EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2013
EMA/465765/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Labazenit

International non-proprietary names: **budesonide/salmeterol**

Procedure No. **EMEA/H/C/002201/0000**

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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List of abbreviations

ACTH	Adrenocorticotropic hormone
ALP	Alkaline phosphatase
ALT	Alanine transaminase
API	Active product ingredient
ASM	Active substance manufacturer
ATP	Adenosine triphosphate
AUC	Area under the curve
cAMP	Cyclic adenosine monophosphate
BUSAL	Name used for Labazenit during development
CEP	Certificate of Suitability to the European Pharmacopoeia
C_{max}	Maximal concentration
COPD	Chronic Obstructive Pulmonary Disease
CYP	Cytochrome P450
DP	Drug Product
DPI	Dry powder inhaler
EC	European Communities
ECG	ElectroCardiogram
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FDC	Fixed dose combination
FEV1	Forced expiratory volume in one second
FPD	Fine particle dose
FVC	Forced volume capacity
GC	Gas Chromatography
GCP	Good clinical practice
GGT	Gamma glutamyl transferase
GINA	Global Initiative for Asthma
GLP	Good laboratory practice
GMP	Good manufacturing practice
GR	Glucocorticoid receptor
GS	Stimulating guanine-nucleotide–binding protein
HDPE	High density polyethylene

HPLC	High pressure liquid chromatography
ICS	Inhalation corticosteroid
IR	Infrared spectroscopy
LABA	Long acting beta agonist
LC	Liquid chromatography
LD50	Dose which is lethal for 50% of the population
LDPP	Low density polypropylene
MAA	Marketing authorisation application
MLI	Multi-stage liquid impinger
NGI	Next Generation Impactor
PEF	Peak expiratory flow
PFT	Pulmonary function test
Ph. Eur.	European Pharmacopoeia
PIF	Peak inspiratory flow
PK	Pharmacokinetics
p.o.	Oral
PP	Polypropylene
RH	Relative Humidity
SD	Standard deviation
SmPC	Summary of Product Characteristics
T_{max}	Time at maximal concentration
TEAE	Treatment emergent adverse event
UDD	Uniformity of delivered dose
uHPLC	Ultra High Performance Liquid Chromatography
Vd	Volume of distribution
WBC	White blood cells

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant Laboratoires SMB s.a. submitted on 28 September 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Labazenit, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the CHMP on 29 September 2008

The Applicant applied for the following indications:

Labazenit is indicated in the regular treatment of asthma in adults where use of a combination product (inhaled corticosteroid and long-acting β2-agonist) is appropriate:

- Patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting β2-agonists.

or

- Patients already adequately controlled on both inhaled corticosteroids and long-acting β2-agonists.

The legal basis for this application refers to Article 10(b) of Directive 2001/83/EC - fixed combination application.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P047/2010 on 31 March 2010 the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice / Protocol Assistance

The applicant received Scientific Advice from the CHMP on 21 January 2010. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

SMB Technology S.A.
Rue du Parc Industriel, 39
B-6900 Marche en Famenne
Belgium

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Barbara van Zwieten-Boot Co-Rapporteur: David Lyons

- The application was received by the EMA on 28 September 2011.
- The procedure started on 19 October 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 January 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 6 January 2012.
- During the meeting on 13-16 February 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 16 February 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 August 2012.
- The summary report of the GCP inspection of studies SMB-BUSAL-SS071 and SMB-BUSAL-III-02-1 carried out at the following sites: ATC, 033, SGS and KCR between 17 April 2012 and 31 May 2012 was issued on 10 July 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 01 October 2012.
- During the CHMP meeting on 15-18 October 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 January 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's written responses to the List of Outstanding Issues to all CHMP members on 7 February 2013.
- During the CHMP meeting on 20 February 2013, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 18-21 March 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Labazenit.
- The CHMP Assessment Report was finalised by written procedure on 4 April 2013.

1.4. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Harald Enzmann Co-Rapporteur: Piotr Fiedor

- The applicant submitted written notice to the EMA on 25 March 2013 to request a re-examination of Labazenit CHMP opinion of 27 June 2013.
- During its meeting on 25 April 2013, the CHMP appointed Harald Enzmann as Rapporteur and Piotr Fiedor as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 28 April 2013. The re-examination procedure started on 29 April 2013.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 28 May 2013. The Co Rapporteur's Assessment Report was circulated to all CHMP members on 28 May 2013.
- During a meeting of the Ad-hoc expert group on 11 June 2013, experts were convened to consider the grounds for re-examination.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 12 June 2013.
- During the CHMP meeting on 24 June 2013, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 27 June 2013, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation.

2. Scientific discussion

2.1. Introduction

Asthma is defined by the Global Initiative for Asthma (GINA) as a chronic inflammatory disorder of the airways; chronic inflammation causes an associated increase in airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night or in the early morning. The episodes are usually associated with widespread but variable airflow obstruction that is usually reversible, either spontaneously or with treatment.

The prevalence of atopy and asthma has increased steeply over the past few decades in western countries and more recently in less-developed nations. In Europe, the prevalence of clinical asthma ranges between 18.4% in Scotland and 4.9% in Scandinavia and the Baltic States. The natural history of the disease is characterised by periodic symptomatic exacerbations making additional treatment needed. In patients with a history of multiple exacerbations there is a risk of long-term progressive decline in lung function. For all these reasons, additional treatment options are desirable.

Labazenit is a new fixed combination medicinal product containing two known components, salmeterol xinafoate and budesonide. Salmeterol and budesonide have different modes of action. Corticosteroid therapy, principally inhaled glucocorticosteroid (ICS) (such as budesonide), is considered the most effective anti-inflammatory treatment and therefore the cornerstone treatment of asthma. In patients not adequately controlled by an ICS alone, the addition of a long-acting β_2-adrenergic agonists (LABA) (such as salmeterol) is preferred to reach clinical control, over increasing the dose of inhaled glucocorticosteroids (GINA recommendations). A fixed combination formulation, in which both components are pre-set, offers an advantage in comparison to the use of the drugs separately, since it improves patient adherence to treatment.

This fixed combination of two well-known, Ph Eur described, active substances, budesonide and salmeterol xinafoate, is formulated in a hard capsule as powder for inhalation in two strengths: budesonide 120 mcg and salmeterol (as the xinafoate) 20 mcg, budesonide 240 mcg and salmeterol (as the xinafoate) 20 mcg. It is the first fixed combination medicinal product of these two active substances. Both budesonide and salmeterol xinafoate are available as single, dry powder inhalation products, e.g. Pulmicort Turbohaler (100, 200, and 400 mcg) and Serevent powder for inhalation (50 mcg). The application is based on new clinical study results relating to this fixed combination. The maximum daily dose is 480 mcg budesonide and 40 mcg salmeterol.

It should be noted that the data submitted in the application dossier referred to Labazenit 150 µg/25 µg and 300 µg/25 µg as the finished medicinal product, which corresponds to the metered dose of both active substances. This was the basis used during the assessment of this application. However in accordance with the "Guideline on Summary of Product Characteristics (SmPC) and QRD Recommendations on the expression of strength in the name of Centrally Authorised Human Medicinal Products" (as stated in Section 1 of the SmPC and in the name section of the Labelling and Package Leaflet), the CHMP agreed that the strength should refer to the delivered dose of both active substances and therefore the name of the medicinal product finally approved by the Committee was expressed as follows: Labazenit 240 µg/20 µg and 120 µg/20 µg, in all official approved documents (CHMP opinion/future EC decision and CHMP opinion). Since 300 µg/25 µg and 150 µg/25 µg (metered dose) were the strengths referred to throughout the non-clinical and clinical development of this medicinal product and the data submitted in the application, this has been left unchanged in the sections of this assessment report relating to the non-clinical and clinical development.

The proposed indication is:

Labazenit is indicated in the regular treatment of asthma in adults where use of a combination product (inhaled corticosteroid and long-acting β_2-agonist) is appropriate:

- Patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting β_2-agonists.

or

- Patients already adequately controlled on both inhaled corticosteroids and long-acting β_2-agonists.

The proposed posology for Labazenit is one inhalation (120 micrograms/20 micrograms or 240 micrograms /20 micrograms) twice daily.

The inhaler device used is called MIAT Monodose Inhaler or Axahaler. Development studies demonstrated that the Monodose inhaler (Axahaler) has a lower airflow resistance than the devices of the comparator products (i.e. Diskus and Turbohaler), which results in inhalation with a higher airflow than these comparator products. This leads to the use of lower doses of salmeterol xinafoate and budesonide in the currently proposed fixed dose combination.

