CLINICAL STUDY REPORT

An 8 week multicenter, randomized, double–blind, double–dummy, parallel group, therapeutic equivalence study of Formoterol (Formopen®) administered with the Elpen*haler*® versus the innovative Formoterol (Foradil®) administered with the Aerolizer®, in patients with mild to moderate asthma..

Name of test drug/investigational product:	Formopen® (Formoterol) DPI
Indication studied:	Mild to Moderate Persistent Asthma
Study design:	Multicenter, randomized, double–blind, double–dummy, parallel group, non–inferiority, single dose study.
Sponsor:	Elpen Pharmaceutical Co. Inc.
Study Code:	2007–FOR–EL–02
EudraCT Number:	2007–002157–23
Development phase of study:	IV (interventional)
Study initiation date:	First patient enrolled : September 5th, 2008
Study completion date:	Last patient completed : January 15th, 2010
Name and affiliation of Sponsor's responsible medical officer:	Dr Katerina Athanassiou, Pharmacist PhD Clinical Trials Director, Elpen Pharmaceutical Co. Inc. 95, Marathonos Av. 190 09 Pikermi, Athens, Greece Tel: +30 210 6039326 Fax: +30 210 6039300 Website: www.elpen.gr
Date of the report:	26/11/2010

STATEMENT

The trial was conducted in accordance with the ethical principles of the 18th World Medical Association Declaration (Helsinki, 1964) and all subsequent amendments and guidelines on Good Clinical Practice. Additionally, the clinical trial protocol complies with the laws and legislations of the country in which the study was conducted, all relevant guidelines, as well as those dealing with protection of personal data.

1. TITLE

An 8 week multicenter, randomized, double–blind, double–dummy, parallel group, therapeutic equivalence study of Formoterol (Formopen®) administered with the Elpen*haler*® versus the innovative Formoterol (Foradil®) administered with the Aerolizer®, in patients with mild to moderate asthma.

2. SYNOPSIS

Name of Sponsor/Company: Elpen Pharmaceutical Co. Inc.	**SYNOPSIS**	
Name of Finished Product: Formopen®		
Name of Active Ingredient: Formoterol		

Study Title:

An 8 week multicenter, randomized, double–blind, double–dummy, parallel group, therapeutic equivalence study of Formoterol (Formopen®) administered with the Elpen*haler*® versus the innovative Formoterol (Foradil®) administered with the Aerolizer®, in patients with mild to moderate asthma.

Principal Investigators:	**Co–investigators:**
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° Dr. Gaga Mina	° Dr. Kainis Elias ° Dr. Petrochilou Kalomira ° Dr. Moraitou Eleni ° Dr. Grigoratou Teo ° Dr. Zervas Elias ° Dr. Economidou Erasmia
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° Dr. Galanis Nikolaos	° Dr. Tryfon Stavros
° Dr. Tatsis Georgios	° Dr. Lazarou Vassiliki

Study centres:

- 2nd Pulmonary Clinic of "Sotiria" General Chest Disease Hospital, Athens
- Asthma Clinic of "Sotiria" General Chest Disease Hospital, Athens
- University Pulmonary Clinic of University General Hospital, Larisa
- 1st University Pulmonary Clinic of General Chest Disease Hospital, Athens
- University Pulmonary Clinic of PEPAGNI Hospital, Heraklion
- A΄ Pulmonary Clinic of "G.Papanikolaou" General Hospital, Thessaloniki

◦ Pulmonology Clinic of "Evaggelismos" General Hospital, Athens
Publication (reference): No scientific publication was released based on the whole or part of the study results until completion of the present report (November 2010).
Studied period: 3 months First patient enrolled: 05/09/2008 Last patient completed: 15/01/2010 — **Phase of development:** Phase IV (interventional)
Objectives: Primary ▪ The primary objective of the study was to establish non–inferiority between a new generic dry powder Formoterol (12μg) formulation (Formopen®) compared to the innovative Formoterol reference formulation (Foradil®). Secondary ▪ To establish the safety and tolerability of a new generic dry powder Formoterol formulation (12μg). ▪ To evaluate the long term bronchodilatory effect of the new dry powder Formoterol formulation (12 μg).
Methodology: This was a multicenter, randomized, double–blind, double–dummy, parallel group, non–inferiority study.
Number of patients: Number of patients planned to be recruited: 92 Number of patients screened:63 Number of patients randomised: 42 Number of patients analyzed: ▪ PP population: 27 ▪ ITT population: 42 ▪ Safety population: 42
Diagnosis and main criteria for inclusion/exclusion: Inclusion Criteria Male or female, aged 18–65 years, diagnosis of mild to moderate persistent asthma of ≥6 months at the screening visit, short acting β_2–agonists and inhaled corticosteroids (ICS) as maintenance treatment, FEV_1 ≥60% and ≤90% of the predicted normal FEV_1 after withholding short–acting inhaled β_2–agonists for at least 6 hours and long–acting β_2–agonists for at least 24, reversibility of at least ≥12% 15 minutes after the inhalation of 400 μg Salbutamol and after withholding short–acting inhaled β_2–agonists for at least 6 hours and long–acting β_2–agonists for at least 24 hours, PIF 30 to 90 lt/min, able to use maximal flow meters properly, able to demonstrate proper use of both inhalation devices, signed and dated written informed consent. Exclusion Criteria *At study entry:* Use of oral ICS, use of pharmacological treatment for infection of the upper respiratory tract, asthma exacerbation, hypersensitivity to Formoterol, Salbutamol or lactose, heavy smoking, pregnancy, lactation, serious hepatic or renal disease, serious heart disease, uncontrolled diabetes, cancer, tuberculosis, evidence or history of severe heart disease, other respiratory tract conditions, hepatic or renal disease, alcohol or drug abuse, patients unlikely to be compliant, patients previously randomised into the study, employees of Elpen Pharmaceuticals Co. Inc. or CROs or hospitals or any other organization involved in the study.

At baseline visit:

Pre–dose FEV_1 variation more than ±15% of the respective FEV_1 measured in the previous visit, use of oral or topical LABAs during the run–in period, treatment for infection of the upper respiratory tract in the prior month, poor compliance during the run–in period (i.e. duration of run in period more than 17 days and/or less than 10 mPEFR and/or less than 10 ePEFR measurements during the specified period), asthma exacerbation, change in patient's ICS treatment during run–in period.

Test product:

Formopen® (Fumaric Formoterol) DPI (Elpen Pharmaceutical Co. Inc.)

Dose: 12 μg bid

Mode of administration: Inhalation

1st Batch number: 70768

2nd Batch Number: 90641

Duration of treatment:8 weeks

Reference product:

Foradil® (Fumaric Formoterol) DPI (Novartis)

Dose: 12 μg bid

Mode of administration: Inhalation

1st Batch number: U0065

2nd Batch Number: U0083

Criteria for evaluation:

Efficacy:

Primary Efficacy:

- Mean change of mean morning PEFR from the run–in period until week 8.

Secondary Efficacy:

- Mean morning and evening PEFR, spirometry values: FEV_1, FVC, FEV_1/FVC, forced expiratory flow fraction at 25% of FVC ($FEF_{25\%}$), FEF between 25 and 75% of FVC ($FEF_{25–75\%}$), number of days with PEFR daily fluctuation of 20%, number of short acting β_2–agonist inhalations utilized, degree of day–night asthma symptoms and usability questionnaire.

Safety:

- Paradoxical bronchospasm, adverse events, vital signs, QTc intervals, serum potassium, blood glucose, haematological and biochemical examinations.

Statistical methods:

Primary analysis aimed to investigate whether Formopen® is therapeutically equivalent to Foradil®.

It was performed by comparing the change of morning PEFR from baseline to final visit between the two treatment groups and was statistically implemented by testing the null hypothesis that the lower 97.5% bound of the between two groups difference in mPEFR change from baseline [Formopen®–Foradil®] is smaller than the non-inferiority margin of –20 *lt/min* (inferiority of Formopen®), at one-sided 0.025 level of confidence.

The analysis was performed in the per protocol (PP) population.

Summary Results:

Primary Efficacy:

PP Population

- The difference between the two groups of mPEFR change is –3.57 *l/min,* 1–sided 97.5%CI: [-57.2, +∞], see Table S1.

Table S1 Estimation of the mean change of mean mPEFR from baseline to final visit in each group and difference in change between groups (Per Protocol Population).

	Change from Baseline	95%CI of change	p–value
mPEFR– *lt/min*			
Formopen®	32.16	[2.47, 61.85]	0.036
Foradil®	35.73	[–11.8, 83.27]	0.126
Formopen®–Foradil®	–3.57	[–57.2, +∞]†	0.265‡

† Lower bound of the 1–sided 97.5% CI.
‡ *p–value* for the null hypothesis Δ<–20 lt/min.

ITT Population

- The difference between the two group of mPEFR change is –3.43*l/min,* 1–sided 97.5%CI : [-49.9, +∞]

Secondary Efficacy:

- No statistically significant differences were observed between the two formulations with respect to mean morning and evening PEFR at each visit.
- No statistically significant differences were observed between the two formulations with respect to the mean value of all spirometric measurements, at each visit.
- The number of days with daily PEFR fluctuation ≥20% were statistically significantly lower at the last study visits compared to baseline (*p-value=0.030*), in both treatment groups.
- The number of short acting β_2–agonist inhalations utilized in the morning and in the evening remained unchanged in both treatment groups.
- There was a similar improvement in both groups in morning and evening asthma symptoms, during the time–course of the study (*p-value<0.0001*).
- According to the results of usability questionnaire, patients exhibited a preference towards Elpen*haler*® compared to Aerolizer® (*p-value<0.05,* at 7 out of 8 questions).

Safety

- *Adverse Events*

Nine patients experienced 11 non-serious adverse events, see following table. All patients were fully recovered. *No Serious Adverse Events were observed in the study.*

Table S2 Table of Adverse Events reported during the study.

Patient No	Treatment	Age (yr)	Sex	Adverse Event Term	Duration	Severity	Action Taken	Causality
10002	Foradil®	62.9	F	Headache	12/1/2009 12/1/2009	Moderate	None	Not Related
10002	Foradil®	62.1	F	Infection of Upper Respiratory Tract	24/1/2009 29/1/2009	Mild	None	Not Related
10407	Foradil®	36.5	M	Infection Of Upper Respiratory Tract	18/1/2009 28/1/2009	Mild	None	Not Related
10411	Formopen®	50.1	M	Tachycardia	12/3/2009 12/3/2009	Mild	None	Not Related
10417	Formopen®	26.7	F	Dyspnoea	23/10/2009 23/10/2009	Mild	None	Not Related
10503	Foradil®	50.5	F	Respiratory Infection	29/10/2008 7/11/2008	Mild	None	Not Related
10504	Formopen®	62.9	F	Respiratory Infection	6/11/2008 18/11/2008	Moderate	None	Not Related
10508	Formopen®	24.4	F	High Levels Of Glucose	22/12/2008 9/2/2009	Mild	None	Related
10511	Formopen®	52.1	F	Shortness Of Breath	31/1/2009 5/2/2009	Moderate	Study Withdrawn	Related
10701	Formopen®	37.9	F	Infection	30/10/2008 8/11/2008	Mild	Study Withdrawn	Not Related
10701	Formopen®	37.9	F	Asthma Exacerbation	1/11/2008 8/11/2008	Moderate	Study Withdrawn	Not Related

- *Other Safety assessments*

ECG: No clinically significant alterations were observed during the trial in both groups.

Vital signs: No clinically significant alterations were observed during the trial in both groups.

Haematology: No clinically significant alterations were observed during the trial in both groups.

Biochemistry: One incidence of clinical significant elevation of blood glucose was observed in the Formopen® group (see *Table S2*). No other clinical significant alterations were reported during the trial in both groups.

CONCLUSION:

The primary objective of the study was to establish the therapeutic equivalence of a novel Formoterol formulation (12 μg) when administered with Elpenhaler® (Formopen®) against the innovative Formoterol formulation DPI (Foradil®–Aerolizer®). A final conclusion on the therapeutic equivalence could not be supported by the data collected in the present study. This was a result of the early termination of the study due to low recruitment rate. Therefore, the limited observed power and the statistical significance could not be attained to support the study hypothesis. Analyses of safety variables concluded on no additional safety issues arising when using Elpenhaler® instead of Aerolizer® for administering Formoterol. Thus, Formopen® and Foradil® present a similar safety profile.

The results of the present study results can not confirm that administration of Formoterol via Elpenhaler® (Formopen®) and Foradil (Aerolizer®) is therapeutically equivalent, thus their similar bronchodilator activity in patients with mild to moderate asthma can not be confirmed.

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Version: 1.0

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AE	Adverse Event
ALAT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ASAT	Aspartate Aminotransferase
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
DAP	Diastolic Arterial Pressure
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
EED	National Ethics Committee of Greece
EMEA	European Medicines Evaluation Agency
EOF	National Organization for Medicines of Greece
FEF	Forced Expiratory Flow
FEV_1	Forced Expiratory Volume in one second
FU	Follow Up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
Hb	Haemoglobin
Hct	Haematocrit
HEENT	Head–eye–ear–neck–throat
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention–To–Treat
LABA	Long–Acting B_2 Agonist
LDH	Lactate Dehydrogenase
MAO	Monoamine Oxidase
NA	Not available
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung, and Blood Institute
OR	Odds Ratio
PEFR	Peak Expiratory Flow Rate
PIF	Peak Inspiratory Flow
PLT	Platelets
PP	Per Protocol
QTc	The interval between Q and T on ECG corrected for heart rate by the Bazett's method
RBC	Red Blood Cells
SABA	Short–Acting B_2 Agonist
SAP	Systolic Arterial Pressure
SD	Standard Deviation
WBC	White Blood Cells

5. ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The present study was conducted in Greece; therefore a full set of study documents was prepared and was submitted to Greek Regulatory Authorities (National Organization for Medicines, EOF). The approvals to initiate study conduct, following review from EOF (Chairman Dr. Miranda Siouti) and National Ethics Committee of Greece (EED, Chairman Prof Ioannis Papadimitriou) were obtained on 30.11.2007 and 03.06.2008 respectively (Appendix 16.1.3). After the study initiation, a notification for the addition of a study centre (Notification of Tatsis study site addition, approval by EOF 04.03.2009, approval by EED 17.02.2009) and a second modification for removal of two study sites (Notification of Kosmas & Tsoukalas study sites removal, approval by EOF 12.05.2009, approval by EED 13.05.2009) were submitted and approved.

Prior to any trial related procedure taking place at the sites, the trial protocol, the patient information sheet and the informed consent form were approved by the National Ethics Committee and the Greek Regulatory Authorities. All correspondence with the aforementioned regulatory authorities was retained in the Investigator Site File and copies of IEC/IRB approvals were forwarded to the CRO.

The approval of the amendments (Protocol amendment, Ammeded Protocol, ICF version 3.0) was obtained on 31/03/2008 by the National Organization for Medicines and on 03/06/2008 by the National Ethics Committee of Greece

The final notification for the study termination was communicated to the regulatory authorities and the National Ethics Committee on 16.04.2010.

A list of the IECs or IRBs consulted and the corresponding approval notes and notifications are provided in Appendix 16.1.3.

5.2 Ethical Conduct of the Study

The trial was conducted in accordance with ICH/GCP 2002 guidelines (1) the ethical principles of the Declaration of Helsinki (2000, Clarification 2002–2004, provided as Appendix 1 in the attached protocol–Appendix 16.1.1) and the applicable national regulatory requirements and laws for the conduct of clinical trials.

5.3 Patient Information and Consent

At the screening visit, prior to any study related procedures and under the Investigator's supervision, each patient (or the patient's acceptable representative) was given full and adequate verbal and written information regarding the study objectives and procedures and the possible risks involved. Provision of information took place prior to any trial–related procedure. Patients were clearly informed about their right to withdraw from the trial at any time, without any affects on the healthcare that are entitled to. Written patient information, approved by the National Ethics Committee and the Greek Regulatory Authorities (National Organization for Medicines, EOF), was also provided to each patient before any trial–related procedure was performed. Furthermore, with the responsibility of the Investigator, a personally signed and dated informed consent was obtained from all patients participating in the study, along with the signature from the person conducting the informed consent discussion, prior to undertaking any trial–related procedure.

A sample of the patient information sheet and the informed consent form are provided in Appendix 16.1.4.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Participating Investigators

A list of the participating Principal Investigators and Co–Investigators of each site is shown in the following tables:

Principal Investigators	**Clinic/Site–Institution**
Dr. Birba Georgia	2nd Pulmonary Clinic of "Sotiria" General Chest Disease Hospital, Athens
Dr. Gaga Mina	Asthma Clinic of "Sotiria" General Chest Disease Hospital, Athens
Dr. Gourgoulianis Konstantinos	University Pulmonary Clinic of University General Hospital, Larisa
Dr. Koulouris Nikolaos	1st University Pulmonary Clinic of General Chest Disease Hospital, Athens
Dr. Siafakas Nikolaos	University Pulmonary Clinic of PEPAGNI Hospital, Heraklion
Dr. Galanis Nikolaos	A΄ Pulmonary Clinic of "G.Papanikolaou" General Hospital, Thessaloniki
Dr. Tatsis Georgios	Pulmonology Clinic of "Evaggelismos" General Hospital, Athens

Co–investigators	**Clinic/Site–Institutions**
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Dr. Kainis Elias	Asthma Clinic of "Sotiria" General Chest Disease Hospital, Athens
Dr. Petrochilou Kalomira	
Dr. Moraitou Eleni	
Dr. Grigoratou Teo	
Dr. Zervas Elias	
Dr. Economidou Erasmia	
Dr. Kostikas Konstantinos	University Pulmonary Clinic of University General Hospital, Larisa
Dr. Daenas Christos	
Dr. Tsaroucha Agori	
Dr. Minas Markos	
Dr. Tagtalianidou Elli	
Dr. Theologi Vassiliki	
Dr. Karetsi Eleni	
Dr. Palamidas Anastasios	1st University Pulmonary Clinic of General Chest Disease Hospital, Athens
Dr. Belladaki Kalliopi	University Pulmonary Clinic of PEPAGNI Hospital, Heraklion
Dr. Stamataki Evangelia	
Dr. Tryfon Stavros	A' Pulmonary Clinic of "G.Papanikolaou" General Hospital, Thessaloniki
Dr. Lazarou Vassiliki	Pulmonology Clinic of "Evaggelismos" General Hospital, Athens

Sponsor's responsible trial director and safety officer

Clinical Trial Director	Dr Katerina Athanassiou Pharmacist, PhD.	Elpen Pharmaceuticals Co. Inc. 95 Marathonos Av. 190 09 Pikermi Athens, Greece Tel: +30–210–6039326 Email: k.athanassiou@elpen.gr
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Investigators' qualifications (curriculum vitae or equivalent) are provided in Appendix 16.1.5.

Sponsor's internal staff

The signature of the Sponsor's responsible medical officer is provided in Appendix 16.1.6.

Contract Research Organisations (CRO)

Study management, data entry, statistical analysis and the elaboration of the clinical study report were carried out by Zeincro Hellas S.A. under the supervision of the Sponsor.

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Central Laboratory Facilities

Biological determinations were performed by Research Diagnostics.

Project Manager	Dr N. Drakoulis	Research Diagnostics 429 Vouliagmenis Av. 163 46 Ilioupoli, Greece Tel: +30 210 9948200 Email: info@research–diagnostics.com

7. INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. It is one of the most common chronic airway diseases worldwide, imposing a substantial social burden on both children and adults (2). Currently, guidelines for the pharmacological treatment of persistent asthma by the Global Initiative for Asthma (GINA) recommend the combination of ICS along with a long–acting β2–adrenergic agonist (LABA) (3). Nowadays, they are predominantly administered as inhaled medications, since this formulation enables direct drug delivery to the airways where they are needed, resulting in potent therapeutic effects with fewer systemic side effects (4). Such drug delivery has pronounced primary clinical advantages related to safety and efficacy: systemic side effects are minimized, high concentrations can be achieved at the intended site of action, onset of action is faster and therapeutic response is achieved more quickly (5). Moreover, dry powder inhalers (DPIs) are preferred because, in addition to their environmental safety and breath actuation, they are able to offer the advantage of ease in administration (4).

Formoterol fumarate is a long–acting β_2–adrenergic agonist (LABA), which has a fast onset and an extended bronchodilatory action of up to 12 hours. Like other LABAs, its action causes smooth muscles in the airway to relax, increases the clearance of mucous membranes, reduces the permeability of blood vessels and may trigger the release of intermediary substances from mast cells and basophils, resulting, thus, in the reduction of asthma exacerbation effects (6, 7). Numerous studies conducted so far have exhibited that frequent use of Formoterol reduces daily fluctuation of peak expiratory flow (PEF), as well as basic lung function compared to placebo or short–acting β_2–agonists (8–16).

The innovative marketed pharmaceutical product combining 12 μg Formoterol fumarate (Foradil®, manufactured by Novartis), is delivered via a DPI; Aerolizer® inhalation device (also manufactured by Novartis). In parallel, a new, multi, single dose DPI (Elpen*haler*®) has been designed, developed and patented by Elpen Pharmaceuticals Co. Inc. The new inhaler is suitable for delivering a range of asthma compounds e.g. budesonide, Formoterol and Fluticasone. Elpen*haler*® can deliver one dose of 12 μg Formoterol which has the trade name Formopen®.

Formopen® is a product with similar in vitro characteristics as Foradil® Aerolizer®. Therapeutic equivalence of these two products has been demonstrated in a single dose cross–over trial (17) as well as through in vitro data acquired by Elpen Pharmaceuticals Co. Inc. The aim of the study presented herein, which includes repeated doses of both formulations for eight weeks, was to further establish therapeutic equivalence (in accordance with the CPMP/EWP/4101 rev1 guideline) in addition to evaluating the stable bronchodilatory effect and similar safety profile of the two products, in patients with mild to moderate persistent asthma.

8. STUDY OBJECTIVES

8.1 Primary objective

The primary objective of the study was to establish therapeutic equivalence between a new generic dry powder Formoterol (12μg) formulation (Formopen®) compared to the innovative Formoterol reference formulation (Foradil®).

8.2 Secondary objectives

The secondary objectives of the study were:

- To establish the safety and tolerability of a new generic Formoterol formulation (12μg).
- To evaluate the long term bronchodilatory effect of the new dry powder Formoterol formulation (12 μg).

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan–Description

Overall study design: This was a multicenter, randomized, double–blind, double–dummy, parallel group, non–inferiority study.

Study treatments: The treatment under study was Formoterol (Formopen®) combination at a dose of 12 μg and the innovative Formoterol (Foradil®) administered at the same dosage.

Patient population and number of patients: 62 male or female adult individuals with mild to moderate persistent asthma, as defined by GINA criteria were enrolled in the trial. Patients were required to comply to a clinical diagnosis of mild to moderate persistent asthma of ≥ 6 months prior to the screening visit, to show $FEV_1 \geq 60\%$ and $\leq 90\%$ predicted, and to complete an airway reversibility test of at least 12% FEV1, with a reversibility PIF 30 to 90 lt/min after inhalation of 400 μg of Salbutamol (for complete inclusion–exclusion criteria refer to section 9.3 "Selection of study population").

Type of control: This study accommodated an active treatment concurrent control.

*Method of assignment to treatment: P*atients were randomly selected to receive either the test product or reference product in a sequence described in Figure 1.

Sequence and duration of all study periods: The sequence and duration of study periods are depicted in Figure 1. The study was comprised of a 2 week run–in period followed by a 6 week treatment period.

Run–in period

Study subjects, after having signed the informed consent form, underwent a screening visit in which eligibility criteria were evaluated. Eligible patients were asked to withhold from LABA use throughout the duration of the run–in period and from the use of short–acting β_2–agonist, 6 hours prior to the next scheduled visit. Additionally, an ICS was administered in accordance to the patients' previous asthma treatment. After a 2 week time interval, study subjects underwent a second visit (baseline visit) during which they were randomly assigned to 2 treatment groups. Each treatment group received a treatment pack containing the exact amount of pharmacological treatment needed for the subsequent 2 weeks in a randomized, double–blind, double–blind manner. The treatment pack was opened at the visits and patients received the following treatments in the specified sequence:

Group A

One inhalation of Formopen® from Elpen*haler*® (Formoterol 12μg) followed (after 1 minute) by one inhalation of Placebo Reference (identical in appearance with Foradil®) from Aerolizer® .

Group B

One inhalation of Foradil® from Aerolizer® (Formoterol 12μg) followed (after 1 minute) by one inhalation of Placebo Reference (identical in appearance with Formopen®) from Elpen*haler*®.

The remaining medication contained in the package was given to the patients for home use. Patients were advised to take the medication twice daily with a gap of 10 hours between doses.

Treatment period

During the treatment period patients underwent 3 treatment visits (visits 3–5) separated by 2 week intervals. At the treatment visits the previously used empty packs were returned and new treatment packs were given according to each patient's respective group. The new pack was opened at the visits and patients received the following treatments in the specified sequence:

Group A

One inhalation of Formopen® from Elpen*haler*® (Formoterol 12μg) followed (after 1 minute) by one inhalation of Placebo Reference (identical in appearance with Foradil®) from Aerolizer® .

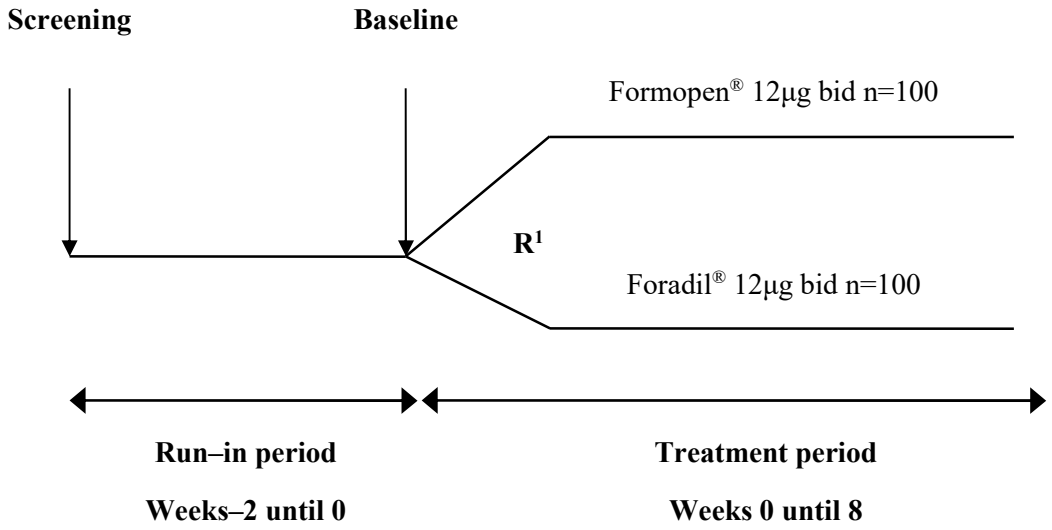
Group B

One inhalation of Foradil® from Aerolizer® (Formoterol 12μg) followed (after 1 minute) by one

inhalation of Placebo Reference (identical in appearance with Formopen®) from Elpen*haler*®.

The remaining medication contained in the pack was given to the patients for home use. Patients were advised to take the medication twice daily with a gap of 10 hours between doses. At the final study visit (visit 6–end of study visit), no medication was administered.

Figure 1: Schematic Representation of Study Design.



1 = Randomization

The actual protocol and its amendments are included in the study report as Appendix 16.1.1 and a sample case report form (unique pages only) is presented in Appendix 16.1.2.

9.2 Discussion of Study Design, including the Choice of Control Groups

In order to adhere to EMEA guidelines regarding the investigation of bioequivalence (18) and the requirements of clinical documentation and demonstration of therapeutic equivalence of orally inhaled products (19) and to best serve the inherent needs of the current stage of development of the investigational product, a multicenter, randomized, double–blind, double–dummy, parallel group design was employed. This design is referred to as a preferred design for orally inhaled products intended for reliever or controller therapy for asthma and COPD (19).

In addition, the “Guideline on the Investigation of Bioequivalence" (20) states that a parallel design is a design of choice for comparison of two formulations consisting of long half life substances. This is in agreement with the previously well documented serum half life of ~12 hours of Formoterol (6, 7). Moreover, the parallel design of the trial ensures that no spontaneous changes in the underlying disease and carry–over effects of administered treatment will occur during the study. In support of the appropriateness of this study design, parallel designs have been previously described in a number of trials aiming at proving or disproving equivalence between active substances or placebo in patients with asthma or COPD (21–28). Additionally, the study was designed as randomized, double–blind and double–dummy which ensures that objective results are produced, since expectations of the Investigator and of the participant about the experimental drug are absent. Hence, the outcome is not affected and any possible subjective bias (selection, confounding and observer) is minimized if not eliminated. Finally, the current study was multicenter in order to allow fast and sufficient patient recruitment

The study was also designed to accommodate an active treatment concurrent control group to facilitate the demonstration of the therapeutic equivalence of the test product formulation (Formopen®–Fumaric

Formoterol, DPI) over the reference product (Foradil®–Fumaric Formoterol, DPI). Foradil® is the marketed Formoterol DPI formulation at a 12 μg dosage form, incorporating a multiple dose inhalation device (Aerolizer®). It was therefore reasonably selected as the reference drug combination, taking into consideration that it is the innovative Formoterol formulation and that the investigational formulation contains also 12 μg of Formoterol DPI delivered by a different inhalation device (Elpen*haler*®). What is more, the choice of the active control group ensures that all patients will receive an active treatment rather than placebo with well documented health benefits (29). Active controls are associated with risks of reduced assay sensitivity and ability to support an efficacy conclusion. These considerations were resolved with the choice of non–inferiority margin of 20lt/min, which based on historical facts (28) and in agreement with the note for guidance of CPMP (30, 31) is an adequate margin capable of maintaining assay sensitivity.

For the present bronchodilation study, a run–in period of at least 2 weeks was chosen, during which all patients withheld from LABA use, but received orally inhaled ICS. This time interval is sufficient, according to published data, for the elimination of any possible bronchodilatory effects carried–over from prior LABA use (32). Furthermore, allowed particularization of asthma therapy to serve the purposes of a basic evaluation. The run–in period was subsequently followed by an 8 week treatment period during which patients received the either the Test or Reference Formoterol formulation. In order to avoid responsive bronchoconstriction, an adverse event associated with the use of inhaled products, any administration of ICS and short/long acting β_2–agonists was withheld for an adequate time window prior to administration of the study treatment. The CPMP guidelines (18, 19) do not specifically define a mandatory treatment period for use of inhaled LABAs in clinical trials, however a 6 week treatment period of ICS is suggested. Moreover, previous data on efficacy and safety of a novel product administered by a new device indicated a 4 week treatment period (32). Therefore, the 8 week treatment period of the trial was considered suitable to show therapeutic equivalence of two Formoterol formulations.

