizabeth Hospital, Birmingham
United Kingdom
-

Study participating centre
Salford Royal Hospital
United Kingdom
-

Study participating centre
Royal Berkshire Hospital
United Kingdom
-

Study participating centre
Royal Devon and Exeter Hospital
United Kingdom
-

Study participating centre
Manchester Royal Infirmary
United Kingdom
-

Study participating centre
Dorset County Hospital, Dorchester
United Kingdom
-

Study participating centre

Sheffield Teaching Hospitals
United Kingdom
-

Study participating centre
University Hospital of North Staffordshire
United Kingdom
-

Study participating centre
Leicester General Hospital
United Kingdom
-

Study participating centre
Southmead Hospital, Bristol
United Kingdom
-

Study participating centre
Plymouth Hospitals
United Kingdom
-

Study participating centre
Nottingham University Hospitals
United Kingdom
-

Study participating centre
Royal Wolverhampton
United Kingdom
-

Study participating centre

Portsmouth Hospitals
United Kingdom
-

Study participating centre
The Princess Royal Hospital, Telford
United Kingdom
-

Study participating centre
York Teaching Hospitals
United Kingdom
-

Study participating centre
University Hospital of Wales
United Kingdom
-

Study participating centre
University Hospitals Coventry and Warwickshire
United Kingdom
-

Study participating centre
The James Cook University Hospital
United Kingdom
-

Study participating centre
Morriston Hospital
United Kingdom
-

Study participating centre

Aberdeen Royal Infirmary
United Kingdom
-

Sponsor information

Organisation
University of Oxford (UK)

Sponsor details
University Offices
Wellington Square
Oxford
England
United Kingdom
OX1 2JD
+44 (0)1865 270000
harp3@ctsu.ox.ac.uk

Sponsor type
University/education

Website
http://www.ox.ac.uk

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Industry

Funder Name
Novartis Pharmaceuticals UK Limited

Alternative Name(s)
Novartis UK, NOVARTIS UK LIMITED

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
This paper is conditionally accepted by a major journal and the trialists are in the process of minor revision.

Intention to publish date

Individual participant data (IPD) sharing plan
Participant level data requests should be made to harp3@ndph.ox.ac.uk and would conform to our department's policy (https://www.ndph.ox.ac.uk/about/data-access-policy).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol and baseline data	01/12/2017		Yes	No
Basic results	results	14/03/2018	09/05/2018	No	No
Results article		09/10/2018		Yes	No
HRA research summary			28/06/2023	No	No