2.2. Quality aspects

2.2.1. Introduction

Labazenit is a fixed-combination product. The drug product is a powder for inhalation in hard capsules, containing budesonide and salmeterol xinafoate. Two strengths are proposed: budesonide 150 µg and salmeterol (as xinafoate) 25 µg and budesonide 300 µg and salmeterol (as xinafoate) 25 µg. The capsule contents equate to delivered doses of budesonide 120 µg and salmeterol (as xinafoate) 20 µg and budesonide 240 µg and salmeterol (as xinafoate) 20 µg. The capsules are presented in an HDPE bottle closed with a polypropylene screw cap which contains desiccant. A single-dose "axahaler" inhalation device made from plastic materials is provided in each pack.

2.2.2. Active Substance

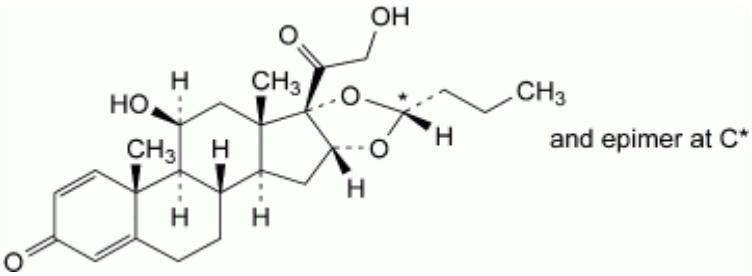
Active Substance

The drug product contains two well-known active substances, salmeterol xinafoate (a long-acting β_2-agonist), and budesonide (a corticosteroid anti-inflammatory), which are described in Ph. Eur. Valid certificates of suitability to the Ph. Eur. monographs (CEP) have been submitted as part of this application for both active substances by their manufacturers. The information provided regarding the manufacturing processes and the control of the active substances was assessed and approved by the European Directorate for the Quality of Medicines. Satisfactory quality of the active substance is ensured through the CEPs. Budesonide is supplied by 2 manufacturers and Salmeterol Xinafoate is manufactured by 2 manufacturers.

Budesonide

Budesonide is a corticosteroid designated chemically as (*R*,*S*)-11β,16α,17,21-tetrahydroxypregna-1,4 diene-3,20-dione cyclic 16,17 acetal with butyraldehyde. The active ingredient budesonide has nine chiral centres. It is a mixture of the two diastereoisomers with *S* and *R* configurations at C*. Budesonide is a white to off-white, tasteless, odourless, crystalline powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform.

The chemical structure of budesonide is:



The manufacturer of the finished product applies a single composite specification to all sources of budesonide. The specification includes all of the controls specified in the monograph for Budesonide performed using the pharmacopoeial test methods, as well as additional specifications for residual solvents and particle size indicated in the CEP.

The release specifications include tests for appearance (Ph. Eur.), solubility (Ph. Eur.), identification (Ph. Eur.), related substances (Ph. Eur.), epimer A (Ph. Eur.), loss on drying (Ph. Eur.), assay (Ph. Eur.), residual solvents (GC) and Particle size (laser diffraction).

The GC methods used for quantification of methanol are described in the respective CEPs and no validation data is presented since it was already assessed by EDQM. The laser diffraction method used by the DP manufacturer has been adequately described and validated.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches from each supplier.

The first manufacturer submitted data for three production scale batches stored for 24 months under long term (25 °C / 60% RH) and 9 batches stored for 6 months under accelerated (40 °C / 75 %RH) conditions as per ICH guidelines. Results on 6 further production scale batches stored for 60 months at long-term conditions and tested for compliance with an older specification for related substance were provided as supporting evidence. All the batches were stored in the proposed commercial packaging. The parameters tested were appearance, identification, assay, loss on drying, epimer A, specified and other impurities, and total impurities.

The second manufacturer provided stability results on 9 production scale batches and 2 pilot scale batches for up to 60 months under long term conditions (25 °C / 60% RH) as per ICH guidelines. No data was provided for batches stored under accelerated conditions, but the results generated under long-term storage conditions indicate that the drug substance is chemically stable. All the batches were stored in the proposed commercial packaging. The parameters tested were identity, assay, loss on drying, purity, epimer A, total related substances and single unknown impurities.

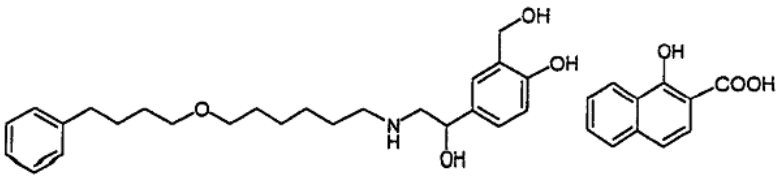
No evidence was presented on stability of the particle size distribution (PSD) of budesonide during the stability studies, but this is a key measure since PSD is a critical quality attribute for inhaled dry powder drugs. Consequently, the particle size distribution is re-tested before use in drug product manufacture.

The stability results are within the specifications and justify the proposed retest period in the proposed container.

Salmeterol xinafoate

Salmeterol xinafoate is a 1:1 salt of 1-hydroxy-2-naphtoic acid and salmeterol. Salmeterol is chiral, having a single stereocentre, and is prepared as the racemate. 36.3 μg of salmeterol xinafoate is equivalent to 25 μg of salmeterol free base. Salmeterol xinafoate is a white or almost white crystalline powder, which is slightly soluble in ethanol, chloroform and isopropanol and sparingly soluble in water. Two polymorphs of salmeterol xinafoate are described in the literature. All the proposed suppliers synthesise the polymorph I which is the most thermodynamically stable form at room temperature.

The chemical structure of salmeterol xinafoate is:



The manufacturer of the finished product applies a single composite specification to all sources. The specification includes all of the controls specified in the monograph for Salmeterol Xinafoate performed using the pharmacopoeial test methods, as well as the additional specifications for residual solvents, particle size, and related substances indicated in the CEP.

The release specifications include tests for appearance (Ph. Eur.), solubility (Ph. Eur.), identification (Ph. Eur.), related substances (Ph. Eur. and HPLC method of Ph.Eur monograph 1765), water (Ph. Eur.), sulphated ash (Ph. Eur.), assay (Ph. Eur.), residual solvents (GC) and particle size (laser diffraction).

The GC methods used are described in the respective CEPs and no validation data is presented since it was already assessed by EDQM. The laser diffraction method used by the DP manufacturer has been adequately described and validated.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches from each supplier.

The first manufacturer submitted data for 3 pilot scale batches stored for 60 months at long term (30 °C / 60% RH) and 6 months at accelerated (40 °C / 75% RH) conditions. All the batches were stored in the proposed commercial packaging. The parameters tested included appearance, identity, water content, appearance of solution, assay, and related substances. The applicant has adopted the re-test period indicated in the CEP for the second manufacturer.

No evidence was presented on stability of the particle size distribution (PSD) of salmeterol xinafoate during the stability studies, but this is a key measure since PSD is a critical quality attribute for inhaled dry powder drugs. Consequently, the particle size distribution is re-tested before use in drug product manufacture.

The stability results are within the specifications and justify the proposed re-test period in the proposed container.

2.2.3. Finished medicinal product

Pharmaceutical Development

The objective was to develop a dry powder for inhalation containing a fixed dose combination of salmeterol xinafoate, a long acting β_2-agonist bronchodilator, and budesonide, a corticosteroid anti-inflammatory, to treat the symptoms of asthma. The dry powder was developed to be used in a Miat Monodose Inhaler, also known as Axahaler. The complete product was designed to be compact, portable, easy to use and accurate. Whilst budesonide and salmeterol xinafoate are both established treatments for asthma and have been dosed to single patients separately, a product with both active substances combined has never been developed, and Labazenit is designed to fill this gap and thereby improve patient compliance by reducing the amount of individual medicines needed to adequately control the disease.

