Safety, tolerability and pharmacokinetics of single and repeat ascending doses of CHF6001, a novel inhaled phosphodiesterase-4 inhibitor: two randomized trials in healthy volunteers

Fabrizia Mariotti, Mirco Govoni, Germano Lucci, Debora Santoro, Marie Anna Nandeuil

Supplementary material

Study 1

Inclusion criteria

Subjects had to meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Provided written informed consent prior to any study-related procedure
2. Healthy male Caucasian volunteers aged 18-55 years inclusive
3. Able to understand the study procedures and the risks involved, and had the ability to be trained to use the devices correctly and to generate sufficient peak inspiratory flow (minimum 60 L/min and optimum 120 L/min using the In-Check device)
4. Body mass index (BMI) between 18.0 and 30.0 kg/m^2 inclusive
5. Non- or ex-smokers who smoked <5 pack years (pack years = the number of cigarette packs per day × the number of years) and stopped smoking >1 year ago
6. Good physical and mental status, determined on the basis of the medical history and a general clinical examination
7. Vital signs: normal BP and HR in supine position (90≤ systolic BP ≤130 mmHg; 60≤ diastolic BP ≤85 mmHg; 45≤ HR ≤100 bpm; 36≤ body temperature ≤37.5°C)
8. 12-lead ECG with computerized protocol interpretation considered as normal (120≤ PR ≤210 ms; QRS ≤120 ms; QTcF or QTcB ≤450 ms)
9. Laboratory test results within the normal ranges; inclusion of subjects with values outside the normal ranges, which were not considered clinically significant and would not have interfered with the study drug assessment, was to be judged by the Investigator
10. Lung function measurements within normal limits: Forced expiratory volume (L) in 1 second (FEV_1) >80% of predicted for the subject's normal value, according to the European Community for Coal and Steel 1993 predicted values
11. Agreed, with their partner, to use two approved methods of contraception from the time of dose administration until 90 days after the last dose of study drug. Agreed not to donate sperm for 90 days after the last dose of study drug.
    Two or more of the following methods were acceptable and at least one barrier method was to be used: Surgical sterilization (i.e. bilateral tubal ligation, hysterectomy for females, vasectomy for males); Hormonal contraception (implantable, patch, oral); Barrier methods (condom or occlusive cap [diaphragm or

cervical vault caps] with spermicide); If the subject had been sterilized, one barrier method of contraception only was acceptable. Alternatively, abstinence was acceptable where it was in line with the subject's preferred and usual lifestyle. Reliable contraception was to be maintained throughout the study.

Exclusion criteria

The presence of any of the following excluded a subject from study enrollment:

1. Abnormal 24 h Holter ECG at screening, as defined in the Holter interpretative guidelines
2. Blood donation (≥450 mL) or blood loss within 8 weeks before inhalation of the study medication
3. Positive human immunodeficiency virus (HIV 1 or 2) immunology result
4. Positive results from the Hepatitis immunology which indicated acute or chronic Hepatitis B or Hepatitis C
5. Unsuitable veins for repeated venipuncture
6. History of substance abuse or drug abuse within 12 months prior to screening or a positive urine drug screen at screening
7. Clinically relevant abnormal laboratory values that suggested an unknown disease requiring further clinical investigation
8. Clinically significant and uncontrolled cardiac, hepatic, renal, gastrointestinal (GI), respiratory, endocrine, metabolic, neurologic, or psychiatric disorder that could have interfered with successful completion of the protocol
9. Participation in another clinical trial where investigation drug was received within 3 months prior to inhalation of the study medication
10. History of hypersensitivity to any of the excipients contained in the formulation used in the trial
11. Any drug treatment, prescribed or over-the-counter medicines as well as vitamins and homeopathic remedies etc., taken in the 14 days (2 months for enzyme-inducing or enzyme-inhibiting drugs e.g. phenobarbital) preceding the first intake of the study drug, with the exception of occasional paracetamol (maximum 2 g per day with a maximum of 10 g per 14 days)
12. Treatment within the previous 3 months to study entry with any drug known to have a well-defined potential for hepatotoxicity (e.g. isoniazide, nimesulide, ketoconazole)
13. Refused to abstain from alcohol, caffeine or grapefruit-containing foods or beverages, from 48 h prior to each intake of study medication until the end of confinement at the clinical center
14. Heavy caffeine drinker (>5 cups or glasses of caffeinated beverages e.g. coffee, tea, cola per day)
15. Positive urine test for cotinine

Study 2

Inclusion criteria

Subjects had to meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Provided written informed consent prior to any study-related procedure
2. Male or female Caucasian healthy volunteers aged 18-55 years, inclusive
3. Able to understand the study procedures, the risks involved and had the ability to be trained to use the device correctly and to generate sufficient PIF (at least 40 L/min) using the In-Check device simulating NEXThaler® device, evaluated at screening

4. Body mass index (BMI) between 18.0 and 32.0 kg/m^2, inclusive
5. Non-smokers or ex-smokers were eligible. Ex-smokers must have smoked <5 pack years (pack-years = the number of cigarette packs per day times the number of years) and had stopped smoking >1 year before the screening visit
6. In good physical and mental status, determined on the basis of the medical history and a general clinical examination
7. Vital signs:
   Subjects aged 18-45 years: Diastolic BP 40-90 mmHg, Systolic BP 90-140 mmHg

