Pharmacokinetics and dose-ranging of tiotropium inhalation solution delivered from the Respimat inhaler in patients with Chronic Obstructive Pulmonary Disease (COPD)

Published: 20-08-2010
Last updated: 04-05-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON34309

Source
ToetsingOnline

Brief title
Tiotropium Respimat PK study 205.458

Condition

- Respiratory disorders NEC

Synonym
chronic bronchitis, emphysema

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: farmaceutische industie; Boehringer Ingelheim

Intervention

Keyword: COPD, efficacy, Inhalation solution and inhalation powder, Pharmacokinetics, Tiotropium

Outcome measures

Primary outcome

The systemic availability after inhalation of different tiotropium doses will

be assessed by the following primary endpointrs:

- Cmax,ss = maximum tiotropium concentration in plasma in steady state

condition,

- AUC(0-6),ss = area under the tiotropium concentration-time curve in plasma in

steady state condition for the time interval till 6 hours post inhalation.

Secondary outcome

Secundary study parameters (outcome of the study) are:

- pharmacokinetics of tiotropium in steady state condition (refer to page 48 of

the protocol): time interval between inhalation and the maximum tiotropium

concentration in plasma [t (max)], terminal elimination halflife (t 1/2), mean

residence time in the body after inhalation (MRTih), clearance (CL/F), volume

of distribution (Vz/F), fraction eliminated via the urine (fe), renal clearance

(CLr), plasma concentration just before inhalation of the last dose (Cpre),

minimum concentration in plasma (Cmin).

- pulmonary function parameters (refer to page 40 of the protocol): trough FEV1

and trough FVC (= value measured just before inhalation of the last dose), FEV1 AUC(0-6) en FVC AUC(0-6) (= areas under the FEV1 and FVC - time curves normalized for time), individual FEV1 and FVC values measured at all time points at the end of each 4-week period.

- safety endpoints: adverse events, continuous ECG recording (Holter during 6 hours) at the end of each period (only in patients participating in the pharmacokinetic assessments).

Study description

Background summary

An existing pharmacokinetic dose-response evaluation of tiotropium solution for inhalation (1.25 mcg - 20 mcg) in COPD is based on renal excretion; in this dose-response pulmonary function tests were also performed. The study included parallel groups and had a small number of patients per dose strenght, meaning that the statistical power could have been insufficient for a proper comparison of the different tiotropium doses. In addition, another comparative study (crossover design) was performed with tiotropium solution for inhalation and inhalation powder in which plasma samples were taken only 10 min after inhalation (refer to page 17 of study protocol).

In the present crossover study the systemic availability of tiotropium solution for inhalation (5 mcg) will be extensively investigated and compared with tiotropium inhalation powder (18 mcg) by frequent blood sampling, in particular in the first 40 min after inhalation. The study includes also two lower doses (1.25 mcg and 2.5 mcg) which could be relevant for future combination therapy with a long-acting sympathicomimetic agent. In addition to pharmacokinetics, pulmonary function tests will provide valuable information on the dose-response relationship in terms of efficacy in COPD.

Study objective

Tiotropium is available in the pharmacy as solution for inhalation (daily dose of 5 mcg) and as inhalation powder (daily dose of 18 mcg). The objective of the present study is to compare three doses of tiotropum solution for inhalation (daily dose of 1.25 mcg, 2.5 mcg and 5 mcg; the latter is the approved daily dose) with the approved daily dose of 18 mcg (inhalation powder) in terms of

pharmacokinetics (systemic availability), efficacy (improvement of lung function) and safety. The pharmacokinetics will provide important information on the systemic availability and renal excretion of tiotropium (following inhalation of different doses and a different formulation). Data on the dose-response relationship in terms of lung function improvement (FEV1, FVC) and systemic availability including the two lower tiotropium doses (as solution for inhalation) is in particular of importance for future combination therapy of tiotropium and other bronchodilators for the treatment of COPD.

Study design

The randomised, placebo-controlled crossover study exists of five 4-week treatment periods: 1 open-label period with inhalation powder (tiotropium 18 µg) and 4 double-blind periods with solution for inhalation (tiotropium 1.25 µg, 2.5 µg, 5 µg and placebo).

Intervention

4 double-blind and 1 open-label treatment periods (crossover);
- double-blind blind (solution for inhalation):
1. placebo (in the morning),
2. tiotropium 1.25 µg (in the morning),
3. tiotropium 2,5 µg (in the morning),
4. tiotropium 5 µg (in the morning),
- open-label (inhalation powder):
5. tiotropium 18 µg (in the morning).

Study burden and risks

Prior to the 5 treatment periods the patient will have to visit the clinic 2 times during the screening period. At the last visit in this period the first dose of study medication of the first treatment period will be inhaled. During the 5 treatment periods of in total 20 weeks the patient will have to visit the clinic 5 times for pulmonary function tests. In case the patient participates in the pharmacokinetic assessments, there are 5 additional visits in this period. Blood sampling (via a catheter) will be performed by an expereinced stud ynurse in order to avoid any burden . All visits are scheduled at the end of each 4- week period. After completion of the last treatment period there will be a final post-study visit.

During each treatment period patients will have active bronchodilator therapy (salmeterol or formoterol and if necessary salbutamol as rescue medication) in addition to the study medication (4 periods with tiotropium and 1 period with placebo). During the washout period of salmeterol and formoterol prior to each test-day salbutamol is allowed; possibly that during the washout period in the treatment period with placebo the patient may suffer from more complaints of

symptoms in case salbutamol provides insufficient relief.

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. All patients must sign an informed consent consistent with ICH-GCP guidelines and local legislations prior to any study-related procedures, including medication washout and restrictions.
2. Male or female patients 40 years of age or older.
3. Patients must be current or ex-smokers with a smoking history of at least 10 pack-years.
4. All patients must have a diagnosis of COPD (refer to page 22 of study protocol).
5. Patients must be able to perform technically acceptable pulmonary function tests.
6. Patients must be able to inhale medication in a competent manner from the Respimat and HandiHaler devices.

Exclusion criteria

1. Significant diseases other than COPD (refer to page 23 of study protocol).
2. Patients with a recent history of myocardial infarction.
3. Patients with any unstable of life-threatening cardiac arrhythmia requiring intervention or change in drug therapy during the past year.
4. Hospitalisation for cardiac failure during the past year.
5. Patients with a history of asthma or who have a total eosinophil count equal to or above 600/mm3.
6. Use of systemic corticosteroid medication at unstable doses (less than 6 weeks on stable dose) or at doses in excess of the equivalent of 10 mg prednisone per day or 20 mg every other day.
7. Pregnant or nursing women.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-11-2010
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	niet van toepassing

Generic name:	placebo inhalation solution
Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	tiotropium inhalation solution; 2 inhalations of 0.625 mcg
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	tiotropium inhalation solution; 2 inhalations of 1.25 mcg
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Spiriva 18 mcg, inhalation powder in hard capsules
Generic name:	tiotropium 18 mcg - inhalation powder
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Spiriva Respimat 2.5 microgram, inhalation solution
Generic name:	tiotropium inhalation solution; 2 inhalations of 2.5 mcg
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-08-2010
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	29-10-2010
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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	EUCTR2009-016251-21-NL
CCMO	NL33405.096.10