FINAL STUDY REPORT (FSR)

1. Contents of The Final Study Report

1.1 Title Page

- **study title:** EFFICACY OF NEBULISED BECLOMETASONE VERSUS PLACEBO IN PREVENTING VIRAL WHEEZING IN PRE-SCHOOL CHILDREN
- **name of test drug or medical device**: beclometasone, Clenil® per aerosol (AIC 023103132)
- **non pharmacological treatment:** placebo
- **brief description of study design**

The study was designed as a two phase study: a randomized controlled trial (phase I) followed by a prospective observational study (phase II) The first phase had the aim to evaluate the effectiveness of beclometasone in preventing viral wheezing recurrence and in reducing symptom severity, while the second phase (observational follow-up) had the objective to monitor the incidence of viral wheezing recurrence and the different therapeutic approaches used by physicians.
A randomized, double blind, parallel group design was used to perform the phase I study.
Pre-school children with a history of viral wheezing attending family paediatricians for a viral upper respiratory tract infection were checked for inclusion and exclusion criteria. Children who fulfilled these criteria and whose parents agreed to participate the study were randomly assigned to receive beclometasone 400 mcg (study drug) or placebo twice daily for 10 days. The primary endpoint was the percentage of children with wheezing diagnosed by paediatricians and occurring during the 10 day treatment period.

- **codice FARM:** FARM7RANLZ
- **EudraCT:** 2009-011116-38
- **Phase:** IV
- **Date of contract:** 16/01/2009
- **Date of Ethic Committee approval:** 04/08/2009
- **Period covered:** 12/10/2010-2/10/2012
- **Name of report author(s):** Antonio Clavenna, Marco Sequi, Massimo Cartabia, Filomena Fortinguerra, Marta Borghi, Livio Garattini, and Maurizio Bonati
- **name, status and affiliation of principal / co-ordinating, investigator** Antonio Clavenna, MD, PhD, Researcher, Laboratorio per la Salute Materno Infantile, IRCCS - Istituto di Ricerche Farmacologiche “Mario Negri”, Milano

The study was conducted in compliance with the protocol, following the instructions and procedures described in it, and adhering to the principles of Good Clinical Practice.

1.2 Study Administration and Investigators

- **name and affiliation of principal investigator** Antonio Clavenna, Laboratorio per la Salute Materno Infantile, IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri", Milano

- **name, affiliation and role in the study of all other investigators** - 40 family paediatricians working in 9 local health units (3 in the North, 3 in the Centre, and 3 in the South of Italy) were involved in the study as investigators. See Appendix I for details.

- **name and affiliation of laboratories used in the study** : Not applicable

- **name and affiliations of all members of any committees involved with the study** e.g.- steering committee independent review committees for specific parameters such as ECGs, X-rays, CT scans etc.

  Steering Committee (scientific coordination): Antonio Clavenna, Maurizio Bonati, *Laboratorio per la Salute Materno Infantile, IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri", Milano*; Livio Garattini, *Centro di Economia Sanitaria Angelo e Angela Valenti, Ranica (BG);* Michele Gangemi, Paolo Siani, *Associazione Culturale Pediatri*

  Research Monitoring Committee: Giancarlo Biasini, *Centro Salute del Bambino*; Luca De Fiore, *Il Pensiero Scientifico Editore*; Roberta Di Turi, *Servizio Farmaceutico ASL RM/A;* Federico Marchetti, *Unità Operativa di Pediatria e Neonatologia, Azienda USL di Ravenna*; Gaia Marsico, *Università degli Studi di Padova*; Rossella Miracapillo, *Osservatorio Farmaci e Salute, Movimento Consumatori;* Ettore Napoleone, *Federazione Italiana Medici Pediatri;* Pietro Panei, *Istituto Superiore di Sanità;* Francesca Rocchi, *Agenzia Italiana del Farmaco e PDCO EMA;*Giacomo Toffol, *Associazione Culturale Pediatri*

  name and affiliation of contract pharmaceutical / research organisations: Unità di Gestione e Monitoraggio della Ricerca Clinica, Consorzio Mario Negri Sud, Santa Maria Imbaro (CH):

- name and address of relevant Sponsor study personnel – See appendix I

The CV of the Principal Investigator is included as Appendix II. CVs of investigators are available for review on request.

1.3 Table of Contents

1.4 List of Abbreviations and Definition of Terms

AED Adverse Drug Event

ADR Adverse Drug Reaction

CC Coordinating Centre

DCF Data Clarification Form

GCP Good Clinical Practice

IMP Investigational Medicinal Product

LHU Local Health Unit

SOP Standard Operative Procedure

URTI Upper Respiratory Tract Infection

2 SYNOPSIS

Title of Study: Efficacy of nebulised beclometasone versus placebo in preventing viral wheezing in pre-school children
Investigators: Principal Investigator: Dr. Antonio Clavenna, Laboratory of Mother and Child Health, Department of Public Health, IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri", via Giuseppe La Masa 19, 20156 Milano
Study centre location 9 Italian local health units (40 family paediatricians)
Study period (years): 2010 –2012
Phase IV
Name of the finished product: Clenil® per aerosol, Chiesi Farmaceutici SpA
Name of the active ingredient: Beclometasone
Objectives of the study. *Primary* To evaluate the efficacy of beclometasone in preventing wheezing in respiratory tract infection. *Secondary* To evaluate: - the efficacy of beclometasone in reducing symptom severity - the efficacy of beclometasone in reducing bronchodilator and/or corticosteroid use - the efficacy of beclometasone in reducing viral wheezing recurrence (during follow-up) - treatment compliance - parental opinion on the treatment - the cost-efficacy ratio of prophylactic treatment with beclometasone.
Methodology The study was designed as a two phase study: a randomized controlled trial (phase I) followed by a prospective observational study (phase II) A randomized double blind controlled parallel group design was used for the phase I study. Enrolled patients were randomly allocated to one of the following treatment groups: - beclometasone suspension 400 mcg twice daily - placebo twice daily Active drug and placebo were administered through a nebulizer, in the morning and in the evening. The duration of the treatment was 10 days. A 6-month observational follow up was performed to monitor the recurrence of respiratory tract infections and viral wheezing. Three visits were scheduled: the entry visit (T_0), the end of treatment visit (T_{0+}11 days), the final visit (T_{0+}180 days).
Number of subjects (planned, analysed): 576 planned (minimum 520), 525 analysed
Inclusion/exclusion criteria. *Inclusion criteria* - Outpatient children 1-5 years old. - Presence of any viral upper respiratory tract infection (URTI) symptoms - At least one episode of viral wheezing (diagnosed by a physician) in the last 12

months.
- No, or minimal, asthma-like symptoms in between separate airway infections.

Exclusion criteria
- Steroid hypersensitivity
- Inhaled and/or oral corticosteroid use in the preceding month
- Chronic respiratory disease (e.g. cystic fibrosis, broncho-pulmonary dysplasia)
- Presence of wheezing at the entry visit

Experimental drug: Beclometasone nebulised suspension 400 mcg administered twice daily (in the morning and in the evening) through a nebulizer

Duration of treatment: 10 days

Reference therapy: placebo

Outcome measures
Primary
a) % of children with wheezing (diagnosed by the paediatrician) during the URTI episode.
Secondary
b)% of patients with moderate/severe wheezing (score >=2 rated by paediatrician);
c) % of patients needing medical care during the treatment period;
d) % of patients receiving rescue medication during the treatment period;
e) % of patients admitted to an emergency department during the treatment period;
f) % of patients with an asthma-like symptom score (rated by parents) ≥ 7;
g) % of parents who consider the treatment helpful;
h) Duration of the respiratory tract infection episode;
i) Mean asthma-like symptom score for each child;
l) Time to the first viral wheezing episode after the end of the treatment;
m) Frequency of respiratory tract infection episodes during the 6 month follow-up period;
n) Frequency of viral wheezing episodes during the 6 month follow-up period;
o) % of patients fully adherent to therapy
p) average cost per patient

Statistical methodology
Analyses included all randomized children (intention to treat population).
The primary outcome measure, as well as the other categorical variables, were compared using the Chi-square test. Patients were stratified according to the number of previous viral wheezing episodes (<= 1 in the preceding 6 months; > 1 in the preceding 6 months).
The proportion of children with no symptoms of respiratory tract infection were compared using the Kaplan-Meier method. Repeated measures analyses of variance was performed to analyse change in the daily asthma-like symptom score. The number of respiratory tract infection episodes and the number of recurrences of viral wheezing during the 6 month follow up period were compared using Poisson regression. Time to first viral wheezing episode after treatment was evaluated using the Nelson-Aalen cumulative hazard function..
A p value <0.05 was considered as statistically significant.

Results
Efficacy
Wheezing was diagnosed by paediatricians in 47 children (9.0%; 95%CI 6.7-11.3%), with no statistically significant differences between treatment groups (6.8%; 95%CI

4.2-10.4 in the beclometasone versus 11.1%; 95%CI 7.7-15.4% in the placebo group). No statistically significant differences were found even after stratification for the number of wheezing episodes in the 6 months preceding the entry visit (Mantel-Haenszel Relative Risk=0.61; 95%CI 0.35-1.08). (a)
Only 7 children (15% of those with wheezing) had an episode rated as moderate by the paediatrician, 2 in the beclometasone and 5 in the placebo group (p=0.43) (b)
In all 75 children (14%) required an extra visit during the 10 day treatment period, with no differences between the two groups (rate: 13% in the beclometasone versus 16% in the placebo group; p=0.35) (c)
The percentage of children receiving rescue medication was 6.5% in the placebo group and 4.2% in the beclometasone group (p=0.23) (d)
No differences were found concerning the rate of emergency department attendance (2.3 in the beclometasone vs 1.5% in the placebo group; p=0.76) (e)
For a total of 80 children (15%) parents the parental score was >6 in at least one day of the treatment period, with no differences between the two groups (12% in beclometasone vs 15% in placebo group; p=0.34) (f)
In all, 62.7% of parents rated the treatment as useful, with no differences between beclometasone and placebo (64 vs 61%, respectively; p=0.46) (g)
No differences were found also for the other secondary outcome measures.
On the average, the cost paid by National Health Service was estimated in 16.50 € per child treated with beclometasone versus 6.35 € per child treated with placebo. (p)

Safety
In all, for 195 children (37%) parents reported at least one adverse drug events (AEDs). No differences were observed in the incidence of AEDs between beclometasone and placebo. Hoarseness and diarrhoea were the most commonly reported AEDs (13% and 12%, respectively).
Two serious AEDs were reported, both unrelated to drug use.

Conclusion.
Our findings confirm that inhaled steroids had little benefit in preventing viral wheezing, and no effect in reducing URTI symptoms. These drugs may have a greater efficacy in children with recurrent episodes of viral wheezing, but this need to be furtherly investigated.

Date of report: 18 April 2013

3 Ethics

3.1 Independent Ethics Committee (IEC)

The study protocol and all informed consent documents were approved by the ethics committee of all the 9 local health units of the paediatricians involved as investigators. See Appendix III for list of IECs

3.2 Ethical Conduct of the Study

The study was conducted in the accordance with the 6th revision of Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subject", approved in the October 2008 by the 59th World Medical Association General Assembly, in Seoul, Korea.

3.3 Subject / Patient Informed Consent

Paediatricians were invited to inform all parents of eligible children about the study and its scopes before the beginning of the trial. Information was provided during ad hoc meeting, or during a visit not necessarily related to ENBe study. A poster with a brief explanation of the ENBe study was provided to all participating paediatricians to be shown in their offices (see appendix IV)

During the entry visit (Visit 1), if inclusion and exclusion criteria were fulfilled, paediatricians proposed parent the participation to the study. They informed the parent(s) about the aims of the study, the procedures, benefits and risks, provided the information leaflet, and asked to sign the informed consent form (see appendix V)

No deviation from the informed consent procedure was reported.

4 Investigational Plan

4.1 Introduction

Viral wheezing (intermittent episodes of wheezing induced by viral infection of the upper respiratory tract) is a common condition in pre-school children. Its incidence is estimated between 6 and 30% and varies depending on criteria, diagnosis, and age definition used [1]. A prospective study performed by a group of Italian paediatricians reported that 19% of children under 18 months had had at least one episode of wheezing associated with an upper respiratory tract infection. In 40% of the cases the wheezing recurred in the following episodes of respiratory tract infection [2]. A prevalence of 45% of children aged 1-5 years reporting recurrent days with cough, wheeze or breathlessness in the preceding 6 winter months was reported in a telephone survey involving 300 Italian households [1]. Viral wheezing, however, is different from atopic asthma, since in 60% of cases symptoms disappear before the age of 6 [3-4]. The efficacy of drug treatments in the prevention and/or treatment of viral wheezing is controversial; short acting beta 2 agonists are often

considered first choice therapies even if evidence is scarce [5] The usefulness of inhaled steroids is also debated: no benefits are documented for maintenance with low dose inhaled corticosteroids, while their episodic use at a high dose may have a modest improvement in symptoms [6-10]. A systematic review by the Cochrane Collaboration regarding the use of episodic high dose inhaled steroids as acute treatment of viral wheezing concluded, on the basis of the results of 2 cross-over RCTs, that inhaled steroids were preferred by the children's parents over placebo (RR=0.64, 95% CI: 0.48-0.87) and that a trend for a reduced requirement of oral corticosteroids was observed (RR=0.53, 95% CI: 0.27-1.04).[11-12] No differences were observed concerning hospitalization rate or bronchodilator use [9]. A prospective, randomized controlled trial included in the Cochrane review reported that episodic high dose budesonide reduced the asthma symptom score, but, in the same study, no differences were observed concerning emergency room attendance, hospitalization rate or bronchodilator use [13] Despite the scant evidence, however, nebulised steroids in particular beclometasone, are widely prescribed in Italy as prophylaxis or treatment for viral wheezing [14-17]. Beclometasone is the second most prescribed drug in Italian children among the medications reimbursed by the National Health Service, with a prevalence estimated around 15% (9-22% depending on the setting).[16-17] Beclometasone prevalence is highest in children 1-4 years old (23%). In 60% of cases it is prescribed occasionally (1 box/patient/year only) and in 98% it is prescribed as a nebulised suspension.[16] Beclometasone is the fourth drug in order of expenditure, and represents 7% of the paediatric pharmaceutical expenditure in charge of the National Health Service [16]. The annual national health service expenditure related to paediatric prescriptions of this drug can be estimated around 24 million Euros. Despite the publication of an open letter in 2001 warning paediatricians about the overuse of this drug, [18] no changes were observed in beclometasone prevalence rate in the 2000-2006 period. Moreover, an analysis of the prescriptions dispensed during 2005 by 1,165 paediatricians in the Lombardy region found that all the paediatricians prescribed nebulised beclometasone at least one time. A median number of 80 children were prescribed beclometasone by each paediatrician.[19] In such a context, a rigorous evaluation of current practice is fundamental.

4.2 Study Objectives

4.2.1 Primary objective.

To evaluate the efficacy of beclometasone in preventing wheezing in respiratory tract infection.

4.2.2 Secondary objectives.

To evaluate:

- the efficacy of beclometasone in reducing symptom severity
- the efficacy of beclometasone in reducing bronchodilator and/or corticosteroid use
- the efficacy of beclometasone in reducing viral wheezing recurrence (during follow-up)
- treatment compliance

- parental opinion on the treatment
- the cost-efficacy ratio of prophylactic treatment with beclometasone.

4.3 Study Design

The study was designed as a two phase study: a randomized controlled trial (phase I) followed by a prospective observational study (phase II) The first phase had the aim to evaluate the effectiveness of beclometasone in preventing viral wheezing recurrence and in reducing symptom severity, while the second phase (observational follow-up) had the objective to monitor the incidence of viral wheezing recurrence and the different therapeutic approaches used by physicians.

A randomized, double blind, parallel group design was used to perform the phase I study.

Pre-school children with a history of viral wheezing attending family paediatricians for a viral upper respiratory tract infection were checked for inclusion and exclusion criteria. Children who fulfilled these criteria and whose parents agreed to participate the study were randomly assigned to receive beclometasone 400 mcg (study drug) or placebo twice daily for 10 days.

Paracetamol for fever and/or pain, nasal saline irrigation and antibiotics if needed were the only concomitant drugs allowed

It was planned to enroll 576 children (minimum: 520).

The scientific coordination of the study was guaranteed by the Steering Committee. An independent Research Monitoring Committee, composed by health professionals and lay people, was also involved with the aim to monitor the management of the trial.

Both the Committees were regularly updated concerning the progress of the study and the data analyses.

Only a non substantial amendment was applied to protocol: due the delay in study approval by the Ethics Committee, the enrollment period was changed from October 2009-March 2010 to September 2010-May 2011. The amended version of the protocol and of the synopsis was sent to the Ethics Committee on the 18th December 2009. The enrollment period was subsequently extended to March 2012 due to some unexpected difficulties in enrolling children. Five investigators abandoned the study in July 2011 and were replaced by other 5 paediatricians, working in the LHUs yet involved in the study.

In all, 40 family paediatricians working in 9 local health units (3 in the North, 3 in the Centre, and 3 in the South of Italy) were involved in the study as investigators.

No interim or exploratory analyses were performed.

The study protocol, The Case Report Form, The Diary 1 and 2, and the Flow Chart of the study are attached as appendices (see appendix VI-X)

4.4 Selection of Study Population

Target population

Pre-school children with a history of viral wheezing presenting to family paediatricians for a respiratory tract infection.

a) Inclusion criteria

- Outpatient children 1-5 years old.
- Presence of any viral upper respiratory tract infection symptoms
- At least one episode of viral wheezing (diagnosed by a physician) in the last 12 months.
- No, or minimal, asthma-like symptoms in between separate airway infections.

b) Exclusion criteria

- Steroid hypersensitivity
- Inhaled and/or oral corticosteroid use in the preceding month
- Chronic respiratory disease (e.g. cystic fibrosis, broncho-pulmonary dysplasia)
- Presence of wheezing at the entry visit

c) Reasons for Withdrawal / Replacement of Study Subjects

Study subjects were replaced only if the parents decided to withdraw the consent before opening the medication package and administering the treatment to their child. In these cases the investigator was instructed to give the medication package to the following eligible child.
In all other cases of withdrawal subjects were not replaced.

4.5 Study Materials

- **name of drug, (generic and trade name, if appropriate):** beclometasone, Clenil® per aerosol
- **formulation:** nebulised suspension
- **dose (including, frequency and duration of administration):** 400 mcg twice daily for 10 days
- **route of administration:** nebulizer
- **storage requirements:** none

Active drug and placebo were administered by parents through a pneumatic nebulizer (Nebula®, Air Liquid Medical System), in the morning and in the evening. In administering the drug, 1 mL of suspension was diluted with 1 mL of saline solution. The nebulizer and the saline solution (20 vials containing 1mL of solution) were provided as part of the study materials and given to parents by the paediatricians at the entry visit (visit 1) together with the medication package.
No diagnostic test was scheduled in the protocol. If needed, paediatricians were allowed to prescribe tests (e.g. C-reactive protein, throat swab) that may be helpful for the diagnosis.

4.6 Methods for Assigning Subjects to Treatment Groups

- **method for generation of randomisation codes:** Patients were allocated to each group according to a computer generated randomization list (see appendix XI). A central randomized block randomization procedure stratified by paediatricians was performed with a block size of 4.

Each paediatrician received 12 to 16 medication packs, each identified by a code. The paediatricians were instructed to give to parents of the enrolled patient the medication pack with the lowest available number.