The choice of the final strength was guided by the FPD determined for the proposed combinations and for the reference products containing the same active ingredients. Reference products available during early development of the proposed formulations were Pulmicort Turbohaler for budesonide (200 μg) and Serevent Discus (50 μg) for salmeterol. The goal was to reach similar *in vitro* lung deposition characteristics for labazenit as for the reference products. Due to the addition of lactose monohydrate to the excipient blend, lower capsule content of active substance is required to achieve comparable fine particle dose to the comparator products (salmeterol: 25 µg vs. 50 µg in Serevent and budesonide:

150 µg vs. 200 µg in Pulmicort). All clinical batches have the commercial composition and have been manufactured at the commercial site. The only differences compared to the commercial process are the batch size and, for some batches, the equipment used for mixing of the blend. However, for all batches blend homogeneity, dose uniformity, and fine particle dose was demonstrated. The applicant has sufficiently demonstrated that the batches used in the clinical study and the batches manufactured in accordance with the proposed commercial process will behave similarly and have comparable pulmonary deposition patterns.

All of the chosen excipients are compendial and widely used in the production of dry powder formulations inhalation. The excipients include: anhydrous lactose (carrier, Ph. Eur.), micronised lactose monohydrate (carrier, Ph. Eur.), and hypermellose (capsule material, Ph. Eur.). Details of minor components of the capsule, carrageenan (gelling agent, USP), potassium chloride (gelling promoter, Ph. Eur.) and black ink (in-house spec., all components Ph. Eur.), are provided but will not appear in the SmPC as they are not ingested.

The drug product contains two different types of lactose i.e. lactose monohydrate and anhydrous lactose. Lactose was chosen as the carrier because of its widespread use in dry powder inhalers. Anhydrous lactose is the major excipient component as the lower moisture content is more compatible with the active substances. Micronised lactose monohydrate was demonstrated to reduce the amount of active substance bound irreversibly to non-inhalable particles of anhydrous lactose and thus improve bioavailability. The ratio of excipients, their particle size specifications, and their relevance to the formulation have been justified. Hard capsules composed of hypromellose were selected because they have lower water content than hard gelatine capsules, and thus proved superior in terms of fine particle dose (FPD) delivered. Furthermore, they are vegetable origin and thus TSE safe.

The inhalation device is CE marked as a Class I Medical Device under 93/42/EEC the Medical Device Directive and applicable amendments and well-known. It has low airflow resistance which makes it suitable for patients with a low peak inspiratory flow. It has been confirmed that no changes were implemented in the design and/or manufacturing process of the delivery device since the early development of the proposed formulations. The overall product is compact, portable, easy to use, and provides accurate doses. The powder for inhalation is stored in hard capsules. On insertion into the inhaler, the capsules are mechanically pierced. On inhalation, the powder is extracted from the capsule and passes through the mouthpiece and into the patient's lungs.

The applicant has adequately described all aspects applicable to inhalation powders that are mentioned in the Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products. The performance of the drug product with the inhalation device was performed by testing with Multistage Liquid Impinger (MLI) and Next Generation Impactor (NGI). Characterisation has been done on the clinical batches with the MLI and control specifications have been set based on these characterisations. The relationship between particle size and the stages of the MLI and the calculation of the FPD has been accurately determined.

The powder blend contains low percentage of salmeterol xinafoate. The mixing process and the homogeneity of the blend are therefore the critical issues of the process. Four slightly different processes have been used during development based on the use of different mixing equipment with different mixing speeds and time. Homogeneity of the blend was always easily achieved and FPD/UDD results were also independent of the process applied, demonstrating the robustness of the proposed formulations. The less time consuming process was therefore chosen.

The capsules will be packaged in HDPE containers with LDPP caps. As the product is sensitive to environmental moisture, a desiccant capsule containing 2 g of silica gel is included in the container.

Adventitious agents

Lactose is the only excipient from ruminant origin contained or used in the manufacture of the drug products. Suitable declarations from the suppliers on the TSE safety of lactose have been provided.

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products

Manufacture of the product

The manufacturing process is equivalent for the two strengths and consists of two blending steps followed by encapsulation and primary and secondary packaging. There is one intermediate isolated during the manufacturing process: the filled, but unpacked capsules. The manufacturing process and equipment are adequately described. Adequate in-process controls have been set.

The method of manufacture of Labazenit is considered to be 'non-standard', as defined in the CHMP guideline on non-standard processes (CPMP/QWP/2054/03), not only because it involves a specialised dose form (dry powder inhaler), but also because both of the drug substances represent less than 2% by weight of the capsule contents. The process has been demonstrated to be capable of manufacturing the finished product of the intended quality on several pilot scale and two commercial scale batches. Furthermore, the applicant has demonstrated significant experience (more than 200 commercial batches) in the manufacture of DPI products requiring dry blending of lactose with small (12 mg) amounts of active substance. In view of the batch analysis data provided and the extensive manufacturing experience of the manufacturer with DPI products, it was considered acceptable that a full validation scheme had not been finalised prior to the CHMP Opinion. The applicant will still need to have finalised the validiation scheme prior to marketing the product in accordance with the current GMP requirements.

Product Specification

The specifications for release and shelf-life include tests for: appearance (visual description), water content (Ph. Eur.), inhalation device identification (visual test) and microbiological purity (Ph. Eur); and for both active substances for uniformity and average of delivered dose (Ph. Eur., HPLC), identification (HPLC, UV), assay (HPLC), fine particle dose (Ph. Eur., HPLC). Related substances are specified and controlled for budesonide (HPLC) and salmeterol (uHPLC). The drug product specification includes a requirement for not more than (NMT) 1% of any specified impurity related to salmeterol. However, the specification lacks information on which individual impurities are covered by the phrase "any specified" and this information needs to be added to the drug product specification.

Other than this minor outstanding issue, control of the drug product is satisfactory. The proposed test procedures and acceptance criteria comply with the requirements of the Ph. Eur. and ICH guidelines. All tests included in the specification have been satisfactorily described and validated. The drug product specification is acceptable and the specification limits are supported by batch data and stability results.

Batch analyses data of seven pilot and two full scale batches of the drug product, confirm compliance with the proposed drug product specifications.

Stability of the product

For both strengths, stability data from three pilot scale batches, stored in the proposed commercial packaging (HDPE bottle) stored under long-term conditions (25 ºC / 60% RH) for up to 36 months, under intermediate conditions (30 ºC / 75% RH) for up to 30 months, and under accelerated conditions (40 ºC / 75% RH) for up to 3 months according to ICH guidelines were provided. Additionally, stability data from three further pilot scale batches stored in aluminium blisters under long-term conditions (25 ºC / 60% RH) for up to 30 months, under intermediate conditions (30 ºC / 60% RH) for up to 12 months, and under accelerated conditions (40 ºC / 75% RH) for up to 6 months according to ICH guidelines were provided. Samples were tested for appearance, average mass, water content, average and uniform delivered dose (UDD), fine particle dose (FPD), assay of budesonide and salmeterol, related substances of budesonide and salmeterol and microbial contamination. The analytical procedures used were stability indicating. The only trend observed is a significant decrease in assay of salmeterol under accelerated storage conditions (20-30%), and a slight decrease under intermediate and long-term stability studies. Temperature rather than humidity was shown to be the main factor in degradation rate. The drug product was demonstrated to be more stable in the commercial HDPE bottle rather than the aluminium blisters.

Two stability studies on commercial scale batches are on-going and will be assessed throughout the proposed shelf-life under long term storage conditions. A long term stability study on a third commercial batch will be carried out post-approval.

No photostability studies were carried out but this is acceptable since the proposed commercial packaging minimises light transmission in compliance with the USP guidelines on light transmission.

Based on available stability data, the proposed shelf-life (24 months) and storage conditions (<30^{o}C) are acceptable. However, the discrepancy between storage temperature proposed in SmPC (<30^{o}C) and that proposed in the answers to day 180 list of outstanding issues (<25^{o}C) needs to be addressed.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, two minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product remained.

Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory manner. Data has been presented to give reassurance on viral/TSE safety.

The CHMP has identified the following measures necessary to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product:

The drug product specification includes a requirement for not more than (NMT) 1% of any specified impurity related to salmeterol. However, the specification lacks information on which individual impurities are covered by the phrase “any specified” and this information needs to be added to the drug product specification.

The discrepancy between storage temperature proposed in SmPC (<30°C) and that proposed in the answers to day 180 list of outstanding issues (<25°C) needs to be reconciled.

2.3. Non-clinical aspects

2.3.1. Introduction

Salmeterol and budesonide are considered well known active substances indicated for the treatment of asthma, with an established non-clinical and clinical safety profile. The Applicant performed an extensive review of published non-clinical data available on salmeterol and on budesonide, therefore no new original data was submitted. In the light of the longstanding clinical use of salmeterol and budesonide, this was considered to be acceptable by the CHMP. Non-clinical studies conducted with the combination of salmeterol and budesonide were limited to repeat-dose toxicity studies in line with the Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005). This was considered acceptable by the CHMP.

