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Impact of DOxofylline compaRed tO THEOphylline in asthma: the DOROTHEO 2 study

Submission date	Recruitment status	[_] Prospectively registered
01/06/2018	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
06/06/2018	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
06/06/2018	Respiratory	

Plain English summary of protocol

Background and study aims
Doxofylline is a drug belonging to the class methylxanthines, which also include theophylline. Doxofylline has shown similar efficacy to theophylline in asthmatic patients but with significantly fewer side effects. Unlike other xanthines such as theophylline, doxofylline does not activate certain specific cellular receptors (i.e. adenosine receptors) and does not alter the movement of calcium into cells. These characteristics may account for the better safety profile of doxofylline compared to theophylline. Conversely, the anti-asthmatic effects of doxophylline involve other mechanisms, mainly reducing the activity of intracellular enzymes (i.e. phosphodiesterases). Thus, the aim of this study is to investigate the beneficial impact of doxofylline versus theophylline with regard to the efficacy and safety in asthmatic patients.

Who can participate?
Adult (over 16 years old) asthmatic patients

What does the study involve?
Participants are randomly allocated to receive oral treatment with placebo (dummy drug), doxofylline 400 mg or theophylline 250 mg, three times a day for 3 months. Lung function tests are carried out at day 1 and at weeks 2, 4, 6, 8, 10 and 12.

What are the possible benefits and risks of participating?
The possible benefits of participating in this study are the improvement in lung function, reduction in the rate of asthma attacks and reduced use of as needed bronchodilator therapy. The possible risks of participating in this study are the non-serious side effects of methylxanthine drugs such as headache, nausea, dyspepsia, insomnia, nervousness and vomiting.

Where is the study run from?
Bernstein Allergy Group, Cincinnati, OH (US); Allergy, Asthma & Immunology Center of Rochester, Rochester, NY (US); Cummins, Kozak, Gillman, & Ellis, Inc., Orange, CA (US); Pulmonary Association of Tampa, Tampa, FL (US); Clinical Research Center, New Orleans, LA (US); Medical Specialties Clinic, Duke South Hospita, Durham, NC (US); University of South Florida, Tampa, FL

(US); Clinical Physiology Associate, Fort Meyers, FL, (US); National Jewish Center for Immunology and Respiratory Medicine, Denver, CO (US); Allergy Associates, P.C., Colorado Springs, CO (US); Cleveland Clinic, Cleveland, OH (US); The Jackson Foundation, Madison, WI (US); Mountain Allergy and Asthma Associates, P.A., Asheville, NC (US); Piedmont Research Associates, Inc., Winston-Salem, NC (US); Chicago Center for Clinical Research, Chicago, IL (US); National Association for Clinical Research, Philadelphia, PA (US); Atlanta Allergy and Immunology Research Foundation, Atlanta, GA (US); Washington University School of Medicine Research Office, St. Louise, MO (US); Allergy & Asthma Research Center-Toledo, Sylvania, OH (US).

When is the study starting and how long is it expected to run for?
September 1990 to February 1997

Who is funding the study?
Roberts Pharmaceutical Corporation (USA)

Who is the main contact?
Dr Alberto Giraudi
alberto.giraudi@abcfarmaceutici.it

Contact information

Type(s)
Scientific

Contact name
Dr Alberto Giraudi

Contact details
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
30,722-302D

Study information

Scientific Title

A double-blind Phase III evaluation of doxofylline, theophylline, and placebo in patients with chronic reversible asthma

Acronym
DOROTHEO 2

Study objectives
Doxofylline [2-(7'-theophylline-methyl)-1,3-dioxolane] is a methylxanthine derivative with the presence of a dioxolane group in position 7. As a drug used in the treatment of asthma, doxofylline has shown similar efficacy to theophylline but with significantly fewer side effects in animal and human studies. Unlike other xanthines, doxofylline lacks any significant affinity for adenosine A1 or A2 receptors and does not produce stimulant effects. Decreased affinity for adenosine receptors may account for the better safety profile of doxofylline compared to theophylline. Unlike theophylline, doxofylline does not affect calcium influx and does not antagonize the actions of calcium channel blockers which could explain reduced cardiac adverse reactions associated with the drug. The anti-asthmatic effects of doxophylline are mediated by other mechanisms, primarily through inhibiting the activities of the phosphodiesterase (PDE) enzymes.