- **holders of the randomisation codes:**

The randomization list with the treatment assignation was kept by dr Guido Bertolini, head of the Laboratory of Clinical Epidemiology at Mario Negri Institute, a researcher not involved in the study. The treatment assignments were unconcealed only after the completion of the analyses regarding the (primary and the secondary) endpoints collected during the experimental phase of the study.

- **any code breaks and reasons for the code breaks:** None

4.7 Dosage Regimen

Beclometasone suspension 400 mcg (Clenil® per aerosol, Chiesi Farmaceutici SpA) and placebo were administered twice daily, for 10 days.
The dosage regimen was consistent with the regimen recommended in the Summary of Product Characteristics.

4.8 Study Blinding

The identity of the active and placebo treatments were concealed by the use of study drugs that were all identical in packaging, labeling, schedule of administration and appearance. Each medication pack contained a total of twenty identical 1 mL ampoules and was identified by a code. A person not involved in the study evaluation labeled the medication packages. The statistical analyses were performed by investigators unaware of the treatment allocation.

4.9 Drug Accountability

A Standard Operative Procedure (SOP) was set up by the Coordinating Centre (CC) of the clinical study concerning drug handling and accountability (see appendix XII) to ensure that the drug management was compliant to GCP and followed the requirements of the relevant regulatory authority, in collaboration with the pharmaceutical company, the pharmacy departments of the Local Health Units (LHUs) and local investigators, through a system of templates (annexes to SOP 5) for notifying and documenting the traceability of the drug used in the clinical trial.
The pharmaceutical company Chiesi Farmaceutici S.p.A. was committed by the Coordinating Centre (CC) to manufacture and supply the investigational medicinal product (IMP) for the clinical study according to GMP and to communicate its availability to the CC. Then the CC committed the designed forwarder to pick up the drug packs from the manufacturer's warehouse and send them to the pharmacy departments the LHUs, through a form "Ordine di Invio Farmaco Sperimentale – Tabella Riassuntiva" (Appendix XII, Annex 1).

Upon the request of the CC, the forwarder delivered the drug packs to each pharmacy departments using the form “Ordine di Invio Farmaco Sperimentale - Consegna alla Farmacia ASL” (Appendix XII, Annex 2), in which is clearly indicated the list of local investigators (identified with a centre code number) and their assigned patient codes (identified by the randomization code).
The forwarder notified the CC of the successful drug delivery by faxing a signed copy of the Annex 2.
Subsequently the pharmacist of the each LHU

- Checked the drug packages, verifying the correspondence of the contents with the packing slip;
- Stored and managed the drug in accordance with the same standards as licensed medicines;
- Dispensed all drug packs to each local investigator indicated by the CC, filling the required data in the form “Dettaglio Farmaco Sperimentale” (Annex 3) provided by the CC;
- Faxed a copy of Annex 3, notifying the CC of the successful delivery of the all drug packs to the local investigators, and archived it.

After the notification of all drug packs’ delivery, the CC invited (by e-mail or phone call) the local investigators to pick up the assigned drug packs at the LHU’s pharmacy departments.
Each local investigator managed and stored the assigned drug packs in his ambulatory, in accordance with the procedure indicated by CC.
During the enrollment period the investigator registered in an appropriate form “Inventario del Farmaco Sperimentale” (Appendix XII, Annex 4):
- the drug packs assigned to each patient recruited in the clinical study (randomization number);
- the number of unused vials for all drug packs returned by each enrolled patient at the end of the 10 days of treatment (visit 2).

At the end of the enrollment period the local investigator:
- faxed a copy of the fulfilled “Inventory of the Investigational Drug” to the CC, and archived it;
- collected any unused medication vial from the enrolled patients and returned them to the LHU’s pharmacy departments.

The pharmacy department informed the CC about the return of unused medication through the form "Dettaglio del Farmaco Sperimentale Reso” (Appendix XII, Annex 5).
Upon request of the CC, the forwarder picked up the unused medication from the pharmacies and delivered it to the site designated by pharmaceutical company for the drug disposal.

On July 2011, 56 medication packages were returned from investigators who abandoned the study, re-labeled and distributed to the 5 investigators subsequently involved. The re-labeling of medication packages was performed by the CC, in accordance with the SOP “Redistribuzione farmaco” (see appendix XIII)

4.10 Treatment Compliance

Each day parents had to record on the diary the number of doses administered to their child.

Moreover, at the end of the treatment period parents were asked to return paediatricians the vials not administered to child. The number of missed doses was reported by paediatricians on the CRF.

4.11 Prior and Concomitant Medication

Children receiving inhaled or oral steroids in the month preceding the baseline visit were excluded.

No medications were allowed during the 10 day treatment period, with the following exceptions:

- Paracetamol as symptomatic treatment for fever and/or pain
- Nasal saline irrigation.
- Antibiotics, if needed.

If viral wheezing occurred during the 10 day treatment period, paediatricians were allowed to prescribe as rescue medications:

- nebulised salbutamol
- nebulised beclometasone
- oral steroids.

During the follow up period (observational phase) paediatricians were allowed to treat children with viral wheezing according to their routine practice.

5 Study Assessments (including efficacy and safety variables)

5.1 Primary Variables

Percentage of children with wheezing (diagnosed by the paediatrician) during the URTI episode.

5.2 Secondary Variables

- % of patients with moderate/severe wheezing (score ≥ 2 rated by paediatrician);
- % of patients needing medical care during the treatment period;
- % of patients receiving rescue medication during the treatment period;
- % of patients admitted to an emergency department during the treatment period;
- Duration of the respiratory tract infection episode;
- % of patients with an asthma-like symptom score (rated by parents) ≥ 7;
- Mean asthma-like symptom score for each child;
- Time to the first viral wheezing episode after the end of the treatment;
- Frequency of respiratory tract infection episodes during the 6 month follow-up period;
- Frequency of viral wheezing episodes during the 6 month follow-up period;
- % of parents who consider the treatment helpful;
- % of patients fully adherent to therapy
- average cost per patient

5.3 Measurements / Assessments

Study plan

Three visits were scheduled: the entry visit (visit 1, day 0), the end treatment visit (visit 2, day 11 with a tolerance of 2 days), and the end follow up period visit (visit 3, day 180 with a tolerance of 2 days) (see the Flow Chart of the study, appendix X)

At visit 1, each paediatrician had to:

- explain the aim of the study,
- assess inclusion/exclusion criteria
- collect informed consent form signed by the parent(s),
- visit the child and collect demographic, anamnestic and clinical data.
- give parent(s) the medication packs
- give parent(s) the nebulizer and the saline solution
- give parent(s) the diary number 1

At visit 2 each paediatrician had to:

- visit the child and collect clinical data
- collect diary number 1 and check the data for quality and completeness
- collect the medication not administered
- give parent(s) diary number 2

At visit 3 each paediatrician had to:

- visit the child and collect clinical data
- collect diary number 2 and check the data for quality and completeness.

Besides these scheduled visits, paediatricians were requested to visit the children in case of wheezing and/or lack of improvement within 72 hours of the start of the therapy (extra visit, visit 1A). Paediatrician had to visit the child within 24 hours from the parent request.

During the follow up period all the visits performed for upper respiratory tract infections were recorded (visit 2A, 2B…).

Clinical evaluation performed by paediatricians.

At the entry visit (visit 1) the paediatrician filled in a case report form (CRF, appendix VII) collecting demographic, anamnestic, clinical data and information regarding familiarity for asthma or allergy. During the treatment period, in case of wheezing and/or lack of improvement within 72 hours from the start of therapy, paediatricians should visit the child, evaluate the presence of wheezing and rate it (extra visit or visit 1A). A wheeze score was assigned as follows: 0 = no wheezing, 1 = end-expiratory wheeze only (mild), 2 = wheeze during entire expiratory with or without inspiratory phase, audible with stethoscope only (moderate), 3 = inspiratory and expiratory wheezing audible without stethoscope (severe).

At the end of the treatment period (visit 2) paediatricians visited the patients and evaluated the presence of URTI symptoms and of wheezing, and also collected information concerning treatment compliance through an interview with the parents.
A visit was also be performed at the end of the 6 month follow up period (visit 3). During this visit the paediatricians recorded information concerning the number of times he/she visited the patient, the number of emergency department visits and hospitalizations, and the drugs and laboratory tests prescribed to the patient.
During all the visit performed for upper respiratory tract infections during the follow up period (visit 2A, 2B…) data concerning symptoms, presence and severity of wheezing, drug used before the visit, drugs prescribed by paediatricians were collected.

Evaluation performed by parents.

During the 10 day treatment period, symptoms were recorded by parents on a diary (diary number 1, appendix VIII). The parents scored the asthma-like symptoms subjectively. Symptoms were divided into cough, wheeze, noisy breathing and breathlessness and were scored daily along a 4-graded scale (none=0; mild=1; moderate=2; severe=3). This scale was used in other clinical trials evaluating the efficacy of steroids in viral wheezing [11-13]. The presence (yes/no) of URTI symptoms (fever, blocked nose, runny nose, sore throat, watery eyes), the number of night awakenings and the number of doses administered to the child were also recorded daily. At the end of the treatment period, the parents expressed a judgement on the treatment (Helpful, Not helpful). Adverse events and the use of other medications were recorded on the diary by the parents. Diary cards were collected by the paediatricians at the end of the treatment period. On that occasion, the paediatrician checked the data for quality and completeness with the parents.
During the follow up period parents recorded on a diary (diary number 2, appendix IX) the number of respiratory tract infection episodes and their duration, the presence (yes/no) of cough, wheeze, noisy breathing and breathlessness, the number of paediatrician visits, emergency room visits, hospitalizations, and the medications administered to the child. Diary cards were collected by the paediatricians at the end of the follow up period (visit 3). On that occasion, the paediatrician checked and validated the data.

Cost analysis

The health care costs were estimated from the payer's (National Health Service) perspective. Costs were assessed using per-patient resource consumption as observed in the study, and national tariffs and prices as unit costs of resources (table 1). The costs of drugs were estimated on the basis of the costs reported in the National Formulary (Prontuario Farmaceutico Nazionale) at 31 December 2011. For the cost of the extra visit was an estimate used in a previous study involving General Practitioners. For the Emergency Department visits the fees reported in the *Sistema Tariffario Ospedaliero* were applied.

The following unit costs (€) were applied:

	€
Beclometasone	11.69
Placebo	0
Other drugs*	
Amoxicillin	2.57
Amoxicillin+clavulanic acid	14.65
Azithromycin	7.93
Clarithromycin	11.69
Salbutamol	7.70
Extra visit	12.32
Emergency Department	28.13
Diagnostic tests*	
C-reactive protein	5.8
Throat swab	6.3

* Only most commonly prescribed drugs or tests were reported as an example

Definition of adverse event, adverse drug reaction and serious adverse event

Adverse events (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse drug reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose were considered adverse drug reactions (ADRs). The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out.

Serious adverse event or reaction/experience

A serious AE (experience) (SAE) or reaction (SAR) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is an important medical event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in cases of important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room, or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Methods of recording and assessing adverse events

All adverse events occurring during the 10 day treatment period were recorded by the parents on the diary. Data were checked by the paediatricians during the visit 2.

Procedure for reporting serious adverse events

In the event of the occurrence of any clinical AE or abnormal laboratory test value that was serious or medically important during the course of the study or the post-treatment period, irrespective of the treatment received by the patient, the investigator had to immediately inform the coordinating centre.

Following a report by phone, written information had to be sent by fax or e-mail. For written reports, the SAE report Form should have been used (see appendix XIV for details).

6 Data Quality Assurance

Data were collected through a web based electronic CRF available at . http://giviti2.marionegri.it/war/ENBe.html

A data validation plan was used in order to check the consistency, completeness and accuracy of the data entered and data clarification forms (DCFs) were sent to the investigators. Each participating investigator was responsible for ensuring data quality.

Two monitoring visits were performed by clinical monitors belonging to the Unità di Gestione e Monitoraggio della Ricerca Clinica, Consorzio Mario Negri Sud, Santa Maria Imbaro (CH). Each visit involved all the investigators of the same local health unit. A SOP was set up to describe how to plan, conduct and document the activities performed during monitoring visits (see Appendix XV)

In particular, the monitor checked:

- the registry of the enrolled patients;
- the inform consent of all enrolled patients;
- all returned diaries for parents;
- the electronic Case Report Forms;
- the unresolved DCFs;
- the Investigator's Study File (ISF) and any other study documents;
- the management and storage conditions of the Investigational Drug;
- the inventory of the Investigational Drug.

During the visit the monitor discussed with the local investigators of any deviation or violation from the protocol or any other issue related to the study conduction, advised them to take the appropriate measures to avoid their recurrence and helped them to solve the requests.
After the monitoring visit, the monitor compiled the “monitoring report”, documenting all actions taken during the visit; the report was sent to the CC within a week; in addition, a letter was sent to each local investigator, which summarizes the activities carried out during the monitoring visit.

7 Data Management Procedures

Data were collected through an electronic Case Report Form, available at the address http://giviti2.marionegri.it/war/ENBe.html
The Case Report Form was developed in JAVA language using Google Web Toolkit and the database was hosted on a server based in the Mario Negri Institute.
Paediatricians could access the eCRF after logging in with username and password. The username was provided by the coordinating centre, while at the first access paediatricians had to reset the password. Password should have been composed by at least 8 characters, with at least two numeric variables. Paediatricians were forced to change their password every 3 months.
Appendix XVI reports the handbook of the eCRF.
To ensure that operators had the right to perform certain actions, a privilege system was implemented by defining user roles (clinical investigators, data managers, and system administrators).
Specific checks were implemented to guarantee validity of data (e.g. existence of date of birth, sex, and informed consent at the time of new patient insert, inclusion and exclusion criteria), and warnings for values outside the normal range.
In case of mistake, investigator could change the value inserted in the eCRF. Every change was recorded together with the timestamp, the user ID of the person doing the operation, the old and new values of the changed field, and the reason for the modification.
All database instances were scheduled for daily backup.

8 Statistical Considerations

8.1 Planned Statistical Methods

Analyses included all randomized children (intention to treat population).
No interim analyses were performed.
The primary outcome measure, as well as the other categorical variables, were compared using the chi-square test. For the analysis concerning the primary endpoint, patients were stratified according to the number of viral wheezing episodes in the previous 6 months ($\leq$ 1versus > 1).
The proportion of children with no symptoms of respiratory tract infection were compared using the Kaplan-Meier method. Repeated measures analyses of variance was performed to analyse change in the daily asthma-like symptom score. The ”last observation carried forward method“ was used to deal with the missing data, when applicable.

The number of respiratory tract infection episodes and the number of recurrences of viral wheezing during the 6 month follow up period were compared using Poisson regression. Time to first viral wheezing episode after treatment was evaluated using the Nelson-Aalen cumulative hazard function.
A Kruskal Wallis non parametric test was performed to compare the costs between the two groups.
A p value <0.05 was considered as statistically significant, with the exception of the evaluation of costs (in that case the level of significance was set at p-value ≤ 0.005).

8.2 Determination of Sample Size

The risk of recurrent viral wheezing in children who had one or more episodes was estimated around 40%. [2] At least 260 children per group were therefore needed to detect a 30% reduction of the risk of viral wheezing (from 40% to 28%), with a statistical power of 0.8 and a two sided alpha error of 0.05.
Taking into account a 10% drop-out rate, it was planned to randomize 576 children.

9 Changes in the Conduct of the Study or Planned Analysis

A few subgroup analyses, not originally planned, were performed in the cohort of children enrolled during the autumn season (between October and December of each year). The main objective of these analyses was to monitor the incidence and the number of the wheezing recurrences during the entire 6 month study period in an homogeneous sample. Given the seasonal variations in the incidence of URTIs, and consequently of the risk of wheezing recurrence, it may important to monitor children in the same period.
In particular, a comparison between demographic and anamnestic characteristics of children presenting versus non presenting wheezing recurrence during the entire study period was performed to identify factors that could be associated to an increased risk of viral wheezing.

10 Results

10.1 Study Subjects / Patients

a) Disposition of Subjects

From October 2010 to March 2012, 1,371 children with an history of viral wheezing were visited by paediatricians for an URTI.
In all, 714 (52%) were not eligible mainly for the presence of wheezing at the baseline visit (63% of not eligible children) and/or the use of steroids in the 30 days before the visit (53%) (Figure 1)
Of the 657 provisionally eligible children, the parents of 132 (20%) declined participation,
and 525 children were enrolled: 264 have been randomized to beclomethasone and 261 to placebo.
Of the enrolled children, 172 lived in the North, 172 in the Centre and 181 in the South of Italy.

The parents of 2 children withdrew the consent after the randomization, and 2 children were lost at follow-up (see Appendix XVII). Thus, a total of 521 patients were visited at the end of the treatment period (visit 2).
In all, 507 were visited at the end of the observational follow up phase (visit 3): 259 in the beclometasone and 248 in the placebo group, since 14 children were lost at follow-up.

b) Protocol Deviations

Protocol deviations were observed for 274 children (52% of the enrolled children): 137 in the beclometasone and 137 in the placebo group.
In particular, 204 children did not complete the therapy (lack of compliance), 109 were visited more than 2 days after the end of the therapy (lack of adherence with the timing of the scheduled visit), and 20 took a not allowed drug during the 10 day treatment period.
Appendix XVIII reports the listings of protocol deviations for individual subjects.

10.2 Efficacy Evaluation

a) Data Sets Analysed

The analyses concerned all the 525 enrolled subjects (intention to treat population).
Only for data collected during the observational follow-up period the analyses concerned the 507 children who completed the study and were visited at the end of the 6 months period (visit 3).

b) Demographic and Other Baseline Characteristics

Table 1 reports the characteristics of the enrolled children by treatment group. No differences were found between the two groups, with the exception for the percentage of children treated with drugs in the 30 days preceding the baseline visits (36% in placebo versus 27% in beclomethasone group; p=0.02), but similar rates were found when comparing single drug classes.

c) Treatment Compliance

In all, 208 children (40%) did not complete the entire therapy: 102 children were randomized to beclometasone and 106 to placebo (chi-square=0.14; p=0.66). The mean number of administered doses was 18.3 (SD: 3.8) in beclometasone group versus 17.6 (SD: 4.4) in placebo group, respectively (p=0.06).
A total of 471 children (90%) received at least 14 out of 20 doses (7 day therapy): 243 in the beclometasone and 228 in the placebo group (p=0.10). In half of the cases the non complete adherence was due to difficulties in performing nebulization, mainly for child refusal or scant cooperation
Appendix XIX reports the information for each subject regarding the compliance to treatment and the number of missed doses.

d) Efficacy Results

Primary and secondary outcome measures

Wheezing was diagnosed by paediatricians in 47 children (9.0%; 95%CI 6.7-11.3%), with no statistically significant differences between treatment groups (6.8%; 95%CI 4.2-10.4% in beclometasone versus 11.1%; 95%CI 7.7-15.4% in placebo group) (table 2).

No statistically significant differences were found even after stratification for the number of wheezing episodes in the 6 months preceding the entry visit (Mantel-Haenszel Relative Risk=0.61; 95%CI 0.35-1.08).

No differences were found also when considering the "per protocol population": the number of children with wheezing were 5 out of 125 (4%) in beclometasone group versus 6 out of 122 (5%) in placebo group (p=0.73)

A different incidence of wheezing was observed in the 3 geographic areas, ranging from 6.1% in the South to 11.6% in the Centre of Italy. No statistically significant differences were found between incidence of wheezing in the beclometasone versus the placebo group after stratification for geographic area of residence (Mantel-Haenszel Chi-square= 2.95; p=0.09)

In 40 cases the wheezing was scored by the paediatrician as mild, in 7 as moderate. For 26 children the wheezing was diagnosed during an extra visit performed in the 10 day treatment period, for 21 after its end, during visit 2.