Pivotal studies regarding the combination of salmeterol and budesonide were performed in compliance with GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Salmeterol

Salmeterol is an inhaled long-acting β2-adrenergic agonist. β2-Adrenergic agonists produce their effects through interaction with specific β2-adrenergic receptors present in high concentration in lung tissue. The receptors consist of a protein that traverses cell membrane seven times, forming three extracellular and three intracellular loops. The receptor is linked to a stimulatory guanine-nucleotide-binding protein (GS). Occupancy of the β2-adrenergic receptor changes the conformation of GS, leading to activation of adenylate cyclase, which in turn catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Protein kinase A is activated by the cAMP. Activated protein kinase A inhibits phosphorylation of key muscle proteins involved in the control of smooth muscle tone; cAMP also results in inhibition of calcium ion release from intracellular stores. Together, these events lead to a general relaxing effect of the airway smooth muscle. In rat left atria and guinea pig gastric fundus preparations, salmeterol was also shown to be a weak partial agonist of β1 and β3-adrenergic receptors. β-receptors are located in virtually every tissue of the organism. β1-receptors increase cardiac output, renin secretion and lipolysis. β2-receptors produce smooth muscle relaxation, dilation of coronary arteries and increase striated muscle contraction. In addition β2-receptors inhibit the release of histamine. β3-adrenoreceptors are also described in the heart tissue, they are activated at high catecholamine concentrations, producing a negative inotropic effect that antagonizes β1-and β2-adrenoreceptor activity. Putative β4 adrenoreceptor has also been described. However, β4-adrenoreceptors have been characterized as a different state of the β1-adrenoreceptor protein. The prolonged action of salmeterol is thought to be mediated by the extended side chain of

salmeterol which allows prolonged activation of the receptor for 12 hours or more. The "tail" binds into the β receptor at an exosite, preventing the molecule from dissociating from the receptor. Meanwhile, the "head" binds to and activates the β2 receptor. The head continually attaches and detaches from the receptor site. This repeating attachment process prolongs the drug's action.

Budesonide

Budesonide is an inhaled glucocorticosteroid. The anti-inflammatory properties of glucocorticoids are manifested by repression of inflammatory genes expression, including cytokines, chemokines, adhesion molecules, inflammatory molecules and many others. Budesonide possesses a good degree of topical potency (local anti-inflammatory activity) compared to systemic effects. Corticosteroids are the most potent antiinflammatory agents currently used to treat asthma. Glucocorticoid receptors are widely distributed in the airways and are expressed on inflammatory and structural cells. The target receptor for corticosteroids is the intracellular glucocorticoid receptor (GR). Under resting conditions, the inactive GR is largely located in the cytosol, associated with multiple chaperon proteins. The glucocorticoid molecule first penetrates the cell membrane, then binds to the GR through the glucocorticoid-binding domain. This induces a conformational change in the receptor protein, dissociation of the chaperone proteins, and the formation of an active glucocorticoid- GR complex. The complex may then form a dimer and translocate from the cytosol to the nucleus of the cell, where it binds to specific DNA sequences (glucocorticoid response elements) in the promoter region of target genes, leading to cofactor activation and either an increase or decrease in gene transcription. This process is termed transactivation. Alternatively, the active glucocorticoid- GR complex, as a monomer, can interact directly with intracellular transcription factors such as activator protein-1 (AP-1) or nuclear factor (NF)-B, through a protein- protein interaction, to attenuate the proinflammatory processes mediated by those transcription factors. This process, termed transrepression, involves recruitment of histone deacetylases and modulation of chromatin structure. The altered transcription of many different genes is involved in the anti-asthma effect of glucocorticoids, but the most important action may be to inhibit transcription of the genes for the cytokines implicated in asthmatic inflammation.

Glucocorticoids may have direct inhibitory effects on many of the cells involved in airway inflammation in asthma, including macrophages, T-lymphocytes, eosinophils, and airway epithelial cells. They may not inhibit the release of mediators of allergic reactions from mast cells, but they do reduce the number of mast cells within the airway. In addition to their suppressive effects on inflammatory cells, glucocorticoids may also inhibit plasma exudation and mucus secretion in inflamed airways. Inhaled glucocorticoids have local anti-inflammatory effects on the bronchial mucosa in patients with asthma. Furthermore, glucocorticoids reverse the shedding of epithelial cells and the goblet-cell hyperplasia characteristically seen in biopsy specimens of bronchial epithelium from patients with asthma.

Budesonide has stronger local and systemic anti-inflammatory properties compared to other molecules of the same pharmaceutical class such as bethamethasone 17-valerate, fluosinolone acetonide, hydrocortisone 17-butyrate or hydrocortisone 21-acetate. Results of experiments in rats indicate that budesonide has strong antiinflammatory properties with fewer systemic side effects than other glucocorticoids. This is probably explained by the important first pass hepatic metabolism observed after oral administration.

Salmeterol / budesonide

No primary pharmacodynamic studies were performed on the fixed dose combination salmeterol/budesonide based on the data available for each compound which was considered acceptable.

Secondary pharmacodynamic studies

Salmeterol

Salmeterol possesses anti-inflammatory properties in both laboratory animals and human that are beneficial in the improvement of airway functions. Its immunomodulatory action probably depends on long-lasting inhibition of the release of pro-inflammatory mediators from lung mast cells, impairment of plasma protein extravasation and inhibition of eosinophils accumulation in lung tissue. These anti-inflammatory properties of salmeterol are explained by the presence of low number of ß2-receptors on inflammatory cells involved in asthma, including eosinophils, neutrophils, T lymphocytes, and macrophages. Inhaled ß2-agonists inhibit the release of histamine and cysteinyl-leukotrienes from chopped human lung and purified human lung mast cells. They have a greater protective effect against adenosine-induced bronchoconstriction, which is mediated by mast cell degranulation, than against histamine- and methacholine-induced bronchoconstriction, which are direct constrictor effects of airway smooth muscle. This indicates the additional inhibitory effect of inhaled ß2-agonists on mast cells. This may be important in the use of ß2-agonists in preventing allergen- and exercise-induced asthma as well as in severe asthma and acute exacerbations, all of which involve mast cell activation. ß2-Agonists also inhibit the release of acetylcholine from cholinergic nerves, thus reducing cholinergic neural (reflex) bronchoconstriction. Exudation of plasma from postcapillary venules is an important component of acute inflammation. ß2-Receptors are present on postcapillary venular endothelial cells, and ß2-agonists inhibit plasma exudation by preventing separation of endothelial cells in postcapillary venules. In addition, ß-Agonists have multiple effects on airway epithelial cells, including stimulating ciliary beat frequency and stimulation of chloride secretion toward the airway lumen, which theoretically could improve the hydration state of the mucus by increasing the water secretion onto the airway surface. Both of these mechanisms could contribute to the enhanced mucociliary clearance (MCC) observed in vivo with ß-adrenergics. Impaired airway MCC is a central component of the pathophysiology of asthma, COPD, and cystic fibrosis.

Budesonide

It is well established now that corticosteroids stimulate the transcription of ß2-receptors. This stimulation is done via binding to specific DNA sequences located in the 5'-noncoding promoter region of the ß2-receptor gene. Both systemic corticosteroids and inhaled corticosteroids reverse ß2-receptor downregulation after exposure to high doses of short-acting ß2-agonists. Corticosteroids also reportedly modulate the efficiency of coupling between the ß2-receptor and its associated stimulatory guanine-nucleotide–binding protein (GS). As a result, ß2-receptor–stimulated adenylate cyclase activity and cAMP accumulation increase after corticosteroid treatment. Animals that have been depleted of corticosteroids by adrenalectomy, in contrast, lose the sensitivity of the ß2-receptor-coupled adenylate cyclase system.

Salmeterol / budesonide

No secondary pharmacodynamic studies were performed on the fixed dose combination salmeterol/budesonide based on the data available for each compound which was considered acceptable.

Safety pharmacology programme

Salmeterol

The pharmacological side effects of β2-agonist treatment, such as tremor, subjective palpitations and headache, have been reported, but tend to be transient and to reduce with regular therapy.