Finally, a group of asthmatic patients with mild to moderate asthma was selected. The trial was carried out in patients with mild to moderate persistent asthma who demonstrated reversibility of airway function, as assessed by measurement of FEV_1, of at least 12% and a 200 ml absolute improvement in 15 minutes after inhalation of an inhaled short–acting β_2–agonist (in our case Salbutamol). The group of patients selected is deemed as representative of the target population (asthmatic patients with mild to moderate persistent asthma) according to the recent guideline on the requirements for clinical documentation for orally inhaled products (20).

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Study subjects eligible for participation met all of the following criteria:

<u>At Study Entry (Visit 1–Screening Visit)</u>

1. Age 18–65 male or female.
2. Signed and dated written informed consent.
3. Documented history of mild to moderate persistent asthma of ≥ 6 months at the screening visit.
4. Concurrent use of a short acting inhaled β_2–agonist for symptom relief and ICS as maintenance treatment.
5. FEV_1 >60% and ≤90% of the predicted normal FEV_1 after withholding short–acting inhaled β_2–agonists for at least 6 hours and long–acting β_2–agonists for at least 24.
6. Demonstration at study entry of airway reversibility (increase in FEV_1 ≥12% of the pre–medication value and an absolute increase of at least 0.200 lt) 15 minutes after the inhalation of 400 μg Salbutamol, after withholding short–acting inhaled β_2–agonists for at least 6 hours and long–acting β_2–agonists for at least 24 hours.
7. PIF between 30 and 90 lt/min measured with the InCheck device.

8. Ability to use both types of inhalers with a satisfactory technique.
9. Ability to use a Peak Flow Meter correctly and to produce reliable PEFR readings.
10. In the opinion of the Investigator, subjects that were able to fill and maintain a diary card, to fill a Questionnaire related to the usability of the inhalers, and understand the procedures of the specific trial.

At Baseline Visit (Visit 2–Randomisation Visit)

1. FEV_1 > 60% and ≤90% of the predicted value for age, height and gender after withholding for 6 hours from short acting β_2–agonists and from long acting β_2–agonists for the duration of the run–in period (at least 14 days plus a maximum of 3 days).

9.3.2 Exclusion Criteria

Patients who met any of the following exclusion criteria were not eligible for enrolment into the study:

At Study Entry (Visit 1–Screening Visit)

1. Patients receiving oral corticosteroid therapy or who had received oral corticosteroid therapy in the 3 months prior to the start of the study, or who had received more than 3 short courses (up to 5 days each) of oral corticosteroid therapy in the last year of other obstructive, pulmonary disease, such as COPD, tuberculosis, cystic fibrosis, bronchiectasis.
2. Patients receiving any of the following medications at the time of the visit:
    a. anticholinergics
    b. theophylline or methylxanthines
    c. cromones
    d. MAO inhibitors or tricyclic antidepressants
    e. use of oral or topical beta–blockers agents (like antihypertensive drugs or eye drops)
    f. use of leukotriene antagonists, either currently or during the last week preceding the screening visit
3. Patients that were received therapy for an upper respiratory tract infection or that had received one during the 2 weeks prior to visit 1.
4. Patients who had been hospitalized or had received emergency treatment for an exacerbation of asthma in the 3 months prior to the start of the study.
5. Patients with a known or suspected hypersensitivity to Formoterol, Salbutamol or lactose.
6. Heavy smokers (> 10 cigarettes per day) or ex smokers who smoked more than 10 packs years.
7. Patients with any of the following concurrent conditions:
    a. uncontrolled diabetes mellitus
    b. evidence or history of neoplastic disease other than adequately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the uterine cervix
    c. evidence or history of tuberculosis
    d. evidence or history of ischemic heart disease, severe heart failure, myocardial infarction, tachyarrhythmias, cardiac arrhythmias, third degree atrioventricular block, decompensated heart failure, idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, severe hypertension, prolongation of the QTc>0.44s, aneurysm, convulsive disorders, thyreotoxicosis, pheochromocytoma
    e. respiratory disorders other than asthma or rhinitis
    f. clinically significant hepatic (transaminase levels > 2 x ULN value) or renal disease (serum creatinine > 3 x ULN value)
    g. evidence or history of alcohol or drug abuse

8. Female patients that were pregnant or lactating. Women of childbearing potential that refused to take adequate contraceptive precautions.
9. In the opinion of the Investigator, patients who were unlikely to be compliant, take their medication as directed, complete the diary card or attend scheduled clinic visits as required.
10. Patients that received other investigational drugs or who had received investigational medication in the month prior to the start of the study.
11. Patients previously randomised into the study.
12. Employees of Elpen Pharmaceuticals Co. Inc. or CROs or hospitals or any other organization involved in the study.

At Baseline Visit (Visit 2–Randomisation Visit)

13. Patients with a pre–dose FEV_1 variation more than ±15% of the respective FEV_1 measured in the previous visit.
14. Use of oral or topical LABAs during the run–in period.
15. Patients that received therapy for an upper respiratory tract infection or who had received such a treatment in the month prior to visit 2.
16. Poor compliance during the run–in period (i.e. duration of run in period more than 17 days and/or less than 10 mPEFR and/or less than 10 ePEFR measurements during the specified period).
17. Asthma exacerbation that required hospitalization and/or administration of oral and/or parenteral steroids during run–in period.
18. Any change in patient's ICS treatment during run–in period (i.e. change of active substance and/or dosage).

9.3.3 Removal of Patients from Therapy or Assessment

Study subjects could be prematurely withdrawn from the trial if any of the following occurred:

- Protocol violation
- Subject's non–compliance
- Intolerable adverse event, including paradoxical bronchospasm.
- Any change in the ICS that the received during the study (in relation to the dosage and/or the active substance).
- Asthma exacerbation requiring hospitalisation or oral and/or parenteral administration of corticosteroids.
- Refusal of the participant to continued the study treatment or any study procedure.
- Non–related illness or complication that does not allow continuation of the study.
- Investigator's decision that termination of the study was to the medical benefit of the participant.
- Discontinuation of monitoring.
- Death of the participant
- Pregnancy
- Administrative reasons
- Serious adverse event

9.4 Treatments

9.4.1 Treatments Administered

The study medications were the following:

- Formopen® DPI containing 12 μg of Formoterol administered with Elpen*haler*®, manufactured by

Elpen Pharmaceuticals Co. Inc. (Test product) and matching placebo identical in appearance.

- Foradil® DPI containing 12 μg of Formoterol administered with Aerolizer®, manufactured by Novartis (Reference product) and matching placebo identical in appearance.

Study medications were administered by inhalation as follows:

Group A

Patients received Formopen® Elpen*haler*® inhaled Formoterol 12mg twice a day for eight weeks. The treatment period was preceded by a preparatory period lasting two weeks. The study drug was added to the existing treatment of each patient, which included ICS. Subjects that were in this treatment group used virtual Aerolizer®, one inhalation twice daily along with the active drug substance.

Group B

Patients received Foradil® Aerolizer® inhaled Formoterol 12mg twice a day for eight weeks. The treatment period was preceded by a preparatory period lasting two weeks. The study drug was added to the existing treatment of each patient, which included ICS. Subjects that were in this treatment group used virtual Elpen*haler*®, one inhalation twice daily along with the active drug substance.

9.4.2 Identity of Investigational Product(s)

Test Formoterol (Formopen®): Inhalation powder, in a single dose blister, containing 12 μg Formoterol delivered by the novel DPI device Elpen*haler*® – 1st Batch number: 70768, Elpen Pharmaceutical Co. Inc. Due to expiration of the batch on 5/2009, a second batch was provided – 2nd Batch Number: 90641.

Reference Formoterol (Foradil®): Inhalation powder, containing 12 μg Formoterol delivered by the DPI device Aerolizer® – 1st Batch number: U0065, Novartis. Due to expiration of the batch on 2/2009, a second batch was provided – 2nd Batch Number: U0083.

Sufficient Test and Reference products were retained and are available for retrospective analysis if, for at least one year after the expiration date.

The use and design of Elpen*haler*® and Aerolizer® used in this study are provided as Appendix 2 & 3 in the attached protocol–Appendix 16.1.1.

9.4.3 Method of Assigning Patients to Treatment Groups

Study patients were randomly assigned to treatment groups at each study centre, as dictated by the randomization list. Then randomisation was central and the randomization list was and sequentially numbered starting from the number "R–501. This number was denoted as patient's randomization number corresponded to a unique outer study treatment package distributed at the study centre.

A table exhibiting the randomisation codes, patient number, and treatment sequence assigned is presented for each centre in Appendix 16.1.8.

9.4.3.1 Generation of allocation sequence

A computer generated permutted block randomisation list (blocks of four) was developed by Zeincro Hellas SA with the use of SAS sofware. Each treatment was coded as A or B and labelled with the letters R followed by a three digit sequential number starting from 501 (e.g. R501). This number was the randomisation number assigned to each patient.

The Master Randomisation List was kept by the sponsor

9.4.3.2 Allocation Concealment

The random allocation of treatments was concealed with the use of blinded and sequentially numbered (by the randomisation number) outer treatment boxes, containing appropriately labelled (by visit) treatment packs, which were directly provided to the sites.

9.4.3.3 Implementation

The sponsor was responsible to assign treatment codes, A or B, to treatment groups. The sponsor assigned A to Formopen® Elpen*haler*® treatment and B to Foradil® Aerolizer® treatment and was specified in the Master Randomisation list (this was not revealed to the statistician until the database lock).

The randomisation number was matched to a treatment box with the same number pre–printed on the outer surface. After randomization, the patient number was written on the outer treatment box by the investigator on the corresponding area.

9.4.4 Selection of Doses in the Study

During the treatment period patients received a single dose of either study treatment twice daily, which could have been:

1. **Test:** Formoterol (12 μg) combination with Elpen*haler*® and Placebo
2. **Reference:** Formoterol (12 μg) combination with Aerolizer® and Placebo

Study visits were planned with a 2 week interval.

Patients inhaled via the inhalation devices in the same order for the duration of the treatment period. Both formulations delivered Formoterol at a dose of 12 μg per inhalation. This dose was selected since it is the standard daily dose of Formoterol combination, most frequently used in clinical trials (33–36).

9.4.5 Selection and Timing of Dose for each Patient

Patients were given a treatment pack and were asked to receive the medication (Formopen® or Foradil®–12 μg of Formoterol) twice daily. The first dose was received in the morning (after morning PEFR measurement) and the second dose was received in the evening, at least 10 hours after the first dose and after the evening PEFR measurement.

The morning PEFR (mPEFR) measurement was performed with the "mini–Wright Peak Flow Meter" (Clement Clark, UK) by the patient, at least 10 hours after the last drug administration and approximately 15 min before receiving the morning dose of the study treatment. After the mPEFR measurement was performed, one actuation from each inhalation device was received by the patients.

The evening PEFR (ePEFR) measurement was performed with the "mini–Wright Peak Flow Meter" (Clement Clark, UK) by the patient, at least 10 hours after administration of the morning dose and immediately before receiving the evening dose of the study treatment. After the ePEFR measurement was performed, one actuation from each inhalation device was received by the patients.

The actuation of Formopen® through Elpen*haler*® could contain 12 μg of active Formoterol or placebo, and the actuation of Foradil® through Aerolizer® could contain 12 μg of active Formoterol or placebo, originating from the double dummy design. Inhalation devices were used in the same order each day; patients first inhaled the dose from the Aerolizer® inhaler and after 1 minute, the patients inhaled the dose from Elpen*haler*®. Patients were given detailed information on accurate PEFR measurement and were properly trained and examined on correct inhaler use.

9.4.6 Blinding

During the treatment period, no participating member (Investigators, Patients, Study Monitors, Data Managers or Statisticians) were aware of the treatment being administered to each patient.

In order to achieve the blind design, the double dummy technique was applied.

At the screening visit and after confirmation of eligibility, patients were assigned a randomisation number. At the same time, each patient was assigned a treatment medication box labelled with the same randomisation number.

Each outer treatment box included the study medication in four different treatment packs. Each of the treatment packs contained two boxes that included two different inhalation devices: the Elpen*haler*® device, with its matching strips and the Aerolizer® device. The Elpen*haler*® device could contain either the active substance of Formoterol or its Placebo. The Aerolizer® device could also contain either the active substance of Formoterol or its Placebo. Patients were supplied with one treatment box at each treatment visit (visits 3–5) that contained enough medication for 2 week home use. The visit/randomization number was pre–printed on each of the three treatment packs of the treatment box in order to ensure the site personnel would distribute the appropriate pack according to the patient's visit and randomization number.

In order to preserve the dummy design of the study each patient inhaled from both devices one of which was "dummy". The first "dummy" inhalation device was indistinguishable to Aerolizer® device in terms of size, weight and colour as developed by Novartis and the second "dummy" was indistinguishable Elpen*haler*® in size, weight and colour, as developed by Elpen Pharmaceuticals Co. Inc. No codes or signs printed on the labels on the devices or the treatment pack per visit could reveal the nature (active drug or placebo) of the inhaled product.

The packaging and labelling of the study medication container is illustrated further below (Figures 2–5).

Figure 2: Label text of the outer treatment box, with all treatment packs for each patient

MEDICINE FOR CLINICAL TRIAL ONLY
Protocol number: 2007–FOR–EL–02
EUDRA CT number: 2007–002157–23

This package contains 4 therapeutic packages. Each therapeutic package contains one box of Formopen® Elpen*haler*® (active or placebo) and one box of Foradil® Aerolizer® (active or placebo).

Store below 25ºC protected from moisture. Keep out of the reach of children.

Patient number:
Randomisation number:

Investigator's name:

Figure 3: Label text of the treatment pack containing the two devices, corresponding to one visit

MEDICINE FOR CLINICAL TRIAL ONLY
Protocol number: 2007–FOR–EL–02
EUDRA CT number: 2007–002157–23

This package contains one box of Formopen® Elpen*haler*® (active or placebo) and one box of Foradil® Aerolizer® (active or placebo).

Store below 25ºC protected from moisture. Keep out of the reach of children.
To be taken according to the instructions given by the investigator.

Patient number:
Randomisation number:
Visit number: Date:
Investigator's name:

Figure 4: Text of the labels on the Formopen® Elpenhaler® box (active or placebo)

35 doses Dry powder for inhalation on single dose strip

Formopen® Elpen*haler*®
Dihydrofumaric Formoterol 12μg or placebo

Lot No: 70768 (1st batch) Exp. Date:05/2009

Lot No: 90641 (2nd batch) Exp.Date: 04/2011

Store below 25ºC away from moisture. Keep out of the reach of children.
To be taken according to the instructions given by the investigator.
Sponsor: Elpen Pharmaceutical Co. Inc
MEDICINE FOR CLINICAL TRIAL ONLY
Protocol number: 2007–FOR–EL–02
EUDRA CT number: 2007–002157–23

Patient number:
Randomization number:
Visit number: Date:
Investigator's name:

Figure 5: Text of the labels on the Foradil® Aerolizer® box (active or placebo)

35 capsules for
inhalation

Foradil® Aerolizer®
Dihydrofumaric Formoterol 12μg or placebo

Lot No: U0065 (1st batch) Exp. Date: 02/2009

Lot No: U0083 Exp. Date 07/2010

Store below 25ºC away from moisture. Keep out of the reach of children.
To be taken according to the instructions given by the investigator.
Sponsor: Elpen Pharmaceutical Co. Inc
MEDICINE FOR CLINICAL TRIAL ONLY
Protocol number: 2007–FOR–EL–02
EUDRA CT number: 2007–002157–23

Patient number:
Randomization number:
Visit number: Date:
Investigator's name:

Labelling and packaging of the study medication was conducted by Elpen Pharmaceuticals Co. Inc. according to Annex 13 of the GMP guidelines, ICH/GCP requirements and the local low.

9.4.6.1 Un–blinding

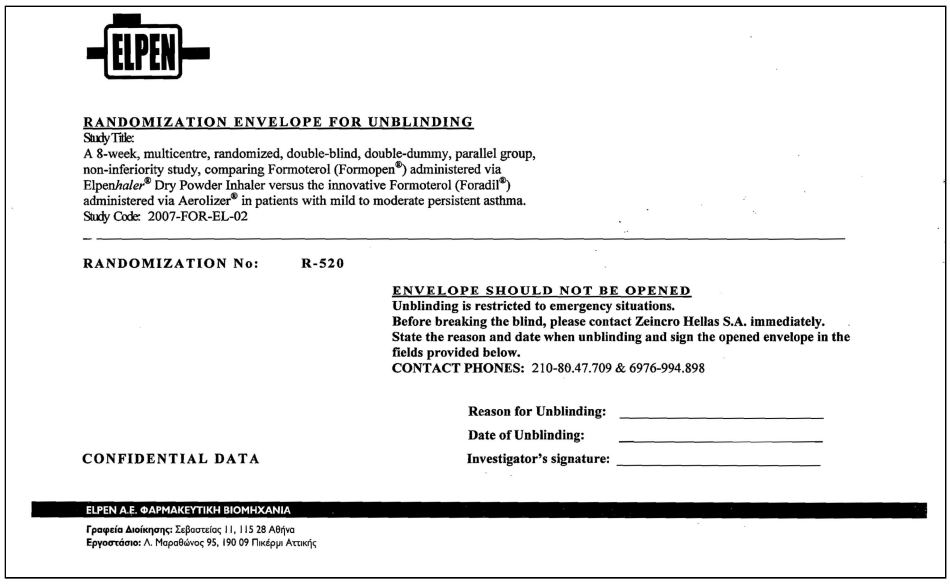
Each study treatment box corresponded to an opaque sealed envelope sequentially numbered according to the randomisation list, containing information on the exact treatment for each patient.

A copy of the sealed drug disclosure envelopes was kept by the Sponsor.

The treatment blind was broken for all patients at September 29th 2010 which is after study completion and database lock (June 30th, 2010).

An example of the randomisation envelopes is shown below (Figure 6):

Figure 6: Example of randomization envelope



ELPEN

RANDOMIZATION ENVELOPE FOR UNBLINDING

Study Title:
A 8-week, multicentre, randomized, double-blind, double-dummy, parallel group, non-inferiority study, comparing Formoterol (Formopen®) administered via Elpen*haler*® Dry Powder Inhaler versus the innovative Formoterol (Foradil®) administered via Aerolizer® in patients with mild to moderate persistent asthma.
Study Code: 2007-FOR-EL-02

RANDOMIZATION No: **R-520**

ENVELOPE SHOULD NOT BE OPENED
Unblinding is restricted to emergency situations.
Before breaking the blind, please contact Zeincro Hellas S.A. immediately.
State the reason and date when unblinding and sign the opened envelope in the fields provided below.
CONTACT PHONES: 210-80.47.709 & 6976-994.898

Reason for Unblinding: _____
Date of Unblinding: _____
CONFIDENTIAL DATA **Investigator's signature:** _____

ΕΛΠΕΝ Α.Ε. ΦΑΡΜΑΚΕΥΤΙΚΗ ΒΙΟΜΗΧΑΝΙΑ
Γραφεία Διοίκησης: Σεβαστείας 11, 115 28 Αθήνα
Εργοστάσιο: Λ. Μαραθώνος 95, 190 09 Πικέρμι Αττικής

In the event of an emergency, each site's principal Investigator was be able to un–blind patient treatment allocation by opening the respective sealed envelope. Un–blinding was restricted to emergency and safety situations and could be practised when knowledge of the study drug allocation was deemed necessary. However un–blinding was not necessary at any time during the study, since no serious adverse events or other emergency situations occurred.

9.4.7 Prior and Concomitant Therapy

Eligible patients for the study were asked to stop or withhold administration of the following medications prior to commencing any study related procedure:

- 12 weeks prior to screening visit: any investigational medication or device.
- 12 weeks prior to screening visit: orally or parenterally administered corticosteroids.
- 2 weeks prior to screening visit: medication administered for upper respiratory tract infection.
- 24 hours prior to screening visit and for the duration of the study (run–in and treatment period): inhaled LABAs monotherapy or combination (except for study medication test or reference).

Eligible patients continued their routine asthma treatment for the duration of the study. However, they were asked to withhold from certain medication administered for other co–morbidities (Table 1). In addition, ICS were administered at a fixed dose, that was determined at the screening visit, depending on each patient's asthma severity and in accordance with GINA guidelines (37) (provided as Appendix 6 in the attached protocol–Appendix 16.1.1).

Prior to each study visit patients were asked to withhold from short–acting oral β_2–agonist use 6 hours prior to each treatment visit and the end of study visit (visit 3–6). Each patient was instructed both in writing and verbally regarding drug withholding times by the study physician.

Table 1: List of prohibited medications (by therapeutic category) for the duration of the trial

Therapeutic category	Medication	
β–blockers (antihypertensive medication)	Atenolol	Nadolol
	Betaxolol	Nebivolol
	Bisoprolol	Oxprenolol
	Esmolol	Pindolol
	Carvedilol	Propranolol
	Labetalol	Celiprolol
	Metoprolol	

Therapeutic category	Medication	
β–blockers (anti galucome medication)	Betaxolol Levobunonol Carteolol	Metipranolol+BenzalkoniumChloride Fenoterol Timolol
β_2–adrenergic receptor agonists	(monotherapy or in combination) Salmeterol Terbutaline Clenbuterol Orciprenaline	Salbutamol+Ipratropium Bromide (in combination) Levalbuterol Metaproterenol Pirvuterol
ICS/LABA combinations	Budesonide+Formoterol	Fluticasone+Salmeterol
Cromones	Cromoglycate Sodium	Nedocromil Sodium
Xanthine derivatives	Aminophylline Diprophylline	Theophylline
Anticholinergic medication	Ipratropium Bromide Tiotropium Bromide	Oxitropium Bromide
Leukotriene antagonists	Montelukast Praklukast	Zileuton Zafirlukast
Tricyclic antidepressants	Amitriptyline Doxepin Imipramine	Nortriptyline Chrorimipramine
MAO inhibitors	Moclobemide	Selegiline

For the duration of the trial, Salbutamol was administered as rescue medication for the management of dyspnoea episodes. The number of Salbutamol doses was recorded in the patient's diary card (see Appendix 16.1.2).

9.4.8 Treatment Compliance

Patients received the study treatments by inhalation twice daily from home. In order to assure that the drug was administered properly, demo devices identical to both Elpen*haler*®/Aerolizer® and placebo capsules/blisters were provided at the screening visit. During the visit, patients were given specific instructions and proceeded with demonstrating proper inhaler use until the study doctor or nurse deemed that they were properly trained. Subsequently, patients were supplied with an adequate quantity of demo devices and placebo capsules/blisters to continue their training at home, throughout the run–in period. In addition, at the screening visit patients were provided with a peak flow meter and patients' diary cards for the performance and recording of the morning and evening PEFR measurements. Detailed instructions on the Flow Meter use and on how to correctly fill in the diary cards were also given (see Appendix 16.1.2).

The receipt, use, recovery, loss or other disposal of the study medication, inhalation devices and peak flow meters was recorded in accountability logs, provided by Zeincro Hellas SA. Information describing the quantities of study drug supplied to each patient was recorded and signed by the Investigator (or pharmacist or the person that supplied the drug) and collected by the study Monitors. Essential data included relevant dates, quantities, batch numbers or codes, and data on patients who received the study drug.

Each capsule of Foradil®/placebo, each blister of Formopen®/placebo, as well as the study inhalation devices/demo devices were accounted for during the study.

In addition, patients were asked to return any partially used, empty or unused demo devices, which were supplied for home training at the screening visit.

At the end of the study, all unused products were collected by the Monitors and returned to Elpen Pharmaceuticals Co. Inc.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

9.5.1.1 Efficacy measurements

Mean morning PEFR (mPEFR) determination (in house measurements)

Using the "Mini–Wright Peak Flow Meter" the mPEFR was measured by the patients at home daily, at least 10 hours after the previous treatment dose administration and approximately 15 mins before administration of the morning treatment dose. The Mini–Wright Peak Flow Meter is a simple spring–loaded piston device that measures PEFR in lt/min during maximal forced expiration. The instrument is widely used among asthmatic patients, including small children, because its proper use can be quickly learned and PEFR measurements can be easily made at home (38). PEFR measurements were performed in triplicate, in accordance with detailed instructions given to each patient at the screening visit. All three PEFR values were recorded in the patient's diary card and used to determine the primary efficacy variable (mean change in the mean mPEFR; section 9.5.3). Of the three values documented each day, the highest value was used for mPEFR estimation.

Mean evening PEFR (ePEFR) determination (in house measurements)

Using the "Mini–Wright Peak Flow Meter" the ePEFR was measured daily at home, at least 10 hours after the morning treatment dose administration and exactly before administration of the evening treatment dose. PEFR measurements were performed in triplicates and in accordance with detailed instructions given to each patient at the screening visit. All three PEFR values were recorded in the patient's diary card and used to determine the mean change in the ePEFR (see section 9.7.1.2). Of the three values documented each day, the highest value was used for ePEFR estimation.

For the determination of both mPEFR and ePEFR measurements all recorded values were utilised. In the case that a patient had recorded less than 10 measurements, he/she was removed due to reduced compliance. Subjects with <85% overall compliance were also removed.

Spirometric values

Spirometry was performed at all study visits (visits 1–6) (with an 11–17 day interval between visits). In order to assure the accurateness and repeatability, all spirometric evaluations were conducted, whenever possible, by the same person (study investigator or nurse) and within a time window of ±2 hours, for each patient. In addition, the same graduated spirometry device was utilised, according to established harmonised procedures (39). Spirometric measurements were carried out 10 mins after the patient's arrival in the study centre (at rest). Patients were asked to perform 3 consecutive measurements. If a >5% difference between measurements was observed, patients were asked to perform up to 8 additional measurements.

- **FEV_1 determination:** The highest FEV_1 value was recorded and used to determine the following spirometric parameters: FVC, FEV_1/FVC, $FEF_{25\%}$ and $FEF_{25–75\%}$. Acceptable FEV_1 values were > 60 and ≤90% of the predicted according to the patient's age, race and sex.
- **PIF measurement:** Using the In–Check dial device, peak inspiratory flow (PIF) was measured at the screening visit in order to determine whether each patient's PIF is sufficient for using inhalation devices like Elpen*haler*® or Aerolizer®. Acceptable PIF for production of therapeutic doses is > 30 and <90 lt/min. Stable asthmatics are reported to produce "acceptable" and "optimal" PIF values at 100% and 81–93% respectively (11). "In–Check" dial device incorporates the resistance generated by the device to the estimation of the value, so as to make sure that asthmatic patients can adequately inhale from the specific device. PIF measurement was performed by the study site's responsible investigator.
- **Reversibility test:** Pre–study FEV_1 measurement was performed by spirometry at the screening visit in order to verify the reversibility of the patient's asthma condition and responsiveness to pharmacological therapy. A positive reversibility test was considered as a ≥12% increase (and an absolute increase of ≥0.2 lt) in pre–study FEV_1 within 15 minutes after 2 actuations of 200 μg (400

μg in total) of Salbutamol. FEV_1 was determined by the study site's responsible investigator. Patients that failed to exhibit a ≥12% increase were not included in the study. However, patients were allowed to return to the study to perform one additional reversibility test within 3 days.

Daily PEFR fluctuation

The number of days with >20% were assessed. The highest ePEFR and mPEFR measurement recorded by the patient in the diary card was used. Daily PEFR fluctuation was calculated as:

% daily PEFR fluctuation = [(ePFER–mPEFER)/ePEFR]*100.

Number of rescue medication nebulisations

The number of Salbutamol nebulisations during the treatment period was recorded by the patients in the diary card.

Degree of asthma symptoms

Recording of the asthma symptoms was performed twice daily by the patients, for the run–in and for the treatment period.

The degree of the day asthma symptoms was noted down right before the evening treatment dose administration in the patient's diary card, according to the following scale:

0 No symptoms during the day
1 Mild symptoms during the day that did not affected daily activities
2 Moderate symptoms during the day that did not affected daily activities
3 Severe symptoms during the day that affected daily activities

The degree of the night asthma symptoms was noted down right before the morning treatment dose administration in the patient's diary card, according to the following scale:

0 No symptoms during the night
1 Mild symptoms that awoke the patient once during the night
2 Moderate symptoms that awoke the patient twice or more during the night
3 Severe symptoms that kept the patient awake for the better part of the night

Usability questionnaire

An appropriate questionnaire (Usability Questionnaire– provided as Appendix 7 in the attached protocol–Appendix 16.1.1) intended to measure the ease of use of Elpen*haler*® or Aerolizer® was distributed to he patients at the termination visit (visit 6). The questionnaire included the same set of questions twice, once for each inhalation device. Answers were rated using a Linkage scale, where 1 was the most positive answer and 5 the most negative.

9.5.1.2 Safety measurements

Paradoxical bronchospasm assessment: Paradoxical bronchospasm was assessed at the baseline visit (visit 2) in the study centre, after randomisation was completed. Patients underwent spiromertry before and 15 mins after LABA administration. If the lowest FEV_1 value recorded after drug administration was lower than the lowest FEV_1 value recorded before drug administration (paradoxical bronchospasm), the patient was removed from the study.

Vital signs: Blood pressure, respiratory rate, SAP & DAP and heart rate were measured at all study visits (visits 1–6) with a ±3 day interval between visits.

12–lead ECG/QTc intervals: 12–lead ECG was performed and QTc interval was recorded at screening visit and at the final visit with a ±3 day interval between visits. Additional ECGs were performed at treatment visits when necessary for safety reasons (see Serum potassium and glucose levels below). Patients that exhibited aberrant ECG findings or a prolonged QTc interval (QTc >44s) were removed from the study.

ECG tests were performed locally at the study centre. All electrocardiographic equipment were calibrated and maintained according to manufacturer's instructions.

Haematology & Biochemistry: Blood sampling was performed at the screening and termination visits (with a ±3 day interval between visits) to conduct a complete set of haematology (Hb, Hct, RBC, WBC with differential & PLTs) and biochemistry (potassium, sodium, urea, creatinine, uric acid, ALP, ALAT/ASAT, bilirubin and glucose levels) tests.

All clinical analyses were conducted at "Research Diagnostics" Central Laboratory (Ilioupoli, Greece) (Appendix 16.1.11).