No differences were found for all the secondary outcome measures (table 3).

Parental perception of symptom severity and treatment efficacy

In all, 62.7% of parents rated the treatment as useful, with no differences between beclomethasone and placebo (table 3).

At day 1 the overall mean score was 2.85 (SD 2.04) in the beclometasone group and 2.94 (SD 2.06) in the placebo group. At the end of the therapy (day 10) it decrease to 1.20 (1.66) and to 1.53 (2.01) in beclometasone and placebo groups, respectively. No statistically significant differences were found, also when evaluating each symptom (cough, noisy breathing, breathlessness, wheezing). (figure 2)

A slightly higher percentage of children had a total score > 6 for one or more days in the placebo group compared to beclometasone group (14.9% versus 11.7%; p=0.34).

At the end of the treatment period for 48% of children in both groups parents did not report any symptom of upper respiratory tract infection. No differences were found in the distribution of the proportion of symptom-free children by group during the treatment period (Beclomethasone vs placebo: Hazard Ratio = 1.02; 95% CI 0.86 – 1.22) (figure 3).

Cost analysis

On the average each child treated with beclometasone would cost to the National Health Service 16.50 euro vs 6.35 euro of each child receiving placebo (p<0.001: Table 4) Nearly all of this difference was due to the cost of beclometasone. The cost for other drugs prescribed during the

extra visit was slightly higher in the placebo group (3.89 vs 2.55€), while, independently from statistical significance, the differences were negligible for the other variables (Table 4).

Follow up period (phase II)

Phase II was an observational follow-up study. The analyses concerned the 507 children visited at the end of the 6 month period (visit 3). Children were grouped according to the treatment (beclometasone versus placebo) received during the phase I.

In all, 249 (49%) children had at least one visit for an URTI episode after the completion of phase I, with an identical prevalence in the two groups (table 5). Of these, 116 had one or more viral wheezing recurrences: 56 (22%) in the beclometasone group and 60 (24%) in the placebo group (Table 5). The number of children with wheezing occurred exclusively during the follow-up period was 99 (51 in beclometasone and 48 in placebo group, respectively, table 6).

On the average, each child was visited 2.4 times for URTIs. The mean number of viral wheezing recurrence was 1.50 (SD 0.89) in the beclometasone group and 1.60 (SD 1.03) in the placebo group (p=0.58).

No statistically significant differences were observed in wheezing severity between children assigned to beclometasone and those assigned to placebo (chi-square=0.88; p=0.64; Table 7). In all, 55% of the children had at least one episode classified as moderate or severe.

A total of 48 children were admitted to an emergency department during the follow-up period, 14 of which for wheezing: 5 (2%) in beclometasone and 9 (4%) in placebo group (p=0.37) (Table 5)

The mean interval before wheezing occurrence was 61.4 (SD 47.9) days in beclometasone versus 53.1 (SD 43.5) in placebo group. (p=0.33)

No differences were found in the cumulative incidence of viral wheezing recurrence between beclometasone and placebo (HR adjusted for enrolment period = 0.84, 95%CI 0.58 – 1.21; p = 0.35). (Figure 4)

In all. 68% of the parents administered drugs to their children with URTIs before the physician's visit (Table 8). The most commonly drugs administered by parents were paracetamol (23% of the URTI episodes), salbutamol (16%) and beclometasone (8%) (Table 9).

A total of 219 (88%) children with URTIs received at least one drug prescription (Table 10). Drugs most commonly prescribed in cases of URTIs were salbutamol (25% of the URTI episodes), saline solution (24%), amoxicillin (13%), and beclometasone (13%) (Table 11).

In all, 96% of children with viral wheezing received at least one drug prescription (Table 12). Salbutamol was the drug most commonly prescribed to children with wheezing (71% of wheezing episodes), followed by betamethasone (26%) and saline (24%) (Table 13).

Beclometasone was prescribed in 21% of the cases of wheezing.

The rate of children with viral wheezing treated with beclometasone was higher in those previously assigned to placebo compared to those assigned to study drug (39 versus 16%; chi-square:=7; p=0.01; Table 14). Beclometasone was prescribed by 13 out of 25 paediatricians who visited children with viral wheezing during the follow-up period.

Considering the entire study period (phase I + phase II) the number of enrolled children with one wheezing recurrence was 145 (29%) (Table 15). The rate was slightly higher in children who received placebo in the experimental phase compared to those assigned to beclometasone (31 versus 26%; chi square=0.96; p=0.33).

Focus on children enrolled between October and December

Given the seasonal variation of the incidence of URTIs, and consequently of the risk of viral wheezing occurrence, we performed a subgroup analysis on children enrolled during the autumn (October-December) period, and therefore followed-up during winter and spring.

The number of children enrolled in the above period was 258, 251 of which were visited at the end of the study.

In this group, the incidence of viral wheezing during the phase I study was 12.7%, consistent with those observed in the overall cohort (Table 16). No differences were found between children treated with beclometasone and those treated with placebo (Mantel-Haenszel chi-square= 0.82; p=0.36).

The rate of wheezing recurrence during the entire study period (independently from the phase) was 41% (37 versus 44% in beclometasone versus placebo group; Mantel-Haenszel chi-square= 1.25; p=0.27) (Table 17). In particular, the rate of recurrence in children who had more than 1 wheezing episode before the entry visit was 50%.

Fourty-four percent of the children were visited 3 or more times during the follow-up period (Table 18)

In all, 38 out of 251 children (15%) had 2 or more wheezing recurrence during the 6 months observation period (Table 19).

Finally, a comparison was performed between the demographic and anamnestic characteristics of children with and without wheezing recurrence, with the aim to identify determinant or risk factors.

No statistically significant differences were found for the analysed variables. Only for the time since the last wheezing episode before the entry visit (≤ 3 versus > 3 months) a p value of 0.05 was estimated (Table 20).

e) Statistical Issues

Analyses included all randomized children (intention to treat population).

Results regarding “per protocol” population are reported only for the primary endpoint.

No interim analyses were performed.

The primary outcome measure, as well as the other categorical variables, were compared using the Chi-square test. For the analyses of the main outcome measure, patients were stratified according to the number of viral wheezing episodes in the previous 6 months (≤ 1versus > 1).

The proportion of children with no symptoms of respiratory tract infection were compared using the Kaplan-Meier method. Repeated measures analyses of variance was performed to analyse change in the daily asthma-like symptom score. The ”last observation carried forward method“ was used to deal with the missing data, when applicable.

The number of respiratory tract infection episodes and the number of recurrences of viral wheezing during the 6 month follow up period were compared using Poisson regression. Time to first viral wheezing episode after treatment was evaluated using the Nelson-Aalen cumulative hazard function.
A Kruskal Wallis non parametric test was performer to compare the costs between the two groups. A p value <0.05 was considered as statistically significant, with the exception of the evaluation of costs (in that case the level of significance was set at p-value ≤ 0.005).

f) Drug Dose, Drug Concentration and Relationship to Response

Not pertinent

g) Drug-drug and drug-disease interactions

Not pertinent

h) Efficacy Conclusions

No statistically significant differences were found between children receiving beclometasone and those receiving placebo for all the endpoints of the trial.
Wheezing occurred in a lower percentage of children in the beclometasone group compared with the placebo group, in particular when taking into account those with a recent history of recurrent episodes, but with no statistically significant differences.
We estimated that on the average each child with URTI treated with beclometasone would cost to the Italian National Health Service 10 € more than children receiving placebo (i.e. saline solution). This difference is nearly almost due to the cost of the drug.

10.3 Safety Evaluation

All 525 children randomized were considered for the safety evaluation.

a) Extent of Exposure

The mean number of administered doses was 18.3 (SD: 3.8) in beclometasone group versus 17.6 (SD: 4.4) in placebo group, respectively.

b) Adverse Events

In all, for 195 children (37%) parents reported at least one adverse drug events (AEDs) (table 21)..
No differences were observed in the incidence and type of AEDs between beclometasone and placebo. Hoarseness and diarrhea were the most commonly reported AEDs (13% and 12%, respectively).

c) Deaths

None observed

d) Other Serious Adverse Events

Two serious adverse events were reported by paediatricians: one hospital admission for urinary tract infection in the beclomethasone group (a 21 months old girl, ID code 561) and one hospitalization

for adenoidectomy and tonsillectomy in the placebo group (a 71 months old boy, ID code 548). None of them was drug related.

e) Adverse Events Leading to Withdrawal

None.

f) Other Significant Adverse Events

None

g) Narratives

Not applicable

h) Clinical Laboratory Evaluations

Not applicable

i) Vital Signs, Physical Findings and Other Observations Related to Safety

Not applicable

j) Safety Conclusions

Beclometasone nebulised suspension has been marketed in Italy for more than 20 years, has been administered to hundreds of thousands children and no safety concerns have ever been raised.
In this regard, the safety evaluation was not a main objective of this study.
In our study no differences in the incidence of adverse events were found between children treated with beclometasone and those treated with placebo. Nearly all AEs were mild and expected (i.e. reported in the Summary of Product Characteristics). Only two serious AEs were reported, but none of them was drug related.

11 Discussion and Overall Conclusions

This is the first NHS funded randomized double blind controlled trial performed in the pediatric primary care setting in Italy and, to the best of our knowledge, one of the few performed all over the world.
It can be considered a pragmatic trial, since it evaluated the efficacy of the beclometasone in the real life context. The prescription of beclometasone in children with URTI is a widespread "attitude" in Italy, and in this regard the study tried to address a relevant topic.
No statistically significant differences were found between children receiving beclometasone and those receiving placebo for all the endpoints of the trial.
Wheezing occurred in a lower percentage of children in the beclometasone group compared with the placebo group, in particular when taking into account those with a recent history of recurrent episodes, but with no statistically significant differences.
In our study, we observed a lower incidence of wheezing than expected. In a previous observational study a risk of recurrence of 40% was reported in infants who had at least one episode of viral wheezing. [2] In our study only 11% of children in the placebo group developed wheezing. We estimated the sample size with the aim to observe a reduction of at least 30% (from 40 to 28%) in the risk of wheezing recurrence, and it is possible that the study is not adequately powered. With a sample of 525 children and a rate of 11% it is possible to detect a relative risk difference $\geq 45\%$,

that is clinically relevant. Moreover, according to our results, the number needed to treat with beclometasone for obtaining an additional benefit can be estimated in 23, therefore the efficacy of the drug prophylaxis appears small, independently from the statistical significance.
It should be considered that during the experimental phase we monitored only one single episode of URTI. When looking at the 6 month observation period, the rate of recurrence was 29%. From this point of view, children enrolled in this study are not different from children at risk of viral wheezing. [1,2]
One of the main strengths of this study was to combine the clinical evaluation of paediatricians with the perception of parents. Previous studies regarding the prevention of episodic viral wheezing used outcome measures almost exclusively based on parental scores and/or symptoms recorded on a diary. [11-13]
Since scores depend greatly on subjective perception and differences exist in parents understanding of what wheezing means [19,20] we decided to use a stronger primary endpoint: the incidence of wheezing diagnosed by paediatricians. It is possible that some cases of children with wheezing were missed because not visited by paediatricians, but the same occurs in the daily practice. In this regards, it should be underlined that 21 out of 47 (45%) cases of wheezing were not recognized by parents and were detected by paediatricians after the end of treatment, during visit 2.
The parental score was used as a secondary outcome measure, but also when considering the parents' perception of the severity of asthma-like symptoms few differences were found.
A greater preference by the children's parents for inhaled steroids versus placebo was previously found in cross-over trials. [11,12] On the contrary, in our study the percentage of parents who considered helpful the treatment were similar in the two groups.
Many Italian paediatricians prescribe beclometasone routinely as treatment of URTI symptoms (e.g. cough, sore throat), besides from wheezing prevention.[14] In this regard, our findings prove that the duration of symptoms are similar in children receiving beclometasone and placebo, and that 48% had one or more symptoms after 10 days of treatment, independently from the drug taken.
It should be considered that for each individual treatment with beclometasone there would be a 10 euro difference in the costs for the National Health Service compared with saline solution treatment.
A low compliance was observed. Only 6 out of 10 children completed all the 10 day therapy. In nearly half of the cases the non complete adherence was due to difficulties in performing nebulization, mainly for child refusal or scant cooperation. This should be taken into account by paediatricians when prescribing drugs that should be administered through a nebulizer.
In our opinion, also the observational phase of the study provided useful findings. Our results confirm that the rate of recurrence is relevant in children with a recent history of viral wheezing, not only in the younger ones. The risk resulted greater in those with frequent episodes, in particular during the winter season, with 50% of them having a recurrence.
Moreover, our findings confirm that most children with URTI received drugs both administered by parents and prescribed by paediatricians. Concerning the wheezing treatment, salbutamol was

prescribed by paediatricians in ¾ of the wheezing recurrences, even if also for this drug the evidence of efficacy are debated. [5]

In conclusion, our findings confirm that inhaled steroids had scant benefit in preventing viral wheezing, and no effect in reducing URTI symptoms.

Despite some limitations, clinical trials performed in primary care setting can provides useful evidence for health professionals, regulatory agencies, and national health service officers, with the aim to improve rational drug use in children.

12 Tables, Figures and Graphs

Figure 1 -Flow Diagram

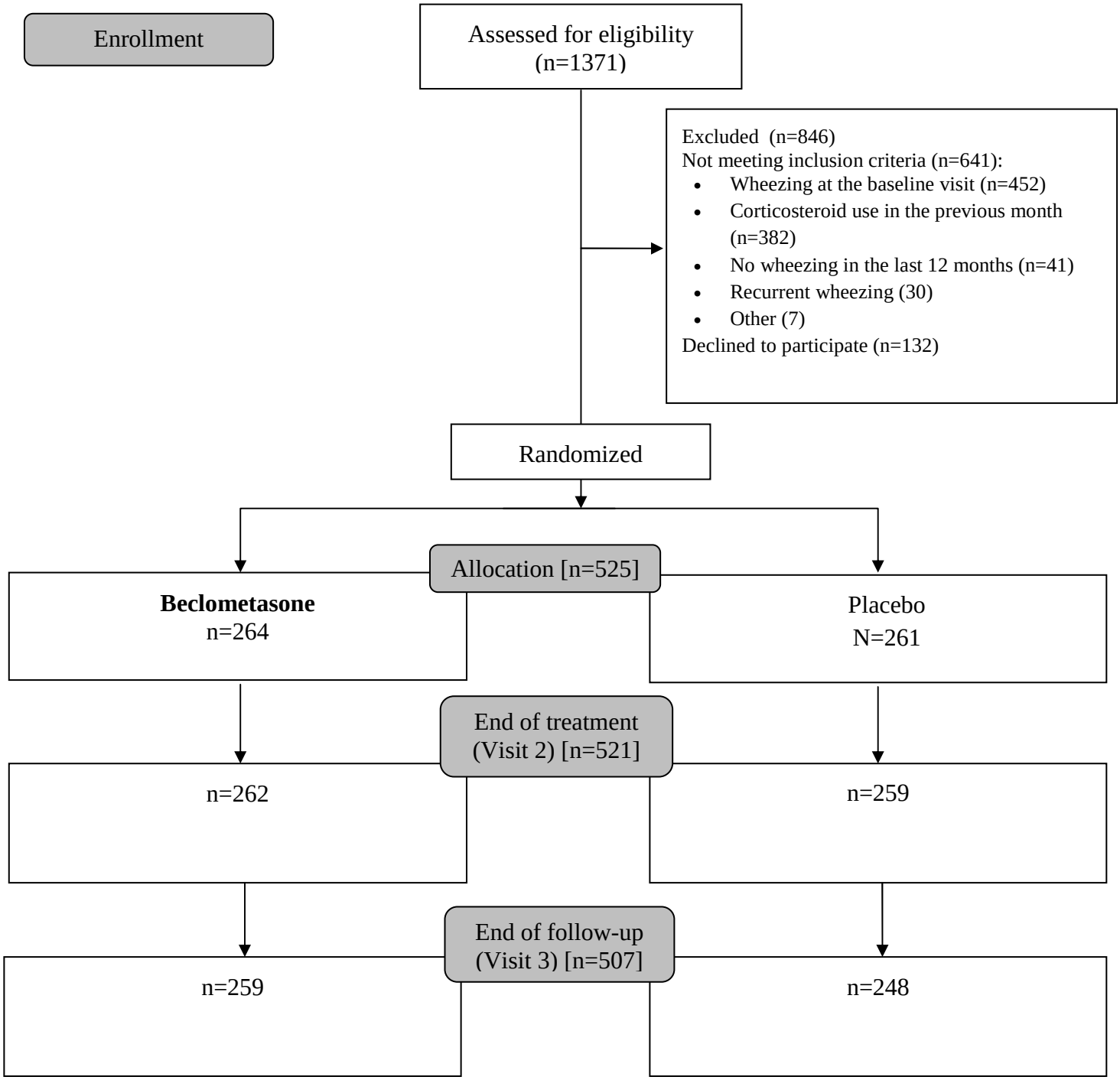


Table 1 -Baseline patient characteristics by group (data are reported as number, percentage, unless otherwise specified).