The coexistence of β1- and β2-adrenoceptors in the heart clearly indicates that β2-agonists do have some effect on the heart, such as increase of heart rate, even when they are highly selective. β2-agonist use has been associated with an increased risk of myocardial infarction, congestive heart failure, cardiac arrest and sudden cardiac death. Some of the major adverse effects of β-adrenergic agonists in the treatment of asthma are caused by stimulation of β1-adrenergic receptors in the heart. Accordingly, drugs with preferential affinity for β2-receptors compared with β1-receptors have been developed. However, this selectivity is not absolute. In rats, myocardial fibrosis was observed after 7-days treatment with β2-agonists salbutamol and terbutaline. This showed a relation with β1-adrenergic receptor occupancy.

β-agonists are also known to decrease plasma potassium levels by stimulation of β2-adrenoreceptors in the liver and skeletal muscle. This reduction is produced by an increase in the transport of potassium ions into cells through the activation of NA+/K+ adenosine triphosphatase which increases the uptake of potassium. Compared to formoterol (another β2-agonist), salmeterol had a lower impact on plasma potassium concentrations in asthma patients treated with a 100 µg dose.

β2-adrenoceptor agonists (β2-agonists) have potent muscle anabolic effects. β-2-receptors have indeed been identified in skeletal muscle and β-agonists may bond directly to skeletal muscle membrane and activate a sequence of events leading to protein accretion. β-agonists may also activate non-muscle β-receptors leading to the production of hormones or other factors. Those may in turn act on the muscle or create an environment conductive to the stimulation of protein accretion.

Budesonide

Budesonide had no effect on the spontaneous motor activity of mice at doses up to 10.0 mg/kg. There was no effect on the normal body temperature of mice or rabbits and no muscle-relaxing effect, anesthesia-potentiating effect, or analgesic effect in mice in doses up to 10.0 mg/kg. 10.0 mg/kg of budesonide potentiated maximal electroshock induced convulsions in mice, but had no effect on pentetrazol-induced convulsions. There were no evident changes in the spinal reflexes or EEG of cats. No obvious changes could be found in the respiration, circulatory system, or behavior of unanesthetized beagle dogs. There was also no effect on the blood pressure response induced by adrenalin or acetylcholine in anesthetized cats at doses up to 10.0 mg/kg. Doses up to 10 mg/kg had no effect on the blood coagulation system of rats or the bleeding time of mice. As for the effects on renal function in rats, doses of at least 0.01 mg/kg of budesonide increased K+ excretion and doses of at least 0.03 mg/kg increased urine volume and Na+ and Cl- excretion. In human, systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. The effect is probably dependent on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity. As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases. The major local side effects of inhaled corticosteroids include oral candidiasis, hoarseness and disphonia. Facial skin irritation has occurred in some cases when a nebulizer with a face mask has been used. To prevent irritation, the facial skin should be washed with water after use of the face mask. Glucocorticoid receptors are very widely distributed outside the lungs, so systemic side effects on bone, growth, skin, skeletal muscles, and blood vessels are common; this provides the rationale for the use of inhaled corticosteroids to reduce systemic exposure.

Salmeterol / budesonide

No safety pharmacology studies were performed on the fixed dose combination salmeterol/budesonide based on the data available for each compound which was considered acceptable.

Pharmacodynamic drug interactions

Beta-adrenergic blockers can weaken or inhibit the effect of salmeterol. Labazenit should therefore not be given together with β-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. The relaxing actions observed in guinea-pig trachea or human bronchus are rapidly and fully reversed by the β-adrenoceptor blocking drug, propranolol (0.1 microM). Another β-adrenoceptor blocking drug, sotalol (10 microM), also fully and rapidly reverses established sub-maximal responses to salmeterol in superfused guinea-pig trachea. However, after administration of sotalol was stopped, the antagonism waned, and salmeterol responses were reasserted without the addition of further agonist. Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors and tricyclic anti-depressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias. In addition L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards β2-sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors, including agents with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions. There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons. Concomitant use of other β-adrenergic drugs can have a potentially additive effect. Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Salmeterol / budesonide

No pharmacodynamic drug interactions studies were performed on the fixed dose combination salmeterol/budesonide based on the data available for each compound which was considered acceptable.

2.3.3. Pharmacokinetics

Methods of analysis

Salmeterol

The LC/MS assay for the quantification of salmeterol has been validated adequately in horse urine. Acceptable linearity, precision and specificity of salmeterol were observed. The limit of quantitative detection was 0.25 ng/mL and the limit of detection was 0.125 ng/mL.

Another method describes the determination of the 1-hydroxy-2-naphtoic acid (HNA) a salt of salmeterol in human plasma. This semi-automated procedure with solid-phase extraction using an automated analytical sample processor (AASP) and high-performance liquid chromatography (HPLC) with fluorescence detection. The method was sensitive to 10 ng/ml. The method is specific for HNA with respect to endogenous plasma components and has been shown to be robust, accurate and precise.

A sensitive, accurate, and precise high-performance liquid chromatographic method for the determination of salmeterol in rat and dog plasma was reported by Colthup Ph. V. *et al.* Samples were prepared by solid-phase extraction and, after chromatography of the extracts on a reversed-phase styrene/divinylbenzene analytical column, salmeterol was detected by fluorescence monitoring (excitation wavelength, 230 nm; emission wavelength, 305 nm).

Budesonide

The HPLC combined with tritiated drug assay for the quantification of budesonide has been validated adequately in beagle dog plasma. Acceptable linearity, precision and specificity of budesonide were observed. To study the pulmonary disposition of 3H-budesonide in rat lungs, the a liquid chromatograph assay has been used.

Salmeterol / budesonide

A validated HPLC assay to determine parameters in the toxicokinetic part of the repeated dose toxicology studies conducted in rats and dogs using various dosages of budesonide and salmeterol as monotherapies or in combination was developed. This validated method is similar to the one used to quantify plasma concentrations in human pharmacokinetic studies. In dog plasma, the method was found to be linear over the calibration range ~15 to 1000 pg/mL for salmeterol, ~40 to 2750 pg/mL for budesonide epimer A and ~50 to 3270 pg/mL for budesonide epimer B. Accuracy and precision were within 15% for all compounds, and recovery was >85.

Absorption

The route of administration of salmeterol and budesonide is via inhalation. However, it is recognised that much of an inhaled dose is eventually swallowed and can be absorbed into the systemic circulation from the gastrointestinal tract. For this reason, the disposition of salmeterol and budesonide in laboratory animals and human is reported after oral administration. In addition, pharmacokinetic data after IV administration in rats and dogs is available.

Salmeterol

Salmeterol is rapidly absorbed following oral administration to both laboratory animals and humans with peak concentrations of drug in plasma achieved within 2 hours in all species. The C_{max}-values are similar for mice, rats and rabbits when normalised for dose level. In dogs, however, dose-normalised C_{max}-values are much higher, reflecting greater systemic absorption in this species. The dose-normalised peak concentrations of salmeterol in human plasma are higher than those observed in rodents/lagomorphs, being more closely related to dogs.

Budesonide

The systemic absorption of budesonide from the gastrointestinal tract is relatively poor with oral bioavailability ranging form 2% or less in monkeys, 9-20% in dogs and 30-35% in rats and mice. In dogs, the systemic availability of budesonide following oral administration ranges form 9.2 to 16.2% at 10 µg/kg and from 18.3 to 18.8% at 100 µg/kg. In humans, the systemic availability is ~11% which points to an extensive first pass metabolism in the liver.

In dogs administered oral doses of 10 and 100 µg/kg, the maximal plasma concentrations are achieved within one hour indicating a fast absorption.

Budesonide has relatively high water solubility and is readily dissolved in mucosal fluids. As a consequence, budesonide is rapidly absorbed into airway tissues. Importantly, the absorption of budesonide into airway tissue does not appear to be affected by lung function, with comparable plasma concentrations achieved following pulmonary delivery in healthy and asthmatic individuals. Once absorbed intracellularly, budesonide undergoes reversible conjugation with intracellular fatty acids, which prolongs its retention within the airways and its duration of action.

After intratracheal administration of a clinically relevant dose of ^{3}H-budesonide via infusion into the pulmonary circulation using isolated perfused and ventilated rat lungs, a rapid initial absorption was found. About half of the given dose was slowly released into the lung perfusate. The lung uptake of budesonide from the pulmonary circulation is relatively high, showing a high lung affinity for budesonide.