Serum potassium and glucose levels: Blood sampling was performed at treatment visits (visits 3–5) (with a ±3 day interval between visits) for potassium and glucose levels measurement. If serum levels of potassium were lower than indicated an additional ECG was performed. Aberrant ECG findings required removal of the patient.

Pregnancy tests: Urine hCG tests were performed for all female subjects of child–bearing potential at the screening and termination visits (with a ±3 day interval between visits).

Adverse Events: Adverse events (self–reported or questioned by the physician) were recorded at study visits 2–6 (with a ±3 day interval between visits) according to protocol definitions, giving additional attention in manifestation of paradoxical bronchospasm after inhalation of treatments, prolonged QTc interval, hypokalaemia and hyperglycaemia. Seriousness, severity, causality and relatedness of the AEs were assessed by the site investigator. After the end of the study, a follow–up telephone call was made by the investigator with a 2–7 day interval for all study participants that received at least one dose to record any potential adverse events. In certain instances, if clinically indicated, an additional visit was scheduled.

9.5.1.3 Flow Chart of the study

Table 2: Flow Chart of the study

	Run–in Period		Treatment Period			
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Description	Screening Visit	Baseline Visit	1st Treatment Visit	2nd Treatment Visit	3rd Treatment Visit	End of study or premature termination[21]
Day	–14	0	14	28	42	56
Time window (days)	maximum–17	0	11–17	25–31	39–45	53–59
Study evaluations						
Informed Consent[1]	X					
Eligibility check[2]	X	X				
Demographics[3]	X					
Asthma history[4]	X					
Medical history[5]	X					
Smoking history[6]	X					
Physical examination[7]	X					X
Pregnancy test (urine)[8]	X					X
Vital signs[9]	X	X	X	X	X	X
Demo inhalation devices distribution	X					

	Run–in Period		Treatment Period			
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Description	Screening Visit	Baseline Visit	1st Treatment Visit	2nd Treatment Visit	3rd Treatment Visit	End of study or premature termination[21]
Day	–14	0	14	28	42	56
Time window (days)	maximum–17	0	11–17	25–31	39–45	53–59
Study evaluations						
Return of demo inhalation devices		X				
Distribution of Peak Flow Meters	X					
Distribution of Patients' daily diary cards	X	X	X	X	X	
Return of Patients' daily diary cards		X	X	X	X	X
Patient training[10]	X	X				
Asthma medication withholding	X[11]	X[12]	X[13]	X[13]	X[13]	X[13]
Spirometry	X	X	X	X	X	X
Reversibility test[14]	X					
Paradoxical bronchospasm assessment		X				
12–lead ECG	X		X[(15)]	X[(15)]	X[(15)]	X
Haematology[16]	X					X
Biochemistry[17]	X		X[(18)]	X[(18)]	X[(18)]	X
Randomisation		X				
Concomitant medication[19]	X	X	X	X	X	X
Adverse events[20]		X	X	X	X	X
Usability questionnaire						X

1 Informed consent took place at the screening visit before any trial related procedure.
2 Eligibility was checked at screening visit and at baseline visit according to GINA guidelines (provided as Appendix 6 in the attached protocol–Appendix 16.1.1).
3 Gender, race, weight, height and date of birth were recorded.
4 Asthma history and degree of asthma symptoms were recorded at the screening visit.
5 Past, controlled and current medical conditions were recorded.
6 Smoking history was fully checked and recorded as appropriate.
7 A full body and organ examination was performed.
8 A pregnancy test (urine) was performed for all female subjects of child–bearing potential. Patients with a positive result were removed from randomization.
9 Blood pressure (SAP/DAP), body temperature, respiratory rate and heart rate were examined.
10 Patients were trained and asked to display proper usage of demo inhalation devices identical to Elpen*haler*® and Aerolizer®.
11 24 hours for long–acting β2 agonists and 6 hours for short–acting β2 agonists.
12 6 hours for short–acting β2 agonists and throughout the run–in period for long–acting β2 agonists (2 weeks ±3 days).
13 12 hours for long–acting β2 agonists and 6 hours for short–acting β2 agonists.
14 A positive reversibility test was considered as a ≥12% increase (and an absolute increase of ≥0.2 lt) in pre–study FEV1 within 15 minutes after 2 actuations of 200 μg of Salbutamol.
15 Only if clinically necessary.
16 Blood sampling for haematology (Hb, Hct, RBC, WBC with differential & PLTs) was performed at the screening visit and at the termination visit.
17 Blood sampling for biochemistry (potassium, sodium, urea, creatinine, uric acid, ALP, ALAT/ASAT, bilirubin and glucose levels) tests
18 Only serum potassium and glucose levels were measured at visits 3, 4 and 5.
19 Concomitant medications were recorded throughout the study period.

[20] Adverse Events were recorded at study visit 2–6 according to protocol definitions.
[21] A telephone contact/follow–up was performed for all patients who received at least one dose of study medication. It may have been replaced by a visit if clinically indicated with a 2–7 day window.

9.5.2 Appropriateness of Measurements

PEFR measurement is a simple method of measuring airway obstruction in mild, moderate and severe disease that can be easily performed by properly trained patients at home. Due to the simplicity of the method, it has been recognised by the National Asthma Education and Prevention Program (NAEPP) as a means for self–monitoring by asthmatic patients that can further provide the patient and the clinician with objective data upon which to base disease management decisions (40). Thus, long–term or short–term daily PEFR monitoring by the patients has been widely used in assessing asthma severity in clinical trials and everyday clinical practice (41–45).

In addition, efficacy assessments such as PIF and FEV_1 are two spirometry based measurements, worldwide considered as objective measures of pulmonary function, in healthy subjects and asthmatic patients (12). Furthermore, according to international medicinal guidelines, FEV_1 is proposed as the most sensitive measure of pulmonary function in clinical trials on patients with asthma (7). As far as safety variables are concerned, recording of all vital signs, ECG, blood haematology and biochemistry changes, as well as recording presentation of all adverse events, self–reported or questioned by the physician, constitute the full panel of safety assessments employed during clinical trials. Therefore, both the efficacy and safety assessments chosen for the purposes of this study are recognised as standard, i.e., widely used, reliable, accurate and relevant to describe safety profiles of the investigational products.

9.5.3 Primary Efficacy Variables

Primary efficacy variable was the mean change of the mean mPEFR observed from the run–in period until the end of the treatment period. It was derived by subtracting the baseline mean mPEFR from the mean mPEFR at the end of the treatment (week 8).

Change of the mean mPEFR from baseline to week 8 was calculated by subtracting the mean mPEFR of the run in period from the mean mPEFR at the end of treatment period (week 8):

$$\Delta mPEFR = mPEFR_{42d–56d} - mPEFR_{–14d–0d}$$

Mean mPEFR baseline value ($mPEFR_{–14d–0d}$) was calculated as the average of more than 10 values of the 14 days of the run–in period. If less than 10 values were recorded then patient should be considered as non–eligible for the study due to poor compliance.

Mean mPEFR end of treatment value ($mPEFR_{42d–56d}$) was calculated as the average of more that 10 values of the 14 days of the last 2 weeks of the treatment period. If patient had less than 10 measurements, then the total compliance percentage was checked (>85%).

Since the mPEFR was measured each time in triplicates, the maximum mPEFR value was considered for the calculation of the respective average value.

Mean mPEFR at visit days 14, 28 and 42 was calculated as the average of all available values recorded by the patient in the respective period: $mPEFR_{1d–14d}$, $mPEFR_{15d–28d}$, and $mPEFR_{29d–42d}$ were used in conjunction with the baseline and end of treatment values for secondary analysis.

For the determination of both mPEFR measurements all recorded values were utilised. In the case that a patient had recorded less than 10 measurements, he/she was removed due to reduced compliance. Subjects with <85% overall compliance were also removed.

9.5.4 Drug Concentration Measurements

Not applicable for the current trial.

9.6 Data Quality Assurance

To assure quality of data collected during the study, an Investigators' meeting, held in Athens, Greece on 9 & 10 February 2008, was organised by Elpen Pharmaceuticals Co. Inc. before any patient was screened and enrolled in the study, in order to inform and train the participating investigators on the following:

- Study Background
- Protocol design and objectives,
- Inclusion/exclusion criteria,
- Informed Consent Form and patients' documents,
- Recruitment period,
- CRF completion,
- Description and handling of IN–Check device,
- Instructions for use of Elpen*haler* and Foradil,
- GCP guidelines and Adverse Event reporting.

The Principle Investigator, at least one co–investigator, and/or study nurse from each study centre were present in this Investigators meeting.

Each recruiting site received 3–7 regularly scheduled interim monitoring visits. At each monitoring visit, 100% review of source documents and CRF variables for all enrolled subjects was conducted. To exclude laboratory variations (on equipment used, sensitivity and accuracy results) between the sites, all laboratory blood analyses were performed centrally, by Research Diagnostics. Details on correct handling procedures and instructions regarding shipment were provided as well as a laboratory manual to all study sites by Research Diagnostics.

No external or internal audits were planned for this study. Elpen however, performed co–initiation visits along with the monitor of the designated CRO (Zeincro Hellas SA), at all sites, and also co monitoring visits at randomly selected sites.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Study Populations

Three populations were considered during the study.

- The Per–Protocol (PP) population consisted of all the ITT patients with no major protocol violation and completed all study visits as described in the study protocol. The PP population was considered as the primary analysis population.
- The Intention–To–Treat (ITT) population consisted of all randomized patients who were administered at least once with the study medication and have at least one valid mPEFR during the trial.
- The safety population comprised of all patients who received at least one dose of study medication.

9.7.1.1 Primary analysis

The statistical hypothesis testing of non–inferiority of Formopen® compared to Foradil® was formulated as follows:

$$H_o: \mu_{Fp} - \mu_{Fd} + \Delta_0 \leq 0 \quad \text{(Inferiority)}$$

$$H_1: \mu_{Fp} - \mu_{Fd} + \Delta_0 > 0 \quad \text{(Non–Inferiority)}$$

Where μ_{Fp} and μ_{Fd} stand for the mean change of mPEFR ($\Delta mPEFR$) in Formopen® and Foradil® groups

respectively, from baseline to final visit. Δ_0 is the non–inferiority margin which was set to 20 lt/min. The hypothesis was tested at at a 2.5% 1-sided significance level.

The hypothesis testing was based on the fact that the null hypothesis $\frac{\hat{\mu}_{Fp} - \hat{\mu}_{Fd} + \Delta_0}{S\mu_{Fp-Fd}}$ follows a standard normal distribution The sample from each treatment group was regarded as independent of the other and of equal variance. The null hypothesis (inferiority) would be rejected in the case that the value of this statistic is greater than the 97.5% percentile of the standard normal distribution, which leads to a non–inferiority conclusion.

9.7.1.2 Secondary analyses

Mean morning and evening PEFR

Mean morning and mean evening PEFR were analyzed at each visit by means of measures of central tendency and dispersion. Comparisons between the two therapy groups were performed by Wilcoxon's rank sum test.

The mean percentage change of mean mPEFR between each visit and baseline was estimated by fitting a linear mixed–effects model to the data.

Fixed covariates were selected among all the baseline clinical and demographic characteristics, according to analysis of variance methods. Random covariates were selected according to the values of Akaike Information Criterion (AIC). The autocorrelation structure was assumed to follow a first–order autoregressive process AR (1). The response variable (mPEFR) was transformed into logarithmic scale to meet the assumption of normality.

Spirometry values

All spirometric measurements ($FEV_{1,}$ FVC, FEV_1/FVC, $FEF_{25\%,}$ $FEF_{25–75\%}$) were presented at each visit by means of measures of central tendency and dispersion. Comparison between the two therapy groups was implemented by Wilcoxon's rank sum test.

Patient's usability questionnaire

Patient's usability questionnaire was illustrated by frequency distribution tables for each treatment device. The difference in usability the usability between the two devices (Elpen*haler*®, Aerolizer®) was tested by Wilcoxon's sign rank sum test.

Other secondary variables

Number of days with PEFR diurnal variation >20%, day and night asthma symptom score and number of morning and evening puffs of concomitant short acting β_2–agonist, were all analyzed by fitting ordinal mixed–effects models.

Time trend was analyzed by exploring the statistical significance of "visite" as fixed covariate; relation with therapy was analyzed by exploring the statistical significance of the fixed covariate "treatment group". The patient number was regarded as a random covariate that follows a normal distribution with zero mean.

The percentage of patients within each asthma intensity category at each visit (morning and evening), was calculated based on patients' daily asthma symptoms, averaged across the time interval between visits.

The percentage of patients that performed one, two or no inhalations (morning and evening), was calculated based on patients' daily inhalations, averaged across the time interval between visits.

All tests in the secondary analysis were 2–sided and the level of statistical significance was set to 5%.

Statistical analysis was performed in SAS V9.2.

9.7.1.3 Safety analysis

Safety analysis includes:

- Frequency distribution tables and lists of patients with AEs by preferred term as in MedDRA 12.0 coding and by causality to the study medication, as assessed by the investigator .
- Descriptive statistics for laboratory measurements during the study visits and frequency tables for the abnormal laboratory values, or ECG.

9.7.1.4 Interim analysis

No interim analysis of the results was performed during the study.

9.7.1.5 Excluded Patients

All patients with at least one major protocol violation or that withdrew their consent to participate in the study, were excluded from the analysis of the primary and secondary endpoints.

9.7.1.6 Data Monitoring Committee

No Independent Data Monitoring Committee was present at the study.

9.7.2 Determination of Sample Size

A sample of 92 patients (46 per treatment arm), was calculated to have 80% power to demonstrate the non–inferiority of generic Formoterol Elpen*haler*® versus the innovative one administered with Aerolizer® at 2.5% level of significance to reject the null hypothesis:

$$H_o: \mu_{Fp} - \mu_{Fd} \leq -\Delta_0$$

$$H_1: \mu_{Fp} - \mu_{Fd} > -\Delta_0$$

Where μ_{Fp} and μ_{Fd} stand for the mean change of mPEFR (*ΔmPEFR)* in Formopen® and Foradil® groups respectively, from baseline to final visit, assuming that the non–inferiority margin (Δ_0) is 20*lt/min* and the common standard deviation 32.5*lt/min* (46).

Δ_0 was based on historical data (47) and is in accordance with the CPMP guidelines (30, 31). It is also a satisfactory range to preserve the assay sensitivity of Formoterol.

9.8 Changes in the Conduct of the Study or Planned Analyses

During the conduct of the study two protocol amendments were submitted and approved by the regulatory authorities. The first amendment regarded the addition of a further study site and the second the removal of two study sites. Additionally, the study was prematurely terminated, following communication to the regulatory authorities, in consequence of low recruitment rates (see section 5.1).

Planned Analysis Changes:

Although 92 patients were planned to participate in the trial, only 42 were actually recruited, due to early termination of the study. In contrast to the planned analysis, all spirometric measurements were analyzed by means of descriptive statistical merthods. The exploration of differences between groups, regarding spirometric and safety measurements was performed by Wilcoxon's rank sum test.

Statistical analysis regarding the number of days with PEFR diurnal variation >20%, day time and night time asthma symptom score and number of morning and evening puffs of concomitant short acting β_2–agonist, were all analyzed by means of ordinal mixed–effects models, instead of applying the Mann-

Whitney U statistic. Time and treatment group were regarded as fixed covariates and patient noumber as random covariate.

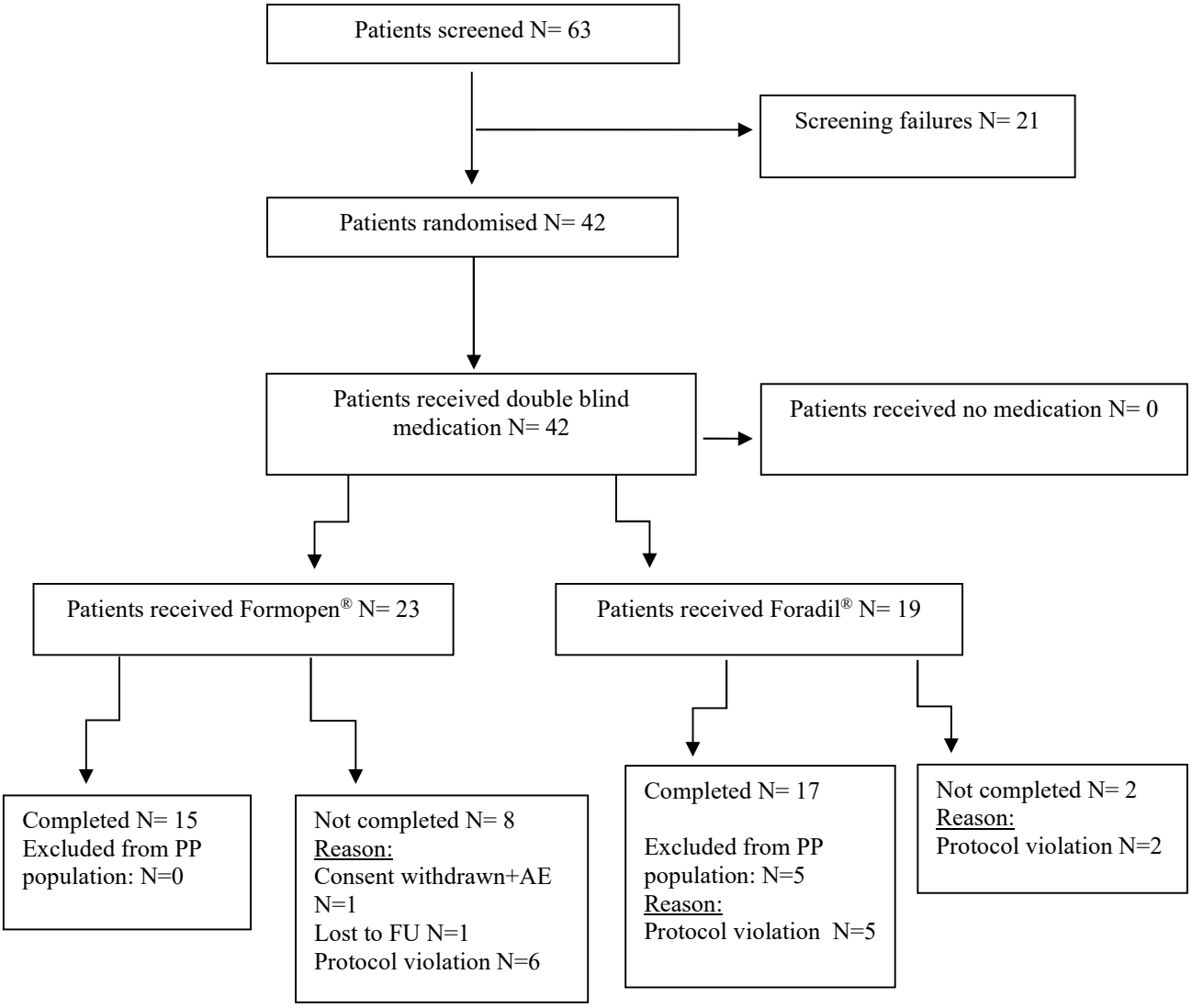
10. STUDY PATIENTS

10.1 Disposition of Patients

Totally, 63 patients were screened and 42 of them were randomized into Formopen® or Foradil®. 10 out of the 42 patients discontinued the treatment. A listing of patients who discontinued the treatment is provided in Appendix 16.2.1.

10.2 Protocol Deviations

In total, 14 protocol deviations were observed.



- 12 patients entered the study even though they did not satisfy the entry criteria.
- 1 patient developed withdrawal criteria during the study but was not withdrawn.
- None of the patients received the wrong treatment or incorrect dose
- None of the patients received an excluded concomitant treatment.

A listing of patients that exhibited a protocol deviation is provided in Appendix 16.2.2.

11. EFFICACY EVALUATION

11.1 Data Sets Analysed

The statistical analysis was performed in PP population (27 patients).

Primary endpoint was also analyzed in ITT population (42 patients).

Safety analysis was performed in all patients that received at least one dose of study medication (42 patients).

11.2 Demographic and Other Baseline Characteristics

Table 3: Demographics and Baseline Clinical Characteristics (PP population)

	Treatment Group		
	Formopen® (n=15)	**Foradil® (n=12)**	**p–value**
Gender – *no. (%)*			
Male	7 (46.7)	5 (41.7)	0.795
Female	8 (53.3)	7 (58.3)	
Age – *yr*			
Mean ± SD	45.6 ± 12.6	46.1 ± 12.8	0.802
Range	24.4 – 64.5	26.2 – 63.4	
BMI – *kg/height²*			
Mean ± SD	27.5 ± 8.2	29.0 ± 6.8	0.150
Range	21.1 – 52.1	20.3 – 42.2	
Race – *no. (%)*			
Caucasian	15 (100.0)	12 (100.0)	–
Duration of asthma – *months*			
Mean ± SD	166.4 ± 93.2	175.5 ± 150.6	0.490
Range	36.0 – 396.0	6.0 – 480.0	
Asthma symptoms – *no. (%)*			
Mild	9 (60.0)	5 (41.7)	0.450
Moderate	6 (40.0)	7 (58.3)	
Asthma classification (Gina) – *no. (%)*			
Mild	11 (73.3)	3 (25.0)	0.021
Moderate	4 (26.7)	9 (75.0)	
Smoking – *no. (%)*			
Never used	12 (80.0)	7 (58.3)	0.580
Ex–smoker	2 (13.3)	3 (25.0)	
Smoker	1 (6.7)	2 (16.7)	

	Treatment Group		
	Formopen® (n=15)	**Foradil® (n=12)**	**p–value**

Table 4: Summary statistics on spirometry & reversibility tests at screening visit (PP population)

	Treatment Group		
	Formopen® (n=15)	**Foradil® (n=12)**	**p–value**
FEV_1–*(lt)*			
Mean ± SD	2.3 ± 0.65	2.3 ± 0.88	0.733
Range	1.5 – 3.5	1.3 – 3.8	
FVC–*(lt)*			
Mean ± SD	3.6 ± 1.19	3.6 ± 1.66	0.807
Range	1.9 – 5.9	1.5 – 6.6	
FEV_1 % of predicted			
Mean ± SD	75.9 ± 9.12	72.9 ± 8.87	0.525
Range	60.0 – 90.0	63.0 – 90.0	
FEV_1/FVC – *(lt/min)*			
Mean ± SD	67.0 ± 8.73	69.8 ± 11.06	0.542
Range	53.3 – 80.0	55.0 – 94.0	
$FEF_{25\%}$ – (*lt/min)*			
Mean ± SD	4.0 ± 1.38	7.1 ± 10.16	0.464
Range	1.8 – 5.8	2.0 – 39.2	
$FEF_{25–75\%}$ – *(lt/min)*			
Mean ± SD	2.4 ± 2.27	1.6 ± 0.67	0.558
Range	0.7 – 9.6	0.7 – 3.1	
PIF – *(lt/min)*			
Mean ± SD	76.7 ± 7.0	82.5 ± 7.8	0.037
Range	65.0 – 90.0	65.0 – 90.0	

Table 5: Concomitant medication for asthma during the study

	Treatment Group		
	Formopen® (n=15)	**Foradil® (n=12)**	**p–value**
Medication – *no. %*			
Salbutamol	6 (40.0)	8 (66.7)	0.322
Aerolin	8 (53.3)	4 (33.3)	0.516
Fluticasone	8 (53.3)	4 (33.3)	0.516
Budesonide	4 (26.7)	2 (16.7)	0.877
Pulmicort	3 (20.0)	2 (16.7)	1
Fluticapen	1 (6.7)	2 (16.7)	0.837
Flixotide	0 (0.0)	2 (16.7)	0.366
Bleclomethasone Hfa	0 (0.0)	0 (0.0)	–
Inuvair	0 (0.0)	1 (8.3)	0.909
Symbicort	0 (0.0)	0 (0.0)	–

Table 6: Other concomitant medication that was received during the study (ITT population)

Formopen® (n=23)			**Foradil® (n=19)**		
Patient No	**Indication**	**Drug**	**Patient No**	**Indication**	**Drug**
10411	Angina Pectoris	Vastarel	10503	Arterial Hypertension	Atacand plus
10104	Arterial Hypert.	Ramipril	10503	Atrhritis Reumatoid	Methotraxate
10511	Esophagitis	Losec	10503		Humira
10409	Hypertension	Diovan	10503		Filicine
10409		Crestor	10004	Coronary Artery Disease	Tildiem 90
10411		Fysiotens	10004		Plavix
10511	Mitral Prolapse	Vascase	10004		Micardis plus
10511	Osteoporosis	Ideos	10004		Nitrodyl
10511		Actonel	10004		Crestor 20
10409		Calcitonin	10004		Ezetrol
10409		Fosamax	10004		Rythmonorm
10504	Respiratory Infection	Zinadol	10109	Diabetes Mellitus	Solosa
			10109		Glugophage
			10109		Actos
			10004	Hypothyroidism	Thyrohormone
			10506	Osteoporosis	Fosamax
			10506		Anarthil
			10506		Naprosin
			10506		Pentin
			10503	Respiratory Infection	Zinadol
			10506	Sideropenic Anaemia	Resoferon
			10004	Stress	Lyrica 75
			10410		Xanax
			10410		Nootrop
			10410		Seroxat

Formopen® (n=23)			Foradil® (n=19)		
			10506	Surgical Excession Of Thyroid	Thyrohormone
			10002	Upper Respiratory Tract Infection	Azithromycin

Table 7: Summary Statistics on Medical and Surgical History

	Formopen® (n=9)	Foradil® (n=9)	Total
Historical medical event – *no. (%)*			
Cardiovascular	4 (44.4)	5 (55.5)	9
Respiratory	3 (33.3)	3 (33.3)	6
Endocrine/Metabolic	1 (11.1)	5 (55.6)	6
Allergy/Drug Sensitivity	2 (22.2)	3 (33.3)	5
Musculoskeletal	2 (22.2)	2 (22.2)	4
Gastrointestinal	3 (33.3)	0 (0.00)	3
Hepatic/Biliary	2 (22.2)	1 (11.1)	3
Renal/Genitourinary–Reproductive	1 (11.1)	1 (11.1)	2
Neurological/Psychiatric	0 (0.0)	2(22.2)	2
HEENT (Head-Eyes-Ears-Nose-Throat)	1 (11.1)	1 (11.1)	2
Haematological/Lymphatic	0 (0.0)	1 (11.1)	1
Immunologic	0 (0.0)	1 (11.1)	1
Dermatologic	0 (0.0)	0 (0.0)	0
Neoplastic	0 (0.0)	0 (0.0)	0
NA	14	10	

11.3 Measurements of Treatment Compliance

No metrics for treatment compliance were present in the current study. However, no significant deviations from treatment program administration were observed.

11.4 Efficacy Results and Tabulations of Individual Patient Data

11.4.1 Analysis of Efficacy

11.4.1.1 Primary analysis

Table 8: Estimation of the mean change of mean mPEFR from baseline to final visit in each group

	Change from Baseline	95%CI of change	p–value

mPEFR – *lt/min*	Change from Baseline	95%CI of change	p–value
Formopen®	32.16	[2.47, 61.85]	0.036
Foradil®	35.73	[–11.8, 83.27]	0.126
Formopen®–Foradil®	–3.57	[–57.2, +∞]†	0.265‡

† Lower bound of the 1–sided 97.5% CI.
‡ *p–value* for the null hypothesis Δ_0<–20 lt/min

Based on the observed values, the difference between the two groups with respect to change from baseline of mPEFR is -3.57lt/min with 97.5%CI: [–57.2, +∞] *p–value=0.265*. Since [–57.2, +∞] is not a subset of [–Δ_0, +∞]= [–20, +∞], the non inferiority of Test over the Reference product cannot be confirmed, see figure 7.

Thus, the assessment regarding the non-inferiority of Formopen® over Foradil® is inconclusive.