Characteristic	Beclometasone N = 264	Placebo N = 261	p value
Age (mean± SD)	2.05 ± 1.03	2.05 ± 1.03	0.73
Male gender	161 *(61)*	158 *(60)*	0.92
Delivery			
natural	154 *(58.3)*	147 *(56.3)*	0.64
cesarean	110 *(41.7)*	114 *(43.7)*	-
Gestational age (weeks)			
≤37	58 *(21.6)*	43 *(16.5)*	0.13
>37	206 *(78.0)*	218 *(83.5)*	-
Atopic dermatitis (Yes)	64 *(24.2)*	68 *(26.1)*	0.63
Allergic Rhinitis (Yes)	13 *(4.9)*	8 *(3.1)*	0.28
At least one case with allergy in family (Yes)	136 *(51.5)*	130 *(49.8)*	0.70
At least one case with asthma in family (Yes)	67 *(25.4)*	59 *(22.6)*	0.46
At least one smoker in family (Yes)	107 *(40.5)*	97 *(37.2)*	0.43
Enrollment period:			
October-December	129 *(48.9)*	129 *(49.4*	0.91
January-March	100 *(37.9)*	101 *(38.7)*	
April-September	35 *(10.6)*	31 *(10.7)*	
N. Upper respiratory tract infections in the last 12 months (mean ± DS)	3.1 ± 2	3 ± 1.9	0.66
N. wheezing episodes in the last 12 months (mean ± DS)	2.06 ± 1.09	2.04 ± 1.07	0.10
N. wheezing episodes in the last 6 months			
0	91 *(34.5)*	77 *(29.5)*	0.40
1	98 *(37.1)*	110 *(42.1)*	-
>1	75 *(28.4)*	74 *(28.4)*	-
Time (months) from the last wheezing episode**:**			
1-3	137 *(51.9)*	137 *(52.5)*	0.74
4-6	46 *(17.4)*	51 *(19.5)*	-
7-9	45 *(17.0)*	45 *(17.2)*	-
10-12	36 *(13.6)*	28 *(10.7)*	-
Children using drug in the preceding month	72 *(27.3)*	95 *(36.4)*	**0.02**
Kind of infection at baseline visit			
Rhinitis	233 *(88.3)*	230 *(88.1)*	0.51
Pharyngotonsillitis	85 *(32.2)*	73 *(28.0)*	-
Laringite	41 *(15.5)*	40 *(15.3)*	-
Otitis	25 *(9.5)*	37 *(14.2)*	-
Others	74 *(28.0)*	70 *(26.8)*	-
Fever in the last 12 hours (Yes)	58 *(22.0)*	69 *(26.4)*	0.23

Table 2 - Children (N, %) with an occurrence of viral wheezing during the study period

Wheezing episodes in the preceding 6 months	Treatment group		p value
	Beclometasone	Placebo	
≤1	13/189 (6.9)	20/187 (10.7)	0.19
>1	5/75 (6.7)	9/74 (12.2)	0.25
Overall	**18/264 (6.8)**	**29/261 (11.1)**	**0.09**

See Appendix XX for the listings of primary endpoint by individual subject

Table 3 - Secondary outcome measures (concerning the experimental phase of the study)

	Beclometasone (N=264)	Placebo (N=261)	p value	Relative Risk (95%CI)
Extra visits, *n* (%)	34 (12.9)	41 (15.7)	0.35	0.82 (0.54-1.25)
Wheezing moderate/severe, *n* (%)	2 (0.8)	5 (1.9)	0.43	0.40 (0.08-2.02)
Prescription of rescue drugs, *n* (%)	11 (4.2)	17 (6.5)	0.23	0.64 (0.31-1.34)
Emergency room attendance, *n* (%)	6 (2.3)	4 (1.5)	0.76	1.48 (0.42-5.19)
Children fully adherent to therapy , *n* (%)	162 (61.4)	155 (59.4)	0.68	1.03(0.90-1.19)
Children with URTI symptoms at visit 2, *n* (%)	108 (41.2)	115 (44.4)	0.46	0.93 (0.76-1.13)
Parents who rated the treatment as helpful, *n* (%)	170 (64.4)	160 (61.3)	0.46	1.05 (0.92-1.20)
Parental score ≥ 7, *n* (%)	31 (11.7)	39 (14.9)	0.34	0.79 (0.51-1.22)

See Appendix XXI for the details of subjects with an extra visit during the 10 day treatment period

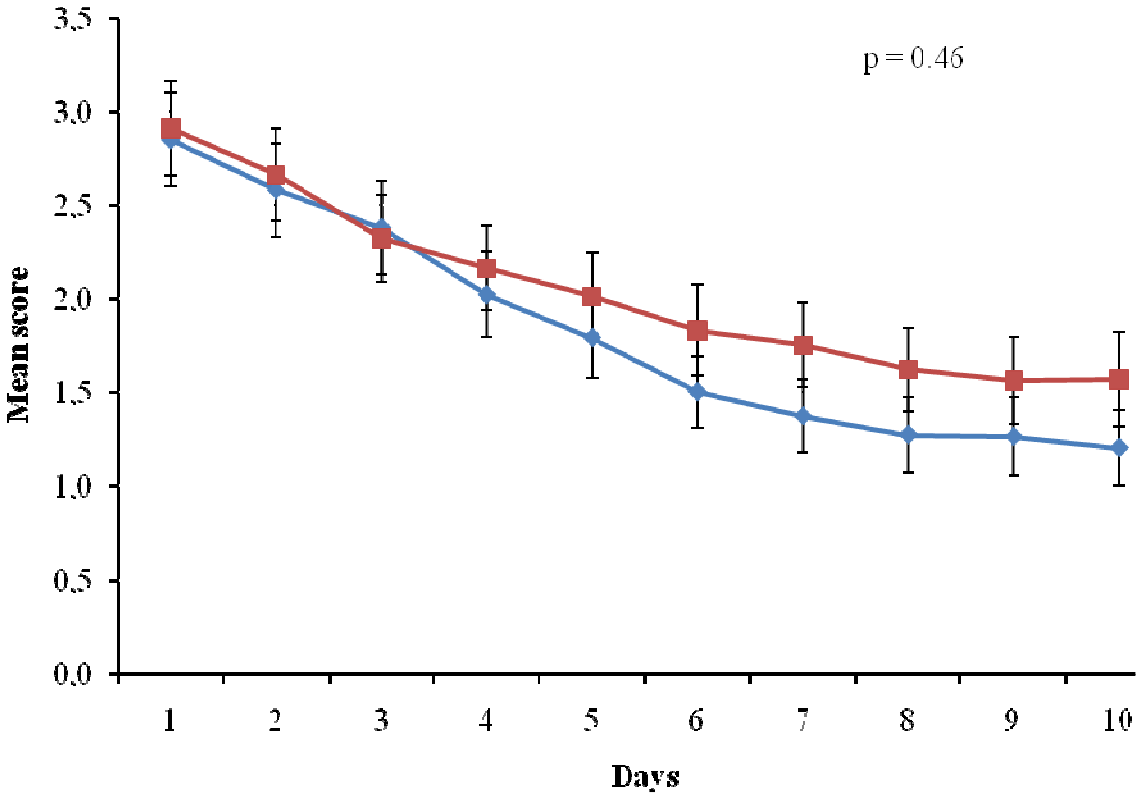
Table 4 - Mean cost per patient (€)

	Beclometasone N=264	Placebo N=261	p-value[§]
Drug treatment	11.69	0	
Other drugs	2.55	3.89	0.0081
Extra visit	1.60	1.98	0.0001
Emergency department attendance	0.64	0.43	0.0001
Lab tests	0.02	0.05	0.0001
Overall cost	**16.50**	**6.35**	**0.0001**

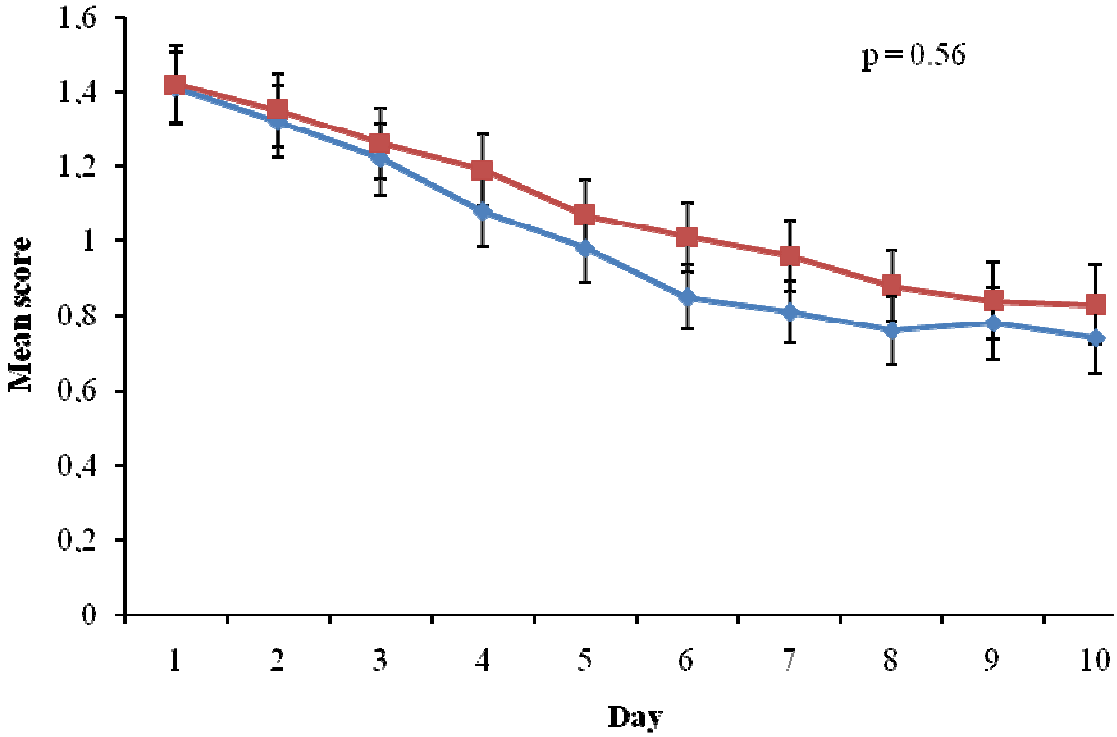
§ Kruskal-wallis test

Figure 2 - Day-by day scores (Mean and 95%Confidence Interval) (Beclometasone ◆; Placebo ■)

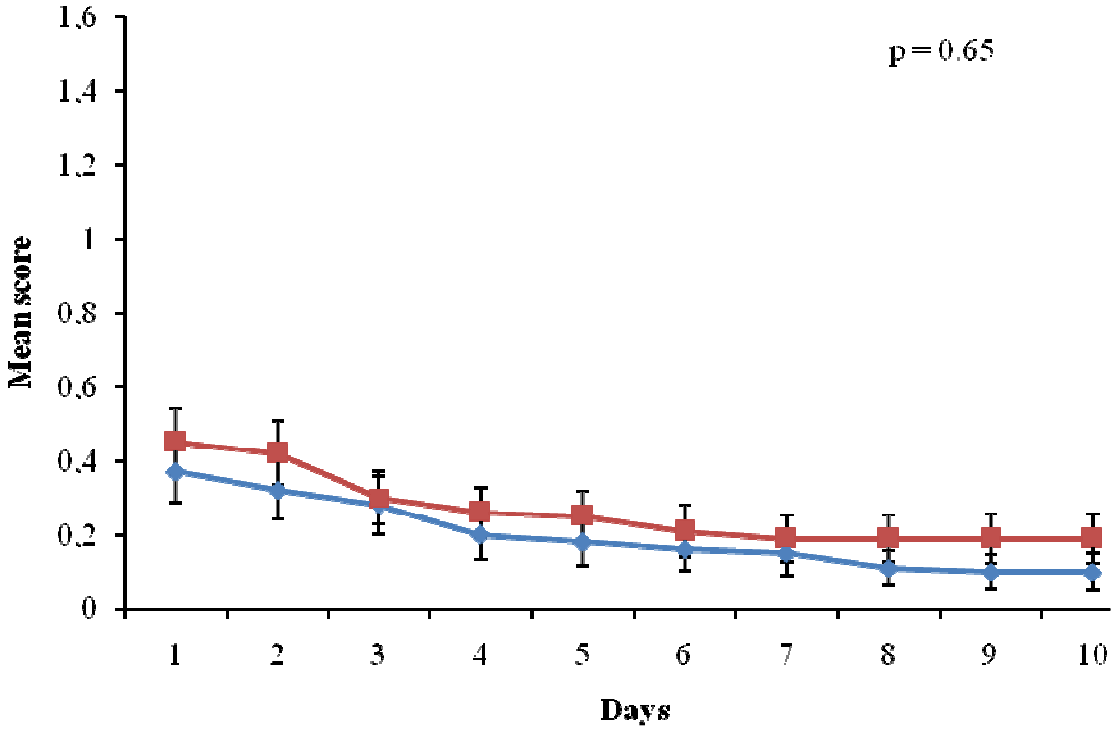
A) Overall



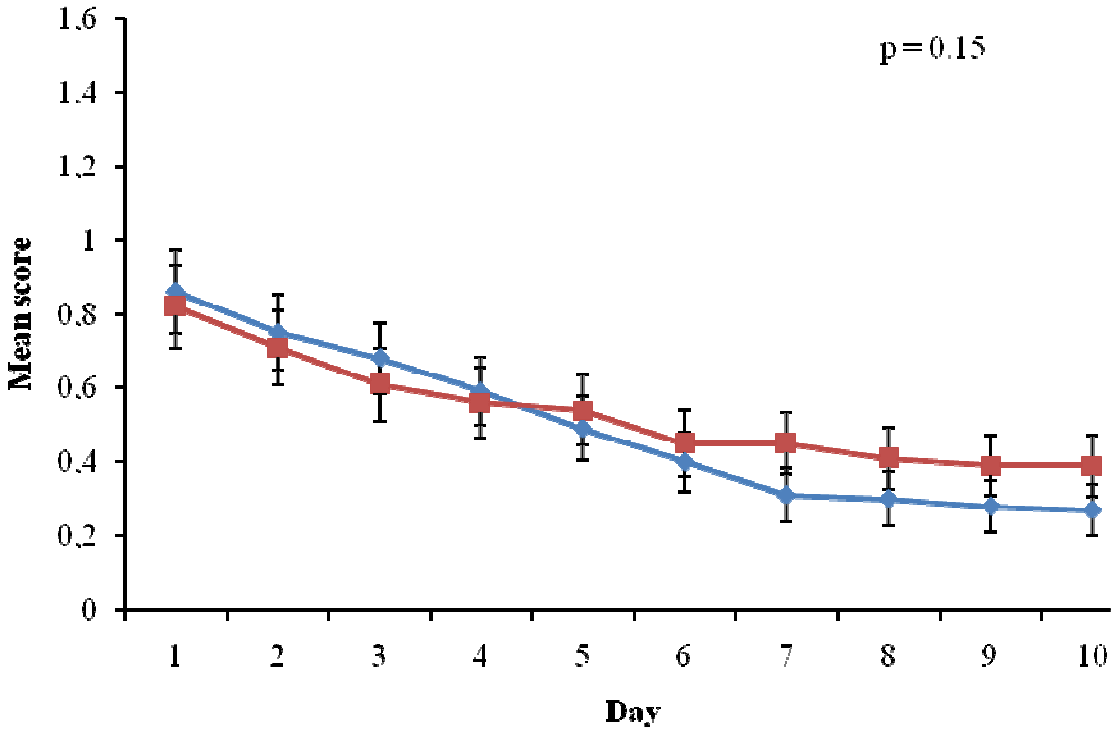
B) Cough



C) Breathlessness



D) Noisy breathing



E) Wheezing

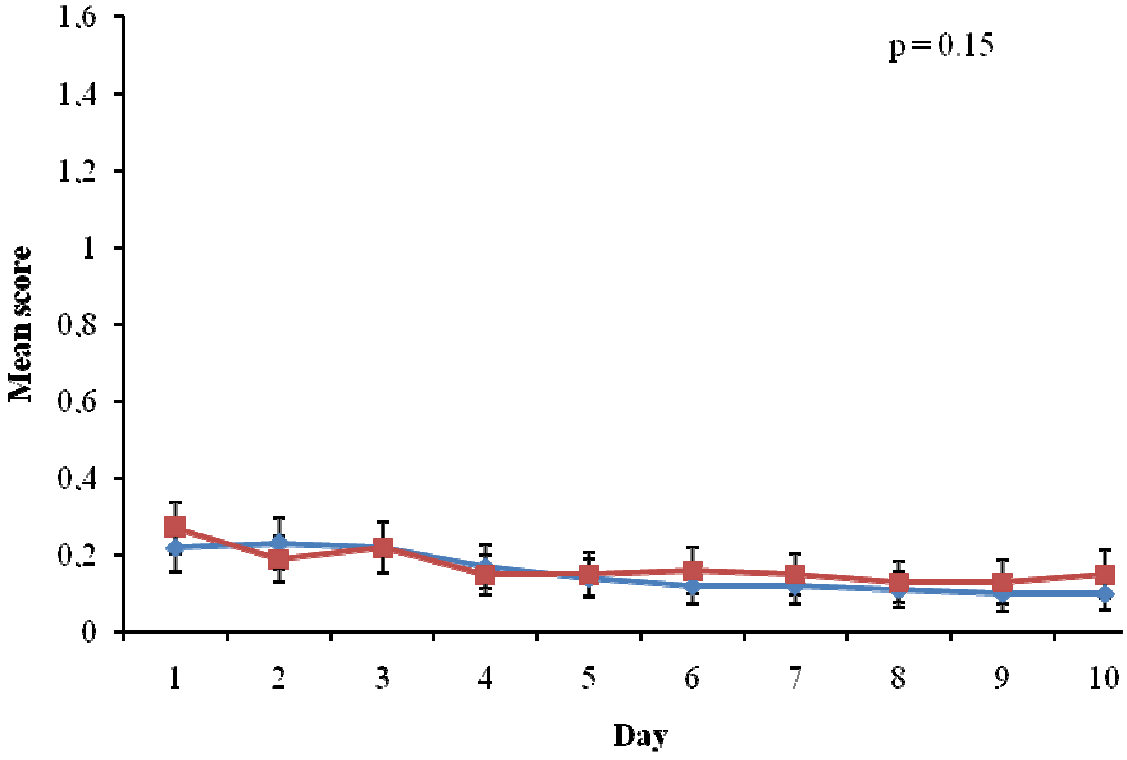
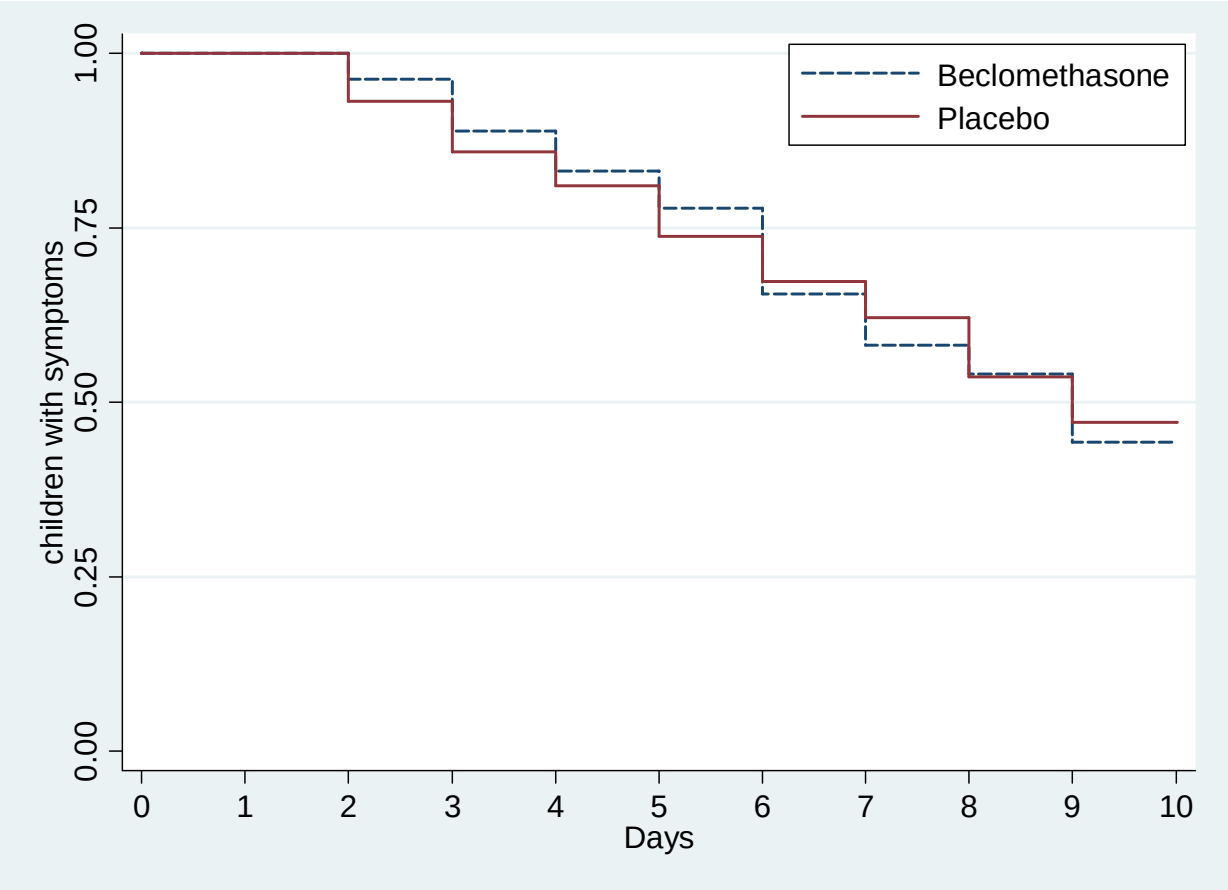


