A Phase 2, Randomized, Double-blind, Placebo-controlled, Efficacy and Safety Study of Inhaled JNJ-49095397 (RV568) in Subjects With Moderate to Severe Chronic Obstructive Pulmonary Disease

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Primary ObjectiveThe primary objective is to assess the efficacy (as measured by change from baseline in prebronchodilator [preBD] percent predicted forced expiratory volume in one second [FEV1]) of JNJ-49095397 compared with placebo in subjects...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory tract infections
Study type	Interventional

Summary

ID

NL-OMON40384

Source
ToetsingOnline

Brief title
Phase 2 trial in COPD patients with medication JNJ-49095397 (RV568)

Condition

- Respiratory tract infections

Synonym
chronic lung inflammation, COPD

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: JNJ-49095397 (RV568), moderate to severe COPD patients, Phase 2

Outcome measures

Primary outcome

The primary endpoint is the change from baseline in preBD percent-predicted FEV1 at Study Visit 7 (Week 12).

All efficacy analyses will be performed on the modified intent-to-treat (mITT) analysis set. The mITT analysis set will include all randomized subjects who receive at least 1 dose of study agent and have at least 1 post-treatment efficacy measurement.

To address the primary objective, the primary endpoint will be analyzed by using an analysis of covariance (ANCOVA) model, which includes treatment, ICS usage at baseline as fixed factors, and baseline preBD percent-predicted FEV1 as a covariate.

Secondary outcome

Major Secondary Endpoints

- Change from baseline in postBD FEV1 (expressed as percentage of predicted) at Study Visit 7 (Week 12)

- Change from baseline in weekly average number of occasions in a day that

rescue medication is used at Study Visit 7 (Week 12)

The weekly average is based on the last 7 days prior to a visit.

-Change from baseline in E-RS* at Study Visit 7 (Week 12) Study Visit 7 E-RS* is defined as the average of the E-RS* assessments in the last 7 days prior to Study Visit 7. Baseline will be the average of last 7 days pretreatment assessments.

-Change from baseline in the total score of the SGRQ-C at Study Visit 7 (Week 12)

All major secondary endpoints will be analyzed with the same ANCOVA model as that for the primary

endpoint.

Other Endpoints

-Change from baseline in other spirometry assessments as measured in the clinic (pre- and postBD peak expiratory flow rate (PEFR), preBD and postBD FVC, forced expiratory flow at 25% and 75% of vital capacity (FEF25-75%), FEV1/FVC ratio

- Change from baseline in weekly average of daytime and night-time symptoms, and weekly average number of occasions in a day that rescue medication is used

- Change from baseline in weekly average of daytime and night-time domiciliary peak flow measurements

- Number of protocol-defined moderate or severe COPD exacerbations and time to the first moderate or severe exacerbation

- Number, intensity and duration of COPD exacerbation events as reported

through EXACTPRO*

-PGIC and proportion of subjects in each response category

Exploratory Endpoints

- Changes in systemic markers of inflammation.

-Changes in lung biomarkers of inflammation.

-Changes in measures of static lung function as measured by plethysmography in

a subgroup of COPD subjects (FRC, residual volume [RV], IC, sGaw, TLC).

Study description

Background summary

JNJ-49095397 (also known as RV568 or R605020) is a narrow-spectrum kinase inhibitor (NSKI) that inhibits the serine/threonine p38 mitogen activated protein kinases (MAPK) and tyrosine kinase Src. JNJ-49095397 has been demonstrated to inhibit inflammatory responses such as those induced by cigarette smoke (the major cause of chronic obstructive pulmonary disease [COPD]) and respiratory viruses (the major cause of COPD exacerbations) which are resistant to corticosteroid inhibition.

Chronic treatment with JNJ-49095397 via delivery to the lungs is expected to reduce the ongoing inflammation, improve airflow limitation and symptoms in the short term, and reduce the occurrence of COPD exacerbations in the long term.

Study objective

Primary Objective
The primary objective is to assess the efficacy (as measured by change from baseline in prebronchodilator [preBD] percent predicted forced expiratory volume in one second [FEV1]) of JNJ-49095397 compared with placebo in subjects with symptomatic moderate (GOLD Grade II) to
severe (GOLD Grade III) COPD.