   Subjects aged 45-55 years: Diastolic BP 40-90 mmHg, Systolic BP 90-150 mmHg

   (as mean of three measures performed after at least 5 minutes of resting); checked at screening visit and Day -1

8. 12-lead digitized Electrocardiogram (12-lead ECG) considered as normal (40 bpm ≤ Heart rate ≤110 bpm;120 msec ≤ PR ≤ 210 msec; QRS ≤ 120 msec; QT interval corrected using Fridericia's formula (QTcF) ≤ 450 msec for males and ≤ 470 msec for females) checked at screening visit and Day -1
9. Lung function measurements within normal limits: FEV1 >80% of predicted normal value (according to the Global Lung Function Initiative, ERS Task Force Lung Function Reference Values) and FEV1/forced vital capacity (FVC) ratio >0.70
10. Male subjects: they and/or their partner of childbearing potential must have been willing to use two reliable methods of contraception** from the time of dose administration and until 90 days after the last dose of study drug. Subjects were not to donate sperm for 90 days after the last dose of study drug
11. Female subjects: women not of childbearing potential, defined as post-menopausal women having at least 12 months of natural (spontaneous) amenorrhea and women permanently sterilized (e.g. hysterectomy, bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation). Women of childbearing potential (defined as all women physiologically capable of becoming pregnant) providing they and/or their partner use two reliable** methods of contraception;
    **Reliable methods of contraception for male and female subjects and/or their partner of childbearing potential, if applicable, must have been at least two of the following methods: a) Male sterilization; b) Placement of an intrauterine device (IUD) or intrauterine system (IUS); c) Hormonal contraception (implantable, patch, oral, injectable); d) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical vaults/caps) with spermicidal foam/gel/film/cream/suppository.

    Abstinence was acceptable where it was in line with the subject's preferred and usual lifestyle.

    Two reliable forms of contraception were to be maintained throughout the study duration and for the following three months.

Exclusion criteria

The presence of any of the following excluded a subject from study enrolment

1. Clinically significant abnormal 24 hours Holter ECG at screening as defined in the Holter interpretative guidelines
2. History of sustained and non-sustained cardiac arrhythmias (ECG demonstrated) and family history of sudden cardiac death
3. Blood donation or blood loss (equal or more than 450 mL) less than 8 weeks prior to screening
4. Female subjects: pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until the termination of the gestation, confirmed

by a positive serum human chorionic gonadotropin laboratory test (>5 mIU/mL). Serum pregnancy test performed at Screening and on Day -1
5. Positive human immunodeficiency virus (HIV)1 or HIV2 serology
6. Positive results from the Hepatitis serology which indicated acute or chronic Hepatitis B or Hepatitis C
7. Clinically relevant and uncontrolled hepatic, gastrointestinal, endocrine, metabolic, neurologic, or psychiatric disorder that may have interfered with successful completion of this study
8. Any clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further clinical investigation or which could impact the safety of the subject or the evaluation of the result of the study according to the Investigator's judgment
9. Unsuitable veins for repeated venipuncture
10. Had taken regular (or course of) medication, whether prescribed or not, including vitamins, homeopathic and herbal remedies such as St John’s Wort, in the 14 days before the screening visit with the exception of occasional paracetamol (maximum 2 g per day with a maximum of 10 g per 14 days) or any other medication not considered to interfere with the study objectives as agreed by the PI and Sponsor's medical expert
11. Had been treated within the 2 months prior to screening with enzyme-inducing or inhibiting drugs (e.g., glucocorticoids, phenobarbital)
12. Had been treated within the 3 months prior to screening with any drug known to have a well-defined potential for hepatotoxicity (e.g. isoniazid, ketoconazole)
13. History of substance abuse or drug abuse within 12 months prior to screening visit or with a positive urine drug screen evaluated at screening and at Day -1
14. Participation in another clinical trial where investigational drug was received less than 3 months prior to screening
15. The subject had a lower respiratory tract infection within 4 weeks before screening
16. History of hypersensitivity to any of the excipients contained in the formulation used in the trial
17. Refused to abstain from alcohol or caffeine containing foods or beverages or grapefruit containing foods or beverages from 48 hours prior to each intake of study medication until the end of confinement at the clinical center
18. Heavy caffeine drinker (>5 cups or glasses of caffeinated beverages e.g., coffee, tea, cola per day)
19. Had a positive urine test for cotinine at screening

Food and beverage restrictions

Subjects in both studies were not to consume beverages or food containing alcohol, xanthine or grapefruit from 48 h before the first study drug administration until the assessments were completed in each study period. Subjects in Study 1 were instructed to avoid lying down for 2 h after dosing, remaining seated as much as possible and avoiding strenuous activities. Subjects in Study 2 were to have no food intake from 10 h prior to study drug administration on Day 1 (both parts) and Day 14 (Part 2) until 2 h post-dose, and from 10 h prior to any safety assessment. Standardized breakfast and lunch were served at 2 and 4 h post-dose. Subjects in Study 2 were also to avoid strenuous activities within 24 h prior to the screening visit until the end of each visit, and were to have no fluid intake from 1 h prior to study drug administration on Day 1 (both parts) and Day 14 (Part 2) until 1 h post-dose, after which timepoint they were to drink at least 240 mL of water every 2 h for the following 6 h.