Figure 3 - Proportion of children with symptoms of upper respiratory tract infection during the 10 day treatment period



OUTCOME MEASURES EVALUATED DURING THE OBSERVATIONAL FOLLOW-UP PERIOD

Table 5 – Secondary endpoints (measured during follow-up period)

	Group			
	Beclometasone N=259	**Placebo N=248**	**Overall N=507**	**p-value**
Children with URTI visits*	128 (*49%*)	121 (*49%*)	249 (*49%*)	0.96
Children with ≥ 1 wheezing episode*	56 (*22%*)	60 (*24%*)	116 (*23%*)	0.49
Visits for URTI				
N	313	275	588	0.20†
mean±SD	2.5±1.6	2.3±1.5	2.4±1.6	
median	2	2	2	
N. URTI episodes (reported by parents)				
N	786	719	1505	0.93
mean±SD	3.0±1.6	2.9±1.6	3.0±1.6	
median	3	3	3	
Wheezing recurrence				
N	85	97	182	0.22†
mean±SD	1.5±0.9	1.6±1.0	1.6±1.0	
median	1	1	1	
Lenght of interval before wheezing occurrence (days)				
mean± SD	61.4±47.9	53.1±43.5	57.0±45.6	0.33
median	51	48	51	
Emergency Department attendance*	23 (9)	25 (10)	48 (*9*)	0.76
*ED attendance for wheezing**	*5 (2)*	*9 (4)*	14 (*3*)	0.37
Hospitalized children*	10 (4)	6 (2)	16 (*3*)	0.50
*Children hospitalized for wheezing**	*2 (1)*	*1 (1)*	*3 (1)*	*1*

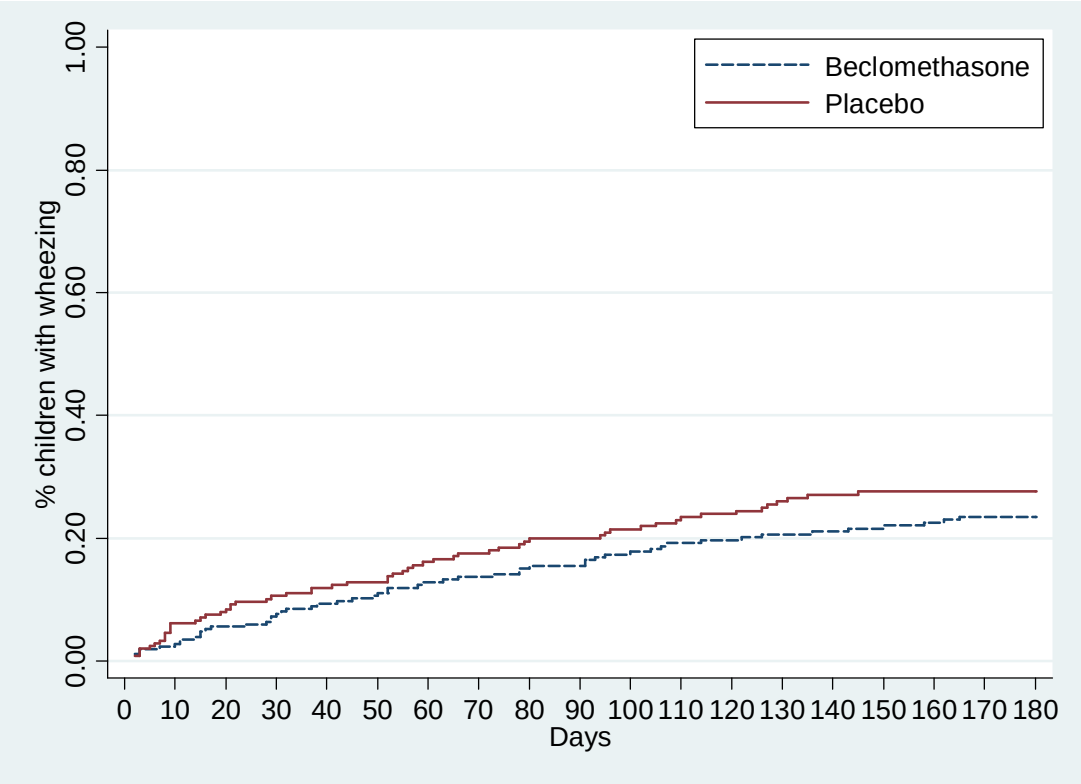
** N (%)*

*** Difference between the date of first wheezing recurrence and end of the treatment period.*

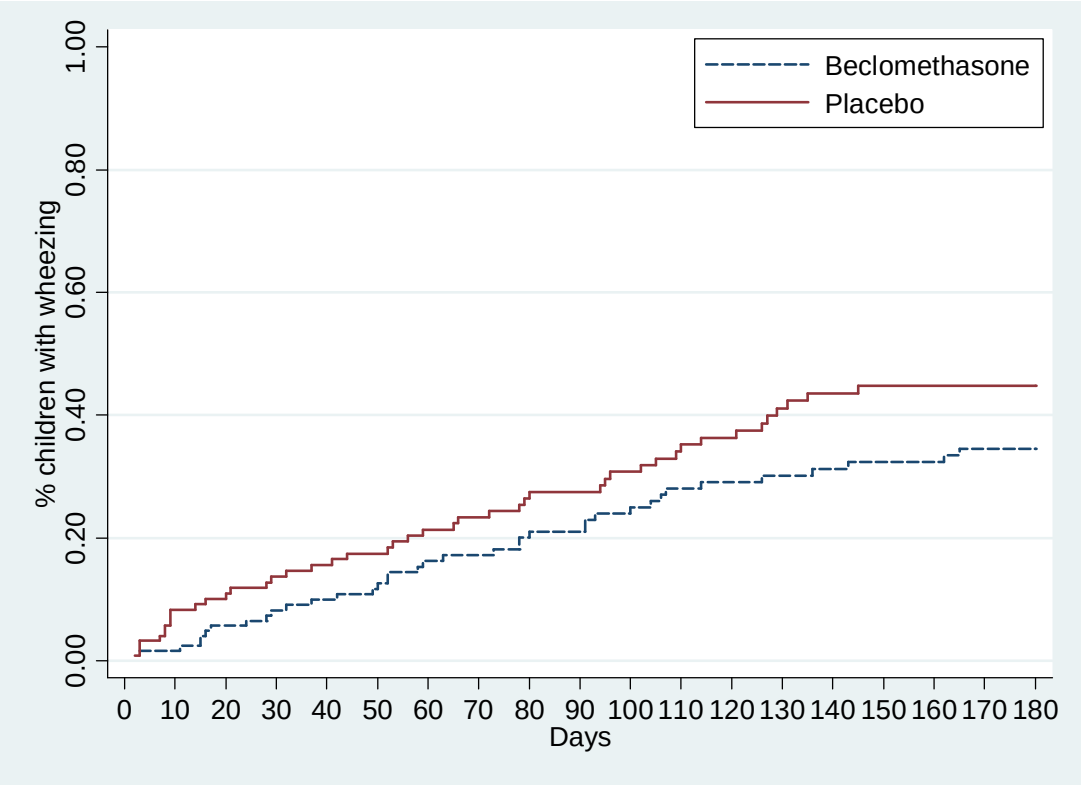
† *Poisson Regression analysis, adjusted for enrollment period*

Figure 4 – Cumulative incidence of viral wheezing recurrence during the follow-up period

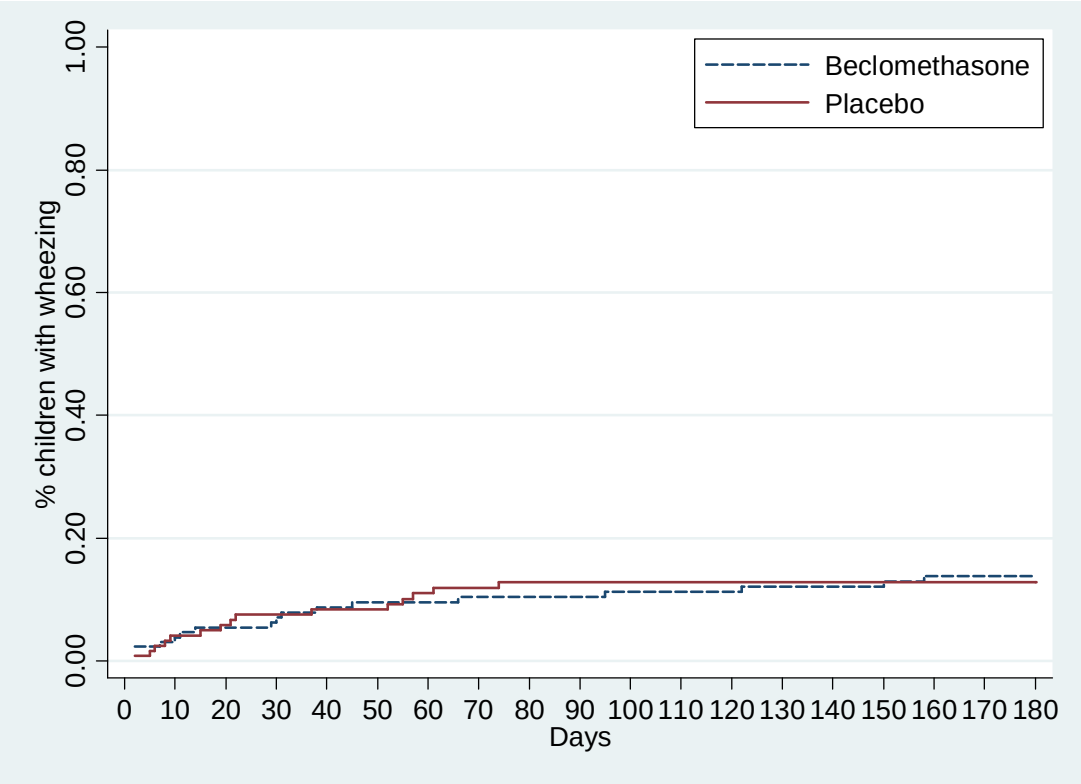
A) Overall population



B) Children enrolled between October and January



C) Children enrolled between February and May



Beclometasone vs Placebo (adjusted for enrollment period): HR = 0.84 (95%CI 0.58 – 1.21); p = 0.35

Table 6 – Children with wheezing occurred ONLY during the follow-up period

Wheezing episodes in the preceding 6 months	Group		
	Beclometasone	Placebo	Overall
≤1	35/187 (*19*)*	32/176 (*18*)*	67/363 (*18*)*
>1	16/72 (*22*)	16/72 (*22*)	32/144 (*22*)
Overall	51/259 (*20*)	48/248 (*19*)	99/507 (*20*)

** N (%)*

Table 7 – Wheezing severity

	Group		
	Beclometasone N=56	Placebo N=60	Overall N=116
Wheezing severity			
End-expiratory wheeze only	26 (*46*)*	27 (*45*)*	53 (*46*)*
Wheeze during entire expiratory phase	27 (*48*)	27 (*45*)	54 (*47*)
Wheezing audible without stethoscope	3 (*5*)	6 (*10*)	9 (*8*)

** N (%)*

Table 8 – N. children visited for URTI who were administered drugs before the visit

	Group		
	Beclometasone N=128	**Placebo N=121**	**Overall N=249**
Drug use			
No	38 (*30*)*	42 (*35*)*	80 (*32*)*
Yes	90 (70)	79 (*65*)	169 (*68*)

** N (%)*

Table 9 – Drugs most commonly administered by parents before the URTI visit

	Group		
	Beclometasone N=313*	**Placebo N=275***	**Overall N=525***
Drug			
Paracetamol	84 *(27)***	54 *(20)***	138 *(23)***
Salbutamol	45 *(14)*	48 *(17)*	93 *(16)*
Beclometasone	26 *(8)*	23 *(8)*	49 *(8)*
Bethametasone	18 *(6)*	15 *(5)*	33 *(6)*

*N. of URTI visits; **N (%)

Table 10 – Children with at least one drug prescribed by paediatricians for URTI

	Group		
	Beclometasone N=128	**Placebo N=121**	**Overall N=249**
Drug prescription			
No	14 (*11*)*	16 (*13*)*	30 (*12*)*
Yes	114 (*89*)	105 (*87*)	219 (*88*)

** N (%)*

Table 11 – Drugs most commonly prescribed by paediatricians for URTI

	Group		
	Beclometasone N=313*	**Placebo N=275***	**Overall N=588***
Drug			
Salbutamol	66 *(21)***	80 *(29)***	146 *(25)***
Saline	80 *(26)*	60 *(22)*	140 *(24)*
Amoxicillin	41 *(13)*	35 *(13)*	76 *(13)*
Beclometasone	33 *(11)*	43 *(16)*	76 *(13*)
Betamethasone	27 *(9)*	29 *(11)*	56 *(10)*
Paracetamol	23 *(7)*	15 *(5)*	38 *(6)*
Amoxicillin+Clavulanic Acid	16 *(5)*	13 *(5)*	29 *(5)*

*N. of URTI visits; **N (%)

Table 12 – N. Children with wheezing recurrence with at least one drug prescribed by paediatrician

	Group		Overall
	Beclometasone	Placebo	
	N=56	N=60	N=116
Drug prescription			
No	2 (*4*)*	3 (*5*)*	5 (*4*)*
Yes	54 (*96*)	57 (*95*)	111 (*96*)

* *N (%)*

Table 13 - Drugs most commonly prescribed by paediatricians to children with wheezing

	Group		
	Beclometasone	Placebo	Overall
	N=85*	N=97*	N=182*
Drug			
Salbutamol	58 *(68)***	72 *(74)***	130 *(71)***
Betamethasone	21 *(25)*	26 *(27)*	47 *(26)*
Saline	17 *(20)*	26 *(27)*	43 *(24)*
Beclometasone	9 *(11)*	29 *(30)*	38 *(21)*
Amoxicillin+Clavulanic Acid	8 *(9)*	10 *(10)*	18 *(10)*

*N. of wheezing recurrences; **N (%)

Table 14 – N. children with wheezing who received a beclometasone prescription

	Group		Overall
	Beclometasone N=56	Placebo N=60	N=116
Beclometasone prescription			
No	47 (*84*)*	37 (*62*)*	84 (*72*)*
Yes	9 (*16*)	23 (*38*)	32 (*28*)

** N (%)*

Table 15 – Children with at least one wheezing episode in the entire study period (experimental+observational phases)

	Group		Totale
	Beclometasone	Placebo	
Wheezing episodes in the preceding 6 months			
≤1	48/187 (*26*)*	51/176 (*29*)*	99/363 (*27*)*
>1	21/72 (*29*)	25/72 (*35*)	46/144 (*32*)
Overall	69/259 (*26*)	76/248 (*31*)	145/507 (*29*)

** N (%)*

FOCUS ON THE COHORT OF 258 CHILDREN ENROLLED DURING THE OCTOBER-DECEMBER PERIOD.

Results presented in tables 16-20 regard only the 258 children enrolled in the october-december period. In all, 251 of them completed the study.

Table 16 – Children with wheezing occurred during the 10 day treatment period

Wheezing episodes in the preceding 6 months	Group		p value
	Beclometasone	Placebo	
≤1	11/104 (*10.6*)*	14/99 (*14.1*)*	0.44
>1	3/25 (*12.0*)	5/30 (*16.7*)	0.72
Overall	14/129 (*10.9*)	19/129 (*14.7*)	0.36

** N (%)*

Table 17 – Children with ≥1 viral wheezing episode occurred during the entire study period (experimental+observational phases)

Wheezing episodes in the preceding 6 months	Group		
	Beclometasone	Placebo	Overall
≤1	37/102 (*36.3*)*	38/95 (*40*)*	75/197 (*38*)
>1	10/25 (*40*)	17/29 (*58.6*)	27/54 (*50*)
Overall	47/127 (*37*)	55/124 (*44.4*)	102/251 (*41*)

** N (%)*

Table 18 – Distribution of children by number of upper respiratory tract infection episodes occurred during the entire study period

	Group		
	Beclometasone N=127	**Placebo N=124**	**Overall N=251**
N. URTI episodes			
1	44 (*34.6*)*	36 (*29*)*	80 (*31.9*)
2	28 (*22*)	31 (*25*)	59 (*23.5*)
3	9 (*7.1*)	21 (*16.9*)	30 (*12*)
4	24 (*18.9*)	12 (*9.7*)	36 (*14.3*)
>4	22 (*17.3*)	24 (*19.4*)	46 (*18.3*)

** N (%)*

Table 19 – Distribution of children by number of viral wheezing episodes occurred during the entire study period (experimental+observational phases)

	Group		
	Beclometasone N=127	**Placebo N=124**	**Overall N=251**
N. wheezing episodes			
0	80 (*63*)*	69 (*55.6*)*	149 (*59.4*)*
1	29 (*22.8*)	35 (*28.2*)	64 (*25.5*)
2	14 (*11.0*)	10 (*8.1*)	24 (*9.6*)
≥3	4 (*3.1*)	10 (*8.1*)	14 (*5.6*)

** N (%)*

Table 20 – Demographic and anamnestic characteristics of children with versus without wheezing recurrence during the entire study period (independently from the phase)

	Wheezing recurrence		
	Yes N=102	**No N=149**	**p value**
Age (months)			
mean ± SD	37.3 ± 15.1	36.3 ± 16.8	0.65
median	33.5	34	-
min - max	12 - 69	12 - 71	-
Gender			
M	67 (*66*)*	88 (*59*)*	0.29
F	35 (*34*)	61 (*41*)	-
Delivery			
natural	61 (*60*)	87 (*58*)	0.82
cesarean	41 (*40*)	62 (*42*)	-
Gestational age (weeks)			
<37	11 (*11*)	13 (*9*)	0.59
≥37	91 (*89*)	136 (*91*)	
Atopic dermatitis (Yes)	28 (*27*)	42 (*28*)	0.90
Allergic Rhinitis (Yes)	8 (*8*)	7 (*5*)	0.30
At least one case with allergy in family (Yes)	48 (*47*)	78 (*52*)	0.41
At least one case with asthma in family (Yes)	29 (*28*)	28 (*19*)	0.07
At least one smoker in family (Yes)	45 (*44*)	52 (*35*)	0.14
N. Upper respiratory tract infections in the preceding 12 months			
mean ± SD	2.8 ± 1.8	2.5 ± 1.8	0.18
median	2	2	-
min -max	0 - 11	0 - 10	
N. wheezing episodes in the preceding 12 months			
mean ± SD	2.6 ± 1.7	2.2 ± 1.6	0.06
median	2	2	-
min - max	1 - 8	1 - 8	
N. wheezing episodes in the last 6 months			
≤1	75 (*74*)	122 (*82*)	0.15
>1	27 (*26*)	27 (*18*)	-
Time (months) from the last wheezing episode**:**			
≤3	48 (*47*)	52 (*35*)	0.05
>3	54 (*22*)	97 (*65*)	-

** N (%)*

Table 21– Adverse events (AE) reported by parents at the end of the treatment period

	Beclometasone* (N=264)	**Placebo* (N=261)**	**p-value**
Any AEs	**97 *(37)***	**98 *(37)***	**0.86**
Hoarseness	34 *(13)*	34 *(13)*	0.97
Diarrhea	27 (*10)*	35 *(13)*	0.30
Skin eruption	19 (*7)*	22 *(8)*	0.69
Vomiting	19 *(7)*	20 *(8)*	0.95
Candidosis	12 *(5)*	15 *(6)*	0.65
Restlessness	*12 (5)*	*7 (3)*	0.36
Perioral dermatitis	*1 (0.4)*	*6 (2)*	0.12
Others	*12 (5)*	*13 (5)*	0.98

** N (%)*

13 Reference

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14 Appendices

I List of the investigators and study personnel

II Antonio Clavenna's CV

III List of IEC

IV Study poster

V Patient information leaflet and informed consent

VI Study protocol

VII Case Report Form

VIII Diary number 1

IX Diary number 2

X Flow chart

XI Randomization list

XII SOP Gestione del farmaco

XIII SOP Redistribuzione farmaco

XIV SOP Eventi Avversi

XV SOP Monitoraggio

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XVII listings of individual subject withdrawal

XVIII Listing of protocol deviation

XIX Evaluation of subjects compliance

XX Primary endpoint by individual subjects

XXI Details of the 75 children having an extra visit (visit 1A) during the treatment period

Appendices

The Final Study Report of the ENBe study was originally submitted to the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) on the 24th April 2013.

