

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

<b>Submission date</b> 01/06/2018	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 06/06/2018	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 06/06/2018	<b>Condition category</b> Respiratory	<input type="checkbox"/> Individual participant data

## 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 doxofylline 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**  
Via Canton Moretti, 29  
Località San Bernardo, Ivrea (TO)  
Italy  
10090  
+39 (0)125 240111  
alberto.giraudi@abcfarmaceutici.it

## Additional identifiers

**Protocol serial number**  
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 doxofylline 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 Hospital, 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. Louis, 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

### **Primary study design**

Interventional

### **Study design**

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

### **Study type(s)**

Treatment

### **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(s)**

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.

## **Key secondary outcome(s)**

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.

**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  $\beta$ -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  $\mu$ g) 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

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

All

**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**  
Tampa  
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**  
Sylvania  
43617

## **Sponsor information**

**Organisation**  
Roberts Pharmaceutical Corporation

**Organisation**  
ABC farmaceutici

**Organisation**  
Takeda (United States)

**ROR**  
<https://ror.org/03bygaq51>

## **Funder(s)**

**Funder type**

Industry

**Funder Name**

Roberts Pharmaceutical Corporation

**Funder Name**

ABC farmaceutici

## Results and Publications

**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?
<a href="#">Basic results</a>		05/06/2018	06/06/2018	No	No