In humans, the plasma half-life was ~3 hours after intravenous administration and ~2 hours after inhalation. In dogs, plasma t1/2 after oral administration ranged from 1.8 to 3 hours depending on the dose. Elimination in rat, mouse and monkey was rapid with plasma t1/2 after intravenous administration of 1.1, 1.6 and 3.8 hours, respectively.

Salmeterol / budesonide

One 14-day toxicokinetic inhalation study (study V9015/01) in dogs has been provided by the Applicant, in which dogs were daily dosed with 10.4 mg/m^3 salmeterol only for 5 minutes, 112 mg/m^3 budesonide only for 5 minutes or a combination of both for different exposure durations (1 minute vs. 5 minutes) leading to a low concentration and a high concentration group. For budesonide, the results showed that for both epimers the time to attain the maximum plasma concentration and C_{max} were similar among groups. Exposure values after a single dose were higher in the budesonide-only group but those differences tended to decrease at steady state and the AUC values were closer when taking into account the standard deviation values. The AUC values were not higher in the combination groups versus the budesonide-only group and those values did not show significant accumulation even at high doses.

For salmeterol, the results showed that the C_{max} values were similar among the dosing groups after a single dose and at steady state. The T_{max} values were also close together (~0.08h), except for the low concentration combination group at steady state. However, this value was associated with a high variability which hampered a proper interpretation (2.5h±2.9). The AUC values were slightly higher in the single compound group compared to those in the combination group at single dose and at steady state. However, this difference is most probably not significant given the observed standard deviation (between 39 and 92%). At steady state, the AUC value for salmeterol in the low concentration combination group was 3 times greater than that after a single dose. However, the variability was very high for the AUC value at steady state (SD=92%). According to the Applicant, salmeterol seems to be slowly eliminated in the low concentration combination group, while in the other groups exposures tended to remain constant during the exposure period.

Table 1. Kinetic parameters after single and repeated dosing (14 days) in dogs via inhalation of salmeterol only, budesonide only or a combination for 5 minutes or via inhalation of a combination for 1 minute.

	group	dose salm (mg/m3)	dose bud (mg/m3)	exposure time (min)	AUC salm (ng*h/mL)	AUC bud A (ng*h/mL)	AUC bud B (ng*h/mL)	Cmax salm (ng/mL)	Cmax bud A (ng/mL)	Cmax bud B (ng/mL)	Tmax salm (h)	Tmax bud A (h)	Tmax bud B (h)
single dose	budesonide only	0	112	5	0	28 (7.9)	27 (6.6)	0	19 (1.6)	22 (2.4)	-	0.22	0.22
	salmeterol only	10.4	0	5	26 (34)/ 12 (6.6)*	0	0	3.6 (2.3)/ 2.6 (0.6)*	0	0	0.48/ 0.08*	-	-
	combination low	10.4	112	1	18 (0.8)	6.3 (0.6)	6.5 (0.8)	0.5 (0.2)	5.6 (0.7)	6.9 (1.2)	0.09	0.12	0.13
	combination high	10.4	112	5	8.0 (5.7)	16 (4.3)	15 (3.9)	2.9 (1.0)	15 (4.2)	16 (4.7)	0.08	0.13	0.13
repeated dose	budesonide only	0	112	5	0	27 (4.2)	25 (4.8)	0	17 (4.9)	18 (5.0)	-	0.13	0.12
	salmeterol only	10.4	0	5	13 (9.5)	0	0	3.3 (1.9)	0	0	0.08	-	-
	combination low	10.4	112	1	5.7 (5.2)	10 (3.1)	8.7 (2.8)	0.6 (0.3)	4.3 (0.8)	4.7 (1.0)	2.5	0.25	0.15
	combination high	10.4	112	5	7.8 (3.0)	20 (4.9)	17 (3.2)	2.6 (0.8)	14 (4.1)	15 (4.0)	0.08	0.12	0.15

Distribution

Salmeterol

The extent of binding of salmeterol to mouse, rat, rabbit, dog and human plasma proteins *in vitro* was ~95% and was independent of drug concentration. Salmeterol distributed equally between erythrocytes and plasma in all species.

After oral administration of ^{14}C-salmeterol xinafoate in rats, radioactive drug-related material was rapidly absorbed and widely distributed although tissue concentrations are significantly lower than after a corresponding intravenous dose. Autoradiographic studies performed in the rat showed that within 15 minutes of intravenous administration of ^{14}C-salmeterol xinafoate, radioactive drug-related material was distributed throughout the tissues. By 30 minutes, the highest concentrations of radioactive material were found in the kidneys, liver, followed by intestinal content, heart, pituitary, bone marrow, lung and stomach/small intestine wall. Lower concentrations of radioactivity were retrieved in blood, whereas only trace amounts were detected in the central nervous system. The levels of radioactivity declined beyond 48 hours and became undetectable 168 hours post-dose.

In pregnant rats, the concentrations of radioactive drug-related material were low in mammary tissue, placenta and foetus after oral administration of ^{14}C-salmeterol xinafoate and comparable to those in maternal blood up to 6 hours post-dose. At 24 hours, radioactivity in the foetus was primarily located in the gastrointestinal tract.

Budesonide

The plasma protein binding of budesonide is 85% in rabbits, 86% in mice and human, 89% in dogs and 92% in rats. Budesonide is equally distributed between erythrocytes and plasma.

The pulmonary disposition of budesonide was studied *in vitro* in rat lungs. Budesonide was found to have longer tissue retention compared to that of other molecules also administered by inhalation (formoterol and terbutaline). This experiment showed that the amount of budesonide that penetrates the air/blood barrier is low; therefore the resulting concentration in plasma is low decreasing the potential for systemic side effects.

After intravenous administration of radiolabeled budesonide in mice, budesonide was rapidly and extensively distributed into tissues. Radioactivity was mainly localized in the liver, kidney, lungs and lymphatic tissues. The radioactivity observed in lung parenchyma was higher than that in the blood. In particular, the bronchi showed a higher content than the rest of the lungs, confirming the high lung affinity of budesonide. Low levels of radioactivity were detected in the CNS. A high uptake of budesonide was also noted in organs and tissues from the reproductive system, such as the epithelium of the head of the epididymis and ductus deferens.

In the pregnant mouse, high amounts of radioactivity were found in the corpora lutea, the placenta and the foetal membranes. In the foetus, the distribution of radioactivity is similar to that of the mother.

Salmeterol / budesonide

No distribution PK studies were performed on the fixed dose combination salmeterol/budesonide which was considered acceptable based on the data provided for the individual compounds.

Metabolism

Salmeterol

In vivo metabolism

Significant differences in the metabolism of salmeterol were evidenced across species In rat, mouse and rabbit, the predominant metabolic route is via glucuronidation of the parent drug. Rat bile contained one major metabolite and a number of minor metabolites. The major metabolite is a phenolic glucuronide conjugate of the parent compound. Two minor metabolites excreted predominantly in rat urine have been identified as products of O-dealkylation.

In dogs, the identity of the major metabolite proved refractory to chromatographic and spectral analysis due to persistent interference from bile salts. However, deconjugation studies indicated a sulphate conjugate of a metabolite that was not observed in any other species. The major metabolite in dogs was eventually identified as the 3-catechol sulphate of the benzoic acid derivative. This metabolite was shown to have very similar physicochemical properties to a major endogenous component of the bile explaining the difficulty to isolate it.

In human, salmeterol undergoes extensive aliphatic oxidation to α-hydroxysalmeterol. CYP3A was demonstrated by inhibition experiments with ketoconazole (1 μM caused substantial inhibition) to play a major role in the human metabolism of salmeterol.

Metabolites in plasma

In all species, the plasma concentrations of total radioactive drug-related material were higher than those of salmeterol at all sampling times, with this difference being more marked after oral administration. In addition, the total radioactive drug-related material persisted longer in plasma than unchanged salmeterol indicating the presence of circulating metabolites.

Budesonide

In vitro metabolism

The metabolism of budesonide was studied in livers from rat, mouse and man. The systemic inactivation of budesonide is rapid in all species due to extensive liver biotransformation. In man, about 90% is metabolized primarily mediated by CYP3A4. Incubations of budesonide with human liver microsomes in the presence of ketoconazole, troleandomycin, erythromycin and cyclosporine showed that budesonide metabolism was inhibited in presence of those CYP3A4 inhibitors.