Secondary Objectives
-To assess the effect of JNJ-49095397 on additional lung function parameters, health-related quality of life, rescue medication usage, and COPD symptoms in

subjects with symptomatic moderate to severe COPD.
-To assess the safety and tolerability of JNJ-49095397 compared with placebo in subjects with symptomatic moderate to severe COPD.
- To characterize the steady-state pharmacokinetics (PK) of JNJ-49095397 in subjects with symptomatic moderate to severe COPD.

The exploratory objectives are:
-To explore the effect of JNJ-49095397 compared with placebo on nasal and lung biomarkers of inflammation in COPD subjects.
- To explore the effect of JNJ-49095397 compared with placebo on measures of static lung function by plethysmography in a subgroup of COPD subjects. (With subgroup are those patients meant who come to the sites where there is the possibility of plethysmography)

-To explore the pharmacokinetic/pharmacodynamics (PK/PD) relationship with respect to clinical efficacy as appropriate.
-To explore the effect of JNJ-49095397 compared with placebo on systemic markers of inflammation

Study design

This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group study. Approximately 200 subjects will be randomized at approximately 40 investigational sites with 100 subjects planned per treatment group.

This is a proof-of-concept study designed to assess the efficacy and the safety of daily inhalation of JNJ-49095397 for 12 weeks in subjects >=40 and <=80 years of age with a diagnosis of symptomatic moderate to severe COPD defined as having a postbronchodilator (postBD)
percent-predicted FEV1 >=40% to <80% and a FEV1/FVC <0.70. Eligible subjects will be randomly assigned in a 1:1 ratio to receive JNJ-49095397 400 µg or placebo daily for 12 weeks. Randomization will be stratified by baseline ICS use (Yes or No).

An Independent Data Monitoring Committee (DMC) will be commissioned for this study

A pharmacogenomic (PG) blood sample will be collected from subjects who consent separately to this component of the study. Subject participation in PG research is optional.

The maximum duration of the study for each subject will be approximately 19 weeks (approximately 3 weeks of screening with 12 weeks of active treatment and 4 weeks of follow-up).

Intervention

Eligible subjects will be randomly assigned in a 1:1 ratio to receive JNJ-49095397 400 µg or placebo daily for 12 weeks. Subjects will self-administer study agent daily at home except on those days when a study site visit is scheduled. On the days when a study visit is scheduled, subjects will administer that dose at the study site

Study burden and risks

Burden:
1) 8 visits during 19 weeks
2) 10 bloodsamples during 19 weeks

Risks:
1) Adverse events standard of care
2) Adverse events JNJ-49095397 (RV568)
3) Side effects from testing
4) Unknown risks

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Be 40 to 80 years of age, inclusive.;2. Has a body mass index (BMI) <=35.0 kg/m2 at Study Visit 1.;3. Have moderate (Grade II) or severe (Grade III) COPD according to the GOLD Guidelines at Study Visit 1 as determined by a physician.;4. Have a diagnosis of chronic bronchitis (defined as sputum production on most days for
at least 12 weeks per year for at least 2 successive years) reported by the subject at Study Visit 1.;5. Be able to meet at least 1 of the following 2 criteria:
* Have had at least 2 COPD exacerbations requiring antibiotics and/or systemic corticosteroids in the past 2 years, OR
* Be able to spontaneously produce an adequate sputum sample at Study Visit 1 or Study Visit 2.;6. Be a current or ex-smoker who has a smoking history of at least 10 pack-years
(10 pack-years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years, etc.) at Study Visit 1.;7. Have a percent-predicted postBD FEV1 >=40% and <80%, and a postBD FEV1/FVC
<0.70 at Study Visit 1.;8. Have a postBD FEV1 >500 mL at Study Visit 1.;9. Have been treated with stable doses of a LABA and/or a LAMA bronchodilator alone or
in combination with ICS for at least 4 weeks prior to Study Visit 1.;10. Have COPD symptoms that required *as needed* use of a short-acting rescue medication
within the past 4 weeks at Study Visit 1.;11. Has a chest radiograph report available within 6 months prior to Study Visit 1 or a chest
radiograph performed at Study Visit 2 that does not show any abnormality suggestive of a malignancy or current active infection.;12. Have results of the following laboratory tests from Study Visit 1 performed at the
central laboratory that are within the limits specified below. Note: the investigator may consider the subject eligible if the previously abnormal laboratory test result is within normal range on a repeat test in the central laboratory. Only 1 repeat testing is allowed.
* Serum ALT levels: <=1.5 x ULN
* Total bilirubin level: <=1.5 x ULN
* Hemoglobin: >=10 g/dL (International System of Units [SI]: >=100 g/L)
* Serum glucose: <250 mg/dL
* White blood cells: *3.0 x 103 cells/mm3 (SI: *3.0 x109 cells/L)
* Platelets: >=100 x 103 cells/mm3 (SI: 100 x 109 cells/L)
* Neutrophils: >=1.5 x 103 cells/mm3 (SI: 1.5 x 109 cells/L)
Except the tests specified above, if the results of other clinical laboratory tests (including serum chemistry, hematology, and urinalysis) are outside the normal reference ranges, the subject must be medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or

urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be promptly reported to the sponsor*s medical monitor and recorded in the subject's source documents and initialed by the investigator.;13. Before randomization, a woman must be either:
* Not of childbearing potential; postmenopausal (>40 years of age with amenorrhea for at least 18 months or >40 years of age with amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level >40 IU/mL); or
* Permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral oophorectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy.;14. A woman must have a negative serum (*-human chorionic gonadotropin [*-hCG]) at
Study Visit 1.;15. A man who is sexually active with a woman of childbearing potential and has not had a
vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository during the study and for 6 months after receiving the last dose of study drug, and all men must also not donate sperm during the study and for 6 months after receiving the last dose of study drug.;16. Subjects must demonstrate the ability to use the study DPI device properly at Study Visit 1.;17. Subject must be willing and able to adhere to the prohibitions and restrictions specified
in this protocol including prohibited medications (see exclusion criterion 4 and Section 8) throughout the study until the end of the treatment period.;18. Each subject must sign an informed consent form (ICF) indicating that he or she
understands the purpose of and procedures required for the study and are willing to participate in the study.;19. Each subject must sign a separate informed consent form if he or she agrees to provide
optional DNA samples for research (where local regulations permit). Refusal to give consent for the optional DNA research samples does not exclude a subject from participation in the study.;In addition, to be randomized, subjects must meet the following additional criteria at Study
Visit 3.:
20. At Study Visit 3, have not experienced a significant worsening of COPD based on symptoms, daily diaries, and spirometry (in the opinion of the investigator) between Study Visit 1 and Study Visit 3.;21. Have a postBD percent-predicted FEV1 >=38% and <80% and >500 mL at Study Visit 3.;22. At Study Visit 3, have not had a COPD exacerbation requiring antibiotics and/or
systemic steroids or a change in COPD maintenance medications (except short acting bronchodilators) during the Screening Period (Study Visit 1 to Study Visit 3 [prior to randomization]).;23. At Study Visit 3, have not taken any disallowed therapies as noted in exclusion
criterion 4 before the planned first dose of study agent.;24. Have not had an upper or lower respiratory infection from Study Visit 1 through Study
Visit 3.;25. At Study Visit 3, have complied with all study procedures since signing of the informed
consent.;26. Have acceptable compliance with the handheld electronic device usage in the

last 7 days
prior to Visit 3, which should be at least 78% (>=11 out of 14 maximal times of use in 7 days). Lack of compliance due to mechanical malfunction of the device or other unusual, uncontrollable circumstances based upon the investigators* judgment will not be considered as non-compliance. In such cases, the screening period may be extended up to 7 days for subjects to demonstrate acceptable compliance (see Section 9.1.3).

