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Aerosolised liposomal cyclosporin A (L-CsA) versus aerosolised placebo in the prevention of bronchiolitis obliterans (BO) in lung transplant (LT) patients

Submission date
25/06/2008

Registration date
10/07/2008

Last Edited
20/05/2019

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Respiratory

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The aim of this study is to assess the safety and effectiveness of an experimental drug called Aerosolised Liposomal Ciclosporin A (L-CsA) when it is given to lung transplant patients to prevent the development of bronchiolitis obliterans syndrome. Bronchiolitis obliterans syndrome is a long-term (chronic) rejection process that can occur in the transplanted lung.

Who can participate?
Patients aged 18 and over who have received a lung transplant (single lung, two lungs or a heart /lung transplant)

What does the study involve?
All participants receive standard of care basic immunosuppression (drugs that inhibit or prevent activity of the immune system). Participants are randomly allocated to also receive aerosolised L-CsA treatment or placebo (dummy drug) treatment. The effectiveness of L-CsA at preventing the development of bronchiolitis obliterans is assessed.

What are the possible benefits and risks of participating?
L-CsA is an investigational drug, which means that it has not been approved by any of the Regulatory Agencies which are responsible for licensing new medicines. L-CsA has already been tested in several animal studies and in one clinical trial where 12 transplant recipients inhaled a single dose of L-CsA via a nebuliser. In this trial four mild side effects (cough, feeling short of breath, gastro-intestinal disorder and raised blood pressure) were seen in the transplanted patients and the trial showed that the amount of L-CsA measured in the lungs might be sufficient to help prevent the development of BOS.

Where is the study run from?
PARI Pharma GmbH (Germany)

When is the study starting and how long is it expected to run for?
June 2009 to July 2013

Who is funding the study?
PARI Pharma GmbH (Germany)

Who is the main contact?
Stefanie Prante

Contact information

Type(s)
Scientific

Contact name
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Contact details
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Additional identifiers

Clinical Trials Information System (CTIS)
2008-003800-73

ClinicalTrials.gov (NCT)
NCT01334892

Protocol serial number
CLP 12011.201

Study information

Scientific Title
A phase III, multicentre, randomised, double-blind, placebo controlled clinical trial to investigate the efficacy and safety of 10 or 20 mg/day aerosolised liposomal ciclosporin A (L-CsA) versus aerosolised placebo in the prevention of bronchiolitis obliterans syndrome (BOS) in lung transplant (LT) patients

Acronym
L-CsA-LT

Study objectives

Current hypothesis as of 29/06/2015:
To assess the efficacy and safety of the addition of aerosolised L-CsA plus Standard of Care systemic immunosuppression as compared to aerosolised placebo plus Standard of Care therapy for prevention of bronchiolitis obliterans syndrome (BOS) in lung transplant recipients.

Previous hypothesis:
To establish an investigational medicinal product (IMP) dosage with the most favourable risk-benefit ratio for the prevention of bronchiolitis obliterans (BO).

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Austria: Ethics Committee of the University of Vienna and the AKH, 14/09/2009, ref: 345/2009
2. Belgium: Ethics Committee of the University of Brussels, Hospital Erasme, 14/09/2009, ref: P2009/175
3. Germany: Ethics Committee of the University of Munich (LMU), 14/07/2009, ref: 143-09
4. United Kingdom: Cambridgeshire 1 Research Ethics Committee, 27/08/2009, ref: 09/H0304/47
5. France: Ethics Committee Est-III Hôpital de Brabois. Rue de Morvan – 54511 Vandœuvre-lès-Nancy Cedex, ref: 10.09.05
6. Spain: CEIC del hospital Universitari Vall d'Hebrón, Barcelona

Study design
Phase III multicentre randomised double-blind placebo-controlled clinical trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Bronchiolitis obliterans

Interventions
Current interventions as of 29/06/2015:
Basic immunosuppression: All participants regardless of treatment allocation will receive Standard of Care basic immunosuppression consisting of a triple drug therapy (TDT) of tacrolimus, prednisone, and mycophenolate mofetil.