Figure 7: Estimation of the difference (Formopen®–Foradil®) in change of mean mPEFR score, from baseline to final visit and lower one–sided 97.5% confidence bound, between the two treatments

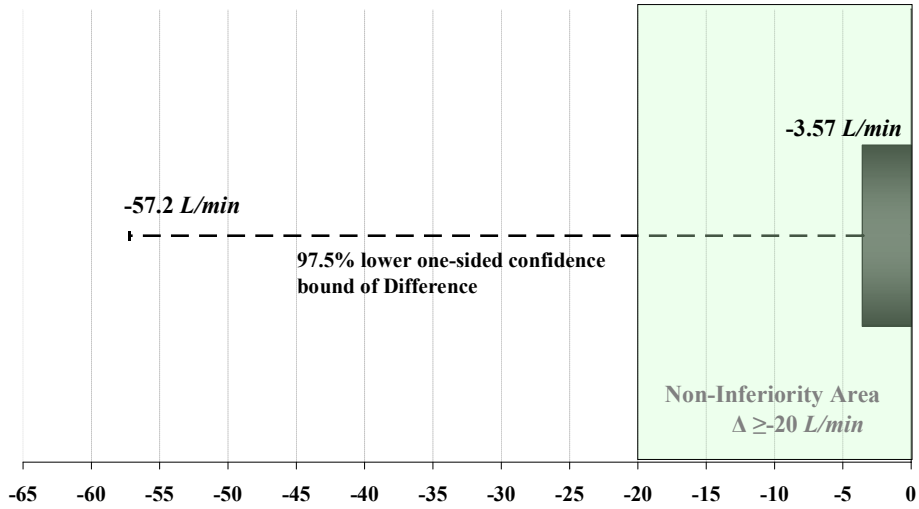
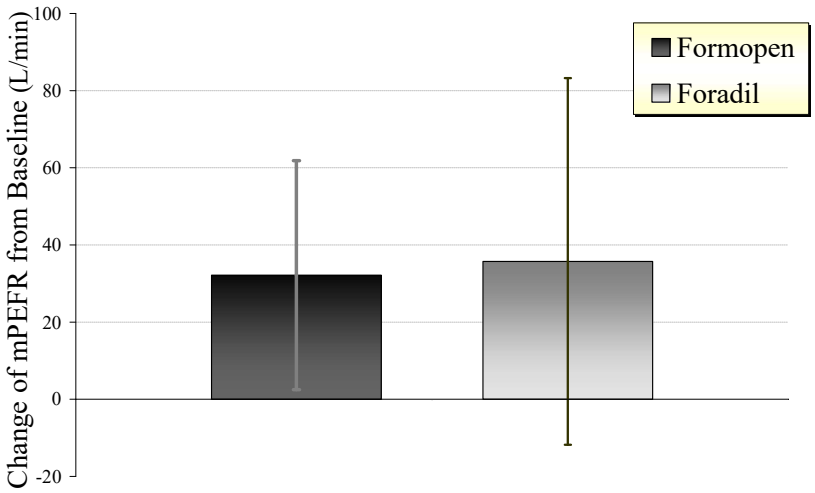


Figure 8: Change of mean mPEFR and 95%CIs from baseline to final visit in each treatment group


Change of mPEFR from Baseline (L/min)
100
80
60
40
20
0
-20
Formopen
Foradil

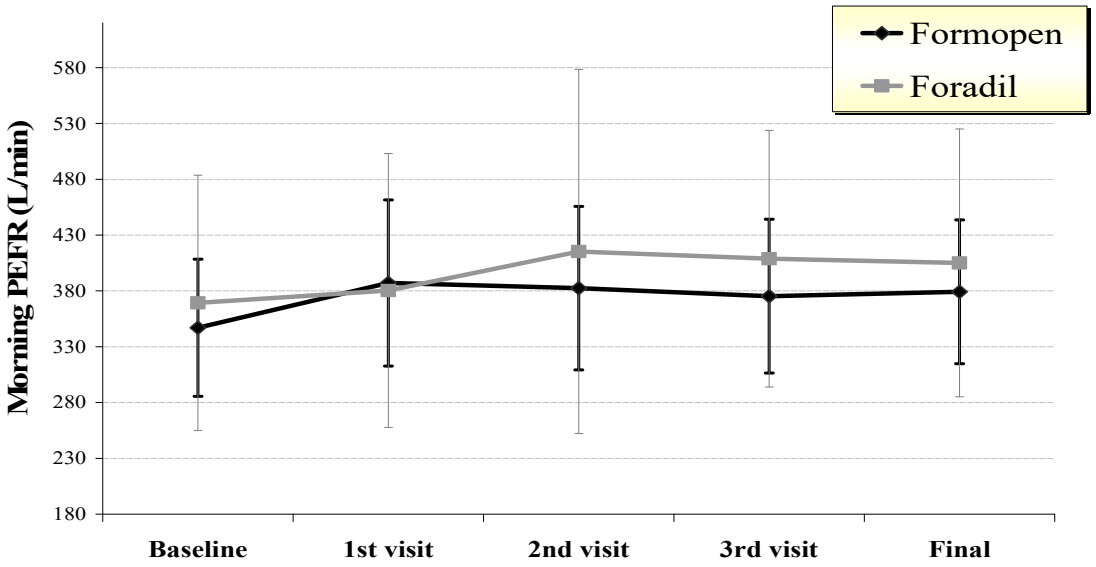
11.4.1.2 Secondary analyses

11.4.1.2.1 Mean mPEFR at treatment visits

Table 9: Summary of statistics of mean mPEFR at each visit for each treatment group.

		Treatment Group		
		Formopen®	**Foradil®**	**p–value**
mPEFR – *lt/min*				
Baseline	n	15	12	0.626
	Mean ± SD	347.0 ± 118.95	369.3 ± 116.63	
	Range	206.0 – 579.3	198.0 – 604.3	
1st FU visit	n	15	12	0.922
	Mean ± SD	387.1 ± 144.18	380.4 ± 111.33	
	Range	162.9 – 656.7	212.5 – 633.3	
2nd FU visit	n	15	11	0.484
	Mean ± SD	382.5 ± 141.66	415.3 ± 115.15	
	Range	173.6 – 645.8	282.5 – 658.0	
3rd FU visit	n	15	12	0.464
	Mean ± SD	375.3 ± 133.48	408.9 ± 137.47	
	Range	208.2 – 656.7	199.1 – 676.9	
End of study	n	15	12	0.591
	Mean ± SD	379.2 ± 124.77	405.1 ± 133.10	
	Range	197.6 – 668.3	207.8 – 644.6	

Figure 9: Graphical display of the estimated mean values and 95%CI of mean mPEFR during the study by treatment group.



Estimations and 95% CIs of the mean percentage (%) change of mean mPEFR from baseline, were calculated by taking into account the effect of the previous factors and are shown at Table 10.

Table 10: Mean Percentage change of mean mPEFR from baseline (both treatment groups)

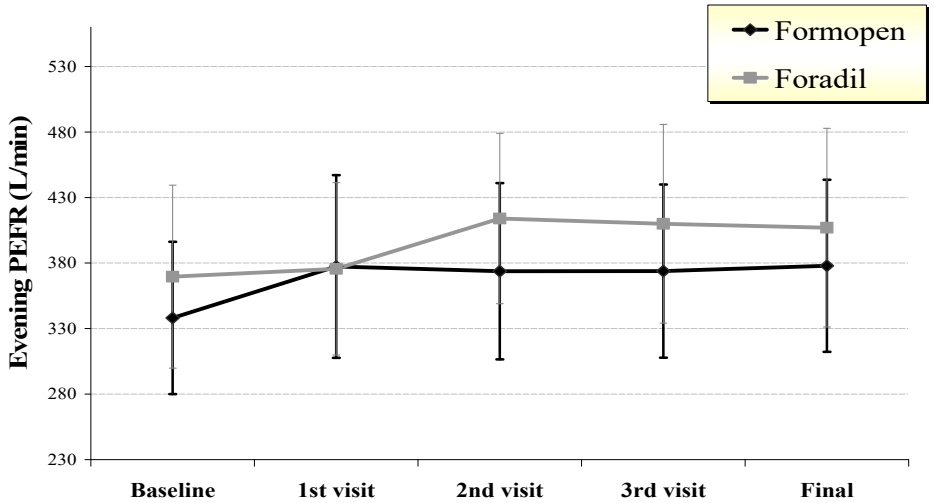
Change (%) of mPEFR	Mean % change	95% CI	p–value
1st FU visit	7.02	[3.55, 10.59]	0.0001
2nd FU visit	8.15	[3.29, 13.24]	0.0012
3rd FU visit	8.48	[2.65, 14.64]	0.0047
End of study	9.22	[2.57, 16.30]	0.0070

11.4.1.2.2 Mean ePEFR

Table 11: Summary statistics of mean ePEFR at each visit for each treatment group

		Treatment Group		
		Formopen®	**Foradil®**	**p–value**
Evening PEFR – *lt/min*				
Baseline	n	15	12	0.559
	Mean ± SD	338.1 ± 112.56	369.6 ± 120.91	
	Range	196.0 – 565.4	186.7 – 618.2	
1st FU visit	n	15	12	1
	Mean ± SD	377.4 ± 135.05	375.6 ± 113.87	
	Range	164.0 – 636.9	202.0 – 624.6	
2nd FU visit	n	15	11	0.337
	Mean ± SD	373.8 ± 130.20	414.0 ± 112.61	
	Range	194.3 – 634.2	248.5 – 648.2	
3rd FU visit	n	15	12	0.354
	Mean ± SD	373.9 ± 127.97	410.0 ± 131.40	
	Range	217.6 – 638.3	205.5 – 655.7	
End of study	n	15	12	0.526
	Mean ± SD	377.9 ± 127.10	407.0 ± 131.33	
	Range	191.8 – 652.5	208.2 – 642.3	

Figure 10: Graphical display of the estimated mean values and 95%CI of mean ePEFR during the study by treatment group.



11.4.1.2.3 Spirometric values

Table 12: Summary statistics of FEV_1at each visit for each treatment group

		Formopen®	Foradil®	p–value
FEV_1–*(lt)*				
Screening visit	n	15	12	0.733
	Mean ± SD	2.3 ± 0.65	2.3 ± 0.88	
	Range	1.5 – 3.5	1.3 – 3.8	
Baseline	n	15	12	0.591
	Mean ± SD	2.4 ± 0.66	2.3 ± 0.73	
	Range	1.5 – 3.6	1.4 – 3.4	
1st FU visit	n	15	12	0.845
	Mean ± SD	2.6 ± 0.79	2.5 ± 0.84	
	Range	1.5 – 3.7	1.4 – 3.7	
2nd FU visit	n	15	12	1
	Mean ± SD	2.5 ± 0.90	2.6 ± 0.82	
	Range	1.4 – 3.9	1.4 – 3.6	
3rd FU visit	n	15	12	0.864
	Mean ± SD	2.6 ± 0.78	2.6 ± 0.89	
	Range	1.5 – 3.7	1.4 – 3.9	
End of study	n	15	12	0.767
	Mean ± SD	2.6 ± 0.81	2.5 ± 0.83	
	Range	1.6 – 4.0	1.4 – 3.6	

Figure 11: Graphical display of the estimated mean values and 95%CI of FEV_1 during the study by treatment group.

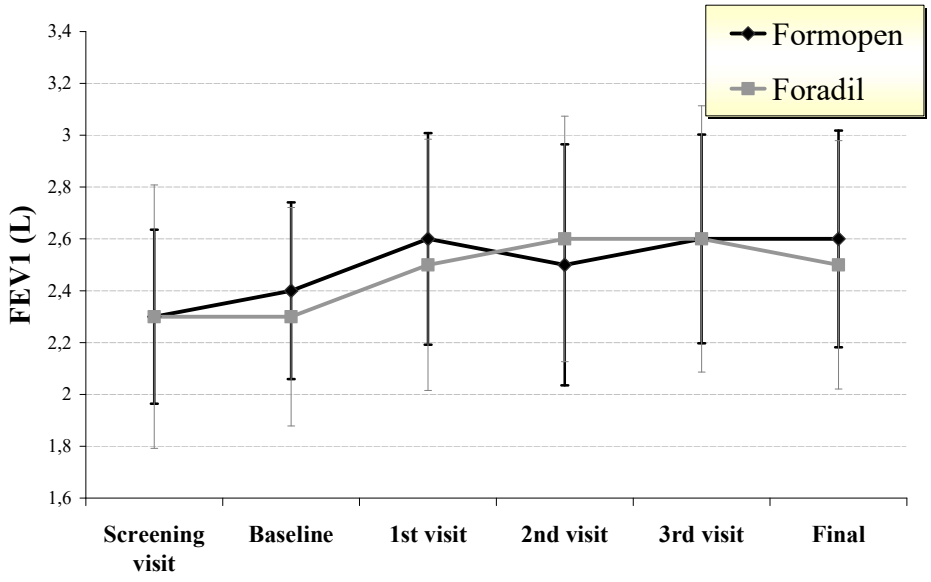


Table 13: Summary statistics of FVC at each visit for each treatment group

		Formopen®	Foradil®	p–value
FVC–*(lt)*				
Screening visit	n	15	12	0.807
	Mean ± SD	3.6 ± 1.19	3.6 ± 1.66	
	Range	1.9 – 5.9	1.5 – 6.6	
Baseline	n	15	12	0.626
	Mean ± SD	3.6 ± 1.21	3.3 ± 1.23	
	Range	2.1 – 5.7	1.5 – 5.1	
1st FU visit	n	15	12	0.788
	Mean ± SD	3.7 ± 1.20	3.7 ± 1.40	
	Range	2.1 – 5.9	1.6 – 5.7	
2nd FU visit	n	15	12	0.961
	Mean ± SD	3.6 ± 1.20	3.6 ± 1.31	
	Range	2.0 – 5.8	1.5 – 5.5	
3rd FU visit	n	15	12	0.807
	Mean ± SD	3.8 ± 1.32	3.7 ± 1.45	
	Range	2.0 – 6.6	1.6 – 5.5	
End of study	n	15	12	0.558
	Mean ± SD	5.8 ± 7.71	3.6 ± 1.35	
	Range	2.0 – 33.3	1.6 – 5.3	

Figure 12: Graphical display of the estimated mean values and 95%CI of FVC during the study by treatment group.

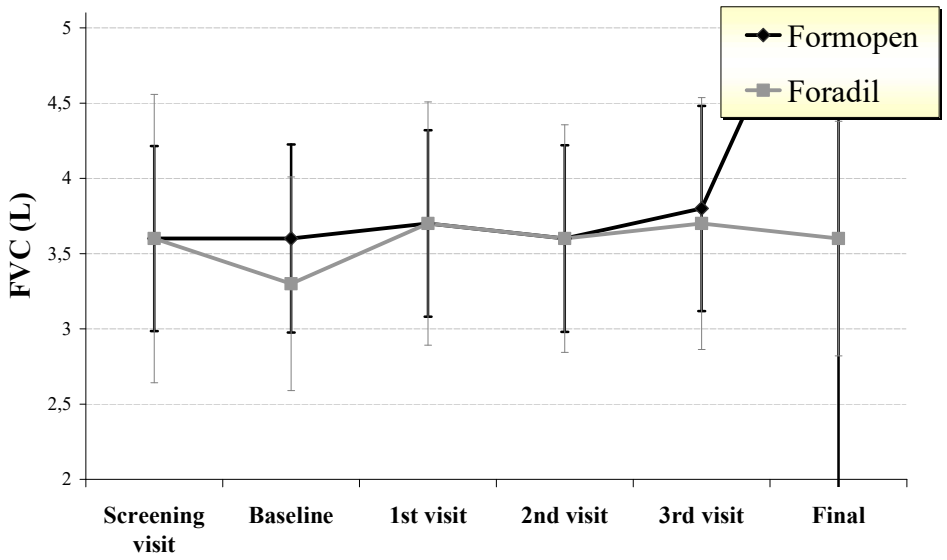


Table 14: Summary statistics of the predicted FEV_1 at each visit for each treatment group

		Formopen®	Foradil®	p–value
FEV_1 % of predicted				
Screening visit	n	15	12	0.525
	Mean ± SD	75.9 ± 9.12	72.9 ± 8.87	
	Range	60.0 – 90.0	63.0 – 90.0	
Baseline	n	15	12	0.196
	Mean ± SD	77.6 ± 8.95	73.1 ± 8.10	
	Range	63.0 – 89.4	62.0 – 88.0	
1st FU visit	n	15	12	0.479
	Mean ± SD	82.6 ± 13.70	79.0 ± 10.08	
	Range	61.0 – 112.0	65.0 – 93.0	
2nd FU visit	n	15	12	0.660
	Mean ± SD	81.2 ± 15.62	82.4 ± 11.22	
	Range	61.0 – 115.0	66.0 – 102.0	
3rd FU visit	n	15	12	0.961
	Mean ± SD	83.3 ± 12.43	84.0 ± 11.01	
	Range	64.0 – 110.0	68.0 – 106.0	
End of study	n	15	12	0.379
	Mean ± SD	84.5 ± 11.71	80.7 ± 9.80	
	Range	69.0 – 105.0	68.0 – 100.0	

Figure 13: Graphical display of the estimated mean values and 95%CI of predicted FEV_1 during the study by treatment group.

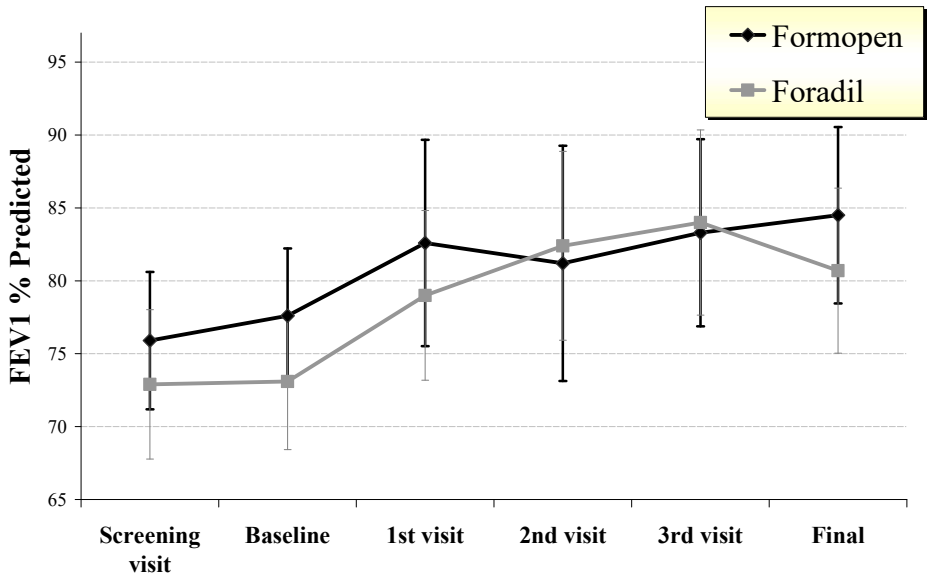


Table 15: Summary statistics of FEV_1/FVC at each visit for each treatment group

		Formopen®	Foradil®	p–value
FEV_1/FVC – *(lt/min)*				
Screening visit	n	15	12	0.542
	Mean ± SD	67.0 ± 8.73	69.8 ± 11.06	
	Range	53.3 – 80.0	55.0 – 94.0	
Baseline	n	15	12	0.510
	Mean ± SD	68.1 ± 7.48	70.9 ± 10.46	
	Range	59.0 – 83.0	55.6 – 93.9	
1st FU visit	n	15	12	0.845
	Mean ± SD	70.4 ± 9.38	71.0 ± 10.20	
	Range	52.2 – 89.0	55.5 – 89.4	
2nd FU visit	n	15	12	0.696
	Mean ± SD	70.5 ± 9.79	73.0 ± 8.99	
	Range	55.1 – 88.0	61.8 – 93.2	
3rd FU visit	n	15	12	0.661
	Mean ± SD	70.8 ± 9.81	73.0 ± 8.74	
	Range	55.0 – 87.0	56.0 – 91.0	
End of study	n	15	12	0.770
	Mean ± SD	71.5 ± 8.79	72.2 ± 8.62	
	Range	55.1 – 88.0	61.0 – 91.0	

Figure 14: Graphical display of the estimated mean values and 95%CI of FEV_1/FVC during the study by treatment group.

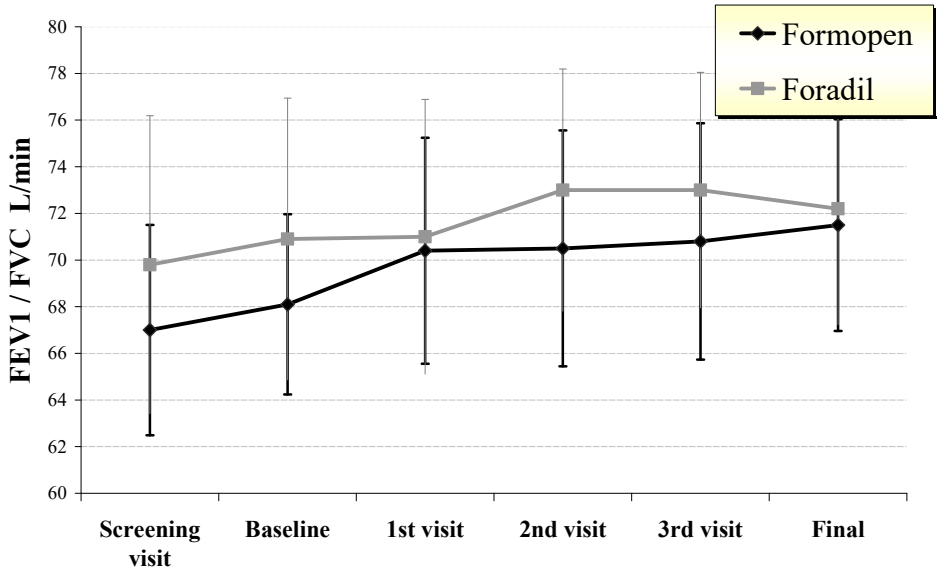


Table 16: Summary statistics of $FEF_{25\%}$ at each visit for each treatment group

		Formopen®	Foradil®	p–value
**$FEF_{25\%}$ – (*lt/min)*				
Screening visit	n	15	12	0.696
	Mean ± SD	4.0 ± 1.38	4.2 ± 1.1	
	Range	1.8 – 5.8	2.0 – 5.9	
Baseline	n	15	12	0.329
	Mean ± SD	3.7 ± 1.09	4.0 ± 1.32	
	Range	2.2 – 5.9	1.5 – 5.9	
1st FU visit	n	15	12	0.495
	Mean ± SD	4.4 ± 1.72	4.8 ± 1.45	
	Range	2.0 – 8.0	2.7 – 7.2	
2nd FU visit	n	15	12	0.407
	Mean ± SD	4.5 ± 1.89	5.0 ± 1.29	
	Range	1.8 – 7.6	2.6 – 6.8	
3rd FU visit	n	15	12	0.510
	Mean ± SD	4.5 ± 1.75	4.8 ± 1.23	
	Range	2.1 – 7.8	2.8 – 7.4	
End of study	n	15	12	0.884
	Mean ± SD	4.8 ± 1.87	4.8 ± 1.31	
	Range	2.2 – 7.9	2.4 – 6.9	

Figure 15: Graphical display of the estimated mean values and 95%CI of $FEF_{25\%}$ during the study by treatment group.

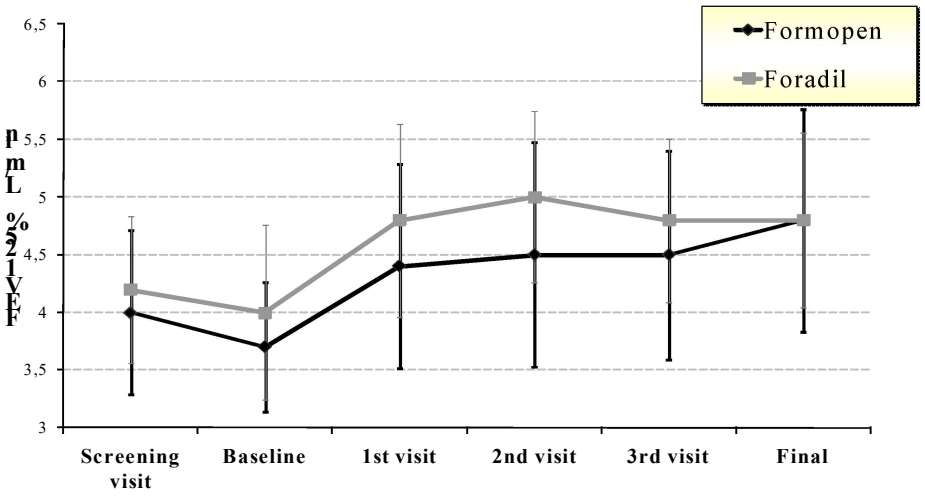
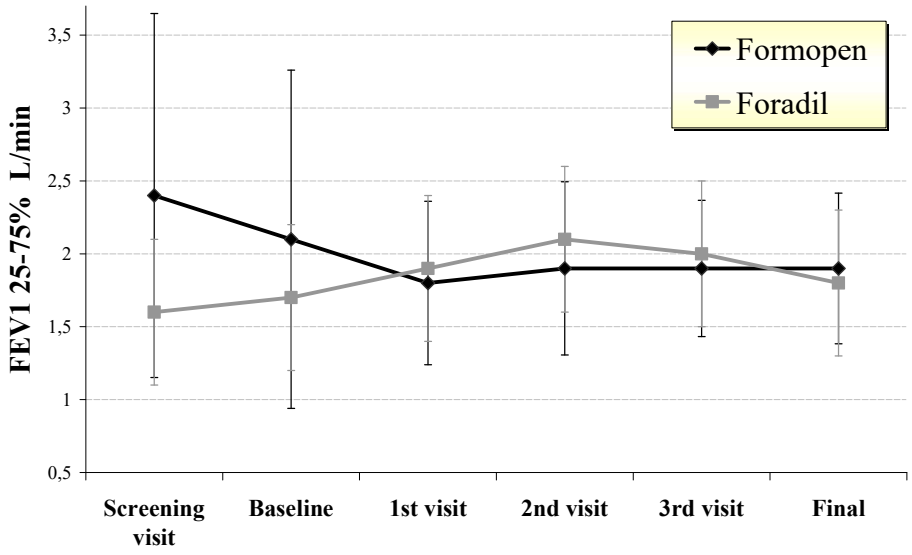


Table 17: Summary statistics of $FEF_{25–75\%}$ at each visit for each treatment group

		Formopen®	Foradil®	p–value
$FEF_{25–75\%}$ – *(lt/min)*				
Screening visit	n	15	12	0.558
	Mean ± SD	2.4 ± 2.27	1.6 ± 0.67	
	Range	0.7 – 9.6	0.7 – 3.1	
Baseline	n	15	12	0.922
	Mean ± SD	2.1 ± 2.11	1.7 ± 0.69	
	Range	0.9 – 9.5	0.8 – 3.2	
1st FU visit	n	15	12	0.449
	Mean ± SD	1.8 ± 1.02	1.9 ± 0.69	
	Range	0.8 – 4.7	0.8 – 3.2	
2nd FU visit	n	15	12	0.317
	Mean ± SD	1.9 ± 1.08	2.1 ± 0.67	
	Range	0.8 – 4.6	0.9 – 3.1	
3rd FU visit	n	15	12	0.770
	Mean ± SD	1.9 ± 0.85	2.0 ± 0.65	
	Range	0.8 – 4.1	1.2 – 2.9	
End of study	n	15	12	0.591
	Mean ± SD	1.9 ± 0.94	1.8 ± 0.57	
	Range	0.9 – 4.1	1.0 – 2.7	

Figure 16: Graphical display of the estimated mean values and 95%CI of $FEF_{25–75\%}$ during the study by treatment group.

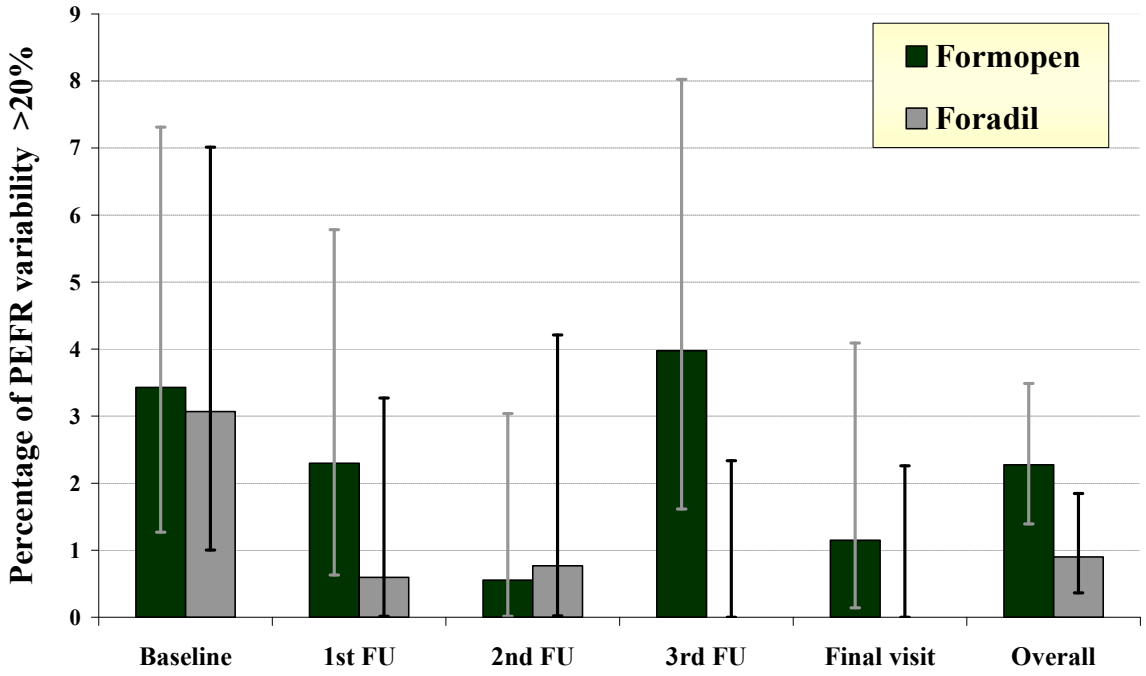


11.4.1.2.4 Daily PEFR fluctuation

Table 18: Number of days with variability in PEFR >20%

Treatment Group		Baseline	1st FU	2nd FU	3rd FU	Final visit	Total
Formopen®	>20%	6	4	1	7	2	20
	Total	175	174	181	176	174	880
	percentage(%)	3.43	2.30	0.55	3.98	1.15	2.27
Foradil®	>20%	5	1	1	0	0	7
	Total	163	168	130	156	161	778
	percentage(%)	3.07	0.60	0.77	0.00	0.00	0.90

Figure 17: Percentage of days where the variability of mean mPEFR is >20%



Statistically significant reduction was observed in the probability of increased variability (>20%) of mean PEFR in the period between the 1st and 2nd FU visit and in the period between 3rd and final FU visit, compared to the period before baseline. Details are given at Table 12.

Table 19: Estimated odds ratio between baseline and each FU visit for the probability that a patient will show variability in PEFR >20% in a particular day.

Baseline vs visit No.	Odds Ratio	95% CI	p–value
1st FU visit	0.510	[0.162, 1.599]	0.248
2nd FU visit	0.197	[0.039, 0.994]	0.049*
3rd FU visit	0.570	[0.199, 1.639]	0.297
End of study	0.166	[0.033, 0.843]	0.030*

*Statistically significant changes from baseline in the odds ratio of PEFR>20%

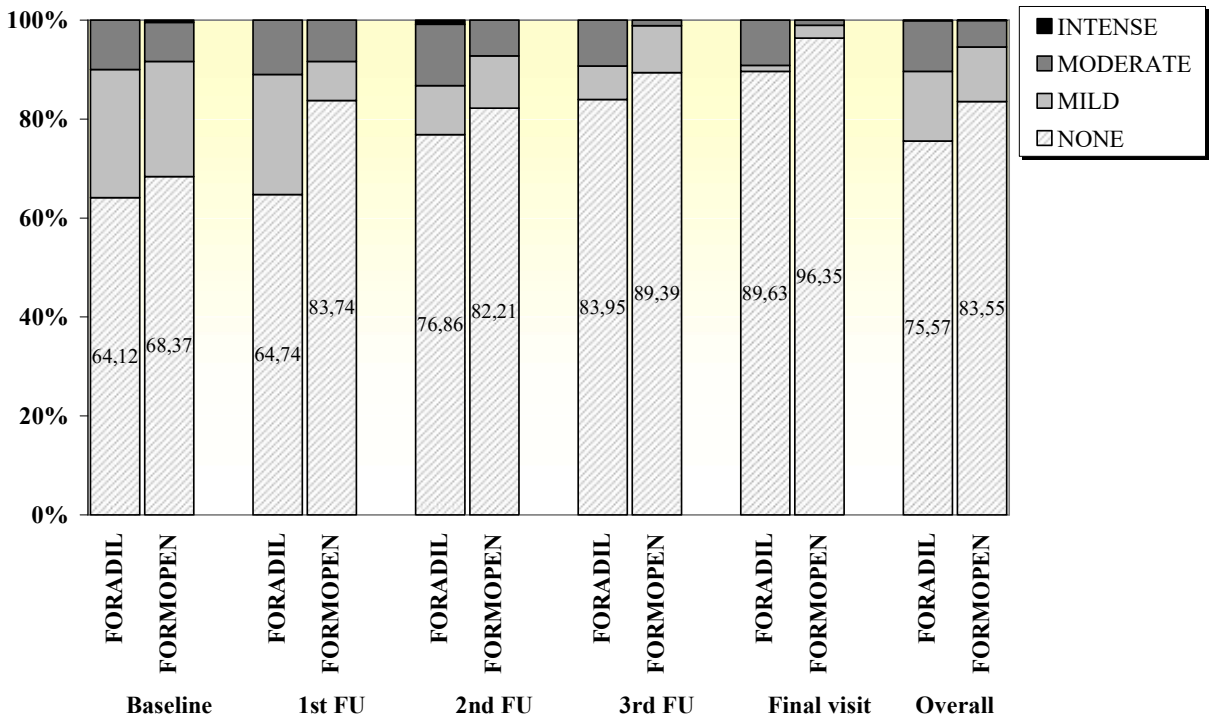
11.4.1.2.5 Morning & evening asthma symptoms

Morning asthma symptoms

Table 20: Asthma severity by treatment group, during the study period.