Here are attached only the appendices (XVII-XXI) relevant for reporting the results of the study.

APPENDIX XVII - LISTING OF WITHDRAWALS

Subjects withdrawn before the end of the treatment visit (not presenting to visit 2)

Randomization code	Pediatrician code	LHU code	Age at the baseline visit (months)	Gender	Group	Reason
253	16	04	20	F	Beclometasone	Consent withdrawal
294	19	05	20	M	Placebo	Consent withdrawal
527	33	09	17	M	Beclometasone	Lost to follow up
637	40	05	65	M	Placebo	Lost to follow up

Subjects withdrawn before the end of the observational follow up (not presenting to visit 3)

Randomization code	Pediatrician code	LHU code	Age at the baseline visit (months)	Gender	Group	Reason
30	02	01	64	M	Placebo	Lost to follow up
167	11	03	18	M	Placebo	Lost to follow up
200	13	04	49	F	Placebo	Lost to follow up
268	17	05	60	M	Placebo	Lost to follow up
279	18	05	24	M	Beclometasone	Lost to follow up
280	18	05	24	F	Placebo	Lost to follow up
303	19	05	71	F	Placebo	Lost to follow up
384	24	06	50	M	Placebo	Lost to follow up
420	27	07	24	F	Beclometasone	Lost to follow up
434	28	07	38	M	Beclometasone	Lost to follow up
438	28	07	25	M	Placebo	Lost to follow up
459	29	08	29	F	Placebo	Lost to follow up
614	38	08	27	M	Placebo	Lost to follow up
639	40	05	29	M	Placebo	Lost to follow up

APPENDIX XVIII - LISTING OF THE PATIENTS WITH PROTOCOL DEVIATIONS (0=abstent; 1=present)

Random_ code	Ped_code	LHU	Drug	Therapy not completed	Visit 2 after 13 days	Not allowed drug use
11	1	1	Beclometasone	1	1	0
17	2	1	Beclometasone	1	1	0
19	2	1	Placebo	0	0	1
20	2	1	Beclometasone	1	0	0
21	2	1	Placebo	0	0	1
22	2	1	Beclometasone	1	0	0
24	2	1	Placebo	1	0	0
25	2	1	Beclometasone	1	0	0
27	2	1	Placebo	0	1	0
28	2	1	Beclometasone	1	1	0
29	2	1	Beclometasone	0	0	1
30	2	1	Placebo	0	1	0
32	2	1	Placebo	1	0	0
33	3	1	Beclometasone	0	0	1
52	4	1	Placebo	1	0	0
54	4	1	Beclometasone	0	1	0
65	5	2	Placebo	1	0	0
66	5	2	Beclometasone	1	0	0
71	5	2	Beclometasone	1	0	0
74	5	2	Placebo	1	1	0
75	5	2	Beclometasone	1	0	0
77	5	2	Placebo	1	0	0
83	6	2	Placebo	1	0	0
95	6	2	Beclometasone	1	0	0
99	7	2	Beclometasone	1	0	0
103	7	2	Placebo	0	1	0
104	7	2	Beclometasone	0	0	1
108	7	2	Placebo	1	0	0
111	7	2	Placebo	1	1	0
112	7	2	Beclometasone	1	1	0
115	8	2	Placebo	1	0	0
116	8	2	Beclometasone	1	0	0
117	8	2	Placebo	1	0	0
119	8	2	Beclometasone	1	0	0
122	8	2	Beclometasone	1	0	0
126	8	2	Beclometasone	1	0	0
127	8	2	Beclometasone	1	0	0
128	8	2	Placebo	0	0	1
130	9	3	Placebo	1	0	0
135	9	3	Beclometasone	1	0	0
138	9	3	Beclometasone	1	0	0

142	9	3	Beclometasone	1	0	0
144	9	3	Beclometasone	0	1	0
148	10	3	Placebo	0	1	0
149	10	3	Placebo	0	1	0
153	10	3	Placebo	0	1	0
154	10	3	Beclometasone	0	1	0
155	10	3	Placebo	1	1	0
156	10	3	Beclometasone	0	1	0
157	10	3	Beclometasone	1	1	0
158	10	3	Placebo	1	1	0
163	11	3	Placebo	1	0	0
164	11	3	Beclometasone	1	1	0
165	11	3	Placebo	0	0	1
167	11	3	Placebo	1	0	0
178	12	3	Beclometasone	1	0	0
181	12	3	Beclometasone	1	0	0
182	12	3	Placebo	1	0	0
185	12	3	Beclometasone	1	0	0
186	12	3	Placebo	1	1	0
189	12	3	Beclometasone	1	0	0
190	12	3	Placebo	1	1	0
191	12	3	Placebo	1	0	0
192	12	3	Beclometasone	1	0	0
193	13	4	Beclometasone	1	0	0
196	13	4	Placebo	1	1	0
198	13	4	Beclometasone	1	1	0
200	13	4	Placebo	1	0	0
203	13	4	Beclometasone	1	0	0
204	13	4	Placebo	0	1	0
206	13	4	Beclometasone	1	0	0
211	14	4	Beclometasone	0	1	0
241	16	4	Placebo	0	0	1
243	16	4	Beclometasone	1	0	0
244	16	4	Placebo	1	1	0
245	16	4	Placebo	1	0	0
247	16	4	Beclometasone	1	0	0
248	16	4	Placebo	1	0	0
249	16	4	Placebo	1	0	0
250	16	4	Beclometasone	1	0	0
252	16	4	Beclometasone	1	1	0
254	16	4	Placebo	1	0	0
255	16	4	Placebo	1	0	0
260	17	5	Placebo	1	0	0
261	17	5	Beclometasone	0	0	1
263	17	5	Beclometasone	0	0	1
265	17	5	Placebo	1	0	0

268	17	5	Placebo	1	0	0
270	17	5	Placebo	1	0	0
271	17	5	Placebo	1	0	0
272	17	5	Beclometasone	0	1	0
275	18	5	Placebo	0	0	1
276	18	5	Beclometasone	1	1	0
277	18	5	Placebo	1	0	0
278	18	5	Beclometasone	1	0	0
279	18	5	Beclometasone	1	0	0
280	18	5	Placebo	1	1	0
282	18	5	Placebo	1	0	0
283	18	5	Placebo	0	0	1
284	18	5	Beclometasone	1	0	0
285	18	5	Placebo	1	0	0
289	19	5	Placebo	1	1	0
290	19	5	Beclometasone	1	0	0
291	19	5	Beclometasone	1	0	0
293	19	5	Beclometasone	1	0	0
295	19	5	Placebo	1	0	0
296	19	5	Beclometasone	0	1	0
298	19	5	Beclometasone	1	1	0
299	19	5	Placebo	1	1	0
300	19	5	Beclometasone	1	0	0
301	19	5	Beclometasone	1	0	0
302	19	5	Placebo	1	0	0
303	19	5	Placebo	1	0	0
304	19	5	Beclometasone	1	0	0
307	20	5	Placebo	1	1	0
313	20	5	Beclometasone	0	1	0
320	20	5	Placebo	0	0	1
322	21	6	Placebo	1	0	0
327	21	6	Beclometasone	1	1	0
328	21	6	Placebo	0	1	0
331	21	6	Beclometasone	1	0	0
338	22	6	Placebo	1	0	0
340	22	6	Beclometasone	1	0	0
341	22	6	Beclometasone	1	0	0
342	22	6	Placebo	1	0	0
343	22	6	Beclometasone	1	0	0
344	22	6	Placebo	0	1	0
346	22	6	Beclometasone	1	1	0
352	22	6	Beclometasone	0	0	1
353	23	6	Beclometasone	0	0	1
354	23	6	Placebo	1	1	0
355	23	6	Placebo	1	1	0
356	23	6	Beclometasone	1	1	0

358	23	6	Placebo	1	0	0
361	23	6	Placebo	1	0	0
362	23	6	Beclometasone	1	0	0
363	23	6	Placebo	1	1	0
369	24	6	Placebo	1	0	0
370	24	6	Beclometasone	1	0	0
371	24	6	Beclometasone	1	0	0
373	24	6	Beclometasone	1	0	0
374	24	6	Placebo	1	0	0
375	24	6	Placebo	1	1	0
376	24	6	Beclometasone	1	0	0
377	24	6	Placebo	1	0	0
378	24	6	Beclometasone	1	0	0
382	24	6	Beclometasone	0	1	0
383	24	6	Beclometasone	1	0	0
384	24	6	Placebo	1	0	0
385	25	7	Beclometasone	0	1	0
387	25	7	Placebo	0	1	0
388	25	7	Beclometasone	0	1	0
393	25	7	Beclometasone	0	1	0
394	25	7	Placebo	1	0	0
395	25	7	Beclometasone	1	0	0
397	25	7	Placebo	1	0	0
398	25	7	Beclometasone	0	1	0
399	25	7	Beclometasone	0	1	0
401	26	7	Beclometasone	1	0	0
402	26	7	Placebo	1	0	0
403	26	7	Beclometasone	1	0	0
405	26	7	Beclometasone	1	0	0
417	27	7	Beclometasone	1	0	0
418	27	7	Placebo	1	0	0
421	27	7	Placebo	1	0	0
422	27	7	Beclometasone	1	0	0
423	27	7	Placebo	1	0	0
425	27	7	Beclometasone	1	1	0
426	27	7	Placebo	1	0	0
427	27	7	Beclometasone	1	1	0
428	27	7	Placebo	1	0	0
429	27	7	Placebo	1	1	0
430	27	7	Beclometasone	1	0	0
432	27	7	Placebo	1	0	0
433	28	7	Placebo	1	0	0
435	28	7	Placebo	0	1	0
438	28	7	Placebo	1	0	0
439	28	7	Placebo	1	0	0
452	29	8	Placebo	0	0	1

453	29	8	Beclometasone	0	1	0
457	29	8	Placebo	0	1	0
458	29	8	Beclometasone	1	1	0
461	29	8	Placebo	1	0	0
462	29	8	Beclometasone	0	1	0
463	29	8	Placebo	0	1	0
465	30	8	Beclometasone	1	1	0
466	30	8	Placebo	1	0	0
467	30	8	Beclometasone	0	1	0
468	30	8	Placebo	1	0	0
469	30	8	Placebo	0	1	0
470	30	8	Beclometasone	0	1	0
471	30	8	Beclometasone	0	1	0
472	30	8	Placebo	1	0	0
476	30	8	Placebo	1	0	0
479	30	8	Placebo	1	1	0
480	30	8	Beclometasone	1	1	0
482	31	8	Placebo	1	0	0
483	31	8	Placebo	1	0	0
484	31	8	Beclometasone	1	0	0
485	31	8	Placebo	1	0	0
489	31	8	Beclometasone	1	0	0
491	31	8	Placebo	0	0	1
493	31	8	Placebo	1	0	0
495	31	8	Placebo	1	1	0
498	32	8	Beclometasone	1	0	0
499	32	8	Beclometasone	0	1	0
500	32	8	Placebo	1	0	0
501	32	8	Beclometasone	1	0	0
503	32	8	Placebo	0	1	0
504	32	8	Beclometasone	1	0	0
506	32	8	Placebo	0	0	1
507	32	8	Beclometasone	1	1	0
508	32	8	Placebo	1	0	0
510	32	8	Beclometasone	1	0	0
511	32	8	Beclometasone	1	0	0
512	32	8	Placebo	1	0	0
513	33	9	Placebo	1	1	0
514	33	9	Beclometasone	0	1	0
515	33	9	Placebo	1	1	0
516	33	9	Beclometasone	1	0	0
517	33	9	Placebo	0	1	0
518	33	9	Beclometasone	1	0	0
519	33	9	Placebo	1	1	0
521	33	9	Beclometasone	1	0	0
522	33	9	Placebo	1	1	0

524	33	9	Beclometasone	1	0	0
526	33	9	Beclometasone	1	0	0
528	33	9	Placebo	0	1	0
531	34	9	Beclometasone	0	1	0
536	34	9	Placebo	1	1	0
537	34	9	Placebo	1	0	0
538	34	9	Beclometasone	0	1	0
539	34	9	Placebo	1	1	0
540	34	9	Beclometasone	1	1	0
541	34	9	Beclometasone	0	1	0
542	34	9	Placebo	0	0	1
543	34	9	Beclometasone	1	1	0
545	35	9	Placebo	1	1	0
546	35	9	Beclometasone	0	1	0
547	35	9	Beclometasone	0	1	0
548	35	9	Placebo	1	1	0
550	35	9	Beclometasone	1	1	0
551	35	9	Placebo	0	1	0
552	35	9	Beclometasone	1	0	0
555	35	9	Placebo	1	1	0
556	35	9	Beclometasone	1	1	0
558	35	9	Placebo	1	1	0
559	35	9	Placebo	0	0	1
560	35	9	Beclometasone	1	1	0
561	36	9	Beclometasone	1	1	0
563	36	9	Placebo	1	1	0
564	36	9	Beclometasone	1	1	0
569	36	9	Placebo	0	1	0
570	36	9	Beclometasone	1	0	0
571	36	9	Placebo	1	1	0
572	36	9	Beclometasone	1	1	0
576	36	9	Placebo	1	1	0
601	37	2	Beclometasone	1	0	0
602	37	2	Placebo	1	0	0
605	37	2	Beclometasone	1	0	0
607	37	2	Placebo	1	0	0
608	37	2	Placebo	1	0	0
609	37	2	Beclometasone	1	0	0
610	37	2	Placebo	1	0	0
611	37	2	Beclometasone	1	0	0
612	38	8	Beclometasone	0	1	0
614	38	8	Placebo	1	0	0
615	38	8	Beclometasone	0	1	0
616	38	8	Placebo	0	1	0
617	38	8	Beclometasone	0	1	0
634	39	5	Beclometasone	1	0	0

636	40	5	Beclometasone	0	1	0
639	40	5	Placebo	1	0	0
642	40	5	Placebo	1	0	0

APPENDIX XIX – EVALUATION OF SUBJECTS COMPLIANCE

Randomization code	Age at entry visit (month)	Gender	Drug	Therapy completed	N. missed doses
1	56	F	Beclometasone	Y	0
2	34	F	Placebo	Y	0
3	16	F	Placebo	Y	0
4	70	F	Beclometasone	Y	0
5	45	F	Beclometasone	Y	0
6	24	M	Placebo	Y	0
7	28	M	Beclometasone	Y	0
8	48	M	Placebo	Y	0
9	38	M	Beclometasone	Y	0
10	57	M	Placebo	Y	0
11	16	M	Beclometasone	N	1
12	12	F	Placebo	Y	0
13	68	M	Placebo	Y	0
14	36	M	Beclometasone	Y	0
15	65	M	Beclometasone	Y	0
16	36	M	Placebo	Y	0
17	32	M	Beclometasone	N	1
18	27	M	Placebo	Y	0
19	49	M	Placebo	Y	0
20	28	M	Beclometasone	N	1
21	28	M	Placebo	Y	0
22	65	M	Beclometasone	N	1
23	56	M	Beclometasone	Y	0
24	29	M	Placebo	N	3
25	15	M	Beclometasone	N	1
26	14	M	Placebo	Y	0
27	33	F	Placebo	Y	0
28	49	M	Beclometasone	N	1
29	49	M	Beclometasone	Y	0
30	64	M	Placebo	Y	0
31	23	F	Beclometasone	Y	0
32	22	F	Placebo	N	2
33	41	F	Beclometasone	Y	0
34	60	F	Placebo	Y	0
35	45	M	Beclometasone	Y	0
49	36	M	Placebo	Y	0
50	19	M	Beclometasone	Y	0
51	19	M	Beclometasone	Y	0
52	51	F	Placebo	N	5
53	12	F	Placebo	Y	0
54	29	M	Beclometasone	Y	0

55	23	F	Beclometasone	Y	0
65	49	F	Placebo	N	6
66	13	M	Beclometasone	N	4
67	29	M	Placebo	Y	0
68	50	M	Beclometasone	Y	0
69	46	F	Beclometasone	Y	0
70	46	M	Placebo	Y	0
71	41	M	Beclometasone	N	2
72	49	F	Placebo	Y	0
73	29	F	Beclometasone	Y	0
74	31	M	Placebo	N	1
75	19	F	Beclometasone	N	1
76	31	M	Placebo	Y	0
77	48	F	Placebo	N	1
78	39	M	Beclometasone	Y	0
79	59	F	Beclometasone	Y	0
80	48	M	Placebo	Y	0
81	57	M	Beclometasone	Y	0
82	26	M	Placebo	Y	0
83	17	M	Placebo	N	11
84	17	M	Beclometasone	Y	0
85	39	F	Placebo	Y	0
86	57	F	Beclometasone	Y	0
87	37	F	Beclometasone	Y	0
88	21	M	Placebo	Y	0
89	45	F	Placebo	Y	0
90	53	M	Beclometasone	Y	0
91	12	F	Placebo	Y	0
92	16	F	Beclometasone	Y	0
93	20	M	Placebo	Y	0
94	20	M	Beclometasone	Y	0
95	45	F	Beclometasone	N	2
96	47	F	Placebo	Y	0
97	57	M	Placebo	Y	0
98	29	M	Beclometasone	Y	0
99	47	M	Beclometasone	N	1
100	33	F	Placebo	Y	0
101	51	F	Placebo	Y	0
102	23	M	Beclometasone	Y	0
103	55	F	Placebo	Y	0
104	47	M	Beclometasone	Y	0
105	51	M	Placebo	Y	0
106	16	F	Beclometasone	Y	0
107	13	M	Beclometasone	Y	0
108	54	F	Placebo	N	3
109	36	F	Placebo	Y	0