Therefore, the hypothesis of this study was that doxofylline may have the same efficacy profile of theophylline, and that doxofylline may have a greater safety profile compared to theophylline in patients with asthma.

Ethics approval required
Old ethics approval format

Ethics approval(s)
The study protocol was reviewed and approved by Institutional Review Boards (IRBs) at the following study sites:
Bernstein Allergy Group, Cincinnati, OH (US); Allergy, Asthma & Immunology Center of Rochester, Rochester, NY (US); Cummins, Kozak, Gillman, & Ellis, Inc., Orange, CA (US); Pulmonary Association of Tampa, Tampa, FL (US); Clinical Research Center, New Orleans, LA (US); Medical Specialties Clinic, Duke South Hospita, Durham, NC (US); University of South Florida, Tampa, FL (US); Clinical Physiology Associate, Fort Meyers, FL, (US); National Jewish Center for Immunology and Respiratory Medicine, Denver, CO (US); Allergy Associates, P.C., Colorado Springs, CO (US); Cleveland Clinic, Cleveland, OH (US); The Jackson Foundation, Madison, WI (US); Mountain Allergy and Asthma Associates, P.A., Asheville, NC (US); Piedmont Research Associates, Inc., Winston-Salem, NC (US); Chicago Center for Clinical Research, Chicago, IL (US); National Association for Clinical Research, Philadelphia, PA (US); Atlanta Allergy and Immunology Research Foundation, Atlanta, GA (US); Washington University School of Medicine Research Office, St. Louise, MO (US); Allergy & Asthma Research Center-Toledo, Sylvania, OH (US).

Lead centre ethics board: The Asthma Center, Philadelphia, PA, USA, 13/05/1991, ref: 30,722-302D-91

Study design
Multicenter double-blind randomized placebo-controlled Phase III clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Home

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Asthma

Interventions
Subjects were randomly assigned to one of the four treatment groups in blocks of three patients according to a computer-generated randomization schedule prepared by the sponsor.

Subjects were randomly assigned to receive oral therapy as follows: placebo, doxofylline 400 mg, or theophylline 250 mg. Each intervention was administered on a t.i.d. regimen for 3 months.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Doxofylline, theophylline

Primary outcome measure
The primary outcome was the forced expiratory volume in 1 s (FEV1). The derived variable that was considered for comparative assessments among treatments was the percent change in the 2 hours FEV1 value from the baseline value (T0, hour 0). The primary time point was the last observation that was reported for each subject during the double-blind treatment period (3 months). FEV1 values were measured by using pulmonary function tests (PFTs) at day 1 (T0) and after at week 2, week 4, week 6, week 8, week 10, week 12.

Secondary outcome measures
1. The secondary outcome variables were forced vital capacity (FVC), FEV1/FVC, forced expiratory flow during the middle half of the FVC (FEF25%-75%) and peak expiratory flow rate (PEFR). These outcomes were expressed as the percent change in the 2 hours values from the baseline value (T0, hour 0). The endpoint was the last observation that was reported for each subject during the double-blind treatment period (3 months). These secondary outcomes were measured by using PFTs at day 1 (T0) and after at week 2, week 4, week 6, week 8, week 10, week 12.
2. Secondary efficacy variables derived from the Medication/Symptom Diaries were asthmatic attack rate (total number of attacks divided by the total number of days on study medication),