Treatment Group	Asthma symptoms	Baseline	1st FU	2nd FU	3rd FU	Final visit	Overall
Formopen®	None	68.37	83.74	82.21	89.39	96.35	83.55
	Mild	23.26	7.88	10.58	9.50	2.60	11.03
	Moderate	7.91	8.37	7.21	1.12	1.04	5.32
	Intense	0.47	0.00	0.00	0.00	0.00	0.10
Foradil®	None	64.12	64.74	76.86	83.95	89.63	75.57
	Mild	25.88	24.28	9.92	6.79	1.22	14.05
	Moderate	10.00	10.98	12.40	9.26	9.15	10.25
	Intense	0.00	0.00	0.83	0.00	0.00	0.13

Figure 18: Percentage of patients belonging in each asthma symptoms classification category.



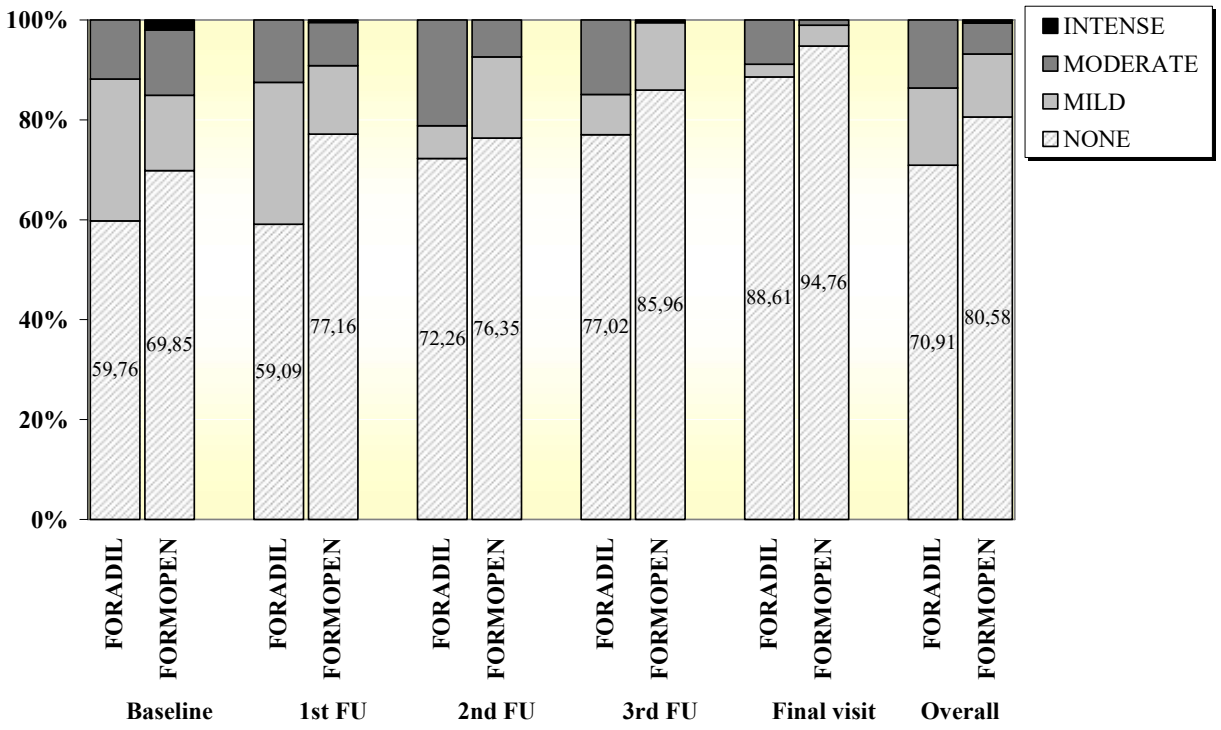
The intensity of symptoms reduces with time (*p-value* <0.0001); the reduction was indipendant of the treatment group (*p-value*>0.05).

Evening asthma symptoms

Table 21: Asthma severity by treatment group, during the study period.

Treatment Group	Asthma symptoms	Baseline	1st FU	2nd FU	3rd FU	Final visit	Overall
Formopen®	None (%)	69.85	77.16	76.35	85.96	94.76	80.58
	Mild (%)	15.08	13.71	16.26	13.48	4.19	12.60
	Moderate (%)	13.07	8.63	7.39	0.00	1.05	6.20
	Intense (%)	2.01	0.51	0.00	0.56	0.00	0.62
Foradil®	None (%)	59.76	59.09	72.26	77.02	88.61	70.91
	Mild (%)	28.40	28.41	6.57	8.07	2.53	15.48
	Moderate (%)	11.83	12.50	21.17	14.91	8.86	13.61
	Intense (%)	0.00	0.00	0.00	0.00	0.00	0.00

Figure 19: Percentage of patients belonging in each asthma symptoms classification category



The intensity of symptoms reduces with time (*p-value* <0.0001); the reduction was indipendant of the treatment group (*p-value*>0.05).

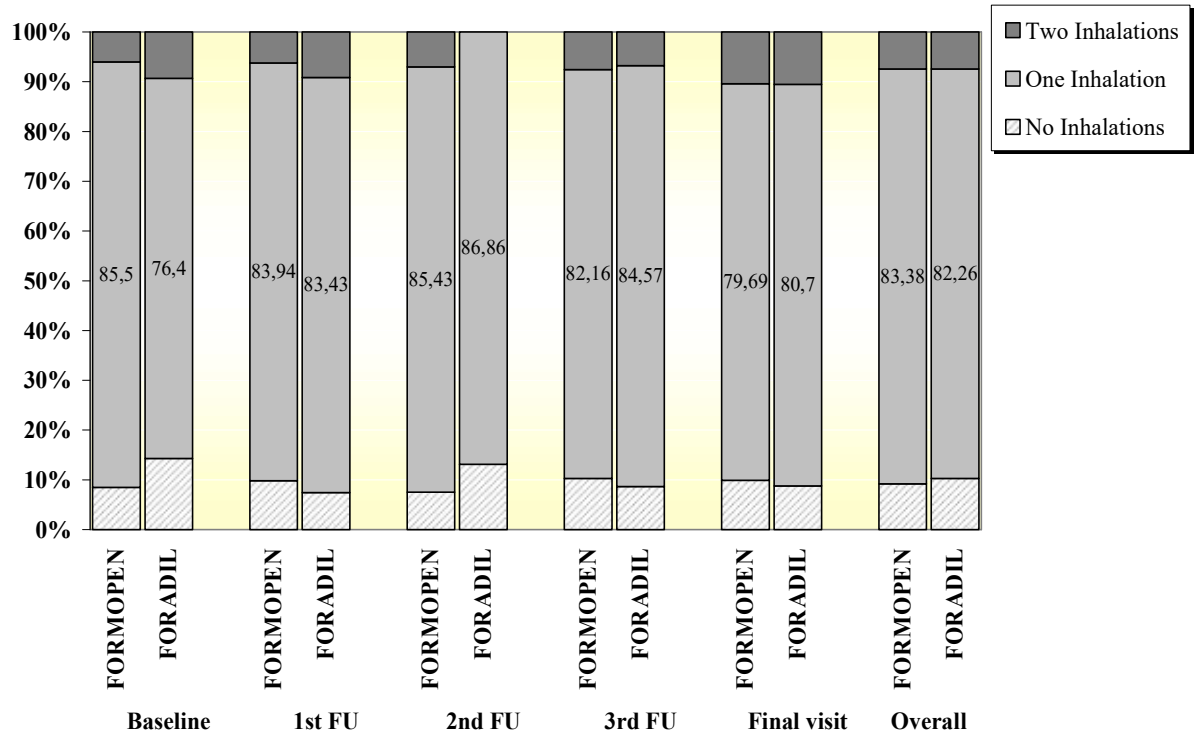
11.4.1.2.6 Number of rescue medication nebulisation

Morning inhalations

Table 22: Number of morning inhalations by treatment group, during the study period

Treatment Group		Baseline	1st FU	2nd FU	3rd FU	Final visit	Overall
Formopen®	0	8.5	9.84	7.54	10.27	9.9	9.18
	1	85.5	83.94	85.43	82.16	79.69	83.38
	2	6	6.22	7.04	7.57	10.42	7.43
Foradil®	0	14.29	7.43	13.14	8.64	8.77	10.3
	1	76.4	83.43	86.86	84.57	80.7	82.26
	2	9.32	9.14	0	6.79	10.53	7.44

Figure 20: Graphical illustration of the percentage of performing 1, 2 ,or no inhalations in the morning, at each study visit



There was no any statistical evidence that the distribution of the number of morning inhalations alters with time (*p-value*>0.05)..

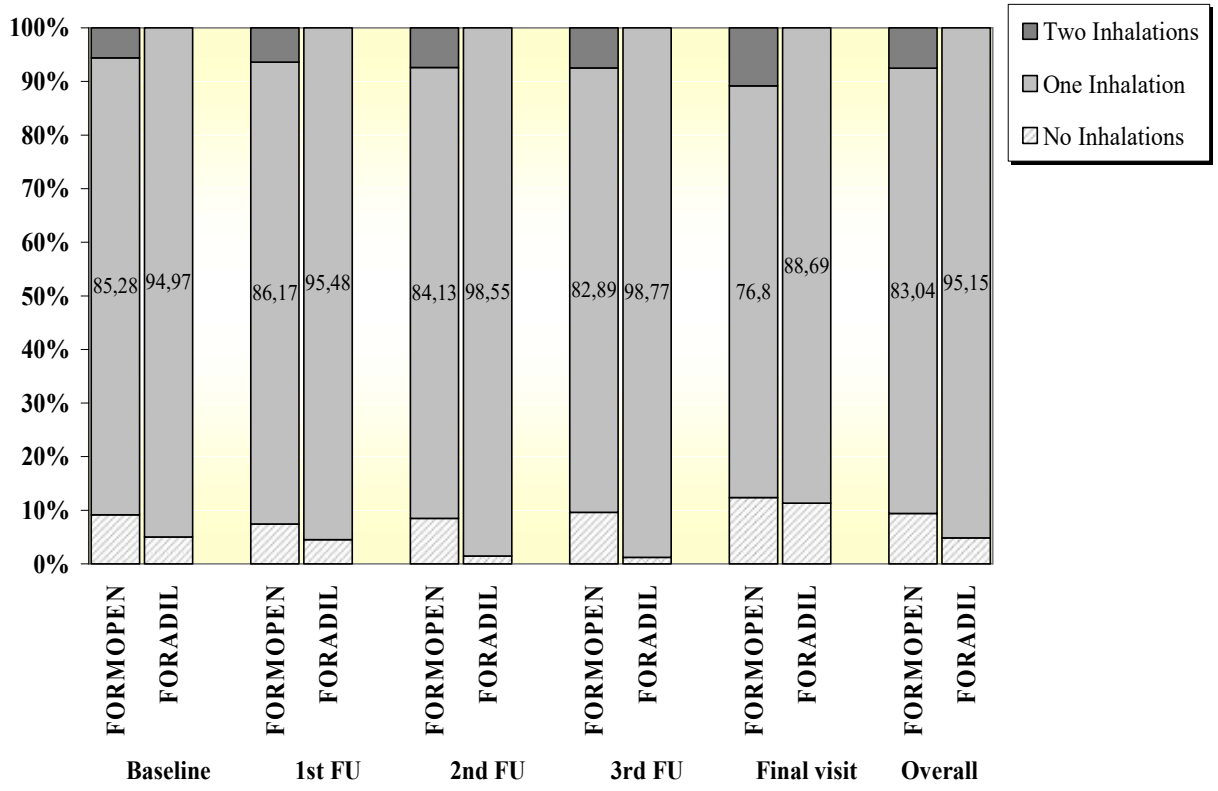
Additionally, the number of inhalations was indipendant of the treatment group (*p-value*>0.05).

Evening Inhalations

Table 23: Number of evening inhalations by treatment group, during the study period.

Treatment Group		Baseline	1st FU	2nd FU	3rd FU	Final visit	Overall
Formopen®	0	9.14	7.45	8.47	9.63	12.37	9.42
	1	85.28	86.17	84.13	82.89	76.8	83.04
	2	5.58	6.38	7.41	7.49	10.82	7.54
Foradil®	0	5.03	4.52	1.45	1.23	11.31	4.85
	1	94.97	95.48	98.55	98.77	88.69	95.15
	2	0	0	0	0	0	0

Figure 21: Graphical illustration of the percentage of performing 1, 2 ,or no inhalations in the evening, at each study visit.



There was no any statistical evidence that the distribution of the number of evening inhalations alters with time (*p-value*>0.05)..

Additionally, the number of inhalations was indipendant of the treatment group (*p-value*>0.05).

11.4.1.2.7 Usability questionnaire

Table 24: Usability questionnaire analysis results

	Aerolizer® n (%)	Elpen*haler*® n (%)	p–value
1. How do you rate the size and shape of the device			
Very attractive and practical	7 (31.8%)	14 (63.6%)	0.003
Attractive and practical	10 (45.5%)	7 (31.8%)	
Moderately attractive and practical	5 (22.7%)	1 (4.6%)	
2 How easy is it to open / close the device			
Very easy	13 (59.1%)	19 (86.4%)	0.039
Easy	7 (31.8%)	1 (4.6%)	
Moderately easy	1 (4.6%)	1 (4.6%)	
Not easy, not difficult	1 (4.6%)	1 (4.6%)	
3. How easy is it to operate the device			
Very easy	11 (50.0%)	17 (77.3%)	0.037
Easy	7 (31.8%)	3 (13.6%)	
Moderately easy	3 (13.6%)	1 (4.6%)	
Not easy, not difficult	1 (4.6%)	1 (4.6%)	
4. How often do you need to inhale more than once so as to obtain the entire dose from the device			
Never	6 (27.3%)	18 (81.8%)	<.0001
Rarely	0 (0.0%)	2 (9.1%)	
Sometimes	7 (31.8%)	2 (9.1%)	
Most of the times	8 (36.4%)	0 (0.0%)	
Almost every time	1 (4.6%)	0 (0.0%)	
5. How easy is it for you to check that you received the dose with the device			
Very easy	7 (31.8%)	20 (90.1%)	0.0002
Easy	8 (36.4%)	1 (4.6%)	
Moderately easy	6 (27.3%)	1 (4.6%)	
Not easy, not difficult	0 (0.0%)	0 (0.0%)	
Difficult	1 (4.6%)	0 (0.0%)	
6. How did you find the taste left in your mouth after inhalation from the device			
Not intense	10 (45.5%)	15 (68.2%)	0.023
Moderately Intense	8 (36.4%)	5 (22.7%)	
Intense	3 (13.6%)	2 (9.1%)	
Very Intense	1 (4.6%)	0 (0.0%)	
7. How did you find the handling / usability instructions of the device			
Very easy	13 (59.1%)	17 (77.3%)	0.563
Easy	8 (36.4%)	2 (9.1%)	
Moderately easy	0 (0.0%)	2 (9.1%)	
Not easy, not difficult	1 (4.6%)	1 (4.6%)	
8. How easy is carrying with you the device and the medication doses			
Very easy	9 (40.9%)	17 (77.3%)	0.0005
Easy	5 (22.7%)	2 (9.1%)	
Moderately easy	6 (27.3)	2 (9.1%)	
Not easy, not difficult	1 (4.6%)	0 (0.0%)	
Difficult	1 (4.6%)	1 (4.6%)	

11.4.2 Statistical/Analytical Issues

11.4.2.1 Handling of Dropouts or Missing Data

In total 10/42 (23.8%) patients dropped out of the study.

At the Formopen® group the drop–out rate was 34.8% (8/23)whereas at the Foradil® group was 10.5% (2/19), p–value=0.057.

The dropouts are not expected to influence the quality of the results as 8/10 patients that dropped out were protocol violators, where the violation occurred before the therapy initiation.

Missing values that occurred in the intermediate visits, were assumed to be absent due to reasons unrelated to the unobserved actual values and no imputation methods were applied.

11.4.2.2 Multicentre Studies

Due to lack of sufficient amount of data, results are not presented by study center.

11.4.2.3 Multiple comparison/Multiplicity

No adjustment of significant level was made, as no multiple comparisons were performed, regarding the analysis of primary efficacy endpoint.

11.4.2.4 Examination of subgroups

The size of the study did not permit the assessment of primary endpoint in separate subgroups.

11.4.3 Tabulation of Individual Response Data

Individual efficacy response data are presented in Appendix 16.2.5.

11.4.3.1 Drug Dose, Drug Concentration, and Relationships to Response

Not applicable.

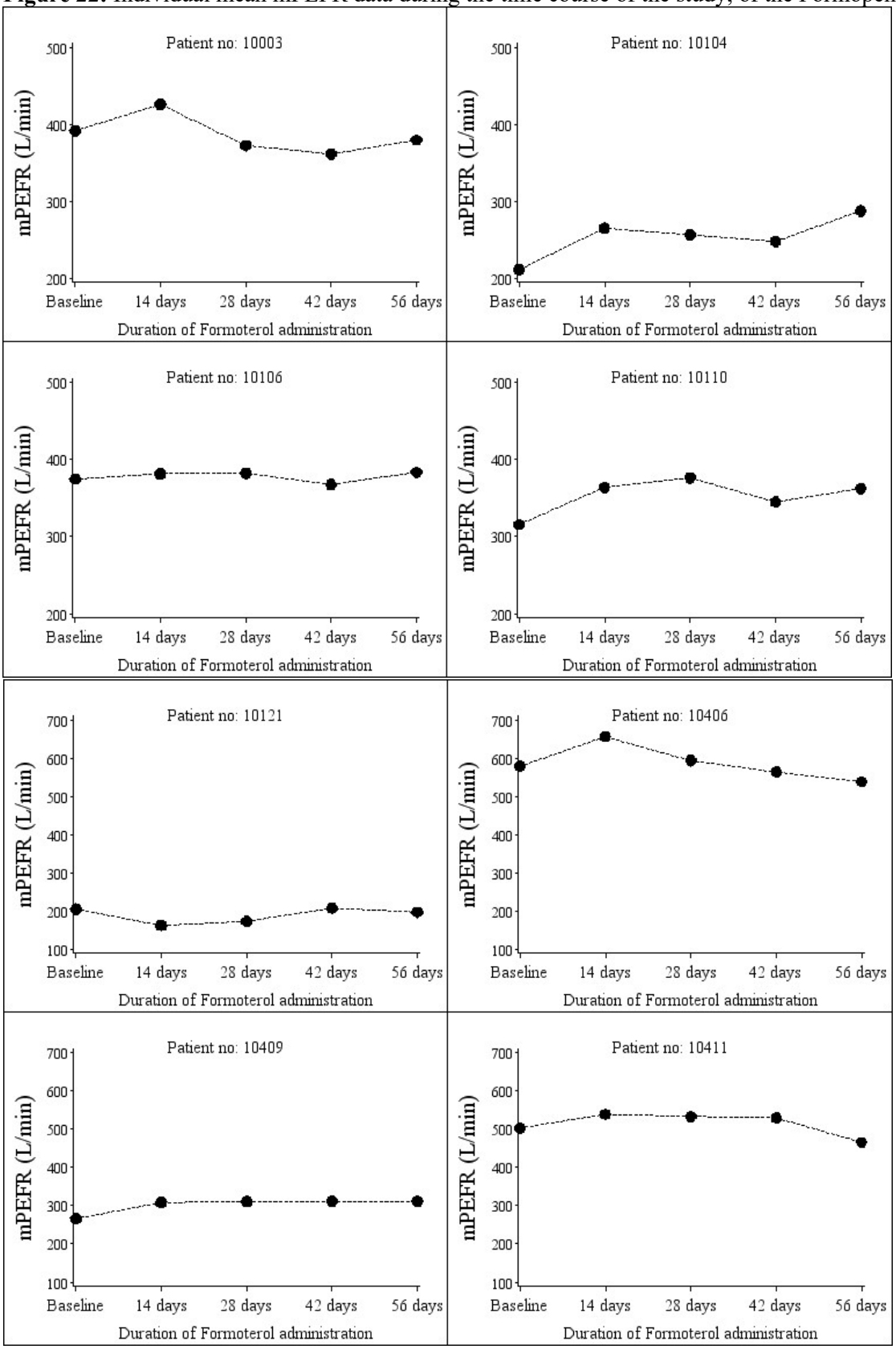
11.4.3.2 Drug–Drug and Drug–Disease Interactions

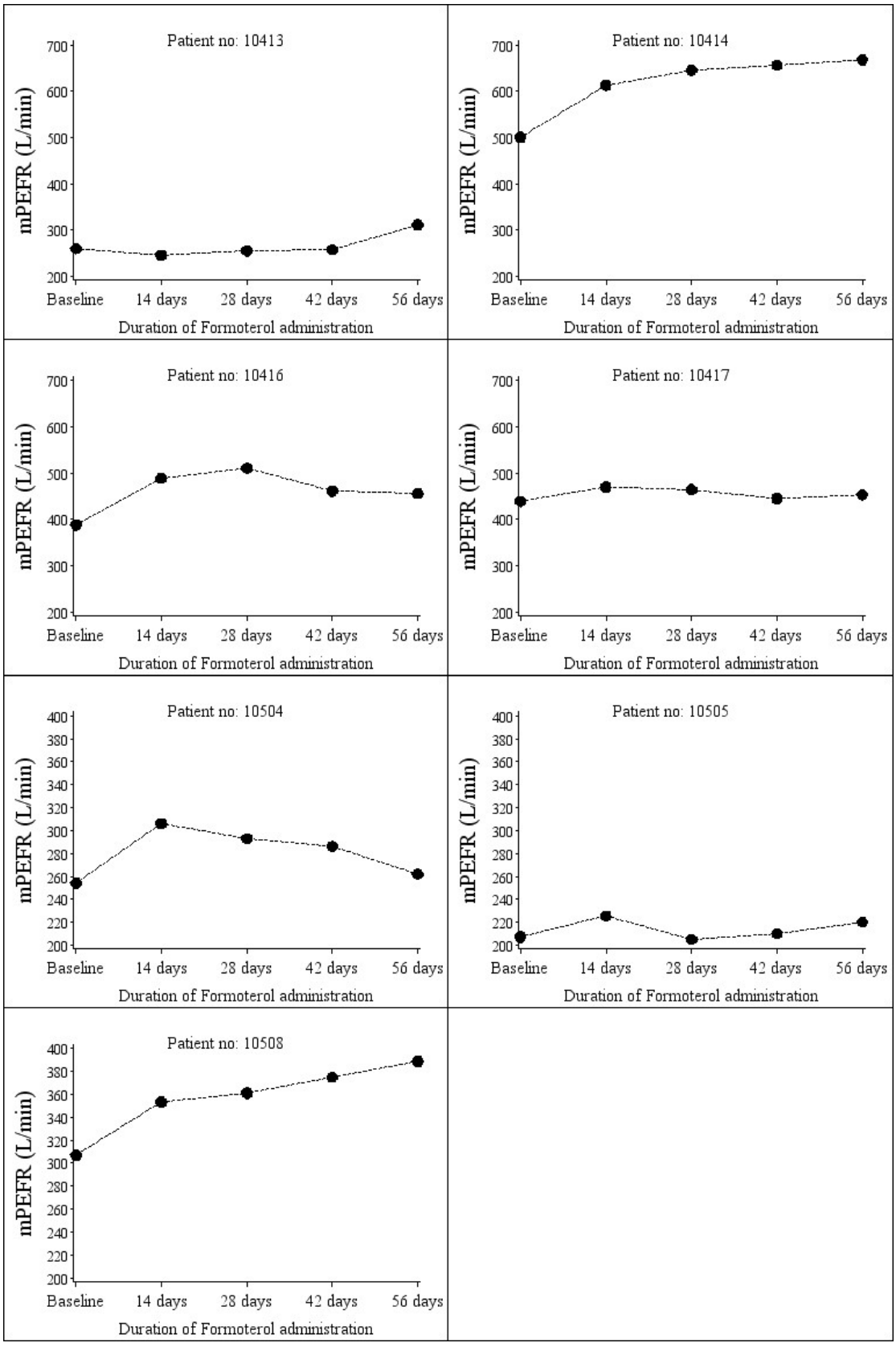
The sample of the trial is not sufficient for the exploration of any potential relation between past and/or concurrent illnesses and treatment response.

11.4.4 By–Patient Displays

11.4.4.1 Formopen® Group

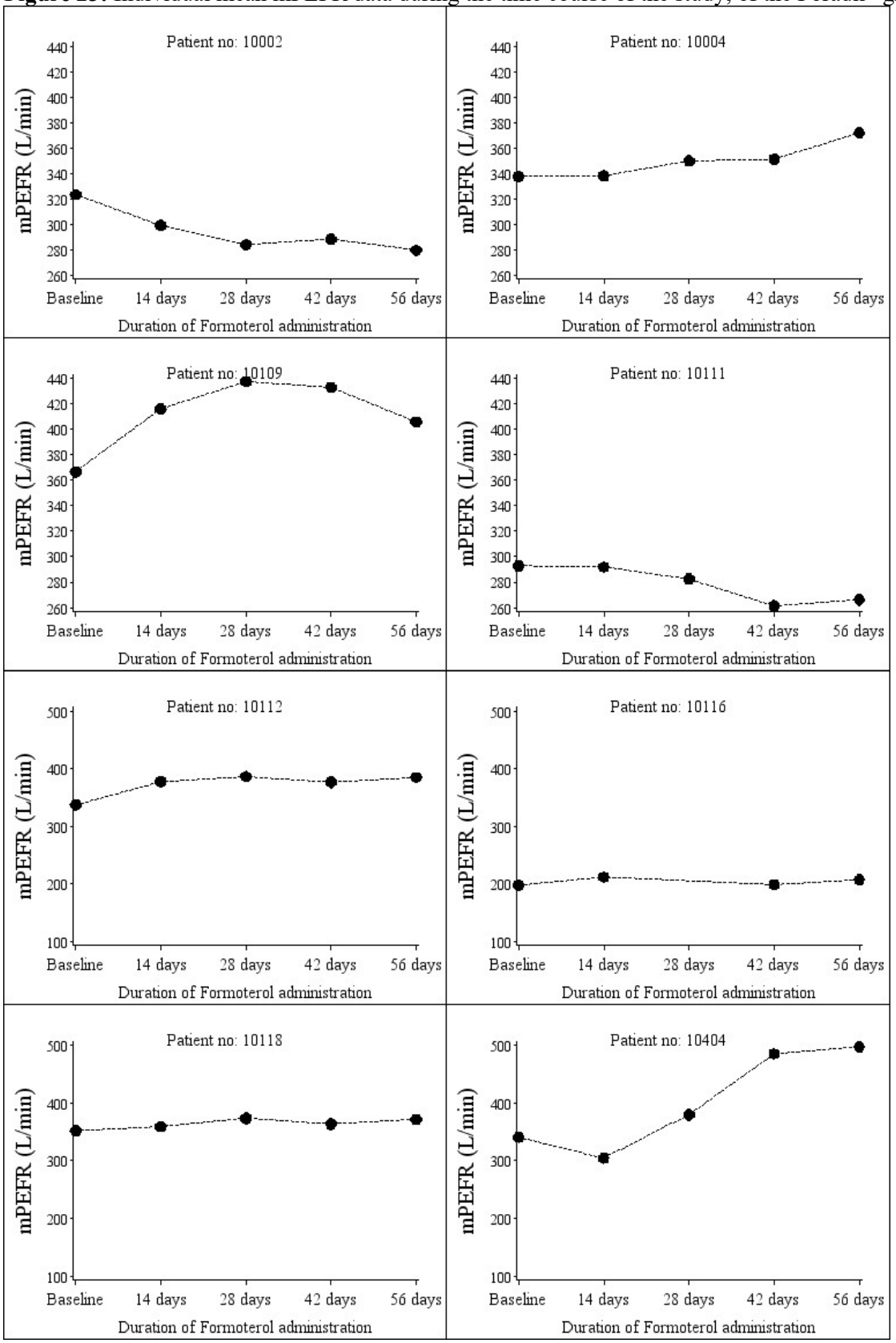
Figure 22: Individual mean mPEFR data during the time course of the study, of the Formopen® group




Patient no: 10413
Patient no: 10414
Patient no: 10416
Patient no: 10417
Patient no: 10504
Patient no: 10505
Patient no: 10508
mPEFR (L/min)
Baseline
14 days
28 days
42 days
56 days
Duration of Formoterol administration

11.4.4.2 Foradil® Group

Figure 23: Individual mean mPEFR data during the time course of the study, of the Foradil® group



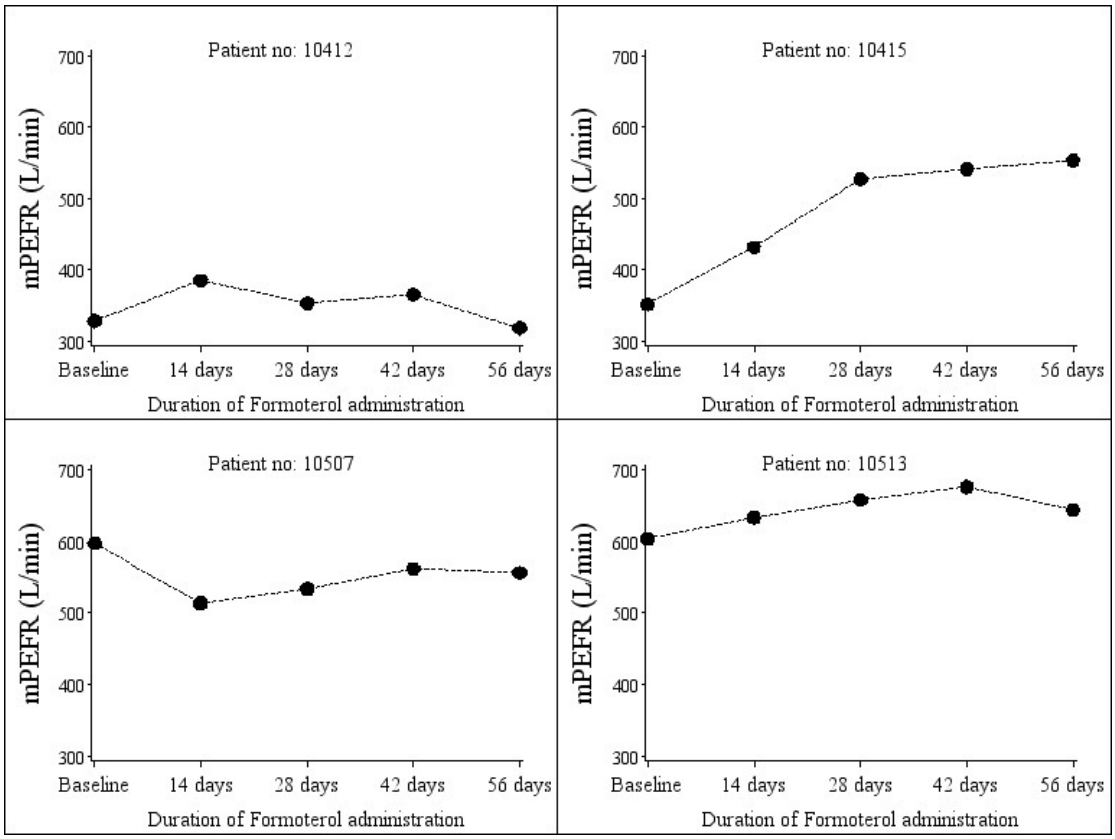

Patient no: 10412
mPEFR (L/min)
700
600
500
400
300
Baseline
14 days
28 days
42 days
56 days
Duration of Formoterol administration
Patient no: 10415
mPEFR (L/min)
700
600
500
400
300
Baseline
14 days
28 days
42 days
56 days
Duration of Formoterol administration
Patient no: 10507
mPEFR (L/min)
700
600
500
400
300
Baseline
14 days
28 days
42 days
56 days
Duration of Formoterol administration
Patient no: 10513
mPEFR (L/min)
700
600
500
400
300
Baseline
14 days
28 days
42 days
56 days
Duration of Formoterol administration

Table 25: Individual tabulation of the values of mean mPEFR at baseline and at the end of study and calculation of its change between these two time points.