The two budesonide epimers produce different metabolites. Epimer 22R gives 16α-hydroxy-prednisolone, while epimer 22S produces a metabolite tentatively identified as 23-hydroxybudesonide. Otherwise, budesonide follows the general metabolic pathways reported for synthetic glucocorticoids. Glucocorticoids are biotransformed and inactivated via oxidative, reductive and conjugation pathways. *In vitro* studies performed in rat livers have shown that this transformation is 5 to 6 times faster for budesonide than for triamcinolone acetonide used as reference compound. Oxidative metabolism predominates, 6β-hydroxybudesonide and Δ-6-budesonide being identified in all investigated species. Reductive metabolism giving 4,5-β-dihydrobudesonide and 3,4,5- β-ditetrahydrobudesonide is most pronounced in the rat. The metabolism in mouse and human was similar being extensive and predominantly oxidative. *In vitro* studies with human livers also showed an extensive first pass metabolism, in agreement with minor effects observed on plasma cortisol after oral doses up to 8 mg in man. Two major metabolites have been isolated: 6β-hydroxybudesonide and 16α-hydroxy-prednisolone. The major metabolic pathway, 16α, 17α-acetal splitting is unique for budesonide within this group of compounds. This biotransformation is catalyzed by microsomal monooxygenases and

proceeds via hydroxylation and subsequent rearrangement to an intermediary ester, which is then cleaved by hydrolysis to 16α-hydroxyprednisolone and butyric acid.

In rat species, there is a marked sex difference in the biotransformation rate of budesonide. The disappearance is more rapid in male rat liver. The greater 6β-hydroxylase activity seems to be the major reason for the observed differences. A marginal sex difference was seen in mouse liver.

The biological activities of 6β-hydroxybudesonide and 16α-hydroxy-prednisolone are less than 1% of budesonide.

Salmeterol / budesonide

No metabolism PK studies were performed on the fixed dose combination salmeterol/budesonide which was considered acceptable based on the data provided for the individual compounds.

Excretion

Salmeterol

After IV administration in rats, levels of radioactivity in blood and most tissues declined after 1 to 2 hours with the exception of the kidney medulla, stomach wall and pituitary gland. By 48 hours, tissue concentration of radioactive drug-related material declined substantially and was eliminated from the body.

It has been demonstrated in humans that 57% of administered radioactivity is recovered in the faeces and 23% in the urine, with the most recovered between 24 and 72 hours after administration by inhalation. Hydroxysalmeterol is eliminated predominantly in the faeces. Unchanged salmeterol accounted for <5% of the excreted dose in the urine in all species.

In another study, recoveries of the radiolabeled dose were incomplete in all species (mouse, rat, dog, rabbit, human) studied after oral and intravenous administration. Since this could not be explained by any retention in the body, it was hypothesised that the metabolism of drug-related material occurred through gut microflora with subsequent loss of the ^{14}C label in gaseous form.

Oral studies in bile duct-cannulated rat and dog indicated that the drug-related material present in the feces is predominantly derived from biliary secretion of metabolites confirming that salmeterol is well-absorbed across the gastro-intestinal tract in these species. There is evidence that some of the metabolites in the rat undergo entero-hepatic circulation. Because the major metabolite in the rat is the glucuronide conjugate of salmeterol, it is likely that the drug is reabsorbed following deconjugation by gut microflora, as only parent drug is detected in the feces. This may contribute to the relatively long half-life in this species.

In the lactating rat, low but persistent concentrations of salmeterol were observed in milk up to 8 hours after oral administration of ^{14}C-salmeterol xinafoate. Substantially higher peak concentrations of total radioactivity were observed in milk and plasma although the observed time to peak was at 24 hours and 6 hours, respectively, indicating a slow equilibration of predominantly metabolites between milk and plasma.

Budesonide

In rats and dogs, after oral or arterial administration, 60-85% of budesonide was excreted as metabolites in the bile and eliminated in the feces, 10-30% appeared as metabolites in urine. This indicates an extensive biliary excretion of the compound and/or its metabolites. No apparent difference between the two epimers prevailed. In rabbits after intravenous administration, 46% was eliminated in the urine and 39% in the feces in 72 hours. Urine and bile samples revealed only traces of unchanged budesonide. After oral and inhalation administration in humans, budesonide was rapidly eliminated with the majority (70%) recovered in the urine.

Salmeterol / budesonide

No excretion PK studies were performed on the fixed dose combination salmeterol/budesonide which was considered acceptable based on the data provided for the individual compounds.

Pharmacokinetic drug interactions

Salmeterol

As stated above, CYP3A4 plays a major role in the metabolism of salmeterol. It has been shown that the co-administration of ketoconazole (400 mg orally once daily) and salmeterol (50 µg inhaled twice daily) in healthy subjects for 7 days resulted in a significant increase in plasma salmeterol exposure (1.4-fold C_{max}, 15-fold AUC). This may lead to an increase in the incidence of other systemic effects of salmeterol treatment compared with salmeterol or ketoconazole treatment alone. Clinically significant effects were not seen on blood pressure, heart rate, blood glucose and blood potassium levels. Co-administration with ketoconazole did not increase the elimination half-life of salmeterol or increase salmeterol accumulation with repeated dosing. There is likely to be a similar risk of interaction with other potent CYP3A4 inhibitors.

Co-administration of erythromycin (500 mg orally three times a day) and salmeterol (50 µg inhaled twice daily) in healthy subjects for 6 days resulted in a small but non-statistically significant increase in salmeterol exposure (1.4-fold C_{max}, 1.2-fold AUC). Co-administration with erythromycin was not associated with any serious adverse effects.

Budesonide

Budesonide administered through inhalation has a high local anti-inflammatory activity and is rapidly and extensively inactivated after absorption. Both characteristics represent a major advantage in terms of adverse events but also in terms of potential pharmacokinetic interactions. Furthermore, as budesonide is primarily metabolised by CYP3A4, the concomitant administration of potent inhibitors of CYP3A4 may increase plasma levels of budesonide.

Substances known to interact with CYP2C (sulfaphenazole, mephenytoin, tolbutamide) and with CYP2D6 (bufuralol, quinidine) do not specifically inhibit the metabolism of budesonide.

Salmeterol / budesonide

Since both products are administered via the inhalation route, the systemic doses are expected to be very low. Therefore, it is unlikely that any clinically relevant interactions will be observed as a consequence of the co-administration with pharmaceutical agents that are metabolised by CYP3A4, as indicated in SmPC of other registered combinations of glucocorticosteroid and β2-agonist.

The pharmacokinetic potential interactions between budesonide and salmeterol have been studied in humans in the pharmacokinetic study BUSAL-SD101. This study showed that when both compounds were administered in combination by the inhalation route, the pharmacokinetic profile of each component was similar to that observed when the drugs were administered separately thereby demonstrating the absence of pharmacokinetic interactions between budesonide and salmeterol.

2.3.4. Toxicology

The toxicity of both budesonide and salmeterol has been evaluated in various animal species and their toxicity profile is well known. Three new repeated dose studies were conducted with the combination of salmeterol and budesonide: a 28-day study in rats and a 14-day and a 3-month studies in dogs. Non-clinical data available from the literature has been provided for both salmeterol and budesonide as monocompound. This is in line with the Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005).

Single dose toxicity

Salmeterol

Acute toxicity studies conducted in mice, juvenile and adult rats and dogs showed salmeterol to be a relatively non-toxic molecule.

In mice, 150 mg/kg per os produced decrease body weight gain and hypothermia.

In juvenile rats, 300 mg/kg p.o. produced a decrease in body weight gain. By the intra-peritoneal (ip) route, doses equal to and above 23 mg/kg caused peritonitis probably due to local irritation and 90 mg/kg was lethal. In adult rats, 600 mg/kg per os caused anal staining, ptosis, watery eyes, rough coat and discolored feces. 1000 mg/kg per os produced heavy rapid breathing, lethargy, ptosis, watery eyes and decreased weight gain. By the ip route doses of 75 mg/kg onwards caused writhing (a response to pain) and peritonitis. By the inhalation route, rats at 2.9 mg/kg showed a slight increase in absolute and relative liver weight.

In dogs, 0.7 mg/kg induced tachycardia, vasodilatation, trembling and mild lung inflammation (route of administration not mentioned, but presumably by inhalation). Kidneys also manifested inflammatory lesions.

Budesonide

The acute toxicity of budesonide was investigated using mice, rats, and dogs.