110	60	M	Beclometasone	Y	0
111	26	M	Placebo	N	3
112	32	M	Beclometasone	N	3
113	30	M	Beclometasone	Y	0
114	15	M	Placebo	Y	0
115	17	M	Placebo	N	3
116	32	F	Beclometasone	N	1
117	31	M	Placebo	N	2
118	31	M	Beclometasone	Y	0
119	57	F	Beclometasone	N	4
120	22	M	Placebo	Y	0
121	63	M	Placebo	Y	0
122	23	M	Beclometasone	N	15
123	46	F	Placebo	Y	0
124	52	M	Beclometasone	Y	0
125	54	M	Placebo	Y	0
126	16	M	Beclometasone	N	2
127	71	M	Beclometasone	N	1
128	50	M	Placebo	Y	0
129	27	M	Beclometasone	Y	0
130	22	M	Placebo	N	10
131	67	M	Beclometasone	Y	0
132	15	M	Placebo	Y	0
133	23	F	Placebo	Y	0
134	30	M	Beclometasone	Y	0
135	34	F	Beclometasone	N	2
136	33	M	Placebo	Y	0
137	55	F	Placebo	Y	0
138	25	M	Beclometasone	N	10
139	17	F	Beclometasone	Y	0
140	42	M	Placebo	Y	0
141	18	M	Placebo	Y	0
142	17	M	Beclometasone	N	6
144	21	F	Beclometasone	Y	0
145	62	M	Placebo	Y	0
146	35	M	Beclometasone	Y	0
147	37	M	Beclometasone	Y	0
148	24	M	Placebo	Y	0
149	12	M	Placebo	Y	0
150	33	M	Beclometasone	Y	0
153	20	M	Placebo	Y	0
154	17	F	Beclometasone	Y	0
155	14	M	Placebo	N	1
156	21	M	Beclometasone	Y	0
157	52	F	Beclometasone	N	10
158	28	M	Placebo	N	17

161	34	F	Placebo	Y	0
162	15	M	Beclometasone	Y	0
163	16	F	Placebo	N	2
164	19	M	Beclometasone	N	2
165	32	M	Placebo	Y	0
166	15	F	Beclometasone	Y	0
167	18	M	Placebo	N	5
177	28	M	Placebo	Y	0
178	37	F	Beclometasone	N	1
179	17	F	Placebo	Y	0
180	54	F	Beclometasone	Y	0
181	54	M	Beclometasone	N	16
182	59	M	Placebo	N	2
183	14	M	Beclometasone	Y	0
184	53	F	Placebo	Y	0
185	29	F	Beclometasone	N	4
186	12	M	Placebo	N	1
187	51	M	Placebo	Y	0
188	18	F	Beclometasone	Y	0
189	31	M	Beclometasone	N	1
190	29	F	Placebo	N	10
191	14	M	Placebo	N	1
192	19	M	Beclometasone	N	1
193	30	M	Beclometasone	N	1
194	40	F	Placebo	Y	0
195	66	M	Beclometasone	Y	0
196	63	M	Placebo	N	1
197	42	F	Placebo	Y	0
198	72	F	Beclometasone	N	1
199	52	F	Beclometasone	Y	0
200	49	F	Placebo	N	16
201	43	F	Placebo	Y	0
202	28	F	Beclometasone	Y	0
203	20	M	Beclometasone	N	1
204	22	M	Placebo	Y	0
205	49	F	Placebo	Y	0
206	44	F	Beclometasone	N	2
207	50	F	Beclometasone	Y	0
208	27	M	Placebo	Y	0
211	59	F	Beclometasone	Y	0
212	22	M	Placebo	Y	0
241	65	M	Placebo	Y	0
242	30	M	Beclometasone	Y	0
243	28	F	Beclometasone	N	1
244	71	F	Placebo	N	16
245	62	F	Placebo	N	3

246	28	M	Beclometasone	Y	0
247	34	M	Beclometasone	N	13
248	23	M	Placebo	N	1
249	68	F	Placebo	N	1
250	36	M	Beclometasone	N	2
251	64	F	Placebo	Y	0
252	27	M	Beclometasone	N	1
253	20	F	Beclometasone	N	20
254	17	M	Placebo	N	2
255	65	M	Placebo	N	3
256	16	F	Beclometasone	Y	0
257	50	M	Placebo	Y	0
258	54	M	Beclometasone	Y	0
259	23	M	Beclometasone	Y	0
260	64	M	Placebo	N	1
261	18	M	Beclometasone	Y	0
262	35	M	Placebo	Y	0
263	44	M	Beclometasone	Y	0
264	45	M	Placebo	Y	0
265	59	M	Placebo	N	1
266	50	M	Beclometasone	Y	0
267	47	M	Beclometasone	Y	0
268	60	M	Placebo	N	14
269	50	M	Beclometasone	Y	0
270	24	F	Placebo	N	1
271	70	M	Placebo	N	2
272	50	F	Beclometasone	Y	0
273	38	M	Beclometasone	Y	0
274	12	M	Placebo	Y	0
275	39	M	Placebo	Y	0
276	19	F	Beclometasone	N	7
277	12	M	Placebo	N	18
278	31	M	Beclometasone	N	3
279	24	M	Beclometasone	N	17
280	24	F	Placebo	N	18
281	22	M	Beclometasone	Y	0
282	31	F	Placebo	N	1
283	15	F	Placebo	Y	0
284	23	M	Beclometasone	N	1
285	16	M	Placebo	N	1
286	20	M	Beclometasone	Y	0
287	40	M	Beclometasone	Y	0
288	28	M	Placebo	Y	0
289	28	F	Placebo	N	3
290	16	M	Beclometasone	N	4
291	14	F	Beclometasone	N	5

292	42	M	Placebo	Y	0
293	18	F	Beclometasone	N	2
294	20	M	Placebo	N	15
295	23	M	Placebo	N	6
296	30	F	Beclometasone	Y	0
297	15	M	Placebo	Y	0
298	15	M	Beclometasone	N	16
299	43	M	Placebo	N	5
300	19	M	Beclometasone	N	3
301	45	F	Beclometasone	N	2
302	24	F	Placebo	N	4
303	71	F	Placebo	N	16
304	32	F	Beclometasone	N	4
305	43	M	Placebo	Y	0
306	33	M	Beclometasone	Y	0
307	55	M	Placebo	N	4
308	17	F	Beclometasone	Y	0
309	25	M	Placebo	Y	0
310	41	M	Beclometasone	Y	0
311	14	M	Beclometasone	Y	0
312	37	M	Placebo	Y	0
313	18	M	Beclometasone	Y	0
314	43	F	Placebo	Y	0
315	21	M	Beclometasone	Y	0
316	56	M	Placebo	Y	0
317	35	F	Beclometasone	Y	0
318	21	M	Placebo	Y	0
319	21	M	Beclometasone	Y	0
320	22	M	Placebo	Y	0
321	12	F	Beclometasone	Y	0
322	58	F	Placebo	N	2
323	16	F	Beclometasone	Y	0
324	32	F	Placebo	Y	0
325	37	F	Beclometasone	Y	0
326	24	F	Placebo	Y	0
327	31	M	Beclometasone	N	2
328	22	M	Placebo	Y	0
329	33	F	Beclometasone	Y	0
330	33	M	Placebo	Y	0
331	32	F	Beclometasone	N	1
332	50	F	Placebo	Y	0
333	36	M	Beclometasone	Y	0
334	46	F	Placebo	Y	0
335	19	F	Placebo	Y	0
336	32	M	Beclometasone	Y	0
337	50	F	Beclometasone	Y	0

338	59	M	Placebo	N	2
339	43	M	Placebo	Y	0
340	58	M	Beclometasone	N	2
341	45	M	Beclometasone	N	1
342	35	F	Placebo	N	3
343	69	M	Beclometasone	N	4
344	30	M	Placebo	Y	0
345	20	M	Placebo	Y	0
346	68	M	Beclometasone	N	6
347	46	M	Placebo	Y	0
348	38	F	Beclometasone	Y	0
349	20	M	Placebo	Y	0
350	59	M	Beclometasone	Y	0
351	19	M	Placebo	Y	0
352	56	M	Beclometasone	Y	0
353	58	M	Beclometasone	Y	0
354	32	F	Placebo	N	6
355	44	F	Placebo	N	2
356	51	M	Beclometasone	N	1
357	45	M	Beclometasone	Y	0
358	23	F	Placebo	N	1
359	65	M	Beclometasone	Y	0
360	70	M	Placebo	Y	0
361	22	F	Placebo	N	8
362	50	M	Beclometasone	N	6
363	37	M	Placebo	N	9
364	33	M	Beclometasone	Y	0
365	64	F	Beclometasone	Y	0
366	27	M	Placebo	Y	0
367	32	F	Beclometasone	Y	0
368	43	F	Placebo	Y	0
369	24	F	Placebo	N	10
370	34	F	Beclometasone	N	1
371	55	M	Beclometasone	N	2
372	50	M	Placebo	Y	0
373	48	M	Beclometasone	N	1
374	26	F	Placebo	N	1
375	43	F	Placebo	N	2
376	35	M	Beclometasone	N	2
377	35	M	Placebo	N	10
378	29	M	Beclometasone	N	4
379	46	M	Beclometasone	Y	0
381	55	M	Placebo	Y	0
382	61	F	Beclometasone	Y	0
383	19	M	Beclometasone	N	2
384	50	M	Placebo	N	5

385	29	F	Beclometasone	Y	0
386	19	M	Placebo	Y	0
387	29	F	Placebo	Y	0
388	63	F	Beclometasone	Y	0
389	45	M	Beclometasone	Y	0
390	59	F	Placebo	Y	0
391	40	F	Placebo	Y	0
392	14	M	Beclometasone	Y	0
393	25	M	Beclometasone	Y	0
394	36	F	Placebo	N	5
395	43	M	Beclometasone	N	4
396	45	M	Placebo	Y	0
397	35	M	Placebo	N	9
398	60	F	Beclometasone	Y	0
399	72	F	Beclometasone	Y	0
400	41	F	Placebo	Y	0
401	26	F	Beclometasone	N	1
402	36	F	Placebo	N	5
403	24	M	Beclometasone	N	2
404	42	M	Placebo	Y	0
405	18	M	Beclometasone	N	1
417	40	M	Beclometasone	N	2
418	35	M	Placebo	N	8
419	23	M	Placebo	Y	0
420	24	F	Beclometasone	Y	0
421	23	M	Placebo	N	2
422	38	M	Beclometasone	N	7
423	42	M	Placebo	N	2
424	60	M	Beclometasone	Y	0
425	33	M	Beclometasone	N	3
426	31	M	Placebo	N	1
427	38	M	Beclometasone	N	1
428	57	M	Placebo	N	3
429	18	M	Placebo	N	4
430	15	F	Beclometasone	N	3
431	38	F	Beclometasone	Y	0
432	27	F	Placebo	N	2
433	13	M	Placebo	N	7
434	38	M	Beclometasone	Y	0
435	21	F	Placebo	Y	0
436	21	M	Beclometasone	Y	0
437	18	M	Beclometasone	Y	0
438	25	M	Placebo	N	3
439	23	F	Placebo	N	3
449	19	F	Placebo	Y	0
450	48	F	Beclometasone	Y	0

451	37	F	Beclometasone	Y	0
452	23	M	Placebo	Y	0
453	14	M	Beclometasone	Y	0
454	22	F	Placebo	Y	0
455	69	F	Placebo	Y	0
456	44	F	Beclometasone	Y	0
457	14	F	Placebo	Y	0
458	13	M	Beclometasone	N	8
459	29	F	Placebo	Y	0
460	14	M	Beclometasone	Y	0
461	59	M	Placebo	N	3
462	58	M	Beclometasone	Y	0
463	54	M	Placebo	Y	0
464	23	M	Beclometasone	Y	0
465	24	M	Beclometasone	N	1
466	26	M	Placebo	N	1
467	55	F	Beclometasone	Y	0
468	20	F	Placebo	N	6
469	55	M	Placebo	Y	0
470	33	M	Beclometasone	Y	0
471	47	M	Beclometasone	Y	0
472	20	F	Placebo	N	4
473	16	M	Beclometasone	Y	0
474	28	F	Placebo	Y	0
475	33	M	Beclometasone	Y	0
476	53	M	Placebo	N	3
477	28	M	Beclometasone	Y	0
478	59	F	Placebo	Y	0
479	39	M	Placebo	N	3
480	22	M	Beclometasone	N	2
481	67	F	Beclometasone	Y	0
482	35	F	Placebo	N	1
483	70	M	Placebo	N	12
484	29	M	Beclometasone	N	1
485	41	M	Placebo	N	2
486	65	M	Beclometasone	Y	0
487	30	F	Placebo	Y	0
488	23	M	Beclometasone	Y	0
489	35	M	Beclometasone	N	3
490	63	M	Placebo	Y	0
491	47	M	Placebo	Y	0
492	46	M	Beclometasone	Y	0
493	17	M	Placebo	N	1
494	72	M	Beclometasone	Y	0
495	14	F	Placebo	N	4
496	43	F	Beclometasone	Y	0

497	36	M	Placebo	Y	0
498	47	M	Beclometasone	N	12
499	58	M	Beclometasone	Y	0
500	15	M	Placebo	N	19
501	56	F	Beclometasone	N	18
502	24	M	Placebo	Y	0
503	45	M	Placebo	Y	0
504	52	F	Beclometasone	N	19
505	40	F	Beclometasone	Y	0
506	34	M	Placebo	Y	0
507	34	M	Beclometasone	N	3
508	34	M	Placebo	N	4
509	57	F	Placebo	Y	0
510	19	F	Beclometasone	N	2
511	70	F	Beclometasone	N	1
512	40	F	Placebo	N	5
513	36	M	Placebo	N	16
514	52	F	Beclometasone	Y	0
515	51	F	Placebo	N	2
516	50	M	Beclometasone	N	2
517	27	F	Placebo	Y	0
518	43	F	Beclometasone	N	2
519	34	M	Placebo	N	13
520	40	M	Beclometasone	Y	0
521	53	M	Beclometasone	N	11
522	49	M	Placebo	N	3
523	19	M	Placebo	Y	0
524	69	M	Beclometasone	N	13
525	27	M	Placebo	Y	0
526	34	F	Beclometasone	N	14
527	17	M	Beclometasone	N	17
528	42	M	Placebo	Y	0
529	14	F	Beclometasone	Y	0
530	35	F	Placebo	Y	0
531	45	M	Beclometasone	Y	0
532	54	F	Placebo	Y	0
533	17	F	Beclometasone	Y	0
534	47	M	Placebo	Y	0
535	22	M	Beclometasone	Y	0
536	37	F	Placebo	N	10
537	52	F	Placebo	N	5
538	45	M	Beclometasone	Y	0
539	49	M	Placebo	N	10
540	19	M	Beclometasone	N	15
541	16	M	Beclometasone	Y	0
542	13	F	Placebo	Y	0

543	25	M	Beclometasone	N	12
545	68	F	Placebo	N	10
546	53	M	Beclometasone	Y	0
547	63	M	Beclometasone	Y	0
548	72	M	Placebo	N	8
549	64	M	Placebo	Y	0
550	17	F	Beclometasone	N	1
551	48	M	Placebo	Y	0
552	23	M	Beclometasone	N	2
553	49	F	Placebo	Y	0
554	45	F	Beclometasone	Y	0
555	24	M	Placebo	N	9
556	56	M	Beclometasone	N	4
557	21	F	Beclometasone	Y	0
558	69	M	Placebo	N	14
559	23	M	Placebo	Y	0
560	40	F	Beclometasone	N	5
561	21	F	Beclometasone	N	6
563	44	F	Placebo	N	17
564	27	F	Beclometasone	N	1
565	27	M	Placebo	Y	0
566	41	M	Beclometasone	Y	0
567	38	M	Placebo	Y	0
568	22	F	Beclometasone	Y	0
569	27	F	Placebo	Y	0
570	64	F	Beclometasone	N	2
571	25	F	Placebo	N	4
572	29	M	Beclometasone	N	2
574	53	F	Beclometasone	Y	0
575	36	M	Beclometasone	Y	0
576	38	F	Placebo	N	5
600	21	M	Placebo	Y	0
601	16	F	Beclometasone	N	1
602	29	M	Placebo	N	2
603	47	F	Beclometasone	Y	0
604	21	F	Placebo	Y	0
605	23	F	Beclometasone	N	7
606	31	F	Beclometasone	Y	0
607	19	M	Placebo	N	7
608	33	M	Placebo	N	6
609	25	F	Beclometasone	N	1
610	39	F	Placebo	N	1
611	14	M	Beclometasone	N	1
612	59	F	Beclometasone	Y	0
613	20	M	Placebo	Y	0
614	27	M	Placebo	N	13

615	16	F	Beclometasone	Y	0
616	43	F	Placebo	Y	0
617	50	F	Beclometasone	Y	0
618	13	F	Beclometasone	Y	0
619	17	M	Placebo	Y	0
620	16	M	Placebo	Y	0
621	33	M	Beclometasone	Y	0
622	72	F	Placebo	Y	0
623	15	M	Placebo	Y	0
624	22	F	Beclometasone	Y	0
625	70	F	Placebo	Y	0
634	56	F	Beclometasone	N	1
635	39	M	Placebo	Y	0
636	30	F	Beclometasone	Y	0
637	65	M	Placebo	N	20
638	58	F	Beclometasone	Y	0
639	29	M	Placebo	N	17
640	19	F	Placebo	Y	0
641	15	M	Beclometasone	Y	0
642	31	M	Placebo	N	1
652	15	M	Placebo	Y	0
653	53	F	Beclometasone	Y	0
654	51	F	Placebo	Y	0
655	38	M	Beclometasone	Y	0

APPENDIX XX - LISTING OF THE PRIMARY ENDPOINT (WHEEZING OCCURRENCE DURING THE 10 DAY TREATMENT PERIOD) BY INDIVIDUAL SUBJECTS

Randomization code	Age at the entry visit (months)	Gender	Treatment	N. wheezing in the last 6 months*	Wheezing (Yes/No)
1	56	F	B	≤1	No
2	34	F	P	>1	No
3	16	F	P	≤1	No
4	70	F	B	≤1	No
5	45	F	B	≤1	No
6	24	M	P	≤1	No
7	28	M	B	≤1	No
8	48	M	P	>1	No
9	38	M	B	≤1	No
10	57	M	P	≤1	No
11	16	M	B	≤1	No
12	12	F	P	≤1	No
13	68	M	P	≤1	No
14	36	M	B	≤1	No
15	65	M	B	≤1	No
16	36	M	P	>1	No
17	32	M	B	≤1	No
18	27	M	P	≤1	No
19	49	M	P	>1	Yes
20	28	M	B	≤1	No
21	28	M	P	>1	Yes
22	65	M	B	>1	No
23	56	M	B	>1	No
24	29	M	P	>1	No
25	15	M	B	≤1	No
26	14	M	P	>1	No
27	33	F	P	≤1	No
28	49	M	B	≤1	No
29	49	M	B	≤1	Yes
30	64	M	P	≤1	Yes
31	23	F	B	>1	No
32	22	F	P	≤1	No
33	41	F	B	>1	No
34	60	F	P	>1	No
35	45	M	B	≤1	No
49	36	M	P	>1	No
50	19	M	B	≤1	No
51	19	M	B	≤1	No

52	51	F	P	≤1	Yes
53	12	F	P	≤1	No
54	29	M	B	≤1	No
55	23	F	B	≤1	No
65	49	F	P	≤1	No
66	13	M	B	≤1	No
67	29	M	P	>1	No
68	50	M	B	≤1	No
69	46	F	B	≤1	No
70	46	M	P	>1	No
71	41	M	B	>1	No
72	49	F	P	≤1	No
73	29	F	B	≤1	No
74	31	M	P	≤1	Yes
75	19	F	B	≤1	No
76	31	M	P	≤1	No
77	48	F	P	≤1	No
78	39	M	B	≤1	No
79	59	F	B	≤1	No
80	48	M	P	>1	No
81	57	M	B	≤1	No
82	26	M	P	>1	No
83	17	M	P	≤1	No
84	17	M	B	≤1	No
85	39	F	P	≤1	No
86	57	F	B	≤1	No
87	37	F	B	≤1	No
88	21	M	P	≤1	No
89	45	F	P	≤1	No
90	53	M	B	>1	No
91	12	F	P	≤1	No
92	16	F	B	≤1	No
93	20	M	P	≤1	No
94	20	M	B	≤1	No
95	45	F	B	≤1	No
96	47	F	P	≤1	No
97	57	M	P	≤1	No
98	29	M	B	≤1	No
99	47	M	B	≤1	No
100	33	F	P	≤1	No
101	51	F	P	≤1	No
102	23	M	B	≤1	No
103	55	F	P	≤1	No