Patient no	Treatment Group	Baseline	End of study	Change
10104	Formopen®	211.538	287.857	76.319
10106	Formopen®	374.615	383.750	9.135
10110	Formopen®	315.833	362.500	46.667
10121	Formopen®	206.000	197.647	–8.353
10406	Formopen®	579.286	538.889	–40.397
10409	Formopen®	266.000	311.667	45.667
10411	Formopen®	503.333	466.154	–37.179
10413	Formopen®	260.000	311.176	51.176
10414	Formopen®	500.833	668.333	167.500
10416	Formopen®	388.333	455.833	67.500
10417	Formopen®	439.167	453.077	13.910
10504	Formopen®	254.286	262.000	7.714
10505	Formopen®	207.273	220.000	12.727
10508	Formopen®	307.000	388.889	81.889
10002	Foradil®	323.571	280.000	–43.571
10004	Foradil®	337.857	372.143	34.286
10109	Foradil®	366.923	406.154	39.231
10111	Foradil®	292.857	266.154	–26.703
10112	Foradil®	337.333	385.294	47.961
10116	Foradil®	198.000	207.778	9.778
10118	Foradil®	352.143	372.000	19.857
10404	Foradil®	340.769	498.000	157.231
10412	Foradil®	328.750	318.667	–10.083
10415	Foradil®	352.000	553.571	201.571
10507	Foradil®	597.500	556.429	–41.071
10513	Foradil®	604.286	644.615	40.330

11.5 Efficacy Conclusions

The purpose of the present study was to demonstrate the therapeutic equivalence of Formopen® DPI administered with Elpen*haler*®, manufactured by Elpen Pharmaceuticals Co. Inc. (Test formulation) over Foradil® DPI administered with Aerolizer®, manufactured by Novartis (Reference formulation), in terms of their bronchodilator effect on the lung function of patients with mild to moderate persistent asthma. According to the applicable guidelines (30), in order to demonstrate therapeutic equivalence between the two formulations, the hypothesis that the primary variable is less than the non–inferiority margin $-\Delta_0$ should be rejected at a 0.025 significance level.

In the present study the primary variable was the difference of the mean change of the mean morning PEFR (mPEFR) between the test and reference formulation, as calculated from the run–in period until the final visit. The non–inferiority margin Δ_0 was set at 20 *lt/min*.

Based on the observed values of the changes in mean mPEFR of patients receiving Test or Reference formulation (Table 8), there was no sufficient evidence to support the hypothesis of therapeutic equivalence (*p–value*=0.265 and 1–sided 97.5%CI: –57.2,+∞ *lt/min*). This could be either the result of absence of actual therapeutic equivalence or the result of the very low observed statistical power, which is a consequence of the low recruitment rate.

Similarly, the demonstration of therapeutic equivalence was not possible when the primary endpoint analysis was conducted in the ITT population, (*p–value*=0.231 and 1–sided 97.5%CI: – 49.09,+∞

lt/min) (Table 45).

Further analyses displayed that mean change in mPEFR was 32.16 (95% CI: 2.47, 61.85, *p–value*=0.036) for patients receiving the Test formulation and 35.73 (95% CI: –11.8, 83.27, *p–value=0.126*) for patients receiving the Reference formulation (Table 8).

In addition, the number of days with PEFR daily fluctuation of >20% was similarly reduced in both treatment groups from baseline to final visit (OR: 0.17 [95%CI: 0.03, 0.84, *p–value* =0.030]) (Table 12). The number of short acting β_2–agonist inhalations utilized in the morning and in the evening remained unchanged in both treatment groups (Table 15, 16). Moreover, a similar improvement morning and evening asthma symptoms was observed for both treatments received (Table 13, 14). Finally, the usability questionnaire exhibited a preference of the patients towards Elpen*haler*® (Table 17). In all variables examined, no statistical significance was achieved due to limited number of observations.

12. SAFETY EVALUATION

12.1 Extent of Exposure

All patients were exposed to equal amounts of Formoterol formulation (test or reference) in terms of dose and drug concentration.

Patients withheld all LABAs during the run–in period, allowing adequate time interval to avoid any carry–over effects from their previous treatment. Thus the patient profile receiving each treatment was identical between study treatments.

Duration

The mean ± SD duration of treatment was 54.2 ± 4.29 days for the patients of the Formopen® group and 55.2 ± 8.33 days for the patients of the Foradil® group (*p–value*=0.149).

Dose

Throughout the treatment period of the study all patients received a single dose of Formoterol (12 μg b.i.d.) (Test or Reference) via inhalation, twice daily.

Drug Concentration

No pharmacokinetic analysis was conducted.

12.2 Adverse Events (AEs)

12.2.1 Brief Summary of Adverse Events

Nine patients out of the 42 patients recruited, developed 11 Non–Serious Adverse Events of mild to moderated intensity during the study (7 reported in the Formopen® group and 4 reported in the Foradil ® group). Only 2 of them (both in the Formopen® group) were reported as related to study drug: High glucose levels and shortness of breath.

6 out of 11 AE's concerned respiratory, thoracic and mediastinal disorders.
3 of the above–mentioned results led to study discontinuation.

All of the patients were recovered whereas no Serious Adverse Events were reported in the study.

Details of the adverse events may be found at Table 54.

12.2.2 Display of Adverse Events

All AEs occurring after initiation of study treatment are displayed in summary tables in section 14.3.1.

Table 26: Adverse events in Foradil® group: number observed and rate, with patients' identification

Foradil N–23	**Mild**		**Moderate**		**Severe**		**Total**		**Total**
	Related	**Not Related**	**Related**	**Not Related**	**Related**	**Not Related**	**Related**	**Not Related**	**R+NR**
Nervous system disorders									
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%) Patno: 10002	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Respiratory, thoracic and mediastinal disorders									
Upper respiratory tract infection	0 (0.0%)	2 (8.7%) Patno: 10002 10407	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2
Respiratory tract infection	0 (0.0%)	1 (4.3%) Patno: 10503	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1

Table 27: Adverse events in Formopen® group: number observed and rate, with patients' identification

Formopen® N=19	**Mild**		**Moderate**		**Severe**		**Total**		**Total**
	Related	**Not Related**	**Related**	**Not Related**	**Related**	**Not Related**	**Related**	**Not Related**	**R+NR**
Respiratory, thoracic and mediastinal disorders									
Respiratory tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%) Patno: 10504	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Asthma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%) Patno: 10701	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2
Cardiac disorders									
Tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Infections and infestations									
Infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Investigations									
Blood glucose increased	1 (5.3%) Patno: 10508	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1

12.2.3 Analysis of Adverse Events

- 6/23 (26.1%) patients of the Formopen® group experienced at least one AE.
- 3/19 (15.8%) patients of the Foradil® group experienced at least one AE.

The probability of occurrence of at least one AE in Formopen® group is estimated to be 1.65 times greater compared to the Foradil® group [95%CI: 0.48, 5.74, *p–value*>0.05].

Table 28: Relation between severity and causality of reported AEs

	Relationship to study drug		
Severity	Related	Not Related	Total
Mild	1 (14.3%)	6 (85.7%)	7
Moderate	1 (25.0%)	3 (75.0%)	4
Total	2	9	11

p–value=1.00 (Fishers's exact test)

Table 29: Relation between treatment group and causality of reported AEs

	Relationship to study drug		
Treatment	Related	Not Related	Total
Formopen®	2 (28.6%)	5 (71.4%)	7
Foradil®	0 (0.0%)	4 (100.0%)	4
Total	2	9	11

p–value=0.491 (Fishers's exact test)

Table 30: Relation between treatment group and severity of reported AEs

	Severity		
Treatment	Mild	Moderate	Total
Formopen®	4 (57.1%)	3 (42.9%)	7
Foradil®	3 (75.0%)	1 (25.0%)	4
Total	7	4	11

p–value=1.00 (Fishers's exact test)

12.2.4 Listing of Adverse Events by Patient

All adverse events for each patient are listed in Appendix 16.2.6.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths or other Serious Adverse Events have been observed during the study.

12.4 Clinical Laboratory Evaluation

12.4.1 Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

Listing of individual laboratory measurements is provided at 14.3.2. The analytes names, respective units and reference ranges are provided at Table 31.

Table 31: Analytical laboratory parameters tested

Analyte Name	SI Units	Reference Range
HAEMATOLOGY		
RED CELL COUNT (RBC)	K/µl	4.200.000–6.300.000
HEAMATOCRIT (Ht)	%	Male: 40.0–52.0/ Female: 36.0–46.0
HAEMOGLOBIN (Hb)	gr/dl	Male: 14.0–18.0/ Female: 12.0–16.0
WHITE CELL COUNT (WBC)	M/ml	4.000–10.000
PLATELET COUNT	K/µl	140–440
NEUTROPHILS	K/µl	40.0–70.0
LYMPHOCYTES	K/µl	19.0–48.0
MONOCYTES	K/µl	3.0–9.0
EOSINOPHILS	K/µl	0.0–7.0
BASOPHILS	K/µl	0.0–2.0
BIOCHEMISTRY		
POTASSIUM	mg/dl	3.5–5.3
SODIUM	mg/dl	136–148
ASAT (SGOT)	mg/dl	Male: 5.0–40.0/ Female: 5.0–35.0
ALAT (SGPT)	mg/dl	Male: 5.0–45.0/ Female: 5.0–40.0
CREATININE	mg/dl	Male: 0.8–1.4/ Female: 0.6–1.2
BILIRUBIN	mg/dl	0.1–1.2
GLUCOSE	mg/dl	60–120
URINE	mg/dl	15–50
γ–GT	mg/dl	5.0–40.0
ALP	mg/dl	30–135
URIC ACID	mg/dl	Male: 3.5–7.2/ Female: 2.4–6.0

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values Over Time

12.4.2.1.1 Haematology Tests

Table 32: Summary statistics of Haematological tests at each visit for each treatment group.

		Formopen®	**Foradil®**	**p–value**
Hb – *gr/dl*				
Screening visit	n	23	19	
	Mean ± SD	13.5 ± 1.03	14.4 ± 1.46	0.083
	Range	11.6 – 15.7	12.2 – 17.6	
	Abnormal – *no (%)*	4 (17.4)	2 (10.5)	
End of study	n	12	13	
	Mean ± SD	13.4 ± 1.03	13.8 ± 1.33	0.478
	Range	12.0 – 16.0	12.4 – 16.9	
	Abnormal – *no (%)*	2 (16.7)	2 (15.4)	
Change	Mean ± SD	–0.13 ± 0.57 (0.210)	–0.40 ± 0.5 (0.042)	0.383
Ht – *%*				
Screening visit	n	23	19	
	Mean ± SD	42.7 ± 3.77	45.1 ± 4.97	0.111
	Range	34.5 – 52.7	38.9 – 57.2	
	Abnormal – *no (%)*	4 (17.4)	2 (10.5)	
End of study	n	12	13	
	Mean ± SD	42.1 ± 2.70	43.3 ± 3.93	0.369
	Range	38.4 – 47.7	38.6 – 50.8	
	Abnormal – *no (%)*	2 (16.7)	0 (0.0)	
Change	Mean ± SD	–0.32 ± 3.01 (0.896)	–14.69 ± 2.56	0.165
RBC ×10^6– *K/µl*				
Screening visit	n	23	19	
	Mean ± SD	4.95 ±0.53	4.98 ± 0.60	0.930
	Range	4.43 –6.38	4.34 –6.70	
	Abnormal	1 (4.4)	1 (5.3)	
End of study	n	12	13	
	Mean ± SD	4.78 ±0.52	4.95 ±0.50	0.242
	Range	4.3 – 6.1	4.3 – 6.3	
	Abnormal – *no (%)*	0 (0.0)	0 (0.0)	
Change	Mean ± SD	–5.58 ± 0.59 (0.266)	–8.54 ± 0.33	0.957
WBC ×10^6– *K/µl*				
Screening visit	n	23	19	
	Mean ± SD	6.5 ± 1.83	6.1 ± 1.93	0.356
	Range	3.3 – 9.9	3.8 –10.0	
	Abnormal – *no (%)*	2 (8.7)	2 (10.5)	
End of study	n	12	13	
	Mean ± SD	7.4 ± 3.18	6.6 ± 2.2	0.765
	Range	3.6 –15.4	3.2 –10.2	
	Abnormal – *no (%)*	3 (25.0)	3 (23.1)	
Change	Mean ± SD	6.18 ± 2.19 (0.519)	3.1 ± 1.66 (0.735)	0.586
PLT – *K/µl*				
Screening visit	n	22	19	

		Formopen®	Foradil®	p–value
	Mean ± SD	272.2 ± 69.35	267.0 ± 131.04	0.239
	Range	148.0 – 422.0	140.0 – 750.0	
	Abnormal – *no (%)*l	0 (0.0)	1 (5.3)	
End of study	n	11	13	
	Mean ± SD	279.4 ± 85.97	252.5 ± 104.26	0.487
	Range	157.0 – 480.0	120.0–480.0	
	Abnormal – *no (%)*	1 (9.1)	2 (15.4)	
Change	Mean ± SD	–11.81±63.1 (0.684)	16.5 ± 85.8 (0.622)	0.885
Neutrophils – *K/µl*				
Screening visit	n	19	15	
	Mean ± SD	56.5 ± 14.78	54.0 ± 14.39	0.849
	Range	39.0 – 99.0	10.0 – 71.0	
	Abnormal – *no (%)*	2 (10.5)	2 (13.3)	
End of study	n	10	11	
	Mean ± SD	58.2 ± 7.84	59.5 ± 12.48	0.596
	Range	41.0 – 67.0	29.0 – 75.0	
	Abnormal – *no (%)*	0 (0.0)	3 (27.3)	
Change	Mean ± SD	–3.8 ± 12.6 (0.375)	1.8 ± 9.3 (0.154)	0.103
Lymphocytes – *K/µl*				
Screening visit	n	19	14	
	Mean ± SD	38.3 ± 17.03	33.8 ± 7.51	0.688
	Range	21.0 – 99.0	22.0 – 47.0	
	Abnormal – *no (%)*	1 (5.3)	0 (0.0)	
End of study	n	10	11	
	Mean ± SD	31.0 ± 5.12	29.4 ± 8.77	0.459
	Range	24.0 – 42.0	19.0 – 48.0	
	Abnormal – *no (%)*	0 (0.0)	0 (0.0)	
Change	Mean ± SD	–7.7 ± 23.6 (0.375)	–3.6 ± 5.6 (0.154)	0.103
Monocytes – *K/µl*				
Screening visit	n	19	14	
	Mean ± SD	10.8 ± 21.41	6.0 ± 1.41	0.737
	Range	3.0 – 99.0	4.0 – 9.0	
	Abnormal – *no (%)*	0 (0.0)	0 (0.0)	
End of study	n	10	11	
	Mean ± SD	6.5 ± 1.72	7.4 ± 3.61	0.943
	Range	4.0 – 9.0	5.0 – 18.0	
	Abnormal – *no (%)*	0 (0.0)	1 (9.1)	
Change	Mean ± SD	–8.0 ± 30.6 (0.258)	1.2 ± 4.0 (0.586)	0.379
Eosinophils – *K/µl*				
Screening visit	n	19	14	
	Mean ± SD	9.6 ± 21.91	2.9 ± 1.41	0.150
	Range	1.0 – 99.0	1.0 – 6.0	
	Abnormal – *no (%)*	3 (15.8)	0 (0.0)	
End of study	n	10	11	
	Mean ± SD	4.3 ± 3.06	3.5 ± 2.50	0.593
	Range	1.0 – 8.0	0.0 – 8.0	
	Abnormal – *no (%)*	3 (30.0)	1 (9.1)	

		Formopen®	Foradil®	p–value
Change	Mean ± SD	–9.9 ± 28.9 (0.219)	0.5 ± 2.3 (0.656)	0.299
Basophils – *K/µl*				
Screening visit	n	19	14	
	Mean ± SD	10.8 ± 21.41	6.0 ± 1.41	1
	Range	3.0 – 99.0	4.0 – 9.0	
	Abnormal – *no (%)*	0 (0.0)	0 (0.0)	
End of study	n	10	11	
	Mean ± SD	6.5 ± 1.72	7.4 ± 3.61	0.231
	Range	4.0 – 9.0	5.0 – 18.0	
	Abnormal – *no (%)*	0 (0.0)	0 (0.0)	
Change	Mean ± SD	–0.17 ± 0.41 (1.00)	0.29 ± 0.49 (0.500)	0.121

12.4.2.1.2 Biochemical Tests

Table 33: Summary statistics of blood glucose at each visit for each treatment group.

Blood Glucose – *mg/dl*		Formopen®	Foradil®	p–value
Screening visit	n	22	17	
	Mean ± SD	85.4 ± 22.38	94.1 ± 18.12	0.097
	Range	12.0 – 135.0	50.0 – 126.0	
	Abnormal – *no (%)*	1 (4.6)	1 (5.9)	
1st FU visit	n	14	16	
	Mean ± SD	89.2 ± 15.46	93.2 ± 16.18	0.328
	Range	69.0 – 130.0	62.0 – 122.0	
	Abnormal – *no (%)*	1 (7.1)	1 (6.3)	
2nd FU visit	n	13	15	
	Mean ± SD	86.5 ± 15.11	93.1 ± 16.94	0.322
	Range	59.0 – 113.0	66.0 – 122.0	
	Abnormal – *no (%)*	0 (0.0)	1 (6.7)	
3rd FU visit	n	9	9	
	Mean ± SD	80.4 ± 35.66	94.7 ± 12.08	0.185
	Range	3.0 – 138.0	80.0 – 118.0	
	Abnormal – *no (%)*	2 (22.2)	0 (0.0)	
End of study	n	13	15	
	Mean ± SD	85.7 ± 13.49	98.3 ± 16.96	0.076
	Range	63.0 – 108.0	75.0 – 135.0	
	Abnormal – *no (%)*	0 (0.0)	2 (13.3)	
Change from BSL	Mean ± SD	0.25 ± 23.9 (0.948)	6.23 ± 20.4 (0.314)	0.430

Table 34: Summary statistics of Potassium at each visit for each treatment group.

Potassium – *mg/dl*		**Formopen®**	**Foradil®**	**p–value**
Screening visit	n	21	17	
	Mean ± SD	4.9 ± 1.10	7.1 ± 9.44	0.508
	Range	3.8 – 8.8	3.9 – 43.2	
	Abnormal – *no (%)*	2 (9.5)	0 (0.0)	
1st FU visit	n	14	16	
	Mean ± SD	4.7 ± 0.63	4.8 ± 1.80	0.738
	Range	3.8 – 6.1	0.4 – 9.5	
	Abnormal – *no (%)*	2 (14.3)	3 (18.8)	
2nd FU visit	n	13	15	
	Mean ± SD	5.0 ± 0.87	4.8 ± 0.97	0.368
	Range	4.1 – 6.8	3.9 – 7.8	
	Abnormal – *no (%)*	4 (30.8)	3 (20.0)	
3rd FU visit	n	9	9	
	Mean ± SD	7.3 ± 7.87	4.9 ± 0.97	0.894
	Range	4.1 – 28.2	4.0 – 7.3	
	Abnormal – *no (%)*	3 (33.3)	1 (11.1)	
End of study	n	13	15	
	Mean ± SD	4.9 ± 1.05	4.6 ± 0.29	0.926
	Range	3.8 – 7.6	4.1 – 5.1	
	Abnormal – *no (%)*	3 (23.1)	0 (0.0)	
Change from BSL	Mean ± SD	–0.01 ± 0.91 (0.754)	–3.35 ± 10.8 (0.804)	

Table 35: Summary statistics of other biochemical tests at each visit for each treatment group.

		Formopen®	Foradil®	p–value
Sodium– *mg/dl*				
Screening visit	n	20	17	
	Mean ± SD	139.9 ± 2.17	137.8 ± 10.16	1
	Range	135.0 – 144.0	100.0 – 145.0	
	Abnormal – *no (%)*	1 (5.0)	2 (11.8)	
End of study	n	13	15	
	Mean ± SD	139.5 ± 1.85	139.7 ± 1.68	0.888
	Range	137.0 – 142.0	137.0 – 144.0	
	Abnormal – *no (%)*	0 (0.0)	0 (0.0)	
Change	Mean ± SD (p–value)	–0.10 ± 2.8 (0.731)	2.46 ± 11.6 (0.721)	0.951
Creatinine – *mg/dl*				
Screening visit	n	20	18	
	Mean ± SD	0.7 ± 0.16	0.8 ± 0.18	0.022
	Range	0.5 – 1.0	0.5 – 1.2	
	Abnormal – *no (%)*	2 (10.0)	1 (5.6)	
End of study	n	13	15	
	Mean ± SD	0.8 ± 0.24	0.8 ± 0.14	0.779
	Range	0.6 – 1.3	0.6 – 1.1	
	Abnormal – *no (%)*	1 (7.7)	1 (6.7)	
Change	Mean ± SD	0.10 ± 0.2 (0.156)	–0.03 ± 0.1 (0.686)	0.198
Urea– *mg/dl*				
Screening visit	n	20	18	
	Mean ± SD	33.2 ± 9.44	33.5 ± 10.11	0.803
	Range	19.0 – 63.0	19.0 – 64.0	
	Abnormal – *no (%)*	1 (5.0)	1 (5.6)	
End of study	n	13	15	
	Mean ± SD	37.1 ± 15.51	31.9 ± 7.81	0.380
	Range	20.0 – 73.0	20.0 – 44.0	
	Abnormal – *no (%)*	2 (15.4)	0 (0.0)	
Change	Mean ± SD	1.9 ± 16.0 (0.717)	–3.2 ± 11.1 (0.437)	0.558
ALAT– *mg/dl*				
Screening visit	n	20	18	
	Mean ± SD	24.0 ± 12.77	27.6 ± 19.32	0.715
	Range	9.0 – 46.0	11.0 – 82.0	
	Abnormal – *no (%)*	4 (20.0)	2 (11.1)	
End of study	n	13	15	
	Mean ± SD	16.5 ± 7.64	30.8 ± 17.36	0.022
	Range	7.0 – 34.0	12.0 – 67.0	
	Abnormal – *no (%)*	0 (0.0)	6 (40.0)	
Change	Mean ± SD	–5.8 ± 12.8 (0.262)	5.8 ± 12.8 (0.161)	0.065
ASAT– *mg/dl*				
Screening visit	n	20	18	
	Mean ± SD	21.0 ± 9.50	27.8 ± 16.99	0.098
	Range	11.0 – 56.0	16.0 – 83.0	
	Abnormal – *no (%)*	1 (5.0)	2 (11.1)	
End of study	n	13	15	
	Mean ± SD	19.3 ± 10.79	21.8 ± 7.88	0.159

		Formopen®	Foradil®	p–value
	Range	7.0 – 47.0	7.0 – 40.0	
	Abnormal – *no (%)*	1 (7.7)	0 (0.0)	
Change	Mean ± SD	–1.4 ± 6.5 (0.272)	–5.8 ± 19.3 (0.399)	0.953
Alk.Phosphatase– *mg/dl*				
Screening visit	n	20	18	
	Mean ± SD	58.2 ± 12.59	70.6 ± 20.73	0.042
	Range	28.0 – 84.0	47.0 – 133.0	
	Abnormal – *no (%)*	1 (5.0)	0 (0.0)	
End of study	n	13	15	
	Mean ± SD	50.2 ± 14.32	64.0 ± 14.39	0.023
	Range	24.0 – 76.0	44.0 – 88.0	
	Abnormal – *no (%)*	1 (7.7)	0 (0.0)	
Change	Mean ± SD	–3.40 ± 6.3 (0.127)	–1.43 ± 9.6 (0.100)	0.930
γ–GT– *mg/dl*				
Screening visit	n	20	18	
	Mean ± SD	17.2 ± 7.94	17.7 ± 12.45	0.618
	Range	5.0 – 37.0	8.0 – 60.0	
	Abnormal – *no (%)*	0 (0.0)	1 (5.6)	
End of study	n	13	15	
	Mean ± SD	14.2 ± 8.22	19.5 ± 12.49	0.121
	Range	7.0 – 35.0	8.0 – 49.0	
	Abnormal – *no (%)*	0 (0.0)	2 (13.3)	
Change	Mean ± SD	–2.10 ± 4.2 (0.148)	5.14 ± 9.1 (0.026)	0.0134
Uric acid– *mg/dl*				
Screening visit	n	20	18	
	Mean ± SD	4.3 ± 1.18	5.4 ± 0.84	0.002
	Range	2.7 – 7.4	3.6 – 6.9	
	Abnormal – *no (%)*	2 (10.0)	0 (0.0)	
End of study	n	13	15	
	Mean ± SD	4.1 ± 1.32	5.3 ± 1.25	0.056
	Range	2.3 – 6.1	2.8 – 7.6	
	Abnormal – *no (%)*	2 (15.4)	2 (13.3)	
Change	Mean ± SD	–0.15 ± 0.7 (0.219)	0.09 ± 1.0 (0.716)	0.253
Bilirubin– *mg/dl*				
Screening visit	n	20	17	
	Mean ± SD	0.2 ± 0.12	0.2 ± 0.12	0.109
	Range	0.1 – 0.6	0.1 – 0.4	
	Abnormal – *no (%)*l	0 (0.0)	0 (0.0)	
End of study	n	12	15	
	Mean ± SD	0.1 ± 0.04	0.2 ± 0.17	0.228
	Range	0.1 – 0.2	0.1 – 0.7	
	Abnormal – *no (%)*	0 (0.0)	0 (0.0)	
Change	Mean ± SD	–0.09 ± 0.2 (0.125)	–0.1 ± 0.2 (0.625)	0.747

12.4.2.2 Individual Clinically Significant Abnormalities

No clinically significant abnormalities were observed but the increase of the blood glucose at one patient of the Formopen group®.

12.4.2.2.1 12– Lead Electrocardiogram

Table 36: Abnormal findings of 12–lead electrocardiogram at first and final visit

	Formopen®	**Foradil®**
Screening visit –*no./ no. total (%)*	1/23 (4.3%)*	1/19 (5.3%)*
QTc interval – *sec*		
(n), Mean ± SD	(23), 0.385 ± 0.052	(19), 0.397 ± 0.040
End of study–*no./ no. total (%)*	0/12 (0.0%)	0/17 (0.0%)
QTc interval – *sec*		
(n), Mean ± SD	(12), 0.358 ± 0.111	(17), 0.515 ± 0.460

**Clinically insignificant finding.*

12.4.3 Individual Patient Changes (Physical Examination)

At the physical examination, the only changes occurred are the following:

- 1 patient of Formopen® group (10405) had abnormal findings in lung examination at the screening visit (Musical lung sounds). No such findings were observed at the final visit.
- 1 patient of Formopen® group (10411) had abnormal findings in cardiovascular examination at the final visit (Tachycardia).
- 1 patient of Foradil® group (104/08) had abnormal findings in lung examination at the screening visit (Musical lung sounds). No such findings were observed at the final visit.

12.5 Vital Signs and ECG findings

Table 37: Summary statistics of systolic blood pressure at each visit for each treatment group.

