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The human nasal lipopolysaccharide (LPS) challenge model reflects inflammatory events in the lower airways, illustrated by CXCR2 inhibition of neutrophil recruitment

Submission date
10/01/2011

Registration date
17/02/2011

Last Edited
03/01/2012

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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Study information

Scientific Title
The human nasal lipopolysaccharide (LPS) challenge model reflects inflammatory events in the lower airways, illustrated by CXCR2 inhibition of neutrophil recruitment: a placebo-controlled double-blind, cross-over study

Study objectives
This study aimed to validate a lipopolysaccharide (LPS) nasal challenge model by investigating the effect of CXCR2 inhibitor AZD8309 on neutrophilic inflammation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Regionala etikprövningsnämnden Lund approved on the 16th February 2009 (ref: LU2008/698)

Primary study design
Interventional

Study design
Placebo-controlled double-blind cross-over study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Neutrophil inflammation in airway disease

Interventions
Study design
This methodology study is a randomised, double-blind, placebo-controlled, two-way crossover study in healthy subjects to assess the effect of AZD8309 on cells and inflammatory biomarkers in nasal lavage and blood after nasal challenge with LPS. The study will comprise of 6 visits; a screening visit (Visit 1), 4 treatment visits (Visits 2 to 5), and a post-study follow-up visit (Visit 6). The healthy subjects will receive 300 mg AZD8309 (oral solution [30 mg/g]) or placebo twice daily for 3 consecutive days. On the third day of dosing (after the fifth dose of study drug, Visits 3 and 5) the subjects will be challenged with 100 µg nasal LPS. The washout period between the LPS challenges will be at least 3 weeks.

Duration of treatment
This study will include a run-in period of less than 3 weeks, followed by Treatment Period 1 (3 days), a washout period of at least 3 weeks, and Treatment Period 2 (3 days). The total duration of the study from Visit 1 (screening) to Visit 6 (follow-up) will be approximately 6 to 12 weeks for an individual subject.

Visit 1 - screening
Visit 1 will be a screening visit where subject informed consent will be obtained, and subject eligibility will be established.

Visits 2, 3, 4 and 5 - treatment
At Visit 2, eligibility criteria will be checked and the subjects will be asked about any AEs prior to dosing. All randomised subjects will also receive a Study Participation Card in Swedish. At Visit 2 and 4, the subjects will be dosed with either AZD8309 or placebo at 08:00 ± 30 minutes and will remain under medical supervision at the study site for at least 1 hour following dosing. Subjects will then be discharged from the study site and will return 7 hours post-dose of study drug for cells and inflammatory biomarker assessments in blood. The subjects will take their second dose of AZD8309 or placebo at home, approximately 12 hours (± 30 minutes) after their first dose.

The subjects will continue to dose with AZD8309 or placebo at home (Day 2) at 08:00 ± 30 minutes and 20:00 ± 30 minutes. The following morning (Day 3), at Visit 3 and 5, the subjects will return to the study site and will be dosed with either AZD8309 or placebo at 08:00 ± 30 minutes. One hour after dosing, nasal challenges with LPS will be performed. The subjects will be confined to the study site until 6 hours post-LPS challenge (7 hours post-dose of study drug), and will then be discharged from the study site. The subjects will take their sixth dose of AZD8309 or placebo at home at 20:00 ± 30 minutes. The following morning, the subjects will return to the study site. Various assessments, such as biomarker assessments in nasal lavage and blood, will be performed 24 hours post-LPS challenge. Subjects will then be discharged from the study site.