104	47	M	B	≤1	Yes
105	51	M	P	≤1	No
106	16	F	B	>1	No
107	13	M	B	≤1	No
108	54	F	P	≤1	No
109	36	F	P	≤1	No
110	60	M	B	≤1	No
111	26	M	P	≤1	No
112	32	M	B	≤1	No
113	30	M	B	≤1	No
114	15	M	P	≤1	No
115	17	M	P	≤1	No
116	32	F	B	≤1	No
117	31	M	P	≤1	No
118	31	M	B	≤1	No
119	57	F	B	≤1	No
120	22	M	P	≤1	No
121	63	M	P	≤1	No
122	23	M	B	≤1	Yes
123	46	F	P	>1	No
124	52	M	B	>1	No
125	54	M	P	>1	No
126	16	M	B	>1	No
127	71	M	B	≤1	No
128	50	M	P	>1	Yes
129	27	M	B	≤1	No
130	22	M	P	≤1	No
131	67	M	B	≤1	No
132	15	M	P	>1	Yes
133	23	F	P	>1	No
134	30	M	B	≤1	No
135	34	F	B	>1	Yes
136	33	M	P	>1	No
137	55	F	P	>1	No
138	25	M	B	≤1	No
139	17	F	B	>1	No
140	42	M	P	≤1	No
141	18	M	P	≤1	No
142	17	M	B	>1	No
144	21	F	B	>1	No
145	62	M	P	≤1	No
146	35	M	B	≤1	No
147	37	M	B	≤1	No

148	24	M	P	≤1	No
149	12	M	P	≤1	No
150	33	M	B	≤1	No
153	20	M	P	≤1	No
154	17	F	B	≤1	No
155	14	M	P	≤1	No
156	21	M	B	≤1	No
157	52	F	B	≤1	No
158	28	M	P	≤1	No
161	34	F	P	≤1	No
162	15	M	B	>1	No
163	16	F	P	>1	No
164	19	M	B	>1	No
165	32	M	P	>1	No
166	15	F	B	>1	No
167	18	M	P	>1	No
177	28	M	P	≤1	No
178	37	F	B	>1	No
179	17	F	P	≤1	No
180	54	F	B	≤1	No
181	54	M	B	>1	Yes
182	59	M	P	≤1	Yes
183	14	M	B	≤1	No
184	53	F	P	≤1	Yes
185	29	F	B	≤1	No
186	12	M	P	≤1	No
187	51	M	P	>1	No
188	18	F	B	≤1	No
189	31	M	B	>1	No
190	29	F	P	≤1	No
191	14	M	P	≤1	Yes
192	19	M	B	≤1	No
193	30	M	B	≤1	No
194	40	F	P	≤1	No
195	66	M	B	≤1	No
196	63	M	P	>1	No
197	42	F	P	≤1	No
198	71	F	B	≤1	No
199	52	F	B	≤1	No
200	49	F	P	>1	No
201	43	F	P	≤1	No
202	28	F	B	≤1	No
203	20	M	B	≤1	No

204	22	M	P	>1	No
205	49	F	P	≤1	No
206	44	F	B	>1	No
207	50	F	B	>1	No
208	27	M	P	≤1	No
211	59	F	B	≤1	No
212	22	M	P	≤1	No
241	65	M	P	≤1	Yes
242	30	M	B	≤1	No
243	28	F	B	≤1	No
244	71	F	P	≤1	No
245	62	F	P	≤1	No
246	28	M	B	≤1	No
247	34	M	B	≤1	Yes
248	23	M	P	≤1	Yes
249	68	F	P	≤1	No
250	36	M	B	≤1	No
251	64	F	P	≤1	No
252	27	M	B	≤1	No
253	20	F	B	>1	No
254	17	M	P	≤1	No
255	65	M	P	≤1	Yes
256	16	F	B	≤1	No
257	50	M	P	≤1	No
258	54	M	B	≤1	No
259	23	M	B	≤1	No
260	64	M	P	≤1	No
261	18	M	B	≤1	Yes
262	35	M	P	≤1	No
263	44	M	B	>1	No
264	45	M	P	≤1	No
265	59	M	P	≤1	No
266	50	M	B	≤1	No
267	47	M	B	≤1	No
268	60	M	P	≤1	No
269	50	M	B	>1	No
270	24	F	P	≤1	No
271	70	M	P	≤1	No
272	50	F	B	≤1	No
273	38	M	B	≤1	No
274	12	M	P	≤1	No
275	39	M	P	≤1	No
276	19	F	B	≤1	No

277	12	M	P	≤1	No
278	31	M	B	≤1	No
279	24	M	B	>1	No
280	24	F	P	≤1	No
281	22	M	B	>1	No
282	31	F	P	>1	No
283	15	F	P	≤1	Yes
284	23	M	B	≤1	No
285	16	M	P	≤1	No
286	20	M	B	≤1	No
287	40	M	B	≤1	No
288	28	M	P	>1	No
289	28	F	P	≤1	No
290	16	M	B	≤1	No
291	14	F	B	≤1	No
292	42	M	P	≤1	No
293	18	F	B	≤1	No
294	20	M	P	≤1	No
295	23	M	P	≤1	No
296	30	F	B	≤1	No
297	15	M	P	≤1	No
298	15	M	B	≤1	No
299	43	M	P	≤1	No
300	19	M	B	>1	No
301	45	F	B	≤1	No
302	24	F	P	≤1	Yes
303	71	F	P	≤1	No
304	32	F	B	>1	No
305	43	M	P	>1	No
306	33	M	B	≤1	Yes
307	55	M	P	≤1	No
308	17	F	B	≤1	No
309	25	M	P	≤1	No
310	41	M	B	>1	No
311	14	M	B	≤1	No
312	37	M	P	>1	No
313	18	M	B	>1	No
314	43	F	P	≤1	No
315	21	M	B	>1	Yes
316	56	M	P	≤1	No
317	35	F	B	≤1	No
318	21	M	P	≤1	No
319	21	M	B	≤1	No

320	22	M	P	>1	No
321	12	F	B	≤1	Yes
322	58	F	P	≤1	No
323	16	F	B	≤1	No
324	32	F	P	≤1	Yes
325	37	F	B	≤1	No
326	24	F	P	≤1	No
327	31	M	B	≤1	No
328	22	M	P	≤1	No
329	33	F	B	≤1	No
330	33	M	P	≤1	No
331	32	F	B	≤1	No
332	50	F	P	>1	No
333	36	M	B	≤1	No
334	46	F	P	>1	No
335	19	F	P	>1	Yes
336	32	M	B	≤1	No
337	50	F	B	≤1	No
338	59	M	P	≤1	No
339	43	M	P	>1	No
340	58	M	B	≤1	Yes
341	45	M	B	>1	No
342	35	F	P	>1	No
343	69	M	B	≤1	Yes
344	30	M	P	≤1	Yes
345	20	M	P	≤1	No
346	68	M	B	≤1	No
347	46	M	P	≤1	No
348	38	F	B	>1	No
349	20	M	P	≤1	Yes
350	59	M	B	>1	No
351	19	M	P	≤1	No
352	56	M	B	>1	Yes
353	58	M	B	≤1	Yes
354	32	F	P	≤1	No
355	44	F	P	>1	No
356	51	M	B	≤1	No
357	45	M	B	≤1	No
358	23	F	P	≤1	No
359	65	M	B	≤1	No
360	70	M	P	≤1	Yes
361	22	F	P	≤1	No
362	50	M	B	≤1	No

363	37	M	P	>1	Yes
364	33	M	B	≤1	No
365	64	F	B	≤1	No
366	27	M	P	≤1	No
367	32	F	B	≤1	No
368	43	F	P	≤1	No
369	24	F	P	≤1	No
370	34	F	B	>1	No
371	55	M	B	≤1	No
372	50	M	P	≤1	No
373	48	M	B	≤1	No
374	26	F	P	≤1	No
375	43	F	P	≤1	No
376	35	M	B	>1	No
377	35	M	P	≤1	No
378	29	M	B	≤1	No
379	46	M	B	>1	No
381	55	M	P	≤1	No
382	61	F	B	≤1	No
383	19	M	B	>1	No
384	50	M	P	≤1	No
385	29	F	B	>1	No
386	19	M	P	≤1	No
387	29	F	P	>1	No
388	63	F	B	>1	No
389	45	M	B	≤1	No
390	59	F	P	≤1	No
391	40	F	P	>1	No
392	14	M	B	>1	No
393	25	M	B	≤1	No
394	36	F	P	≤1	No
395	43	M	B	≤1	No
396	45	M	P	>1	No
397	35	M	P	≤1	No
398	60	F	B	>1	No
399	72	F	B	≤1	No
400	41	F	P	>1	No
401	26	F	B	>1	No
402	36	F	P	>1	No
403	24	M	B	>1	No
404	42	M	P	>1	No
405	18	M	B	≤1	No
417	40	M	B	≤1	No

418	35	M	P	≤1	No
419	23	M	P	≤1	No
420	24	F	B	≤1	No
421	23	M	P	>1	Yes
422	38	M	B	>1	No
423	42	M	P	≤1	No
424	60	M	B	≤1	No
425	33	M	B	>1	No
426	31	M	P	≤1	No
427	38	M	B	≤1	No
428	57	M	P	≤1	No
429	18	M	P	≤1	No
430	15	F	B	≤1	No
431	38	F	B	>1	No
432	27	F	P	≤1	No
433	13	M	P	>1	No
434	38	M	B	≤1	No
435	21	F	P	≤1	No
436	21	M	B	≤1	No
437	18	M	B	≤1	No
438	25	M	P	≤1	No
439	23	F	P	≤1	No
449	19	F	P	≤1	No
450	48	F	B	≤1	No
451	37	F	B	≤1	No
452	23	M	P	≤1	Yes
453	14	M	B	>1	No
454	22	F	P	≤1	No
455	69	F	P	≤1	No
456	44	F	B	≤1	No
457	14	F	P	≤1	No
458	13	M	B	≤1	No
459	29	F	P	≤1	No
460	14	M	B	≤1	No
461	59	M	P	≤1	No
462	58	M	B	≤1	No
463	54	M	P	≤1	No
464	23	M	B	≤1	No
465	24	M	B	≤1	No
466	26	M	P	>1	No
467	55	F	B	≤1	No
468	20	F	P	>1	No
469	55	M	P	≤1	No

470	33	M	B	>1	No
471	47	M	B	>1	No
472	20	F	P	>1	No
473	16	M	B	>1	No
474	28	F	P	>1	No
475	33	M	B	>1	No
476	53	M	P	>1	No
477	28	M	B	>1	No
478	59	F	P	>1	No
479	39	M	P	>1	No
480	22	M	B	>1	No
481	67	F	B	≤1	No
482	35	F	P	≤1	Yes
483	70	M	P	≤1	No
484	29	M	B	≤1	No
485	41	M	P	>1	No
486	65	M	B	≤1	No
487	30	F	P	≤1	No
488	23	M	B	≤1	No
489	35	M	B	≤1	No
490	63	M	P	≤1	No
491	47	M	P	≤1	Yes
492	46	M	B	≤1	No
493	17	M	P	>1	Yes
494	72	M	B	>1	No
495	14	F	P	>1	No
496	43	F	B	≤1	Yes
497	36	M	P	≤1	No
498	47	M	B	≤1	Yes
499	58	M	B	≤1	No
500	15	M	P	≤1	No
501	56	F	B	≤1	No
502	24	M	P	≤1	No
503	45	M	P	>1	No
504	52	F	B	≤1	No
505	40	F	B	≤1	No
506	34	M	P	≤1	Yes
507	34	M	B	≤1	No
508	34	M	P	>1	No
509	57	F	P	≤1	No
510	19	F	B	≤1	No
511	70	F	B	≤1	No
512	40	F	P	≤1	No

513	36	M	P	≤1	Yes
514	52	F	B	≤1	No
515	51	F	P	≤1	No
516	50	M	B	≤1	No
517	27	F	P	>1	No
518	43	F	B	≤1	No
519	34	M	P	>1	Yes
520	40	M	B	>1	No
521	53	M	B	>1	Yes
522	49	M	P	>1	No
523	19	M	P	≤1	No
524	69	M	B	≤1	No
525	27	M	P	>1	No
526	34	F	B	>1	No
527	17	M	B	>1	No
528	42	M	P	≤1	No
529	14	F	B	≤1	No
530	35	F	P	≤1	No
531	45	M	B	>1	No
532	54	F	P	>1	No
533	17	F	B	≤1	No
534	47	M	P	≤1	No
535	22	M	B	>1	No
536	37	F	P	≤1	No
537	52	F	P	≤1	No
538	45	M	B	>1	No
539	49	M	P	≤1	No
540	19	M	B	≤1	No
541	16	M	B	>1	No
542	13	F	P	>1	No
543	25	M	B	>1	No
545	68	F	P	≤1	No
546	53	M	B	>1	No
547	63	M	B	≤1	No
548	71	M	P	≤1	No
549	64	M	P	≤1	No
550	17	F	B	≤1	No
551	48	M	P	≤1	No
552	23	M	B	>1	No
553	49	F	P	≤1	No
554	45	F	B	≤1	No
555	24	M	P	≤1	No
556	56	M	B	≤1	No

557	21	F	B	≤1	No
558	69	M	P	≤1	No
559	23	M	P	≤1	No
560	40	F	B	≤1	No
561	21	F	B	≤1	No
563	44	F	P	>1	No
564	27	F	B	>1	No
565	27	M	P	>1	No
566	41	M	B	>1	No
567	38	M	P	≤1	No
568	22	F	B	>1	No
569	27	F	P	≤1	No
570	64	F	B	≤1	No
571	25	F	P	>1	No
572	29	M	B	≤1	No
574	53	F	B	>1	No
575	36	M	B	>1	No
576	38	F	P	>1	No
600	21	M	P	>1	No
601	16	F	B	>1	No
602	29	M	P	>1	No
603	47	F	B	≤1	No
604	21	F	P	≤1	No
605	23	F	B	≤1	No
606	31	F	B	≤1	Yes
607	19	M	P	≤1	No
608	33	M	P	≤1	No
609	25	F	B	≤1	No
610	39	F	P	>1	No
611	14	M	B	≤1	No
612	59	F	B	≤1	No
613	20	M	P	≤1	No
614	27	M	P	≤1	No
615	16	F	B	≤1	No
616	43	F	P	≤1	No
617	50	F	B	≤1	No
618	13	F	B	≤1	No
619	17	M	P	≤1	No
620	16	M	P	≤1	No
621	33	M	B	≤1	No
622	72	F	P	≤1	No
623	15	M	P	≤1	No
624	22	F	B	>1	No

625	70	F	P	≤1	No
634	56	F	B	≤1	No
635	39	M	P	≤1	No
636	30	F	B	≤1	No
637	65	M	P	≤1	No
638	58	F	B	≤1	No
639	29	M	P	≤1	No
640	19	F	P	>1	No
641	15	M	B	>1	No
642	31	M	P	>1	No
652	15	M	P	≤1	No
653	53	F	B	≤1	No
654	51	F	P	≤1	No
655	38	M	B	≤1	No

* N. of wheezing episodes in the 6 months preceding the entry visit. B=Beclometasone, P=Placebo

APPENDIX XXI - DETAILS OF THE 75 CHILDREN WITH AN EXTRA VISIT (VISIT 1A) DURING THE EXPERIMENTAL PHASE OF THE STUDY

ID_number (randomization code)	Group	Gender	Age at the entry visit (months)	Wheezing score	Rescue drug prescription (Yes/No)	Salb (Yes/No)	Beclo (Yes/No)	OCS (Yes/No)
4	B	F	70	0	N	N	N	N
6	P	M	24	0	N	N	N	N
7	B	M	28	0	N	N	N	N
9	B	M	38	0	N	N	N	N
12	P	F	12	0	N	N	N	N
14	B	M	36	0	N	N	N	N
16	P	M	36	0	N	N	N	N
19	P	M	49	1	Y	Y	N	N
21	P	M	28	1	Y	Y	N	N
29	B	M	49	1	Y	Y	N	N
52	P	F	51	1	Y	Y	N	N
54	B	M	29	0	N	N	N	N
74	P	M	31	1	Y	Y	N	N
98	B	M	29	0	N	N	N	N
101	P	F	51	0	N	N	N	N
103	P	F	55	0	N	N	N	N
104	B	M	47	1	Y	Y	N	N
112	B	M	32	0	N	N	N	N
113	B	M	30	0	N	N	N	N
114	P	M	15	0	N	N	N	N
122	B	M	23	1	Y	Y	N	N
124	B	M	52	0	N	N	N	N
128	P	M	50	2	Y	Y	N	N

148	P	M	24	0	N	N	N	N
165	P	M	32	0	N	N	N	N
182	P	M	59	1	Y	Y	N	N
183	B	M	14	0	N	N	N	N
200	P	F	49	0	N	N	N	N
204	P	M	22	0	N	N	N	N
207	B	F	50	0	N	N	N	N
211	B	F	59	0	N	N	N	N
212	P	M	22	0	N	N	N	N
241	P	M	65	1	Y	Y	N	N
245	P	F	62	0	N	N	N	N
247	B	M	34	1	Y	Y	N	N
249	P	F	68	0	Y	N	N	N
261	B	M	18	2	Y	Y	N	N
263	B	M	44	0	N	N	N	N
265	P	M	59	0	Y	N	N	Y
273	B	M	38	0	N	N	N	N
275	P	M	39	0	N	N	N	N
278	B	M	31	0	N	N	N	N
282	P	F	31	0	N	N	N	N
283	P	F	15	2	Y	Y	N	N
284	B	M	23	0	N	N	N	N
303	P	F	71	0	N	N	N	N
321	B	F	12	1	Y	Y	N	Y
324	P	F	32	1	Y	Y	N	Y
333	B	M	36	0	N	N	N	N
353	B	M	58	1	Y	Y	N	N
362	B	M	50	0	Y	N	N	N
366	P	M	27	0	Y	N	N	N

421	P	M	23	0	N	N	N	N
426	P	M	31	0	Y	Y	N	N
452	P	M	23	1	Y	Y	Y	N
453	B	M	14	0	Y	Y	Y	N
454	P	F	22	0	N	N	N	N
491	P	M	47	1	Y	Y	N	N
493	P	M	17	2	Y	Y	Y	N
494	B	M	72	0	N	N	N	N
496	B	F	43	1	Y	Y	N	N
497	P	M	36	0	N	N	N	N
513	P	M	36	2	Y	Y	N	N
519	P	M	34	2	Y	Y	N	N
521	B	M	53	1	Y	Y	N	N
552	B	M	23	0	N	N	N	N
557	B	F	21	0	N	N	N	N
559	P	M	23	0	Y	Y	Y	N
600	P	M	21	0	N	N	N	N
602	P	M	29	0	N	N	N	N
606	B	F	31	2	Y	Y	Y	N
609	B	F	25	0	N	N	N	N
614	P	M	27	0	N	N	N	N
615	B	F	16	0	N	N	N	N
619	P	M	17	0	N	N	N	N

B=Beclometasone, P=Placebo.
Salb=Salbutamol, Beclo=Beclometasone, OCS=Oral Corticosteroids (Prednisone, Betamethasone)