Systolic blood pressure – (mmHg)		Formopen®	Foradil®	p–value
Screening visit	n	23	19	
	Mean ± SD	128.7 ± 13.50	133.3 ± 13.82	0.252
	min–max	110.0 – 160.0	110.0 – 160.0	
Baseline visit	n	23	19	
	Mean ± SD	128.7 ± 12.27	128.4 ± 17.75	0.689
	min–max	110.0 – 160.0	107.0 – 185.0	
1st FU visit	n	19	19	
	Mean ± SD	127.9 ± 9.76	128.1 ± 7.81	0.856
	Min–Max	110.0 – 140.0	118.0 – 140.0	
2nd FU visit	n	16	17	
	Mean ± SD	122.1 ± 9.35	130.2 ± 14.42	0.046
	Min–Max	110.0 – 140.0	120.0 – 175.0	
3rd FU visit	n	15	17	
	Mean ± SD	129.6 ± 12.29	127.3 ± 9.66	0.576
	Min–Max	110.0 – 159.0	109.0 – 150.0	
End of study	n	16	19	
	Mean ± SD	130.0 ± 17.22	130.9 ± 20.58	0.809
	Min–Max	110.0 – 180.0	110.0 – 193.0	
Change from BSL	Mean ± SD (p–value)	0.00 ± 23.2 (1.00)	–2.37 ± 16.0	0.712

Table 38: Summary statistics of diastolic blood pressure at each visit for each treatment group.

Diastolic blood pressure – (mmHg)		Formopen®	Foradil®	p–value
Screening visit	n	23	19	
	Mean ± SD	74.6 ± 9.64	74.5 ± 11.07	0.768
	min–max	60.0 – 105.0	60.0 – 100.0	
Baseline visit	n	23	19	
	Mean ± SD	71.1 ± 6.39	75.0 ± 11.56	0.338
	min–max	60.0 – 85.0	60.0 – 110.0	
1st FU visit	n	19	19	
	Mean ± SD	70.8 ± 10.09	75.1 ± 7.00	0.061
	Min–Max	60.0 – 100.0	60.0 – 85.0	
2nd FU visit	n	16	17	
	Mean ± SD	70.3 ± 9.91	70.8 ± 8.71	0.722
	Min–Max	60.0 – 100.0	60.0 – 95.0	
3rd FU visit	n	15	17	
	Mean ± SD	73.9 ± 10.70	73.7 ± 8.27	0.744
	Min–Max	60.0 – 106.0	60.0 – 90.0	
End of study	n	16	19	
	Mean ± SD	69.9 ± 11.00	72.7 ± 9.81	0.157
	Min–Max	60.0 – 103.0	55.0 – 102.0	
Change from BSL	Mean ± SD (p–value)	–4.50 ± 9.6	–1.79 ± 10.1 (0.537)	0.242

Table 39: Summary statistics of Heart rate at each visit for each treatment group.

Heart Rate – (bpm)		Formopen®	Foradil®	p–value
Screening visit	n	23	19	
	Mean ± SD	74.7 ± 10.61	73.2 ± 10.01	0.732
	min–max	60.0 – 98.0	53.0 – 95.0	
Baseline visit	n	23	19	
	Mean ± SD	71.0 ± 9.43	73.8 ± 7.95	0.102
	min–max	60.0 – 105.0	60.0 – 87.0	
1st FU visit	n	19	19	
	Mean ± SD	71.5 ± 9.38	72.3 ± 8.74	0.747
	Min–Max	60.0 – 100.0	60.0 – 88.0	
2nd FU visit	n	16	17	
	Mean ± SD	70.6 ± 8.02	71.3 ± 7.74	0.799
	Min–Max	60.0 – 88.0	60.0 – 86.0	
3rd FU visit	n	15	17	
	Mean ± SD	72.5 ± 10.23	73.1 ± 6.91	0.622
	Min–Max	60.0 – 98.0	60.0 – 82.0	
End of study	n	16	19	
	Mean ± SD	71.0 ± 8.91	70.5 ± 8.71	0.881
	Min–Max	58.0 – 90.0	58.0 – 92.0	
Change from BSL	Mean ± SD (p–value)	–2.69 ± 12.7 (0.455)	–2.63 ± 11.3 (0.288)	0.934

Table 40: Summary statistics of breath rate at each visit for each treatment group.

Breath Rate – (bpm)		Formopen®	Foradil®	p–value
Screening visit	n	23	19	
	Mean ± SD	16.3 ± 3.75	15.3 ± 3.59	0.403
	min–max	12.0 – 24.0	12.0 – 22.0	
Baseline visit	n	23	19	
	Mean ± SD	15.7 ± 3.39	15.7 ± 3.40	0.990
	min–max	12.0 – 22.0	12.0 – 24.0	
1st FU visit	n	19	19	
	Mean ± SD	16.1 ± 3.58	15.8 ± 3.71	0.789
	Min–Max	12.0 – 24.0	12.0 – 24.0	
2nd FU visit	n	16	17	
	Mean ± SD	15.1 ± 2.66	14.9 ± 3.03	0.824
	Min–Max	12.0 – 20.0	12.0 – 20.0	
3rd FU visit	n	15	17	
	Mean ± SD	16.1 ± 2.80	15.1 ± 2.99	0.354
	Min–Max	12.0 – 20.0	12.0 – 20.0	
End of study	n	16	19	
	Mean ± SD	16.8 ± 4.10	15.8 ± 3.19	0.523
	Min–Max	12.0 – 25.0	12.0 – 20.0	
Change from BSL	Mean ± SD (p–value)	0.19 ± 3.7 (0.955)	0.47 ± 2.4 (0.547)	0.466

Table 41: Summary statistics of temperature at each visit for each treatment group.

Temperature – (C°)		Formopen®	Foradil®	p–value
Screening visit	n	23	19	
	Mean ± SD	36.6 ± 0.2	36.6 ± 0.2	0.456
	min–max	36.2 – 36.9	36.2 – 36.9	
Baseline visit	n	23	19	
	Mean ± SD	36.5 ± 0.27	36.5 ± 0.25	0.296
	min–max	35.5 – 36.8	36.0 – 36.9	
1st FU visit	n	19	19	
	Mean ± SD	36.4 ± 0.27	36.5 ± 0.23	0.076
	Min–Max	35.6 – 36.7	36.0 – 36.8	
2nd FU visit	n	16	17	
	Mean ± SD	36.5 ± 0.19	36.6 ± 0.15	0.191
	Min–Max	36.0 – 36.8	36.2 – 36.9	
3rd FU visit	n	15	17	
	Mean ± SD	36.5 ± 0.23	36.6 ± 0.23	0.456
	Min–Max	36.0 – 36.8	36.2 – 36.9	
End of study	n	16	19	
	Mean ± SD	36.5 ± 0.26	36.6 ± 0.65	0.920
	Min–Max	36.0 – 36.9	35.4 – 38.9	
Change from BSL	Mean ± SD (p–value)	–0.06 ± 0.3 (0.351)	0.03 ± 0.7 (0.947)	0.641

12.6 Safety Conclusions

During the study no serious adverse events (SAEa) or deaths were reported. Totally, nine patients presented eleven non–serious adverse events (AEs), seven of mild and four of moderate severity. All patients that presented adverse events were treated according to the nature of the adverse event and recovered in the same day of the event's appearance (Table 54). The majority of AEs reported were infections or disorders of the respiratory tract (8 reports). These included a reported case of dyspnoea of moderate severity, an unexpected AE that was related to the study drug and which necessitated withdrawal of the patient. In addition, one patient presented a moderate asthma exacerbation that, however, was unrelated to the study drug, but also required her withdrawal from the study. Moreover, one patient presented a drug related mild increase in blood glucose levels, an expected adverse event, that required no further action to be taken. The remaining AEs included an occurrence of a tachycardia (cardiac disorder), one incidence of moderate headache (nervous system disorder) and one case of infection that was unrelated to the study drug and required the patient's withdrawal.

Assessment of vital signs, including systolic and diastolic blood pressure, heart rate, body temperature and breath rate showed no clinically significant difference between the screening visit and the end of the study, for both treatment groups. Similarly, no clinically significant difference between the screening visit and the end of the study, for both treatment groups was observed in relation to ECG findings (Table 36). Biochemical and haematological examinations did not exhibit clinically important abnormal findings between treatment groups or compared to the values at screening (Table 32, 33–35). A small number of patients in both study groups exhibited few aberrant biochemical or haematological values that were though clinically insignificant (Table 55).

Based on the afore–mentioned results on all safety variables assessed in the present study, it is concluded that Formopen® DPI (Formoterol delivered by Elpen*haler*®, manufactured by Elpen Pharmaceutical Co. Inc) has favourable safety profile, which is comparable to Foradil® (Formoterol delivered by Aerolizer®, manufactured by GlaxoSmithKline).

13. DISCUSSION AND OVERALL CONCLUSIONS

The purpose of the present study was to demonstrate the therapeutic equivalence of Formopen® DPI administered with Elpen*haler*®, manufactured by Elpen Pharmaceuticals Co. Inc. (Test formulation) to Foradil® DPI administered with Aerolizer®, manufactured by Novartis (Reference formulation), in terms of their bronchodilator effect on the lung function of patients with mild to moderate persistent asthma. Both treatments included the same known substance, i.e. 12 μg of Formoterol. In order to investigate the therapeutic equivalence of the two products a multicenter, randomized, double–blind, double–dummy, parallel group design was employed (19). In addition, a group of asthmatic patients with mild to moderate persistent asthma, who demonstrated reversibility of airway function, was selected, as representative subjects of the target population (asthmatic patients with mild to moderate persistent asthma) (20). Patients were assigned randomly to two treatment groups receiving either the test or the reference formulation for eight weeks.

Formoterol is a potent long–acting β_2–agonist (LABA) widely used in the management of asthma and chronic obstructive pulmonary disease (COPD) (48, 49). It has a well established efficacy for improving lung function and asthma symptoms in patients with mild to moderate persistent asthma (50, 51), in addition to a fast onset and longer duration of action (52, 53). Formoterol significantly improves lung function, asthma symptoms, and rescue medication use and reduces the risk of exacerbation. It is therefore recommended by the National Heart, Lung, and Blood Institute (NHLBI) (54) and GINA (55), as a monotherapy or in combination with ICS treatment, for the long term management of asthma and COPD.

Foradil® is the marketed Formoterol 12 μg DPI formulation, delivered by a single–dose dry powder inhaler, Aerolizer®. It was reasonably selected as the reference drug combination, taking into consideration that it is the innovative Formoterol formulation and the only one available in the market. The test formulation also contains 12 μg of Formoterol DPI delivered by a different inhalation device (Elpen*haler*®). When studying the therapeutic equivalence of inhaled bronchodilators, an important indicator proposed for assessing lung function is PEFR recorded daily at home (22). According to the applicable guidelines (30), in order to demonstrate therapeutic equivalence, the null hypothesis that the primary endpoint is lower than $-\Delta_0$ (inferiority), must be rejected at a 0.025 confidence level. In the present study the primary variable was the difference in the mean change of mean morning PEFR (mPEFR) between the test and reference formulation, from the run–in period until the final visit. Statistical analysis performed on the values of mean mPEFR collected from patients receiving both formulations could not support the hypothesis of therapeutic equivalence between the two formulations, as a result of either the absence of such an equivalence or the very low observed statistical power. In the same way, no conclusion could be drawn on the therapeutic equivalence of the test and reference formulation when statistical analysis of the primary variable was conducted in the ITT population. Analysis of the secondary variables exhibited a similar efficacy profile for both formulations.

To establish the therapeutic equivalence of Formopen® DPI compared to the reference product Foradil® DPI both efficacy and safety analyses were conducted. Safety variables in the present study included adverse event occurrence, assessment of paradoxical bronchospasm, changes in hematology and biochemistry values, changes in the 12–lead ECG and vital signs. All cases of safety analyses supported the comparable safety profile of Formopen® DPI administered with Elpen*haler*® with Foradil® DPI administered with Aerolizer®, recording no significant changes between the afore mentioned therapies (Tables 54, 55).

Overall conclusions

The primary objective of the study was to establish the therapeutic equivalence of a novel Formoterol formulation (12 μg) when administered with Elpenhaler® (Formopen®) against the innovative Formoterol formulation DPI (Foradil®–Aerolizer®). A final conclusion on the therapeutic equivalence of the two formulations could not be ascertained. This was a result of the early termination of the study due to low recruitment rate. Therefore, the limited observed power and the statistical significance could not be attained to support the study hypothesis. Analyses of safety variables concluded on no additional safety issues arising when using Elpenhaler® instead of Aerolizer® for administering Formoterol. Thus,

Formopen® and Foradil® present a similar safety profile.
Taken together, the study results are insufficient to provide a firm conclusion on the therapeutic equivalence of administration of Formoterol via Elpenhaler® (Formopen®) or Aerolizer® (Foradil®). Therefore a similar bronchodilator activity of test and reference formulation in patients with mild to moderate asthma can not be confirmed.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic data

Table 42: Demographics and Baseline Clinical Characteristics of ITT population

	Treatment Group		
	Formopen® (n=23)	**Foradil® (n=19)**	**p–value**
Gender – *no. (%)*			
Male	7 (30.4)	10 (52.6)	0.209
Female	16 (69.6)	9 (47.4)	
Age – *yr*			
Mean ± SD	46.2 ± 12.0	44.5 ± 14.4	0.801
Range	24.4 – 69.3	20.7 – 69.3	
BMI – *kg/height²*			
Mean ± SD	27.2 ± 6.9	29.6 ± 6.6	0.143
Range	19.8 – 52.1	20.3 – 52.1	
Race – *no. (%)*			
Caucasian	23 (100.0)	19 (100.0)	–
Duration of asthma – *months*			
Mean ± SD	135.1 ± 93.0	199.9 ± 188.8	0.486
Range	24.0 – 396.0	6.0 – 396.0	
Asthma symptoms – *no. (%)*			
Mild	13 (56.5)	8 (42.1)	0.536
Moderate	10 (43.5)	11 (57.9)	
Asthma classification (Gina) – *no. (%)*			
Mild	16 (69.6)	7 (36.8)	0.034
Moderate	7 (30.4)	12 (63.2)	
Smoking – *no. (%)*			
Never used	19 (82.6)	11 (57.9)	0.207
Ex–smoker	2 (8.7)	5 (26.3)	
Smoker	2 (8.7)	3 (15.8)	

Table 43: Medication for asthma at each visit (ITT population)

	Treatment Group		
	Formopen® (n=23)	**Foradil® (n=19)**	**p–value**
Medication – *no. %*			
Salbutamol	11 (47.8)	9 (47.4)	1
Aerolin	10 (43.5)	10 (52.6)	0.779
Fluticasone	10 (43.5)	6 (31.6)	0.638
Budesonide	6 (26.1)	4 (21.1)	0.986
Pulmicort	4 (17.4)	4 (21.1)	1
Fluticapen	2 (8.7)	3 (15.8)	0.820
Flixotide	0 (0.0)	2 (10.5)	0.386
Bleclomethasone Hfa	1 (4.3)	0 (0.0)	1
Inuvair	0 (0.0)	1 (5.3)	0.923
Symbicort	1 (4.3)	0 (0.0)	1

Table 44: Summary statistics on spirometry & reversibility tests at screening visit (ITT population)

	Treatment Group		
	Formopen® (n=23)	**Foradil® (n=19)**	**p–value**
FEV_1–*(L)*			
Mean ± SD	2.3 ± 0.6	2.4 ± 0.8	0.587
Range	1.5 – 3.5	1.3 – 3.8	
FVC–*(L)*			
Mean ± SD	76.7 ± 10.9	72.4 ± 8.8	0.426
Range	60.0 – 102.0	60.0 – 90.0	
FEV_1 *% of predicted*– (*%)*			
Mean ± SD	76.7 ± 10.9	72.4 ± 8.8	0.245
Range	60.0 – 102.0	60.0 – 90.0	
FEV_1/FVC – *(lt/min)*			
Mean ± SD	70.1 ± 9.5	2.4 ± 0.8	0.479
Range	53.3 – 88.3	1.3 – 3.8	
$FEF_{25\%}$ – (*lt/min)*			
Mean ± SD	3.8 ± 1.5	6.0 ± 8.1	0.353
Range	0.9 – 5.6	1.8 – 39.2	
$FEF_{25–75\%}$ – *(lt/min)*			
Mean ± SD	2.1 ± 1.9	1.9 ± 1.5	0.647
Range	0.7 – 9.6	0.74 – 7.5	
PIF– *(lt/min)*			
Mean ± SD	75.9 7.2	77.9 11.9	0.192
Range	60.0–90.0	50.0–90.0	

14.2 Efficacy Data

14.2.1 Assessment of primary endpoint on ITT

Table 45: Estimation of the mean change of mean mPEFR from baseline to final visit in each group (ITT population)

	Change from Baseline	95%CI of change	p–value
mPEFR– *lt/min*			
Formopen®	32.16	[2.47, 61.85]	0.036
Foradil®	35.59	[–1.74, 72.93]	0.060
Formopen®–Foradil®	–3.43	[–49.09, +∞]†	0.231‡

† Lower bound of the 1–sided 97.5% CI.
‡ *p–value* for the null hypothesis Δ<–20 lt/min

14.2.2 Assessment of secondary endpoints on ITT

Table 46: Summary statistics for ITT population for the mean mPEFR

		Treatment Group		
		Formopen®	**Foradil®**	**p–value**
mPEFR – *lt/min*				
Baseline	n	21	18	0.096
	Mean ± SD	330.7 ± 108.18	397.8 ± 132.66	
	Range	206.0 – 579.3	198.0 – 681.8	
1st FU visit	n	19	19	0.226
	Mean ± SD	365.0 ± 136.29	420.4 ± 135.85	
	Range	162.9 – 656.7	212.5 – 706.9	
2nd FU visit	n	17	18	0.099
	Mean ± SD	366.7 ± 140.68	444.8 ± 133.28	
	Range	173.6 – 645.8	259.3 – 715.0	
3rd FU visit	n	15	17	0.355
	Mean ± SD	375.3 ± 133.48	414.9 ± 129.56	
	Range	208.2 – 656.7	199.1 – 676.9	
End of study	n	16	15	0.607
	Mean ± SD	378.1 ± 120.62	402.0 ± 131.95	
	Range	197.6 – 668.3	207.8 – 644.6	

Table 47: Summary statistics for ITT population for the mean ePEFR

		Treatment Group		
		Formopen®	**Foradil®**	**p–value**
Evening PEFR – *lt/min*				
Baseline	n	21	18	0.099
	Mean ± SD	325.1 ± 102.9	397.9 ± 131.5	
	Range	196.0 – 565.4	186.7 – 642.5	
1st FU visit	n	19	19	0.184
	Mean ± SD	359.4 ± 126.6	420.0 ± 139.0	
	Range	164.0 – 636.9	202.0 – 700.0	
2nd FU visit	n	17	18	0.214
	Mean ± SD	359.0 ± 129.6	446.7 ± 134.8	
	Range	194.3 – 634.2	248.5 – 717.0	
3rd FU visit	n	15	17	0.265
	Mean ± SD	373.9 ± 128.0	418.0 ± 127.7	
	Range	217.6 – 638.3	205.5 – 655.7	
End of study	n	16	15	0.633
	Mean ± SD	376.3 ± 123.0	402.5 ± 131.2	
	Range	191.8 – 652.5	208.2 – 642.3	

Table 48: Summary statistics for ITT population for the variable FEV1

FEV_1		**Formopen®**	**Foradil®**
Screening visit	n	23	19
	Mean ± SD	2.3 ± 0.6	2.4 ± 0.8
	min–max	1.5 – 3.5	1.3 – 3.8
Baseline visit	n	22	19
	Mean ± SD	2.3 ± 0.6	2.6 ± 1.0
	min–max	1.4 – 3.6	1.2 – 4.4
1st FU visit	n	19	19
	Mean ± SD	2.5 ± 0.7	2.9 ± 1.2
	Min–Max	1.5 – 3.7	1.1 – 5.6
2nd FU visit	n	16	17
	Mean ± SD	2.5 ± 0.9	2.8 ± 1.1
	Min–Max	1.4 – 3.9	1.3 – 5.0
3rd FU visit	n	15	17
	Mean ± SD	2.6 ± 0.8	2.8 ± 1.1
	Min–Max	1.5 – 3.7	1.3 – 4.5
End of study	n	16	19
	Mean ± SD	2.6 ± 0.8	2.9 ± 1.1
	Min–Max	1.6 – 4.0	1.4 – 4.8

Table 49: Summary statistics for ITT population for the variable FVC

FVC(L)		Formopen®	Foradil®
Screening visit	n	23	19
	Mean ± SD	3.3 ± 1.1	3.8 ± 1.6
	min–max	1.7 – 5.9	1.5 – 6.6
Baseline visit	n	22	19
	Mean ± SD	3.4 ± 1.1	3.8 ± 1.4
	min–max	1.8 – 5.7	1.5 – 6.1
1st FU visit	n	19	19
	Mean ± SD	3.6 ± 1.1	4.1 ± 1.7
	Min–Max	2.1 – 5.9	1.6 – 7.5
2nd FU visit	n	16	17
	Mean ± SD	3.6 ± 1.2	4.0 ± 1.5
	Min–Max	2.0 – 5.8	1.5 – 6.7
3rd FU visit	n	15	17
	Mean ± SD	3.8 ± 1.3	3.9 ± 1.6
	Min–Max	2.0 – 6.6	1.6 – 6.1
End of study	n	16	19
	Mean ± SD	5.6 ± 7.5	4.0 ± 1.5
	Min–Max	2.0 – 33.3	1.6 – 6.4

Table 50: Summary statistics for ITT population for the variable FEV_1 % Predicted

FEV_1 % Predicted *(L)*		Formopen®	Foradil®
Screening visit	n	23	19
	Mean ± SD	76.7 ± 10.9	72.4 ± 8.8
	min–max	60.0 – 102.0	60.0 – 90.0
Baseline visit	n	22	19
	Mean ± SD	78.5 ± 10.1	77.6 ± 11.9
	min–max	63.0 – 104.4	55.6 – 98.5
1st FU visit	n	19	19
	Mean ± SD	84.4 ± 14.2	83.6 ± 14.8
	Min–Max	61.0 – 112.0	60.9 – 118.7
2nd FU visit	n	16	17
	Mean ± SD	82.2 ± 15.7	84.0 ± 12.8
	Min–Max	61.0 – 115.0	61.0 – 104.5
3rd FU visit	n	15	17
	Mean ± SD	83.3 ± 12.4	84.4 ± 11.8
	Min–Max	64.0 – 110.0	60.1 – 106.0
End of study	n	16	19
	Mean ± SD	83.6 ± 11.9	84.0 ± 11.3
	Min–Max	69.0 – 105.0	65.2 – 100.4

Table 51: Summary statistics for ITT population for the variables FEV1/FVC

FEV_1/FVC		**Formopen®**	**Foradil®**
Screening visit	n	23	19
	Mean ± SD	70.1 ± 9.5	2.4 ± 0.8
	min–max	53.3 – 88.3	1.3 – 3.8
Baseline visit	n	22	19
	Mean ± SD	70.8 ± 8.1	71.4 ± 9.8
	min–max	59.0 – 84.9	55.6 – 93.9
1st FU visit	n	19	19
	Mean ± SD	71.6 ± 9.0	71.3 ± 9.8
	Min–Max	52.2 – 89.0	52.6 – 89.4
2nd FU visit	n	16	17
	Mean ± SD	70.9 ± 9.6	72.8 ± 9.2
	Min–Max	55.1 – 88.0	57.9 – 93.2
3rd FU visit	n	15	17
	Mean ± SD	70.8 ± 9.8	73.0 ± 8.8
	Min–Max	55.0 – 87.0	56.0 – 91.0
End of study	n	16	19
	Mean ± SD	71.6 ± 8.5	72.6 ± 8.2
	Min–Max	55.1 – 88.0	60.9 – 91.0

Table 52: Summary statistics for ITT population for the variable FEF_{25}%

FEF_{25}%*(lt/min)*		**Formopen®**	**Foradil®**
Screening visit	n	22	19
	Mean ± SD	3.8 ± 1.51	6.0 ± 8.12
	min–max	0.9 – 5.6	1.8 – 39.2
Baseline visit	n	22	19
	Mean ± SD	3.7 ± 1.32	4.9 ± 2.19
	min–max	0.5 – 6.3	1.5 – 10.7
1st FU visit	n	19	19
	Mean ± SD	4.5 ± 1.55	5.4 ± 2.18
	Min–Max	2.0 – 8.0	1.4 – 9.8
2nd FU visit	n	16	17
	Mean ± SD	4.5 ± 1.83	5.2 ± 1.68
	Min–Max	1.8 – 7.6	1.7 – 8.0
3rd FU visit	n	15	17
	Mean ± SD	4.5 ± 1.75	5.1 ± 1.65
	Min–Max	2.1 – 7.8	1.9 – 7.9
End of study	n	16	19
	Mean ± SD	4.9 ± 1.85	5.3 ± 1.70
	Min–Max	2.2 – 7.9	1.8 – 8.0

Table 53: Summary statistics for ITT population for the variable $FEF_{25–75\%}$

$FEF_{25–75\%}$*(lt/min)*		**Formopen®**	**Foradil®**
Screening visit	n	22	19
	Mean ± SD	2.1 ± 1.89	1.9 ± 1.49
	min–max	0.7 – 9.6	0.74 – 7.5
Baseline visit	n	22	19
	Mean ± SD	2.0 ± 1.75	2.0 ± 1.03
	min–max	0.9 – 9.5	0.4 – 4.5
1st FU visit	n	19	19
	Mean ± SD	1.8 ± 0.93	2.2 ± 1.03
	Min–Max	0.8 – 4.7	0.4 – 4.4
2nd FU visit	n	16	17
	Mean ± SD	1.9 ± 1.04	2.2 ± 0.90
	Min–Max	0.8 – 4.6	0.4 – 3.7
3rd FU visit	n	15	17
	Mean ± SD	1.9 ± 0.85	2.2 ± 0.86
	Min–Max	0.8 – 4.1	0.5 – 3.5
End of study	n	16	19
	Mean ± SD	1.9 ± 0.91	2.1 ± 0.90
	Min–Max	0.9 – 4.1	0.6 – 4.1

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 54: Table of adverse events

Patient No	Treatment	Age (years)	Sex	BMI (k/m^2)	Adverse Event Term	Preferred Term Class	Duration	Severity	Serious AE	Action Taken	Relationship to Study Drug	Outcome
10002	Foradil®	62.9	Female	31.14	Headache	Headache	12/1/2009 12/1/2009	Moderate	No	None	Not Related	Recovered
10002	Foradil®	62.1	Female	31.15	Infection Of Upper Respiratory Tract	Upper Respiratory Tract Infection	24/1/2009 29/1/2009	Mild	No	None	Not Related	Recovered
10407	Foradil®	36.5	Male	26.0	Infection Of Upper Respiratory Tract	Upper Respiratory Tract Infection	18/1/2009 28/1/2009	Mild	No	None	Not Related	Recovered
10411	Formopen®	50.1	Male	37.1	Tachycardia	Tachycardia	12/3/2009 12/3/2009	Mild	No	None	Not Related	Recovered
10417	Formopen®	26.7	Female	29.3	Dyspnoea	Dyspnoea	23/10/2009 23/10/2009	Mild	No	None	Not Related	Recovered
10503	Foradil®	50.5	Female	37.8	Respiratory Infection	Respiratory Tract Infection	29/10/2008 7/11/2008	Mild	No	None	Not Related	Recovered
10504	Formopen®	62.9	Female	33.7	Respiratory Infection	Respiratory Tract Infection	6/11/2008 18/11/2008	Moderate	No	None	Not Related	Recovered
10508	Formopen®	24.4	Female	23.5	High Levels Of Glucose	Blood Glucose Increased	22/12/2008 9/2/2009	Mild	No	None	Related	Recovered
10511	Formopen®	52.1	Female	30.4	Shortness Of Breath	Dyspnoea	31/1/2009 5/2/2009	Moderate	No	Study Drug Withdrawn	Related	Recovered
10701	Formopen®	37.9	Female	30.4	Infection	Infection	30/10/2008 8/11/2008	Mild	No	Study Drug Withdrawn	Not Related	Recovered
10701	Formopen®	37.9	Female	30.4	Asthma Exacerbation	Asthma	1/11/2008 8/11/2008	Moderate	No	Study Drug Withdrawn	Not Related	Recovered

14.3.2 Abnormal Laboratory Value Listing (Each Patient)

Table 55: Individual patient haematological data with abnormal values

Treatment	Patient no	Visit	Hb	Ht	RBC	WBC	PLT	NEU	LY	MO	EO	BA
Formopen®	10511	Screening	**11.6**	38.8	4430000	7360	361	57	36	6	1	0
		Final	–	–	–	–	–	–	–	–	–	–
Foradil®	10002	Screening	12.2	40.2	4650000	9770	196	58	32	6	4	.
		Final	12.4	38.9	4770000	8820	**120**	64	25	5	6	0
Formopen®	10003	Screening	14.4	42.8	4510000	7500	300	**73**	21	5	1	0
		Final	14.3	42.1	4360000	6450	157	66	24	8	2	0
Foradil®	10004	Screening	12.8	38.9	4530000	6760	140	65	26	8	1	0
		Final	13.4	40.7	4720000	7150	140	**71**	20	7	1	1
Foradil®	10101	Screening	–	–	–	–	–	–	–	–	–	–
		Final	16.9	49.8	5260000	**3830**	180	58	34	6	2	0
Formopen®	10106	Screening	15.4	44.0	5040000	**3800**	244	43	45	6	5	1
		Final	16.0	45.5	5140000	5370	300	56	31	5	**8**	0
Formopen®	10108	Screening	13.8	40.8	4640000	5520	305	41	43	8	7	1
		Final	–	–	–	–	–	–	–	–	–	–
Foradil®	10109	Screening	14.1	44.0	5250000	**10020**	316	–	–	–	–	–
		Final	12.6	38.6	4640000	9930	307	–	–	–	–	–
Foradil®	10112	Screening	14.0	42.1	4580000	4260	250	**10**	–	–	–	–
		Final	–	–	–	–	–	–	–	–	–	–
Formopen®	10121	Screening	12.4	38.2	**6380000**	5730	422	56	27	6	**11**	.
		Final	–	–	–	–	–	–	–	–	–	–
Foradil®	10404	Screening	**13.9**	40.6	4390000	5000	200	55	37	5	3	0
		Final	**13.4**	41.1	5040000	**10230**	**480**	53	32	7	**8**	0
Formopen®	10405	Screening	13.6	41.5	5030000	6960	400	50	36	6	**8**	0
		Final	13.4	41.1	5040000	**10230**	**480**	53	32	7	**8**	0
Foradil®	10407	Screening	15.5	47.3	5330000	7050	192	**71**	22	6	1	0
		Final	14.9	46.4	5110000	6480	203	**75**	19	6	0	0
Foradil®	10408	Screening	16.5	**57.2**	5550000	4840	208	56	37	4	3	0
		Final	15.6	50.8	5400000	4610	140	55	32	6	6	1
Formopen®	10409	Screening	12.9	43.0	4620000	9400	303	68	26	5	1	0
		Final	14.1	43.1	4850000	**15410**	316	67	27	5	1	0
Formopen®	10411	Screening	15.7	**52.7**	5240000	4290	148	**39**	**52**	7	2	0
		Final	–	–	–	–	–	–	–	–	–	–
Formopen®	10414	Screening	**11.9**	**36.5**	6150000	5640	304	42	37	7	**13**	1
		Final	**12.0**	**38.4**	5070000	5810	215	41	42	9	**8**	.
Foradil®	10415	Screening	15.5	**55.4**	5620000	**3760**	**750**	65	27	5	2	1
		Final	–	–	–	–	–	–	–	–	–	–
Formopen®	10416	Screening	**11.8**	**34.5**	5890000	6290	161	–	–	–	–	–
		Final	–	–	–	–	–	–	–	–	–	–
Formopen®	10417	Screening	14.3	44.7	5030000	7650	–	65	27	5	3	0
		Final	13.4	**47.7**	4610000	8270	–	65	29	5	1	0
Formopen®	10505	Screening	**13.1**	40.4	4770000	5100	252	**99**	**99**	**99**	**99**	**99**
		Final	**13.0**	42.3	4510000	**3560**	217	63	26	4	7	.
Foradil®	10507	Screening	**13.6**	46.3	**6700000**	8560	312	63	29	5	3	0
		Final	**13.0**	42.6	6260000	8070	320	66	25	5	4	0
Foradil®	10513	Screening	15.1	46.8	5070000	4310	254	51	37	6	6	0
		Final	14.2	43.1	4950000	**3150**	264	**29**	48	**18**	5	0
Formopen®	10701	Screening	13.5	**47.2**	5210000	**3300**	197	40	47	8	5	0
		Final	–	–	–	–	–	–	–	–	–	–

