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Bosentan, an endothelin-receptor antagonist, in the treatment of pulmonary hypertension in severe chronic obstructive pulmonary disease: a prospective, double-blind, placebo-controlled trial

Submission date
22/03/2006

Registration date
20/04/2006

Last Edited
07/05/2008

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Respiratory

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

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title

Acronym
TOP Study

Study objectives
We hypothesise that the orally administered dual endothelin-receptor antagonist bosentan improves exercise capacity (as measured by the six-minute walk test, mobile spiroergometry) and pulmonary perfusion (as measured by computed tomography single photon emission computed tomography [CT SPECT]) and is well tolerated at a dose of 125 mg, twice daily, in patients with pulmonary hypertension due to severe chronic obstructive pulmonary disease (COPD)

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved by Ethics Committee of Basel (EKBB) on 20/03/2006, reference number: 317/05. This trial was also approved by the Swiss Federal Authority (Swiss Agency for Therapeutic Products [SWISSMEDIC]), protocol reference number: 2006 DR 2086.

Study design
Interventional, prospective, randomised, double-blind, placebo-controlled study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Not specified

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Chronic obstructive pulmonary disease

Interventions

Bosentan dose increases from 62.5 mg twice a day (BID) to 125 mg DIB after 14 days, if there is no increase in AST/ALT greater than 3 x normal values. If there is an increase of AST/ALT greater than 3 times but less than 5 times that of the normal values, the dosage is maintained at 62.5 mg BID. If the increase if greater than 5 times the normal value, therapy with bosentan has to be discontinued. The control group will receive a placebo.

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Bosentan

Primary outcome measure
Improvement in six feet walking distance after three months therapy.

Secondary outcome measures
Improvement or change after three months in regard to:
1. Partial pressure of Oxygen (pO2) measured in the Arterial Blood Gas Analysis (ABGA)
2. Maximal oxygen uptake (VO2 max), Saturation of Oxygen in arterial blood (SaO2) as measured by mobile exercise test
3. Perfusion pattern on the thorax SPECT-CT (SYMBIA T2), comparing different morphologic types of emphysema
4. Systolic pulmonary pressure, right-ventricular enlargement and right-ventricular ejection fraction as measured by echocardiography
5. Bodyplethysmography and Carbon Dioxide (CO2) diffusion capacity
6. Brain natriuretic peptide
7. Liver enzymes (AST, ALT)

Overall study start date
01/04/2006

Completion date
01/12/2006

Eligibility

Key inclusion criteria
1. Patients with a diagnosis of severe (forced expiratory volume in one second [FEV1] less than 50%), or very severe (FEV1 less than 30%) COPD and/or severe emphysema (markedly impaired diffusion capacity), according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines will be included in the study. Post-bronchodilator lung function test will be appreciated, as suggested in the guidelines. Patients will be screened in regard to echocardiographical technical feasibility. Moreover, patients will undergo routine clinical, land laboratory evaluation as well as full lung function testing.
2. Greater than 18 years of age
3. Postmenopausal women or women with negative pre-treatment pregnancy test as well as a reliable method of contraception during study treatment and for at least three months after

study treatment termination. Reliable methods of contraception are:
3.1. Barrier type devices (e.g. female condom, diaphragm, contraceptive sponge) only in combination with a spermicide
3.2. Intra-uterine devices
3.3. Oral, injectable or implantable contraceptives only in combination with a barrier method
3.4. Hormone-based contraceptives alone, regardless of the route of administration, are not considered as reliable methods of contraception
3.5. Abstention, rhythm method, and contraception by the partner alone are not acceptable methods of contraception

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
24

Key exclusion criteria
1. Mental disorder preventing appropriate judgment concerning study participation
2. Significant comorbidity resulting in reduced life expectancy
3. Infectious or non-infections hepatitis
4. Known intolerance to bosentan
5. Significant exacerbation of COPD within the last month
6. Insufficient technical quality in the echocardiographic evaluation
7. Systolic Blood Pressure (BP) less than 85 mmHg
8. Body weight less than 40 kg
9. Hemoglobin concentration less than 75% of the lower limit of the normal range
10. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) values greater than 3 times the upper limit of normal
11. Moderate to severe hepatic impairment (Child-Pugh B or C)
12. Patients with decompensated and/or not corrected right heart failure
13. Concomitant treatment with:
13.1. Calcineurin-inhibitors (e.g. cyclosporine A and tacrolimus, everolimus, sirolimus)
13.2. CYP2C9 and CYP3A4 inhibitors (e.g. fluconazole, amiodarone, miconazole, ketoconazole, itraconazole, ritonavir, voriconazole, metronidazole)
13.3. Protease inhibitors (e.g. ritonavir) or glibenclamide (glyburide) within 1 week of randomisation

Date of first enrolment
01/04/2006

Date of final enrolment
01/12/2006

Locations

Countries of recruitment
Switzerland

Study participating centre
University Hospital Basel
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4031

Sponsor information

Organisation
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Sponsor type
University/education

Website
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ROR
https://ror.org/04k51q396

Funder(s)

Funder type
University/education

Funder Name
University Hospital Basel (USB) (Switzerland) - Department of Pneumology

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

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?
Results article	Results	01/09/2008		Yes	No