Exclusion criteria

1. Has another pulmonary disease (eg, asthma, clinically significant bronchiectasis, cystic fibrosis, sarcoidosis, interstitial lung disorder, moderate or severe sleep apnea or pulmonary hypertension) at Study Visit 1.;2. Has an active infection, including histoplasmosis or coccidioidomycosis, tuberculosis
(TB), or non-tuberculous mycobacterial infection at Study Visit 1.;3. Has experienced life-threatening COPD (eg, requiring intensive care unit [ICU]
admission, intubation, or long-term non-invasive ventilation). Short-term (less than five days), non-invasive ventilation during a hospitalization for an acute exacerbation of COPD is permitted, provided that non-invasive ventilation was not continued at home.;4. Has taken any of the following COPD medications within the specified time prior to
Study Visit 1:
* Oral PDE-4 inhibitors (eg, roflumilast) within 2 weeks prior to Study Visit 1.
* Oral bronchodilators (eg, albuterol) within 2 weeks prior to Study Visit 1.
* Leukotriene modifying agents (eg, montelukast, zileuton) within 2 weeks prior to Study Visit 1.
* Prescription xanthines (eg, theophylline, aminophylline) within 2 weeks prior to Study Visit 1.
* Oral and IV corticosteroids for any indication within 6 weeks prior to Study Visit 1
* Intramuscular (IM) depot corticosteroids for any indication within 12 weeks prior to Study Visit 1.
* Cytotoxic/immunosuppressant/immunomodulatory agents within 12 weeks prior to Study Visit 1.
* Monoclonal antibodies (eg, omalizumab) within 12 weeks prior to Study Visit 1.
* Continuous antibiotic use within 4 weeks prior to Study Visit 1.;5. Has had any of the following respiratory tract conditions within the specified time
interval:
* COPD exacerbation that required systemic corticosteroids and/or antibiotics or required hospitalization within 6 weeks prior to Study Visit 1, or
* Upper or lower respiratory tract infection (including common cold, sinusitis, pneumonia) within 6 weeks prior to Study Visit 1.;6. Has COPD related to α-1 antitrypsin deficiency according to medical history at Study
Visit 1.;7. Is participating in the active phase of a supervised pulmonary rehabilitation program at
Study Visit 1.;8. Has right heart failure or an oxygen saturation (SpO2, as measured by pulse oximetry)

less than 90% at rest on room air at Study Visit 1 or requires oxygen therapy on a daily basis (>12 hours/day) for chronic hypoxemia at Study Visit 1.;9. Has had a lung lobectomy, lung cancer surgery, surgical or nonsurgical lung volume
reduction, or a lung transplant.;10. Has a clinically significant ECG abnormality at Study Visit 1 (eg, prolongation of the
QTc interval >=450 msec [either QTcB or QTcF, males or females], a history of risk factors for Torsade de Pointes such as persistent hypokalemia, or family history of long QT syndrome; or a history of second- or third-degree heart block).;11. Has had major surgery (eg, requiring general anesthesia) within 6 weeks before
Study Visit 1, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study.
Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.;12. Has a transplanted organ (with the exception of a corneal transplant performed more
than 3 months prior to Study Visit 1).;13. Has donated blood or has had a blood loss of more than 400 mL within 4 weeks prior to
Study Visit 1 or plans to donate blood during the study.;14. Has a recent history (within 12 months prior to Study Visit 1) of uncontrolled, chronic
disease including, but not limited to, cardiovascular, endocrine, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological, psychiatric, metabolic disturbances, or ophthalmic diseases that the investigator believes are clinically significant. In case of doubt, the investigator should discuss with the medical monitor.;15. Has any condition that, in the opinion of the investigator, would make participation in the study not be in the best interest (eg, compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments.;16. Has positive serology to human immunodeficiency virus (HIV)-1 or HIV-2, hepatitis B
virus , or hepatitis C virus (HCV) at Study Visit 1.;17. Has any history of malignancy at Study Visit 1 with the exceptions of:
* basal cell carcinoma or squamous cell carcinoma in situ of the skin that has been treated with no evidence of recurrence within 6 months prior to Study Visit 1, or
* squamous cell carcinoma (not in situ) or cervical carcinoma in situ that has been treated with no evidence of recurrence within 5 years prior to Study Visit 1.;18. Has known allergies, hypersensitivity, or intolerance to JNJ-49095397 (RV568) or its
excipients (refer to the latest version of the Investigator's Brochure and Addenda for JNJ-49095397.;19. Has previously received JNJ-49095397 (RV568).;20. Has received an investigational drug (or investigational vaccines) or used an invasive
investigational medical device within 5 half-lives (or 3 months if the half-life is unknown) before the planned first dose of study drug, plans to enroll, or is currently enrolled in an investigational study.;21. Is a woman who is breast-feeding while enrolled in this study or within 12 weeks after
the last dose of study drug.;22. Is a man who plans to father a child while enrolled in this study or within 6 months after
the last dose of study drug.;23. Has, or has had, a substance abuse (drug or alcohol) problem within the previous 3 years
at Study Visit 1.;24. Is, in the opinion of the investigator, known to be unreliable or noncompliant.;25. Is an employee of the investigator or study site, with direct involvement in the proposed

study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-01-2014
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO Date:	19-09-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-11-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	18-11-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-11-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-02-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-005184-27-NL
ClinicalTrials.gov	NCT01867762
CCMO	NL45628.056.13