Table 56: Individual patient biochemical data with abnormal values*

Treatment	Patient no	Visit	Glucose	Potassium	Sodium	Creatinine	Urea	ALAT	ASAT	ALP	γ–gt	Uric Acid	Bilirubin
Foradil®	10002	Screening	86	4.5	145	0.6	39	19	27	76	10	5.6	0.1
		1st Fu	**122**	**0.4**	–	–	–	–	–	–	–	–	–
		2nd Fu	**122**	4.0	–	–	–	–	–	–	–	–	–
		3rd Fu	118	5.0	–	–	–	–	–	–	–	–	–
		Final	**135**	4.7	144	0.6	38	19	20	71	13	**7.6**	0.1
Formopen®	10003	Screening	**135**	4.0	140	1.0	**63**	19	14	48	17	**7.4**	0.2
		Final	87	4.6	139	1.0	42	14	15	42	13	6.1	0.1
Foradil®	10101	Screening	85	4.1	141	1.0	29	22	19	47	27	6.5	0.3
		Final	93	4.7	140	1.1	44	**44**	29	46	28	6.3	0.3
Formopen®	10104	Screening	96	4.4	136	0.6	35	25	21	60	19	4.3	0.1
		1st Fu	92	4.6	–	–	–	–	–	–	–	–	–
		2nd Fu	90	**5.5**	–	–	–	–	–	–	–	–	–
		Final	96	4.9	142	**1.3**	**57**	34	35	42	24	5.6	0.1
Formopen®	10106	Screening	81	4.1	140	**0.6**	24	**46**	**56**	70	20	5.2	0.3
		1st Fu	75	**5.5**	–	–	–	–	–	–	–	–	–
		Final	98	4.5	139	0.7	20	20	**47**	76	12	5.5	–
Formopen®	10108	Screening	83	4.8	**135**	0.6	30	15	22	54	16	4.5	0.1
Foradil®	10109	Screening	111	4.6	138	0.7	20	16	19	90	10	5.7	0.1
		Final	**129**	4.9	139	0.7	22	12	14	81	8	5.1	0.1
Formopen®	10110	Screening	78	5.1	138	0.7	35	10	19	**28**	8	3.7	0.1
		Final	63	4.5	139	0.8	31	11	17	**24**	7	3.8	0.1
Foradil®	10113	Screening	110	4.2	139	1.0	35	**82**	34	133	**60**	5.4	0.3
Foradil®	10116	Screening	83	4.7	141	0.7	39	12	22	60	16	5.1	0.1
		2nd Fu	70	**5.4**	–	–	–	–	–	–	–	–	–
		Final	93	4.4	140	0.9	36	15	21	88	18	5.2	0.7
Formopen®	10119	Screening	109	4.6	143	0.6	29	**41**	21	53	20	3.8	0.1
Foradil®	10404	Screening	104	3.9	142	0.9	31	11	16	49	11	5.1	0.4
		1st Fu	76	**9.5**	–	–	–	–	–	–	–	–	–
		2nd Fu	103	4.6	–	–	–	–	–	–	–	–	–
		3rd Fu	93	**7.3**	–	–	–	–	–	–	–	–	–
		Final	91	4.1	138	**0.7**	20	13	7	51	14	**2.8**	0.1
Formopen®	10405	Screening	98	4.8	139	0.7	19	**44**	13	48	23	3.2	0.1
		Final	91	4.1	138	0.7	20	13	7	51	14	2.8	0.1
Formopen®	10406	Screening	86	5.0	139	1.0	39	36	25	59	25	5.4	0.1
		1st Fu	89	4.4	–	–	–	–	–	–	–	–	–
		2nd Fu	61	**6.2**	–	–	–	–	–	–	–	–	–
Foradil®	10407	Screening	67	11.0	**133**	1.1	36	38	34	73	12	5.5	0.3
		2nd Fu	96	**7.8**	–	–	–	–	–	–	–	–	–
		3rd Fu	92	4.5	–	–	–	–	–	–	–	–	–
		Final	86	5.1	139	1.0	38	**45**	23	59	25	5.0	0.1
Foradil®	10408	Screening	50	4.8	142	1.0	36	24	21	49	15	5.9	0.4
		Final	77	5.1	139	0.9	24	25	19	44	**44**	5.9	0.2
Formopen®	10409	Screening	74	**7.0**	139	0.6	39	19	15	68	37	3.3	0.2
		1st Fu	79	**6.1**	–	–	–	–	–	–	–	–	–
		2nd Fu	82	4.6	–	–	–	–	–	–	–	–	–
		Final	87	**5.9**	141	0.7	**73**	19	16	66	35	3.1	0.1
Formopen®	10413	2nd Fu	98	**6.0**	–	–	–	–	–	–	–	–	–
		3rd Fu	**3**	**28.2**	–	–	–	–	–	–	–	–	–
		Final	94	4.6	137	1.2	39	13	10	39	7	3.8	0.1
Formopen®	10414	Screening	95	4.2	–	–	–	–	–	–	–	–	–
		1st Fu	85	4.2	–	–	–	–	–	–	–	–	–

Treatment	Patient no	Visit	Glucose	Potassium	Sodium	Creatinine	Urea	ALAT	ASAT	ALP	γ–gt	Uric Acid	Bilirubin
		2nd Fu	95	**6.8**	–	–	–	–	–	–	–	–	–
		3rd Fu	78	**5.4**	–	–	–	–	–	–	–	–	–
		Final	88	**6.2**	141	0.9	44	29	24	36	22	5.6	0.1
Foradil®	10415	Screening	.	43.2	**100**	1.2	**64**	34	**83**	92	11	5.3	.
		1st Fu	62	**7.1**	–	–	–	–	–	–	–	–	–
		2nd Fu	66	**5.5**	–	–	–	–	–	–	–	–	–
		Final	86	4.4	140	0.9	38	27	22	88	13	**6.7**	0.1
Formopen®	10416	Screening	12	–	–	–	–	–	–	–	–	–	–
		1st Fu	91	5.2	–	–	–	–	–	–	–	–	–
		2nd Fu	76	4.7	–	–	–	–	–	–	–	–	–
		3rd Fu	70	**5.4**	–	–	–	–	–	–	–	–	–
		Final	63	4.2	142	1.1	39	16	18	61	12	5.2	0.2
Formopen®	10417	Screening	79	**8.8**	139	0.8	35	10	21	48	11	3.4	0.1
		Final	71	**7.6**	137	0.7	24	7	14	47	9	3.0	0.1
Foradil®	10503	Screening	102	5.0	144	0.9	32	**69**	**58**	69	26	5.4	0.1
		Final	99	4.5	140	0.8	25	**46**	31	72	23	5.4	0.1
Formopen®	10504	Screening	90	4.5	141	0.6	37	17	23	63	14	2.7	0.2
		Final	108	4.8	137	0.6	43	16	20	58	13	**2.3**	0.1
Formopen®	10505	Screening	87	4.5	140	0.6	32	15	17	49	10	**3.4**	0.6
		Final	90	4.2	141	0.6	24	9	13	46	9	**3.2**	0.1
Foradil®	10506	Screening	**126**	4.0	140	**0.5**	43	29	23	67	9	4.0	0.1
		Final	109	4.3	140	0.6	29	**36**	25	62	9	4.5	0.1
Foradil®	10507	Screening	82	4.3	138	0.8	25	32	16	67	29	6.5	0.4
		Final	96	4.5	140	0.8	37	**56**	24	66	**49**	6.9	0.3
Formopen®	10508	Screening	92	3.8	142	**0.5**	22	9	14	68	5	3.3	0.2
		1st Fu	**130**	3.8	–	–	–	–	–	–	–	–	–
		2nd Fu	113	4.3	–	–	–	–	–	–	–	–	–
		3rd Fu	**138**	4.2	–	–	–	–	–	–	–	–	–
		Final	78	3.8	140	0.6	26	13	15	64	7	3.0	0.2
Foradil®	10513	Screening	89	4.9	142	0.9	24	23	20	55	8	5.4	0.1
		Final	92	4.4	139	0.8	29	**67**	40	57	9	5.4	0.1
Formopen®	10701	Screening	75	4.6	141	0.6	28	**43**	30	59	16	4.4	0.1

*Visits with no (or missing) information for the laboratory parameters, were excluded from the table.

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16. APPENDICES

16.1 Study Information

16.1.1 Sample Case Report Form & Patients Diary Card

PATIENT DIARY CARD

PATIENT NUMBER: __ __ __ / __ __ __

TREATMENT PERIOD: From ___ / ___ / _____ to ___ / ___ / _____ (dd / mm / yyyy)

Day	_____		_____		_____		_____		_____		_____		_____	
Date (dd / mm)	__ __/__ __		__ __/__ __		__ __/__ __		__ __/__ __		__ __/__ __		__ __/__ __		__ __/__ __	
	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*
ASTHMA SYMPTOMS SCORE														

***Symptom Score**: 0=No symptoms, 1=Mild symptoms, don't affect normal activities, 2=Moderate symptoms, don't affect normal activities, 3=Severe symptoms that affect daily activities*

PEFR	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*
Measurement #1														
Measurement #2														
Measurement #3														
Asthma Medication	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*
FORADIL AEROLIZER *please tick [√]*														
FORMOPEN ELPEN*haler* *please tick [√]*														
INHALED														

CORTICOSTEROIDS *please write the **number** of puffs you inhaled*														
ICS active substance /dose _____														
SALBUTAMOL *please write the **number** of puffs you inhaled*														

***Abreviations:** morn:morning, evng: evening*

PATIENT DIARY CARD

PATIENT NUMBER: __ __ __ / __ __ __

TREATMENT PERIOD: From ___ / ___ / _____ to ___ / ___ / _____ (dd / mm / yyyy)

Day	_____		_____		_____		_____		_____		_____		_____	
Date (dd / mm)	__ __/__ __		__ __/__ __		__ __/__ __		__ __/__ __		__ __/__ __		__ __/__ __		__ __/__ __	
	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*
ASTHMA SYMPTOMS SCORE														

***Symptom Score**: 0=No symptoms, 1=Mild symptoms, don't affect normal activities, 2=Moderate symptoms, don't affect normal activities, 3=Severe symptoms that affect daily activities*

PEFR	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*
Measurement #1														
Measurement #2														

Measurement #3														
Asthma Medication	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*
FORADIL AEROLIZER *please tick [√]*														
FORMOPEN ELPENhaler *please tick [√]*														
INHALED CORTICOSTEROIDS *please write the **number** of puffs you inhaled*														
ICS active substance /dose _____														
SALBUTAMOL *please write the **number** of puffs you inhaled*														

***Abreviations:** morn:morning, evng: evening*

PATIENT DIARY CARD

PATIENT NUMBER: __ __ __ / __ __ __

TREATMENT PERIOD: From ___ / ___ / _____ to ___ / ___ / _____ (dd / mm / yyyy)

Day	_____		_____		_____		_____		_____		_____		_____	
Date (dd / mm)	__ __/__ __		__ __/__ __		__ __/__ __		__ __/__ __		__ __/__ __		__ __/__ __		__ __/__ __	
	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*
ASTHMA SYMPTOMS SCORE														

***Symptom Score**: 0=No symptoms, 1=Mild symptoms, don't affect normal activities, 2=Moderate symptoms, don't affect normal activities, 3=Severe symptoms that affect daily activities*

PEFR	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*
Measurement #1														
Measurement #2														
Measurement #3														

Asthma Medication	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*	morn*	evng*
FORADIL AEROLIZER *please tick [√]*														
FORMOPEN ELPENhaler *please tick [√]*														
INHALED CORTICOSTEROIDS *please write the **number** of puffs you inhaled*														
ICS active substance /dose _____														
SALBUTAMOL *please write the **number** of puffs you inhaled*														

***Abreviations:** morn:morning, evng: evening*

PATIENT DIARY CARD

User's Instructions

All fields in **light yellow** color should be filled by your **study physician** (i.e.: **patient number, treatment period, the first day & date of recordings** and **the ICS active substance and dose).**

General instructions:

You should record daily your asthma symptom score, PEFR measurements, use of study medication (use of study devices: Elpen*haler* and Aerolizer) and use of ICS and rescue medication. The first measurment will be performed at the same day when you will receive your first Diary Card and recorded in the corresponding fields of the first page. Sudsequently, you will continue to record daily measurements until your next scheduled visit. If necessery, recordings will be continued in the 3rd page too. The total number of days with recorded measurements, should **NOT** be over 17 (i.e. 14 days + 3).

At your next scheduled study visit, you should return to your study physician/nurse, your Diary Card with all the necessary information recorded properly, if possible, and receive a new one for the following 14 days of treatment. You will not be given a new Diary Card at your final study visit.

In case of a mistake, you **DO NOT** correct with an eraser/correction fluid. You should rather strike through the mistake and add the proper value in a clear and readable manner.

The Patient Diary Cards are Sponsor's property. If any Card is still in your hands after the termination of your participation in the study, you must return the Card immediately to your study physician/nurse.

Each study day is divided into 2 fields for morning (morn) and evening (evng) measurements according to the following instructions.You are kindly requested to perform and record all measurements in an accurate and consistent way. If by accident you miss a measurement or recording, please leave the corresponding field empty.

Symptoms Score:

You will record your day and night asthma symptom score twice daily, in the morning before using study medications and in the evening before using study medications. The morning score will refer to previous night asthma symptoms and the evening score to the asthma symptoms experienced by you during the day. The detailed asthma symptoms score climax can be found in **page 5** of the Diary Card.

PEFR measurements:

Morning and evening PEFR measurements will be performed by you, at home, with the use of Mini–Wright Peak Flow Meter. Each measurement should be done in triplicate and all of them should be recorded (i.e. Measurement #1, #2 & #3).

Morning PEFR should be measured **NOT** earlier than 10 hours after the previous evening dose of study medications and approximately 15 min before taking the morning dose of study medications. Evening PEFR should be measured just before taking the evening dose of study medications and at least 10 hours after the morning dose of study medications.

NOTICE: For the study purposes, it is vitaly important that you should accurately perform PEFR measurements according to the instructions.

PATIENT DIARY CARD

User's Instructions

All fields in **light yellow** color should be filled by your **study physician** (i.e.: **patient number, treatment period, the first day & date of recordings** and **the ICS active substance and dose).**

Asthma medication:

You should tick in the relevant fields the use of both Aerolizer and Elpenhaler devices, in the morning and in the evening. You should always first use Aerolizer (one inhalation) and after 1 minute Elpenhaler (one inhalation). You must record the **NUMBER** of puffs of your prescribed Inhaled Corticosteroid (ICS) that you have received on the day or night of the corresponding day. Additionaly, you must record the **NUMBER** of puffs of Salbutamol that you have received as a reliever on the day or night of the corresponding day. If you haven't used an ICS and/or Salbutamol, you should write zero **[0]** at the appropriate box.

Day asthma symptoms score	Night asthma symptoms score
0 No symptoms during the day 1 Mild symptoms during the day that did not affect the daily activities 2 Moderate symptoms during the day that did not affect daily activities 3 Severe symptoms during the day that affect normal daily activity	0 No symptoms during the night 1 Mild symptoms that woke you up once during the night 2 Moderate symptoms that woke you up twice or more during the night 3 Severe symptoms that kept you awake for most of the night

NOTICE: If you have any questions regarding this Patient Diary Card, please refer to your study physician/nurse.

16.1.2 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority)–Representative written information for patient and sample consent forms

National Organisation for Medicines approval

Date		Chairman
30 November 2007	Initial approval of the study	Dr. Miranta Siouti
4 March 2009	Addition of Tatsis study site approval	
12 May 2009	Removal of Kosmas study site approval/ Removal of Tsoukalas study site approval	
16 April 2010	Notification of study termination	

National Ethics committee approval

Date		Chairman
3 June 2008	Initial approval of the study	Prof. Ioannis Papadimitriou
17 February 2009	Addition of Tatsis study site approval	
13 May 2009	Removal of Kosmas study site approval/ Removal of Tsoukalas study site approval	
16 April 2010	Notification of study termination	

Institutional review board approvals

Date		Chairman
22 October 2007 (initial approval)	Athens General Hospital for Thoracic Diseases “Sotiria”, Athens	Dr Micahail Toumpis
28 September 2007 (initial approval)	University General Hospital of Larisa, Larisa	Prof. Ioannis Fezoulidis
9 November 2007 (approval of protocol first amendment)	University General Hospital of Larisa, Larisa	Prof. Ioannis Fezoulidis
22 September 2007 (initial approval)	University General Hospital of Heraklion, Crete	Prof. Maria Kalmanti
25 October 2007 (initial approval)	Thessaloniki General Hospital “G. Papanikolaou”, Thessaloniki	Dr. Nikolaos Kitis
26 November 2008 (initial approval)	Athens General Hospital “Evaggelismos”, Athens	Dr. Georgios Tatsis

16.1.3 Sample Patient information sheet & Informed consent form

PATIENT INFORMATION SHEET

Title of the study:	An 8 week multicenter, randomized, double–blind, double–dummy, parallel group, therapeutic equivalence study of Formoterol (Formopen®) administered with the Elpen*haler*® versus the innovative Formoterol (Foradil®) administered with the Aerolizer®, in patients with mild to moderate asthma.
Study Code No:	***2007–FOR–EL–02***
Study Sponsor:	***Elpen Pharmaceuticals Co. Inc.***
Principal Investigator:	
Patient's Name:	

16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

PRINCIPAL INVESTIGATORS	CLINIC/SITE
Dr. Birba Georgia	2nd Pulmonary Clinic of "Sotiria" General Chest Disease Hospital, Athens
Dr. Gaga Mina	Asthma Clinic of "Sotiria" General Chest Disease Hospital, Athens
Dr. Gourgoulianis Konstantinos	University Pulmonary Clinic of University General Hospital, Larisa
Dr. Koulouris Nikolaos	1st University Pulmonary Clinic of General Chest Disease Hospital, Athens
Dr. Siafakas Nikolaos	University Pulmonary Clinic of PEPAGNI Hospital, Heraklion
Dr. Galanis Nikolaos	A' Pulmonary Clinic of "G.Papanikolaou" General Hospital, Thessaloniki
Dr. Tatsis Georgios	Pulmonology Clinic of "Evaggelismos" General Hospital, Athens

CO–INVESTIGATORS	CLINIC/SITE
Dr. Lamprakis Charilaos	2nd Pulmonary Clinic of "Sotiria" General Chest Disease Hospital, Athens
Dr. Kainis Elias Dr. Petrochilou Kalomira Dr. Moraitou Eleni Dr. Grigoratou Teo Dr. Zervas Elias Dr. Economidou Erasmia	Asthma Clinic of "Sotiria" General Chest Disease Hospital, Athens
Dr. Kostikas Konstantinos Dr. Daenas Christos Dr. Tsaroucha Agori Dr. Minas Markos Dr. Tagtalianidou Elli Dr. Theologi Vassiliki Dr. Karetsi Eleni	University Pulmonary Clinic of University General Hospital, Larisa
Dr. Palamidas Anastasios	1st University Pulmonary Clinic of General Chest Disease Hospital, Athens
Dr. Belladaki Kalliopi Dr. Stamataki Evangelia	University Pulmonary Clinic of PEPAGNI Hospital, Heraklion
Dr. Tryfon Stavros	A' Pulmonary Clinic of "G.Papanikolaou" General Hospital, Thessaloniki
Dr. Lazarou Vassiliki	Pulmonology Clinic of "Evaggelismos" General Hospital, Athens

Brief CVs of the above listed personnel, involved in the present study are presented in the following pages, as per site.

Site 100:

2nd Pulmonary Clinic of "Sotiria" General Chest Disease Hospital, Athens

Site 101:

Asthma Clinic of "Sotiria" General Chest Disease Hospital, Athens

Site 102:

University Pulmonary Clinic of University General Hospital, Larisa

Site 104:

1st University Pulmonary Clinic of General Chest Disease Hospital, Athens

Site 105:

University Pulmonary Clinic of PEPAGNI Hospital, Heraklion

Site 107:

A΄ Pulmonary Clinic of "G.Papanikolaou" General Hospital, Thessaloniki

Site 108:

Pulmonology Clinic of "Evaggelismos" General Hospital, Athens

16.1.5 Signatures of sponsor's responsible medical officer and clinical trial report authors

Sponsor's Responsible Medical Officer

STUDY TITLE: An 8 week multicenter, randomized, double–blind, double–dummy, parallel group, therapeutic equivalence study of Formoterol (Formopen®) administered with the Elpen*haler*® versus the innovative Formoterol (Foradil®) administered with the Aerolizer®, in patients with mild to moderate asthma.

STUDY REPORT AUTHORS:

Eumorphia M. Delicha, Data & Biostatistics Manager, Zeincro Hellas SA

Ioannis Elmatzoglou, Biostatistician, Zeincro Hellas SA

Tereza Vogiatzi PhD, Medical Advisor , Zeincro Hellas SA

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

Signature: _____

Date: _____

Katerina Athanasiou,

Clinical Trials Director

Pharmacist, PhD

Clinical Trials Director

ELPEN Pharmaceutical Co, Inc

21st km, Marathonos Ave.,

Athens, Greece

Signature: _____

16.1.6 Listing of patients receiving test drug from specific batches, where more than one batch was used

N/A

16.1.7 Randomisation scheme and codes (patient identification and treatment assigned)

All eligible patients included in the trial were randomized to either test or reference, drug, as dictated by the randomization list generated by the PROC PLAN in SAS® V9.1.3 and executed by Zeincro's personnel.

The method followed for the allocation of a treatment to each patient was equal randomization in random permuted blocks of four. Specifically, all possible combinations for allocating two treatments, A and B, in a sequence of four were considered (1:1 allocation). In total, there were six permutated blocks: AABB, BBAA, ABBA, BAAB, ABAB BABA. A number from 1 to 6 was assigned in each of the 6 blocks and a random sequence of numbers from 1 to 6 was generated. Each patient was assigned with either treatment A or B, according to the produced sequence. The randomization list was numbered starting from the number "R501" in ascending order.

The randomized treatment allocation sequence was sent to the Sponsor and it was Sponsor's responsibility to label A and B to Test or Reference, see following Table (Table 57).

The CRO's personnel including the Trial Biostatistician was blind with respect to treatment allocation until the database lock. The Master Randomization List was kept by the Sponsor.

Table 57: Treatment assigned to each patient

Site Number	Randomization Number	Therapy Group	Treatment
10002	R–527	B	Foradil
10003	R–525	A	Formopen
10004	R–526	B	Foradil
10101	R–521	B	Foradil
10104	R–522	A	Formopen
10106	R–523	A	Formopen
10108	R–553	A	Formopen
10109	R–524	B	Foradil
10110	R–554	A	Formopen
10111	R–555	B	Foradil
10112	R–556	B	Foradil
10113	R–557	B	Foradil
10116	R–545	B	Foradil
10117	R–546	A	Formopen
10118	R–547	B	Foradil
10119	R–548	A	Formopen
10120	R–558	A	Formopen
10121	R–559	A	Formopen
10201	R–509	A	Formopen
10404	R–501	B	Foradil
10405	R–502	A	Formopen
10406	R–503	A	Formopen
10407	R–504	B	Foradil
10408	R–538	B	Foradil
10409	R–537	A	Formopen
10410	R–539	B	Foradil
10411	R–540	A	Formopen
10412	R–551	B	Foradil

Site Number	Randomization Number	Therapy Group	Treatment
10413	R–549	A	Formopen
10414	R–550	A	Formopen
10415	R–552	B	Foradil
10416	R–505	A	Formopen
10417	R–506	A	Formopen
10503	R–513	B	Foradil
10504	R–514	A	Formopen
10505	R–515	A	Formopen
10506	R–516	B	Foradil
10507	R–533	B	Foradil
10508	R–534	A	Formopen
10511	R–535	A	Formopen
10513	R–536	B	Foradil
10701	R–517	A	Formopen

16.1.8 Audit certificates

N/A, no external or internal audits were performed during the study.

16.1.9 Documentation of inter–laboratory standardisation methods and quality assurance procedures

16.1.10 Publications based on the study

Not applicable, no publications of any kind were presented based in the entity of a subset of results from the present study.

16.2 Patient Data Listings

16.2.1 Discontinued patients

Table 58: Listing of patients who discontinued therapy

Treatment	Patient No	Sex	Age	Last visit	Dose	Concomitant medication	Reason for Discontinuation
Formopen®	10108	F	44	2nd FU	12 µg	Budesonide Salbutamol	Protocol violation
Formopen®	10117	F	46	Baseline	12 µg	Fluticasone Salbutamol	Consent withdrawn
Formopen®	10119	F	54	2nd FU	12 µg	Fluticasone Salbutamol	Protocol violation
Formopen®	10120	F	44	1st FU	12 µg	Budesonide Salbutamol	Protocol violation
Formopen®	10201	F	69	Baseline	12 µg	–	Protocol violation

Treatment	Patient No	Sex	Age	Last visit	Dose	Concomitant medication	Reason for Discontinuation
Formopen®	10405	F	31	Baseline	12 µg	Fluticapen Aerolin	Protocol violation
Formopen®	10511	F	52	1st FU	12 µg	Pulmicort Aerolin Symbicort Vascase Ideos Actonel	Lost to FU
Formopen®	10701	F	38	Baseline	12 µg	Bleclomethasone HFA Salbutamol	Protocol violation
Foradil®	10408	M	26	2nd FU	12 µg	Fluticapen Aerolin	Protocol violation
Foradil®	10410	M	64	2nd FU	12 µg	Fluticason Vastarel Fysiotens Aerolin	Protocol violation

16.2.2 Protocol deviations

Table 59: Listing of patients and observations excluded from efficacy analysis due to violation of protocol criteria

Treatment	atient no	Sex	Age	Observation Excluded	Reasons	
					Violation	Protocol Criteria Violated
Formopen®	10108	F	44	All observations	1) 104.4% 2) 17.5%	1)FEV1>60% and FEV1 ≤90% of the predicted normal FEV1 2)FEV1 Visit 2 > FEV1 Visit 1 (by +/– 15%)
Formopen®	10119	F	54	All observations	21.37%	FEV1 Visit 2 > FEV1 Visit 1 (by +/ – 15%)
Formopen®	10120	F	44	All observations	19.68%	FEV1 Visit 2 > FEV1 Visit 1 (by +/ – 15%)
Formopen®	10201	F	69	All observations	Age: 68 years	Male or female subjects aged from 18 to 65 years old
Formopen®	10405	F	31	All observations	42 days between Baseline and 1st FU	Patient should arrive 14 (+3) days after previous Visit
Formopen®	10701	F	38	All observations	1.01%	FEV1 increase in FEV1≥12%
Foradil®	10101	M	31	All observations	90.40%	FEV1>60% and FEV1 ≤90% of the predicted normal FEV1
Foradil®	10113	M	21	All observations	23.80%	FEV1 Visit 2 > FEV1 Visit 1 (by +/– 15%)
Foradil®	10407	M	36	All observations	17.21%	FEV1 Visit 2 > FEV1 Visit 1 (by +/– 15%)
Foradil®	10408	M	26	All observations	33.00%	FEV1 Visit 2 > FEV1 Visit 1 (by +/– 15%)
Foradil®	10410	M	64	All observations	93.00%	FEV1>60% and FEV1 ≤90% of the predicted normal FEV1
Foradil®	10503	F	51	All observations	17.90%	FEV1 Visit 2 > FEV1 Visit 1 (by +/– 15%)
Foradil®	10506	F	63	All observations	15.30%	FEV1 Visit 2 > FEV1 Visit 1 (by +/– 15%)
Foradil®	10118*	F	63	None*	15.67%	FEV1 Visit 2 > FEV1 Visit 1 (by +/– 15%)

*Patient approved by Sponsor

16.2.3 Patients excluded from the efficacy analysis

N/A

16.2.4 Demographic data and baseline asthma characteristics

Table 60: Demographic data

Table 61: Baseline asthma characteristics

16.2.5 Individual efficacy response data

Table 62: Individual efficacy response data

16.2.6 Adverse event listing by patient

Table 63: Adverse Events reported during the trial

16.2.7 Listing of individual safety measurements

Table 64: Biochemistry Data Listing

Table 65: Individual Haematological Data Listing

Table 66: Vital signs Data Listing

Table 67: Individual 12-ECG Data Listing

Table 68: Daily Inhaledled corticosteroids & Salbutamol Data Listing

End of the Report

2007–FOR–EL–02