After screening and consenting patients will be randomly assigned to one of the following treatments:

Treatment arm A (aerosolised L-CsA treatment plus Standard of Care therapy):
Single-Lung Transplant (SLTx) patients: L-CsA 5 mg/1.25 ml twice daily for 96 weeks (24 months)
Plus
Standard of Care systemic immunosuppression

Double-Lung Transplant (DLTx) patients:
L-CsA 10 mg/2.5 ml twice daily for 96 weeks (24 months)
Plus
Standard of Care systemic immunosuppression

Treatment arm B (aerosolised placebo treatment plus Standard of Care therapy):
Single-Lung Transplant (SLTx) patients:
Placebo 1.25 ml twice daily for 96 weeks (24 months)
Plus
Standard of Care systemic immunosuppression

Double-Lung Transplant (DLTx) patients:
Placebo 2.5 ml twice daily for 96 weeks (24 months)
Plus
Standard of Care systemic immunosuppression

Previous interventions from 12/05/2009 to 29/06/2015:
Subjects will be randomised (1:1:1) to one of three treatment arms:
1. 1 x 10 or 5 mg/day L-CsA and 1 x placebo/day
2. 2 x 10 or 5 mg/day L-CsA
3. 2 x placebo

Subjects will be stratified according to several baseline risk factors, e.g. double versus single lung transplantation. Treatment duration will be 96 weeks (2 years) with one month follow-up period.

Initial information at time of registration:
Subjects will be randomised (1:1:1) to one of three treatment arms:
1. 1 x 10 or 5 mg/day L-CsA and 1 x placebo/day
2. 2 x 10 or 5 mg/day L-CsA
3. 2 x placebo

Subjects will be stratified according to several baseline risk factors, e.g. double versus single lung transplantation. Treatment duration will be 96 weeks (2 years) with no follow-up period. After successful completion of the study, the patient may enter the follow-up clinical trial (ref: 12011.203) after fulfilling inclusion/exclusion criteria.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Liposomal cyclosporin A (L-CsA)

Primary outcome(s)
Current primary outcome measures as of 29/06/2015:
BOS-free survival
Bronchiolitis obliterans syndrome (BOS)
Efficacy of L-CsA in preventing the development of bronchiolitis obliterans when given to lung

transplant recipients in addition to Standard of Care systemic immunosuppression. Efficacy failure is the combined endpoint of occurrence of BOS (defined as at least a 20% decline from the initial randomization FEV1 value confirmed by two separate measurements of at least three weeks apart) or re-transplantation or death. BOS stage 1 and higher is considered as BOS for the primary endpoint. BOS-free survival is the time from first IMP intake to either first BOS or re-transplantation or death.

Previous primary outcome measures:
The primary objective is to establish an IMP dosage with the most favourable risk-benefit ratio for the prevention of BO in LT patients.

Key secondary outcome(s))

Current secondary outcome measures as of 29/06/2015:
1. Efficacy: Pulmonary function parameter, incidence of BOS, overall survival, Incidence of graft loss
2. Safety: Treatment-emergent adverse events (AEs), incidence of invasive bacterial, viral or fungal infections, clinical laboratory, vital signs, physical examination and L-CsA and tacrolimus trough blood levels

Previous secondary outcome measures:
The secondary objectives are to compare efficacy and safety data from two different L-CsA doses versus placebo and to evaluate investigational medicinal product (IMP) pharmacokinetic (PK) data in bronchoalveolar lavage (BAL) and in whole blood samples.

Completion date

12/07/2013

Eligibility

Key inclusion criteria

Current information as of 31/03/2010:
The following point has been amended as of the above date:
2. Received a single lung, bilateral lung or heart/lung transplantation between 6 weeks and 26 weeks prior to first IMP administration

Previous information as of 12/05/2009:
1. Patient's written informed consent obtained prior to any screening procedure
2. Received a single lung, bilateral lung or heart/lung transplantation within four weeks prior to first investigational medical product (IMP) administration
3. Male or female greater than or equal to 18 years of age
4. Capable of self-administration of medications
5. Capable of understanding the purpose and risk of the clinical trial
6. Received within one week prior to first IMP administration the following immunosuppressive agents and dosages for maintenance therapy:
6.1. Tacrolimus approximately 0.1 to 0.2 mg/kg/day adjusted to a target serum level (C0, trough) of 8 to 15 µg/L, and
6.2. Mycophenolate mofetil (MMF) 1 to 3 g/day, and
6.3. Prednisone orally; tapered down within the first 3 months after transplantation
7. Female patients with childbearing potential must have a negative serum pregnancy test within 3 days prior to screening. Both women and men must agree to use a medically acceptable method of contraception throughout the IMP treatment period and for 3 months after IMP

