Randomized, double-blind, placebo-controlled, multicenter study comparing Ciprofloxacin DPI 32.5 mg BID intermittently administered for 28 days on / 28 days off or 14 days on / 14 days off versus placebo to evaluate the time to first pulmonary exacerbation and frequency of exacerbations in subjects with non-cystic fibrosis bronchiectasis.

Published: 27-02-2014
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Page 18 of the protocol (v1.0, 4-Nov-2013):The primary objectives of this study are:- To evaluate the efficacy of ciprofloxacin DPI administered BID intermittently for 28 days on study treatment / 28 days off study treatment or 14 days on study…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON41580

Source
ToetsingOnline

Brief title
Respire 2

Condition

- Bronchial disorders (excl neoplasms)

Synonym
non-cystic fibrosis bronchiectasis

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Verrichter

Intervention

Keyword: Ciprofloxacin, Dry Powder Inhalation, Non-cystic fibrosis bronchiectasis, Pulmonary exacerbation

Outcome measures

Primary outcome

Paragraaf 8.3.1.1 - Primary efficacy variable

The primary efficacy variable is the time to first acute exacerbation requiring

an intervention with systemic antibiotics for the US NDA, and frequency of

exacerbations requiring an intervention with systemic antibiotics over 48 weeks

after start of treatment for the EU MAA.

Secondary outcome

Protocol (v1.0, 4-Nov-2013):

Paragraph 8.3.1.2 - Secondary efficacy variablescondary efficacy variables

- Frequency of exacerbations over 48 weeks (US NDA) / Time to first

exacerbation (EU MAA)

- Apparent pathogen eradication present at baseline;

- Changes from baseline in the disease-specific PRO score SGRQ (symptoms component score);

- Occurrence of new pathogens not present at baseline;

- Changes from baseline in FEV1 (post-bronchodilator spirometry).

Confirmatory analyses for pathogen eradication, occurrence of new pathogens and lung function and SGRQ will be evaluated at end of the on-treatment part of the 6th cycle for subjects in the 28 day on/off regimen, at end of the on-treatment part of the 12th cycle for subjects in the 14 day on/off regimen.
Pathogen refers to the list of organisms as defined in Section 7.6.3.

Paragraph 8.3.1.3 - Other efficacy variables

Other efficacy variables are:

- Changes from baseline in the disease-specific PRO score QOL-B respiratory symptom domain;

- Number/time to exacerbation using different definitions of exacerbation (see Section 8.4.2.2)

- Changes from baseline in FVC and FEV1 / FVC (post- bronchodilator spirometry);

- Changes from baseline in inflammatory markers (hsCRP, Polymorphphonuclear leukocytes (PMN) count);

- Exploratory endpoint (at participating centers): Changes from baseline in sputum inflammatory markers IL 8 and MPO.

- Shift in minimal inhibitory concentration (MIC) over time

Paragraph 8.3.2 - Safety variables

- Occurrence of any AEs (including deaths and other SAEs);

- Occurrence of inhalation-induced bronchospasm on the day of the first

administration (defined as pre-post drop in FEV1 of *15% from baseline);

- Changes in safety laboratory values;

- Development of ciprofloxacin-resistant pathogenic bacterial isolates;

- Presence of NTM, and recurring / new pathogens.

Study description

Background summary

See paragraph 1.1 of the protocol (v1.0, 4-Nov-2013). Below some quotes of key phrases.

There is an unmet medical need to reduce the frequency of exacerbations in non-CF BE subjects through a long-term treatment targeting chronic respiratory tract colonization by potentially pathogenic bacteria. Inhaled antibiotic therapy has proven value in the treatment of chronic respiratory conditions such as CF.
[…]
Based on nonclinical, Phase I and Phase II data (Study 12965), ciprofloxacin DPI appears to be a suitable drug for chronic intermittent treatment of non-CF BE subjects.
[…]
Reducing the bacterial load in the airways may translate into a reduced inflammatory response and could contribute to an improved long-term prognosis.

