

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

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		<input type="checkbox"/> Protocol
<b>Registration date</b> 17/06/2010	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan
		<input checked="" type="checkbox"/> Results
<b>Last Edited</b> 10/05/2012	<b>Condition category</b> Respiratory	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

Not provided at time of registration

## Contact information

### Type(s)

Scientific

### Contact name

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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 µg (therapeutic dose), 750 µg or 1000 µg, 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  $\alpha = 0.05$ . Point estimates and their 90% confidence intervals (CI) were calculated. The primary treatment/placebo comparisons were roflumilast 500  $\mu\text{g}$  with placebo on Day 16 and roflumilast 1000  $\mu\text{g}$  with placebo on Day 37. The primary comparison between moxifloxacin and placebo for clinical interpretation was at the moxifloxacin anticipated  $t_{\text{max}}$ , 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  $\text{kg}/\text{m}^2$  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

Germany

78467

## 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?
<a href="#">Results article</a>	results	01/07/2011		Yes	No