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# Assessing the long-term efficacy and safety of doxofylline in treating asthma

**Submission date**
28/03/2019

**Recruitment status**
No longer recruiting

**Registration date**
01/04/2019

**Overall study status**
Completed

**Last Edited**
05/04/2019

**Condition category**
Respiratory

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

## Plain English summary of protocol

Background and study aims
Doxofylline is a drug belonging to the class methylxanthines. Doxofylline has shown similar efficacy to theophylline in asthmatic patients but with significantly fewer side effects. Recent findings from two clinical trials (DOROTHEO1 and DOROTHEO2) performed in asthmatic patients and lasting 12 weeks showed that doxofylline has a favorable efficacy and safety profile, and that this drug provides a meaningful improvement of lung function. 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 specific characteristics may account for the favorable safety profile of doxofylline. The the main anti-asthmatic effects of doxophylline seems to be related with its activity on intracellular enzymes (i. e. phosphodiesterases). Thus, the aim of this study is to investigate the efficacy and safety profile of doxofylline administered for long time, up to one year, in asthmatic patients.

Who can participate?
Adult (over 18 years old) asthmatic patients

What does the study involve?
All participants received for 12 months oral doxofylline 400 mg three times daily . Lung function tests were carried out at day 1 and at months 1, 3, 6, 9, and 12.

What are the possible benefits and risks of participating?
The possible benefits may include increased lung function, reduced asthma events rate, and reduced use of albuterol, leading to an overall increased asthma control. The potential risks may include the occurrence of side effects, namely gastrointestinal symptoms (nausea, vomiting, gastrointestinal distress, stomach ache), tachycardia or palpitations, insomnia, and nervousness. In any case, the overall treatment benefits would overcome the symptoms related with the side effects.

Where is the study run from?
Allergy Associates, Inc., North Dartmouth, MA (US); Allergy, Asthma & Immunology Center of Rochester, Rochester, NY (US); International Medical Technical Consultants, Inc., Prairie Village, KS (US); Advanced Allergy & Asthma, Albany, NY (US); Pulmonary Associates, Philadelphia, PA

(US); Allergic Disease Associates, Philadelphia, PA (US); Doctors' Clinic Research Center, Vero Beach, FL (US); Pharmaco Health Research Center, Austin, TX (US); Cleveland Clinic, Cleveland, OH (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); Washington University School of Medicine Research Office, St. Louise, MO (US).

When is the study starting and how long is it expected to run for?
February 1992 to September 1994

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

### ORCID ID
https://orcid.org/0000-0003-0456-069X

### Contact details
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# Additional identifiers

### Protocol serial number
30,722-303C

# Study information

### Scientific Title
A Long-term clinical trial on the Efficacy and Safety profile of Doxofylline in Asthma: the LESDA study

### Acronym
LESDA

### Study objectives

Doxofylline may have a favorable efficacy and safety profile when administered for a longer time.

## Ethics approval required
Old ethics approval format

## Ethics approval(s)
Approved 19/11/1991, Northeast Medical Research Associates Institutional Review Board (49 State Road, Watuppa Building North Dartmouth, MA, USA 02747; 1-855-636-7287; study@nemra-us.com), ref: 30,722-303C-91.

## Primary study design
Interventional

## Study design
Multicenter, open-label, single-arm , phase III, clinical trial

## Study type(s)
Treatment

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

## Interventions
This is a single-arm study in which asthmatic patients received doxofylline 400 mg (Maxivent 400 mg, tablets; Lot # Dox-049-11/E) three times daily (t.i.d, drug administered at 8 hr interval) administered per os. The total duration of treatment was 12 months, and the follow up lasted 13 months

## Intervention Type
Drug

## Phase
Phase III

## Drug/device/biological/vaccine name(s)
Doxofylline

## Primary outcome(s)
Airway obstruction is measured using “FEV1, detected via pulmonary” function tests at day 1 and months 1, 3, 6, 9, 12.