Study objective

Page 18 of the protocol (v1.0, 4-Nov-2013):

The primary objectives of this study are:
- To evaluate the efficacy of ciprofloxacin DPI administered BID intermittently for 28 days on study treatment / 28 days off study treatment or 14 days on study treatment / 14 days off study treatment to prolong the time to first exacerbation requiring an intervention with systemic antibiotics in subjects

with non CF BE (as agreed with the US FDA(Food and Drug Administration)).
- To evaluate the efficacy of ciprofloxacin dry powder for inhalation (DPI) administered 2 times a day (BID) intermittently for 28 days on study treatment / 28 days off study treatment or 14 days on study treatment / 14 days off study treatment in reducing the frequency of pulmonary exacerbation requiring an intervention with systemic antibiotics in subjects with non-CF BE (as agreed with the EMA (European Medical Agency) /CHMP) within 48 weeks after start of treatment.

The secondary objectives of this study are:
- To assess pathogen eradication and acquisition of new pathogenic organisms not present at baseline;
- To assess the safety and tolerability of different long term regimen of ciprofloxacin DPI;
- To assess the improvement of quality of life by Saint George*s Respiratory Questionnaire (SGRQ);
- To assess changes in lung function as measured by change in FEV1.

Further objectives are:
- To assess the quality of life by Quality of Life-Bronchiectasis (QOL B) questionnaire;
- To assess the inflammatory response measured by the following inflammatory markers: high-sensitivity C-reactive protein (hsCRP), polymorphonuclear leukocytes (PMNs), interleukin-8 (IL-8), and myeloperoxidase (MPO).
- To assess the selection of resistant isolates in the different treatment groups.

Following pharmacokinetic sampling is planned (see also Section 14.4):
Plasma, sputum and fecal concentrations (in a subgroup of subjects) of ciprofloxacin will be determined during two study visits using a sparse sampling approach to avoid interference with study interventions related to the primary outcome parameters.
Pharmacokinetics (PK) samples will be drawn from approx. 40-50 subject selected at approx. 15-20 participating centers. All subjects will sign a separate ICF.

Study design

Relevant part of paragraph 4.1 of the protocol (v1.0, 4-Nov-2013):

This study is a prospective, international, multicenter, parallel-group, randomized, double blinded for treatment medication, placebo-controlled Phase III clinical study with 4 treatment arms comparing ciprofloxacin DPI 32.5 mg administered BID intermittently versus matching placebo in subjects with non CF BE. The study will not be blinded for the treatment regimen, i.e., 28 day on/off treatment versus 14 day on/off treatment.
After a screening period of a maximum of 4 weeks, eligible subjects will be randomized to treatment with either ciprofloxacin DPI 32.5 mg BID or matching

placebo; a treatment cycle will consist either of 28 days on-/ 28 days off-treatment or of 14 days on-/ 14 days off treatment. Initial screening failures may be re-screened one more time at the discretion of the PI.
All subjects will be treated with their cyclic regimen of study medication for 48 weeks. Each subject will be observed for a total follow-up time of 8 weeks after last dose. An end-of-study (EOS) visit will be performed after completion of the follow-up period.

Intervention

Either Placebo or ciprofloxacin DPI is administered. This is done bi-daily during a treatment cycle. Every treatment cycle is followed by a cycle without placebo or ciprofloxacin DPI treatment. Depending on which group the patient is assigned to, a cycle takes 14 or 28 days. In total there are thus 4 groups:
- ciprofloxacin DPI 14 days cycle
- placebo 14 days cycle
- ciprofloxacin DPI 28 days cycle
- placebo 28 days cycle

Study burden and risks

Paragraph1.2 of the Protocol (v1.0, 4-Nov-2013):

1.2 Benefit-risk assessment
Ciprofloxacin DPI is a novel therapeutic option in subjects with non-CF BE. No other inhaled antibiotic treatment is currently approved for the use in this target population. It is expected that ciprofloxacin DPI will lead to additional benefits to those from conventional treatment, especially by reducing the frequency of acute exacerbations in non-CF BE subjects chronically colonized with RBPs. Clinical safety information from Phase II studies of subjects with non CF BE and CF subjects showed that ciprofloxacin DPI 32.5 mg was well tolerated in both groups. Thus, the risk associated with participating in this Phase III study is considered low.
The benefit-risk balance of ciprofloxacin DPI in the target indication of non CF BE is favorable.