albuterol use rate (total number of puffs divided by total number of days on study medication), average daily peak flow meter (PFM) rate, and global assessment. For the daily PFM rate, the percent change from baseline (T0) was calculated. For the remaining efficacy variables derived from the Medication/Symptom Diaries, the absolute change from baseline (T0) was determined. “Baseline” for these variables was defined as the value obtained from the diaries during the placebo run-in phase, after that these secondary outcomes were measured at week 2, week 4, week 6, week 8, week 10, week 12.
3. Safety was assessed by physical examinations, ECGs, and the recording of vital signs, laboratory test results, and adverse events. All clinical adverse events (AE) entered on the Case Report Forms (CRFs) were to be classified as to possible relation to study medication (not related, possibly related, definitely related, or unknown) and severity (mild, moderate, or severe). Also recorded for each AE were the start and stop dates, the action taken (none, study medication discontinued, or treatment prescribed), and the outcome (recovered, recovered with sequelae, under treatment, deceased, unknown, or ongoing). If a subject experienced an AE leading to withdrawal from the study, the investigator was to make an effort to have the subject return to the study center for examination and for obtaining a serum sample for drug level determination. The time and date of the last dose taken were to be entered into the CRF.

Overall study start date
14/09/1990

Completion date
10/02/1997

Eligibility

Key inclusion criteria
1. Males and nonpregnant females. Women of childbearing potential had to use acceptable methods of birth control and have a negative prestudy serum β-hCG pregnancy test. Acceptable methods of birth control were limited to vaginal or intrauterine contraceptive devices or agents and natural (postmenopausal) or surgical sterility. Abstention, oral contraceptives, and use of contraceptive by the woman’s partner were not acceptable methods of birth control
2. Age: adults, 16 years of age or older
3. Health status: nonsmokers for at least 6 months before entering the study, in good physical condition with a more than 1-year history of chronic, extrinsic reversible hyperreactive airway disease (asthma)
4. Willing to undergo the procedures required in the protocol
5. Willing to undergo a chest x-ray if required by the Principal Investigator
6. On screening, subjects must have had a baseline FEV1 value within 50% to 80% of the predicted FEV1 value for their age and height, when immediate-release theophylline or sustained-release theophylline had been withheld for at least 24 hours. Subjects were further required to have abstained from use of any sympathomimetic, including beta-agonist inhalers, for at least 8 hours before the screening pulmonary function tests (PFTs)
7. On screening, subjects had to show at least a 15% increase in FEV1 30 minutes after administration of a standard dose (2 puffs, 180 µg) of albuterol
8. Subjects must have demonstrated, by verbal history, a period of at least 1 month of acceptable clinical control of their asthma in the preceding 3 years using oral theophylline, alone or in combination with a beta-agonist inhaler
9. Subjects had to weight at least 48 kg (105 lb)

Participant type(s)

Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
150

Key exclusion criteria
1. Clinically significant deviation from normal in physical examination, laboratory parameters, ECG, or chest x-ray, as evaluated by the Principal Investigator, that would have precluded the subject's participation in the study
2. Clinically significant coexisting disease, including:
2.1. Clinically significant cardiovascular disease, including a history of congestive heart failure
2.2. Angina pectoris within 1 year
2.3. History of myocardial infarction within 1 year
2.4. Convulsive disorder
2.5. Clinically significant gastrointestinal disease, including active peptic ulcers within the preceding 5 years
2.6. Renal disease
2.7. Hepatic disease
2.8. Hematologic disease
2.9. Insulin-dependent diabetes mellitus
2.10. Nonreversible chronic pulmonary disease
2.11. Known infection with human immunodeficiency virus
2.12. Chronic obstructive pulmonary disease
3. Presence of any acute illness
4. Sensitivity to theophylline or theophylline-like agents
5. A resting heart rate of less than 50 bpm or greater than 100 bpm and/or an arterial blood pressure of less than 100/60 mmHg or greater than 140/90 mmHg when sitting
6. History of alcohol, narcotic, barbiturate, marijuana, or polydrug abuse
7. Participation in other investigational drug studies within 30 days before the start of this study
8. Subjects who were unlikely to be compliant with the protocol requirements
9. Oral contraceptive use was not allowed because of the propensity for these drugs to decrease theophylline clearance. If a woman became pregnant during the study, she was to be withdrawn from the study
10. Nursing mothers
11. Subjects using aerosol steroids were required to discontinue their use at least 1 month before the study and to refrain from using them throughout the entire study. Subjects using oral steroids to control bronchoconstriction were excluded from participation. Subjects using cromolyn sodium or oral steroids were required to discontinue their use at least 1 month before the study and to refrain from using them throughout the entire study, with the exception of acute steroid burst treatment