Visit 6 - follow-up
Visit 6 will be a post-study follow-up visit.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
AZD8309, lipopolysaccharide

Primary outcome(s)
Neutrophil numbers in nasal lavage, measured 24 hours post-LPS challenge

Key secondary outcome(s)
1. Other cells in nasal lavage: total leucocytes, macrophages, lymphocytes, eosinophils and epithelial cells, measured 24 hours post-LPS challenge
2. Inflammatory biomarkers in nasal lavage, which may include, but not be restricted to: IL-8, GROa, LTB4 and neutrophil elastase activity, measured 24 hours post-LPS challenge
3. Cells in blood: total leucocytes, neutrophils, monocytes, lymphocytes, basophils and eosinophils, measured 24 hours post-LPS challenge
4. Inflammatory biomarkers in blood, which may include, but not be restricted to: TNFa, high sensitivity CRP, IL-6, IL-8, GROa and serum amyloid A, measured 24 hours post-LPS challenge
5. Safety:
5.1. Incidence and nature of adverse events
5.2. Nasal symptoms (total nasal symptom scores) and nasal airway resistance (peak nasal inspiratory flow)
5.3. Clinically significant abnormalities in pulse, blood pressure, body temperature and liver enzymes (aspartate aminotransferase, alanine aminotransferase and bilirubin)

Completion date
31/12/2010

Eligibility

Key inclusion criteria
1. Provision of informed consent prior to any study specific procedures
2. Be willing and able to comply with study procedures
3. Healthy men or women aged 18 to 50 years (inclusive). Women must be of non-childbearing

potential, that is women who are permanently sterilized (hysterectomy and/or bilateral oophorectomy or salpingectomy).
4. Have a body mass index (BMI) between 18 and 30 kg/m2 (inclusive) and minimum body weight of 50 kg
5. A blood neutrophil count above 2.2 x 10^9/L
6. Be non-smokers, or ex-smokers who have not smoked (or used any other nicotine products) in the 12 months preceding Visit 1 with a pack-year history of less than 10

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Any clinically relevant disease and/or abnormality (past or present), which, in the opinion of the investigator, may either put the subject at risk because of participation in the study, or influence the results of the study, or the subject's ability to participate in the study
2. A definite or suspected personal or family history of intolerance or hypersensitivity to drugs and/or their excipients, judged to be clinically relevant by the investigator
3. Surgery or significant trauma within 3 months of Visit 1
4. Symptoms, signs or laboratory findings suggestive of an ongoing infective illness, as judged by the investigator, at Visit 1
5. Current or recurrent atopic symptoms, ie, rhinitis, asthma or conjunctivitis of clinical relevance as judged by the investigator
6. Participation in any clinical study with an investigational drug or new formulation of a marketed drug in the 3 months prior to Visit 1, or participation in a methodology study 1 month prior to Visit 1 (Note: participation is identified as the completion of a treatment-related visit)
7. Donation of blood within 3 months and plasma within 14 days prior to Visit 1
8. Use of any medication (other than hormone replacement therapy [HRT]), including vaccinations or "over-the-counter" medication (e.g., herbal remedies, vitamins or nutritional supplements) within 2 weeks in relation to first administration of study drug (or longer if the medication has a half-life long enough to potentially expose the subject to any significant systemic exposure that may interfere with the objectives of the study or the safety of the subjects), as judged by the investigator. Occasional intake of paracetamol, maximum 1 g 4 times daily (qid), is allowed.
9. Past or present alcohol or drug abuse, as judged by the investigator, or positive drugs of abuse test
10. Positive results on screening tests for serum hepatitis B surface antigen, hepatitis C antibodies and/or human immunodeficiency virus (HIV)
11. A suspected/manifested infection according to World Health Organization (WHO) risk classification 2, 3 or 4

12. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
13. Previous randomisation into the present study
14. Subjects, who in the opinion of the investigator, should not participate in the study
15. Subjects being recently extensively exposed to passive smoking or environmental LPS (eg, swine farms) as judged by the investigator
16. Previous participation in another LPS study during the last 12 months
17. Suspicion of Gilbert's syndrome
18. Structural abnormalities of the nose or nasal disorder symptomatic enough to cause significant nasal obstruction, as judged by the investigator

Date of first enrolment
01/03/2009

Date of final enrolment
31/12/2010

Locations

Countries of recruitment
Sweden

Study participating centre
Department of Clinical Science, intervention and technology
Stockholm
Sweden
14186

Sponsor information

Organisation
AstraZeneca (Sweden)

ROR
https://ror.org/04wwrrg31

Funder(s)

Funder type
Industry

Funder Name

AstraZeneca (Sweden)

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics, AZ

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/04/2012		Yes	No