## Key secondary outcome(s)
1. The change from baseline (T0, hour 0) in FEV1 values is measured “via pulmonary function tests” at months 1, 3, 6, 9 and 12.
2. Asthma events rate (total number of events divided by the total number of days on study medication), and albuterol use rate (total number of puffs divided by total number of days on study medication) are determined using Medication/Symptom Diaries at “months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12.”
3. Safety is assessed by physical examinations, ECGs, and the recording of vital signs, laboratory test results, and adverse events “(AE) at months 1, 3, 6, 9 and 12.”

3.1. All “clinical AE” entered on the Case Report Forms (CRFs) are classified as to possible relation to study medication (not related, possibly related, definitely related, or unknown) and severity (mild, moderate, or severe).
3.2. Also recorded for each AE are 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).
3.3. If a subject experiences an AE leading to withdrawal from the study, the investigator is to make an effort to have the subject return to the study centre for examination and obtain a serum sample for drug level determination. The time and date of the last dose taken is to be entered into the CRF.

### Completion date
04/06/1997

## Eligibility

### Key inclusion criteria
1. Males and non-pregnant females.
1.1. Women of childbearing potential had to use acceptable methods of birth control and have a negative prestudy serum β-hCG pregnancy test.
1.1.1. Acceptable methods of birth control were limited to vaginal or intrauterine contraceptive devices or agents and natural (postmenopausal) or surgical sterility.
2. 18 years of age or older.
3. Nonsmokers for at least 6 months before entering the study.
4. In good physical condition with a more than 1-year history of chronic, extrinsic reversible hyperreactive airway disease (asthma).
5. On screening, 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.
6. On screening, at least a 15% increase in FEV1 30 minutes after administration of a standard dose (2 puffs, 180 µg) of albuterol.
7. Stable dose of inhaled corticosteroids (ICS) and/or cromolyn sodium for at least 30 days was permitted. If ICS and/or cromolyn sodium was required during the study, it was recommended that a Doxofylline baseline level be achieved (minimum, 14 days) before the administration of any additional medications.

### 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. Cardiovascular disease, including a history of congestive heart failure, angina pectoris, or myocardial infarction within 1 year
2.2. Convulsive disorder
2.3. Gastrointestinal disease
2.4. Renal disease
2.5. Hepatic disease
2.6. Hematologic disease
2.7. Insulin-dependent diabetes mellitus
2.8. Nonreversible chronic pulmonary disease
2.9. Known infection with human immunodeficiency virus
2.10. 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, except the DOROTHEO1 (ISRCTN65297911) and DOROTHEO2 (ISRCTN22374987) that preceded this study.
8. Subjects using oral steroids or oral B2-agonists
9. Lactating females

### Date of first enrolment
19/02/1992

### Date of final enrolment
07/09/1994

## Locations

### Countries of recruitment
United States of America

### Study participating centre
**Allergy Associates, Inc.**
North Dartmouth
United States of America
02747

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

United States of America
14620

**Study participating centre**
**International Medical Technical Consultants, Inc.**
Prairie Village
United States of America
64108

**Study participating centre**
**Advanced Allergy & Asthma**
Albany
United States of America
12203

**Study participating centre**
**Pulmonary Associates**
Philadelphia
United States of America
United States of America

**Study participating centre**
**Allergic Disease Associates**
Philadelphia
United States of America
19107

**Study participating centre**
**Doctors' Clinic Research Center**
Vero Beach
United States of America
32960

**Study participating centre**
**Pharmaco Health Research Center**
Austin
United States of America
78705

**Study participating centre**
**Cleveland Clinic**
Cleveland
United States of America
44113

**Study participating centre**
**Piedmont Research Associates, Inc.**
Winston-Salem
United States of America
27103

**Study participating centre**
**Chicago Center for Clinical Research**
Chicago
United States of America
60634

**Study participating centre**
**National Association for Clinical Research**
Philadelphia
United States of America
19114

**Study participating centre**
**Washington University School of Medicine Research Office**
St. Louis
United States of America
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) 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 purposes (i. e. post-hoc analyses, pooled analyses) with researchers employed at institutional research departments who will make a formal request to the scientific board of ABC Farmaceutici. If the scientific board determine the proposed analysis is consistent with the local ethics and legal rules, and could provide further evidence than those 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 | | 30/03/2019 | 01/04/2019 | No | No |