12. Due to their effects on theophylline clearance, none of the following could be taken during the study: allopurinol, ciprofloxacin, erythromycin, troleandomycin, lithium carbonate, phenytoin, rifampin, or cimetidine

Date of first enrolment
07/08/1991

Date of final enrolment
29/11/1994

Locations

Countries of recruitment
United States of America

Study participating centre
Bernstein Allergy Group
Cincinnati
45202

Study participating centre
Allergy, Asthma & Immunology Center of Rochester, P.C
Rochester
14620

Study participating centre
Cummins, Kozak, Gillman, & Ellis, Inc.
Orange
92868

Study participating centre
Pulmonary Association of Tampa
Tampa
33614

Study participating centre
Clinical Research Center
New Orleans
70119

Study participating centre
Medical Specialties Clinic, Duke South Hospital
Durham
27710

Study participating centre
University of South Florida
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4202 E Fowler Ave, Tampa, FL

Study participating centre
Clinical Physiology Associates
Fort Meyers
33912

Study participating centre
National Jewish Center for Immunology and Respiratory Medicine
Denver
80206

Study participating centre
Allergy Associates, P.C.
Colorado Springs
80920

Study participating centre
Cleveland Clinic
Cleveland
44113

Study participating centre
The Jackson Foundation
Madison
53703

Study participating centre

Mountain Allergy and Asthma Associates, PA
Asheville
28801

Study participating centre
Piedmont Research Associates, Inc.
Winston-Salem
27103

Study participating centre
Chicago Center for Clinical Research
Chicago
60634

Study participating centre
National Association for Clinical Research
Philadelphia
19114

Study participating centre
Atlanta Allergy and Immunology Research Foundation
Atlanta
30329

Study participating centre
Washington University School of Medicine Research Office
St. Louis
63110

Study participating centre
Allergy & Asthma Research Center-Toledo
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43617

Sponsor information

Organisation
Roberts Pharmaceutical Corporation

Sponsor details
Meridian Center II
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United States of America
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Sponsor type
Industry

Organisation
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Sponsor type
Industry

Website
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Organisation
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Sponsor details

Sponsor type
Not defined

Website
http://www.takeda.com/

ROR
https://ror.org/03bygaq51

Funder(s)

Funder type
Industry

Funder Name
Roberts Pharmaceutical Corporation

Funder Name
ABC farmaceutici

Results and Publications

Publication and dissemination plan
This study is planned to be published in a high-impact peer reviewed journal by 15/12/2018. Additional documents (study protocol and clinical study report) will be publically available by 15 /12/2018.

Intention to publish date
15/12/2018

Individual participant data (IPD) sharing plan
Dr Alberto Giraudi (alberto.giraudi@abcfarmaceutici.it; ABC Farmaceutici S.p.a., Canton Moretti 29, Ivrea (TO) Italy) can be contacted for accessing to the datasets. Available data include patient-by-patient variable recorded at each time-point and will be available for request in one year from the publication of the paper. Informed consent was obtained by all the participants of the study. Data will be shared merely for scientific purpose (i.e. post-hoc analyses, pooled analyses) with researchers employed at institutional research Departments, and that will apply a formal request to the scientific board of ABC Farmaceutici. Whether the scientific board will find that the proposed analysis will be consistent with the local ethics and legal rules, and that it could provide further evidences than those still published, the data will be released in agreement with patients anonymisation. The data will be available for one year from the date of publication in a high-impact peer reviewed journal.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		05/06/2018	06/06/2018	No	No