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An Evaluation of the Effects of Roflumilast on Cardiac Repolarization, Pharmacokinetics, Safety, and Tolerability in Healthy Volunteers

Submission date
08/06/2010

Recruitment status
No longer recruiting

Registration date
17/06/2010

Overall study status
Completed

Last Edited
10/05/2012

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

Protocol serial number
A5821023

Study information

Scientific Title
A Single Centre, Randomised, Placebo- and Active-Controlled, Parallel-Group Study to Investigate the Effects of Roflumilast on Cardiac Repolarization, Pharmacokinetics, Safety, and Tolerability in Healthy Volunteers

Study objectives
The study hypothesis is that supra-therapeutic doses of roflumilast (a phosphodiesterase 4 inhibitor under investigation for treatment of Chronic Obstructive Pulmonary Disease [COPD]) have no effect on cardiac repolarization in healthy subjects.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved by the Institutional Review Board(s) (IRB) at PPD Development Clinics, 706B Ben White Blvd, West Austin, Texas, USA on the 9th of December 2004.

Study design
Single centre randomised placebo and active controlled parallel group Phase I study in 2 cohorts

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
On Day 1, 80 healthy subjects (54 males, 26 females) received either oral moxifloxacin 400 mg (as a positive control for prolongation of QT/heart-rate corrected QT [QTc]) (n = 40) or placebo (n = 40). After a 1-day washout, participants received either placebo or ascending oral doses of roflumilast 500 ìg (therapeutic dose), 750 ìg or 1000 ìg, once daily, for 14, 7 and 14 days, respectively. QT intervals were measured from serial digital 12-lead electrocardiograms (ECGs) and corrected for heart rate with a Fridericia algorithm (QTcF). The primary endpoint was the largest mean time-matched change in QTcF from baseline (Day 1). Safety and tolerability were monitored.

The coordinating investigators for the study were:
1. Dr Thomas Lynn Hunt (MD; Principal Investigator)
2. Katherine L. Batiste (BS; sub-investigator)
3. Michael S. Benedict (BS; sub-investigator)
4. Katherine A. Day (BS; sub-investigator)
5. Dr David D Hoelscher (MD; sub-investigator)
6. Dr Laurent L Aziz (MD; sub-investigator)

Intervention Type
Drug

Phase
Phase I

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

Primary outcome(s)
Time-matched change from baseline in QTcF (Fridericias correction of the QT interval), calculated for each subject by subtracting the QTcF at each nominal time on the baseline day from the QTcF at the same nominal time on Days 1, 16 and 37.
Comparisons between active drug and placebo were made using a repeated analysis of covariance, performed with a significance level of á = 0.05. Point estimates and their 90% confidence intervals (CI) were calculated. The primary treatment/placebo comparisons were roflumilast 500 µg with placebo on Day 16 and roflumilast 1000 µg with placebo on Day 37. The primary comparison between moxifloxacin and placebo for clinical interpretation was at the moxifloxacin anticipated tmax, approximately 2 hours post-dose on Day 1. Pharmacokinetic parameters were summarized using descriptive statistics; effect of roflumilast on RR using time-matched change from baseline day; and effect of roflumilast on QRS using time-matched change from baseline day.

Key secondary outcome(s))
1. Effect of roflumilast on QTcB (QT interval corrected by Bazetts formula) using time-matched change from baseline day
2. Effect of roflumilast on QT (uncorrected QT interval) using time-matched change from baseline day
3. Effect of roflumilast on heart rate (VR) using time-matched change from baseline day
4. Effect of roflumilast on pulse rate using time-matched change from baseline day
5. Pharmacokinetics
6. Safety and tolerability

Completion date
11/04/2005

Eligibility

Key inclusion criteria
Subjects of any race were required to meet all of the following inclusion criteria to be eligible for enrolment into the study:
1. Healthy male and/or female subjects between the ages of 18 and 55 years, inclusive (healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination including blood pressure and pulse rate measurement, 12-lead ECG, and clinical laboratory tests [including magnesium])
2. Body mass index (BMI) of approximately 18 to 30 kg/m2 and a total body weight >50 kg (110 lbs)
3. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) had been informed of all pertinent aspects of the trial
4. Subjects who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group

Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Subjects with evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing)
2. Subjects with any condition possibly affecting drug absorption (eg, gastrectomy)
3. Use of any medication not considered acceptable by the clinical investigators during the 14-day period prior to the start of the study (Day 1)
4. Blood donation of approximately 1 pint (500 mL) within 56 days prior to dosing
5. Participation in a study of investigational or marketed drugs during the 30-day period before the start of the study (Day 1)
6. Known history of clinically significant adverse reaction to roflumilast, moxifloxacin, or quinolone antibiotics
7. Use of any medication known to induce or inhibit CYP3A4 or CYP1A2 during the 14-day period prior to the start of study (Day 1) until Closeout
8. Use of any tobacco containing products during the 14-day period prior to the start of the study (Day 1) until Closeout
9. Use of St. Johns wort during the 14-day period prior to the start of the study (Day 1) until Closeout 10. Consumption of grapefruit juice or food products containing grapefruit during the 7-day period prior to the start of study (Day 1) until Closeout
11. Consumption of caffeine-containing products 48 hours prior to the start of the study (Day 1) until Closeout
12. Subjects with a positive urine drug screen
13. History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks /week for men (1 drink = 5 oz of wine or 12 oz [360 mL] of beer or 1.5 oz [45 mL] of hard liquor) within 6 months of screening
14. Pregnant or nursing females or females of childbearing potential who were unwilling or unable to use acceptable methods of contraception from at least 14 days prior to the first dose of trial medication until completion of follow-up procedures
15. History of sensitivity to heparin or heparin-induced thrombocytopenia
16. Evidence of hypomagnesemia
17. Clinically important or significant conduction abnormalities on ECG at Screening (including QTc intervals >430 msec for men or >450 msec for women)
18. Evidence or history of long QT syndrome
19. Subjects unwilling or unable to comply with the Lifestyle guidelines (Appendix A1, Final Protocol) and/or
20. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial

Date of first enrolment
15/12/2004

Date of final enrolment
11/04/2005

Locations

Countries of recruitment
Germany

United States of America

Study participating centre
Nycomed GmbH
Konstanz
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Sponsor information

Organisation
Pfizer Global Research and Development (USA)

ROR
https://ror.org/01xdqrp08

Funder(s)

Funder type
Industry

Funder Name
Pfizer Global Research and Development (USA)

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?
Results article	results	01/07/2011		Yes	No