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) Age at least 18 years;;2) Proven and documented diagnosis of non-CF idiopathic or post-infectious BE by CT scan (conventional high resolution CT is considered the standard) including 2 or more lobes and dilated airways compatible with BE at initial diagnosis;3) Positive culture from an adequate sputum sample for Pseudomonas aeruginosa, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Streptococcus pneumoniae, Stenotrophomonas maltophilia or Burkholderia cepacia obtained at screening and with history >=2 documented exacerbations in the past 12 months.;4) Stable pulmonary status as indicated by FEV1 (percent of predicted) equal to or more than 30% and less than 90% (post-bronchodilator, if used as standard of treatment);;5) Stable regimen of standard treatment with:;o Bronchodilators, anticholinergics, inhaled corticosteroids, or mucolytics, if used as chronic treatment for BE, at least for the past 4 weeks prior to screening.;Subjects on maintenance therapy with low-dose systemic corticosteroids should be receiving 10 mg/day or less prednisolone equivalent at least for the past 4 weeks before the screening visit;;and/or;o Macrolides if used as chronic treatment for BE for at least 6 months prior to screening.;6) Sputum production on the majority of days;;7) Ability to follow the inhaler device instructions;;8) Ability to complete questionnaires;;9) Written informed consent;;10) Negative urine pregnancy test result for women of childbearing potential before first dose of study drug;;11) Women of childbearing potential and men must agree to use adequate contraception when sexually active. This applies from the time of signing of the informed consent form (ICF) until 3 months after the last study drug administration. Adequate methods of contraception include vasectomy, or condom use, diaphragm with spermicidal gel, coil

(intrauterine device), surgical sterilization, or oral contraceptives.

Exclusion criteria

1) FEV1 less than 30% or more or equal to 90% predicted (post-bronchodilator);;2) Active allergic bronchopulmonary aspergillosis (ABPA);;3) Active and actively-treated non-tuberculosis mycobacterial (NTM) infection or tuberculosis;;4) Diagnosis of common variable immunodeficiency (CVID);;5) Recent significant hemoptysis (300 mL or more or requiring blood transfusion) in the preceding 4 weeks before screening (and during the screening period);;6) Primary diagnosis of COPD;;7) Known CF and / or documented chronic bronchial asthma;;8) Administration of any investigational drug within 4 weeks before screening;;9) Medical history of allergies to quinolones or fluoroquinolones;;10) Women who are pregnant, lactating, or in whom pregnancy cannot be excluded;;11) History of tendon disorders related to quinolone treatment;;12) History of myasthenia gravis;;13) Concomitant administration of tizanidine while on study drug;;14) Systemic or inhaled antibiotic treatment for any indication within 4 weeks prior to the administration of study drug; except for chronic macrolide use (see section 6.9).;15) Systemic corticosteroids at more than 10 mg/day prednisolone equivalent for more than 14 days within 4 weeks prior to the administration of study drug;;16) If participating in or has participated in other investigational interventional studies within the previous 4 weeks before screening; ;17) Subjects with any other conditions (specifically those which are addressed in the warnings and precautions section of the IB) or clinically relevant laboratory findings that the investigator defines as not appropriate for enrollment of a subject into the study ;18) Previous assignment to treatment in this study (randomized in Study 15626); subjects who have participated in RESPIRE 1 will not be enrolled in RESPIRE 2.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-08-2014
Enrollment:	19
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not available yet
Generic name:	ciprofloxacin dry powder for inhalation (DPI)

Ethics review

Approved WMO Date:	27-02-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-04-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-05-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-09-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-01-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	19-01-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-05-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-06-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-12-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-03-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-04-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-04-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-08-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-09-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2013-004659-19-NL
ClinicalTrials.gov	NCT01764841
CCMO	NL47800.028.14