discontinuation.
8. Estimated life expectancy greater than 6 months

Initial information at time of registration:
1. Signed informed consent provided prior to any screening procedure
2. Male or female, 12 years or older
3. Capable of self-administrating medications
4. Capable of understanding the purpose and risk of the study
5. Received a single lung, bilateral lung or heart/lung transplantation within one week prior to first investigational medicinal product (IMP) administration
6. Received within one week prior to first IMP administration the following immunosuppressive agents and dosages for maintenance therapy:
6.1. Tacrolimus 0.1 to 0.2 mg/kg/day adjusted to target serum level (trough concentrations) of 8 to 15 µg/L
6.2. Mycophenolate mofetil (MMF) 1 to 3 g/day, and
6.3. Prednisone orally 0.5 mg/kg/day initial dosing tapered down to approximately 5 mg/week after 2 to 4 weeks
7. Female patients with child bearing potential must have a negative serum pregnancy test within 3 days prior to screening. Both women and men must agree to use a medically-acceptable method of contraception throughout the treatment period and for 3 months after discontinuation of treatment. Acceptable methods of contraception include intra-uterine device (IUD), oral contraceptive, subdermal implant and double barrier (condom with a contraceptive sponge or contraceptive suppository)
8. Estimated life expectancy greater than 6 months

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
130

Key exclusion criteria
Current information as of 12/05/2009:
1. Any previous episode of bronchiolitis obliterans (BO) or bronchiolitis obliterans syndrome (BOS) of grade 1 or higher
2. Any active invasive bacterial, viral or fungal infection within one week prior to first IMP administration
3. Received systemic maintenance immunosuppressive therapy other than listed in the inclusion criteria within one week prior to first IMP administration

4. Received any systemic or topical ciclosporin A within one week prior to first IMP administration and/or during the clinical trial
5. Received any systemic or topical rosuvastatin within one week prior to first IMP administration and/or during the clinical trial
6. Current mechanical ventilation
7. Received a lung re-transplantation
8. Pregnant or breast feeding woman
9. Has known hypersensitivity to ciclosporin A
10. Has a serum creatinine value of more than 265 µmol/L (3 mg/dL) or chronic dialysis (haemodialysis)
11. Unlikely to comply with visits, inhalation procedures or spirometric measurements scheduled in the protocol
12. Receipt of an investigational drug as part of a clinical trial within 4 weeks prior to first administration of IMP
13. Any co-existing medical condition that in the investigator's judgement will substantially increase the risk associated with the patient's participation in the clinical trial
14. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or completion of the necessary procedures
15. Patient was previously enrolled in the present clinical trial

Initial information at time of registration:
1. Any previous episode of acute rejection of grade A2 or higher
2. Any previous episode of bronchiolitis obliterans (BO) or bronchiolitis obliterans syndrome (BOS) of grade 1 or higher
3. An active invasive bacterial, viral or fungal infection within one week prior to IMP administration
4. Received systemic maintenance immunosuppressive therapy other than listed in the inclusion criteria within one week prior to first IMP administration
5. Received any systemic or topical cyclosporin within one week prior to first IMP administration and/or during the clinical trial
6. Received mechanical ventilation
7. Received a lung re-transplantation
8. Pregnant or breast feeding woman
9. Has known hypersensitivity to cyclosporin A
10. Has a serum creatinine value of more than 3 mg/dL
11. Unlikely to comply with visits, inhalation procedures or spirometric measurements scheduled in the protocol
12. Receipt of an investigational drug as part of a clinical trial within 4 weeks prior to first administration of IMP
13. Any co-existing medical condition that in the investigator's judgement will substantially increase the risk associated with the subject's participation in the study
14. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or completion of the necessary procedures
15. Has been previously enrolled in this study

Date of first enrolment
18/12/2009

Date of final enrolment
01/08/2012

Locations

Countries of recruitment
United Kingdom

Austria

Belgium

France

Germany

Spain

Study participating centre
PARI Pharma GmbH
Munich
Germany
81369

Sponsor information

Organisation
PARI Pharma GmbH (Germany)

ROR
https://ror.org/011pcrd91

Funder(s)

Funder type
Industry

Funder Name
PARI Pharma GmbH (Germany)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results				No	No
HRA research summary			28/06/2023	No	No