Intravenous administration of budesonide to mice and rats suppressed spontaneous motor activity and led to prone posture after administration. Many of the animals that died did so within 24 hours. Intraperitoneal administration produced temporary writhing in addition to the aforementioned symptoms. Intraperitoneal, subcutaneous, and oral administration all induced emaciation. Many of the animals that died did so 2 weeks after administration. The LD50 values in mice and rats were approximately 100 mg/kg in intravenous administration, 150-300 mg/kg in intraperitoneal administration, 50-100 mg/kg in subcutaneous administration, and more than 3200 mg/kg in oral administration.

The LD50 value of subcutaneous administration in dogs was 173 mg/kg. No particular differences between species or genders were seen by any administration route.

Histopathologic studies of animals of all species that died and those that survived revealed atrophy of the adrenal cortex, atrophy of the lymphatic system tissue, and ulceration of the digestive tract.

Salmeterol / budesonide

No single dose toxicity studies were performed on the fixed dose combination salmeterol/budesonide which was considered acceptable based on the data available for each compound.

Repeat dose toxicity

Salmeterol

The toxicity profile of salmeterol includes mainly tachycardia, vasodilatation, increased muscle development and hypokaliema. There may be signs of irritation of the respiratory tract when salmeterol is administered at high doses by inhalation and it seems that salmeterol is more toxic in young animals compared to adults.

In a 90-day study conducted in mice *per os*, there was a hypertrophy of the uterus at 1.4 and 10 mg/kg.

In a 2-week oral study in rats, 2 mg/kg produced no significant toxic effects. In a 39-day p.o. study in 3-day rats, doses of 1 and 10 mg/kg p.o. were lethal. Deaths occurred in the high dose groups within the first 10 days. The survivors showed increased body weight gain and acceleration in the rate of eye opening. Juvenile rats seem more sensitive than adults. In a 13-week inhalation/p.o. study in rats at doses up to 0.7 mg/kg by inhalation and 2.0 mg/kg p.o., no significant toxicity was seen. Hypoglycemia, slight increases in cardiac weight and increases in serum enzymes were observed although no histopathology was noted. Extending a similar study to 26-weeks, the observed changes were similar to those seen in the 13-week study. In a 78-week study in rats; doses of 0.06, 0.18 and 0.63 mg/kg were administered by inhalation. There was hypoglycaemia and hypokaliema. Increased food consumption was seen at all doses in both sexes. The males showed a decrease in vacuolated hepatocytes and an increase in vacuolated macrophages. In the females, there were ovarian follicular cysts, bilateral mesovarian leiomyomas and mammary lobular hyperplasia. Both sexes showed laryngeal epithelial hyperplasia accompanied by squamous metaplasia at the mid and high doses. The latter indicated an inflammatory response attributed to the aerosolised salmeterol xinafoate.

In 13-, 28-, and 52-week toxicity studies in dogs, salmeterol was administered p.o. and by inhalation using daily doses of 0.15, 0.5 and 2.0 mg/kg p.o. and twice daily inhalation doses of 5 x 50 µg bursts, 10 x 50 µg bursts and 20 x 50 µg bursts, for the low; mid and high doses respectively. Some animals showed transient tachycardia, vasodilatation, increased muscle development and hypokaliema. At the high dose in the 28 and 52-week studies, the dogs showed seizures and prostration. One animal died following seizures in the 52-week study. Myocardial papillary fibrosis with and without calcification was seen in all 3 studies. The incidences were increased at the mid dose in the 13-week study, at all doses in the 28-week study and at the mid and high dose in the 52-week study.

Budesonide

The toxicity of budesonide – as detailed below - is characterised by a reduction in blood leukocytes and eosinophils, an increase in blood neutrophils due to an inhibition of their apoptosis, elevated AST/ALT, and increase in blood sugar. A reduction in weight and atrophy of the spleen, thymus and all lymph nodes, adrenals, small ulcerative lesions of the stomach and increased liver weight can also be observed. It should be noted that the toxicity of budesonide administered by inhalation is very low, due to its low bioavailability coupled to an extensive first pass metabolism.

Budesonide cream or ointment was administered to male and female Crj:CD (SD) rats by topical administration to the shaved back skin at doses of 200 and 1000 mg/kg for up to 13 weeks followed by a 13-week recovery period. Control groups received base cream or ointment. The results show a trend for decreased body weight with a reduction in food consumption. Inhibition of hair growth on the skin at the application site was noted during the dosing period in each administration group with budesonide with cutaneous thinning at the application site. Biochemistry showed a reduction in blood leukocytes, an increase in serum transaminases, blood sugar and serum iron. At necropsy, a reduction in weight and atrophy of the spleen, thymus, and adrenals, small ulcerative lesions of the stomach, hemosiderosis of the Kupffer cells of the liver, a tendency toward an increase in fat cells of the bone marrow, slight hyperplasia of the breasts, and cutaneous atrophy at the application site were seen in the budesonide groups during the study period. All changes were reversible within 13 weeks.

In longer studies (26 weeks) performed in male and female Wistar rats (10 animals/group), budesonide administered subcutaneously at doses of 0.01, 0.1 and 5 µg/kg/d, and 5, 20 and 80 µg/kg/d (15 animals/group) revealed a dose-dependent decrease in body weight gain in the groups given 5, 20 and 80 µg/kg/d compared with the control group linked to a dose-related reduction in food intake in males receiving 20 or 80 µg/kg/d. Increased values were observed for packed cell volume, hemoglobin concentration and erythrocyte counts in both sexes at the doses of 20 and 80 µg/kg/d. A marked decrease in the number of blood lymphocytes was seen for both sexes at 80 µg/kg/d, and for females also at 20 µg/kg/d. Pathological changes associated with treatment with budesonide were found in the liver, panacinar hepatocytic fine vacuolation in females receiving 80 µg/kg/d, as well as decreased numbers of lymphocytes in lymph nodes and thymus and acinar hyperplasia and secretion in mammary glands were observed in both sexes receiving 20 and 80 µg/kg/d.

In Beagle dogs, a subacute toxicity study by percutaneous absorption was conducted by applying ointment that contained 0.05% budesonide to the skin of the back for 13 weeks followed by a 13-week recovery period. The amounts of budesonide applied corresponded to 0.01 and 0.2 g/kg/day. An untreated group and a group in which 0.2 g/kg/day of the budesonide vehicle was applied were established as control groups. A group in which 0.2 g/kg/day of betamethasone 17-valerate ointment was applied was also established as comparative control group. The recovery study was conducted in the budesonide 0.2 g/kg/day group, vehicle group, and betamethasone 17-valerate group. Budesonide administration produced erythema at the administration site, reduced the skin thickness, and suppressed hair growth. Histopathologic studies revealed atrophy of the skin and reduced subcutaneous adipose tissue. Hematological and biochemical studies found decreases in the blood eosinophil count, lymphocyte count, and WBCs and increases in serum total cholesterol and serum triglycerides. In the organ weights, decreases were seen in thymus and adrenals and increases in the liver. Histopathological studies found lymph follicle atrophy in the spleen and lymph nodes, atrophy of the thymus, atrophy of the fascicular and reticular zones in the adrenals, and hypertrophy of the liver due to increased glycogen content. The betamethasone 17-valerate group exhibited basically the same changes as the budesonide groups. In the recovery study, all of these changes alleviated and increases in blood eosinophil count and hypertrophy of the thymus thought to represent rebound phenomena were noted.

Salmeterol / budesonide

New studies with the combination were performed in rats and dogs (see table below).

Table 2. Repeated dose studies with the combination of salmeterol and budesonide

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (Mg/m^3)	Major findings
TNO V 5452	Rat 5/sex/gp	B/S: 0/0; 0.3/0.025; 1/0.083; 3/0.25; 3/0; 0/0.25 Mg/m^3 By inhalation	28 days	Budesonide: 0.3 mg/m^3 Salmeterol: 0.25 mg/m^3	**Clinical signs** Combi mid+high, bud: Bw gain ↓ or bw loss **Haematology** Combi mid+high, bud: retic↓ (m), WBC↓, lymph↓, mono↑ (m) Combi high, bud: neut↑ (f) bud: thromb↓ (m) **Clinical chemistry** Combi mid+high, bud: Glucose↑, protein↑ Combi mid+high, bud, sal: A/G↓, Ca↑ (f) Combi high, bud: triglycerides↑ (f), phosholipids↑ (f) **Organ weights** Combi high, bud: Adrenals↓ **Histopathology** Combi mid+high, bud: Thymus lymphoid depletion Combi high: Spleen PALS depletion
TNO V 8141	Dog 4/sex/gp	B/S *: 249/0; 0/15; 49/3; 223/15 µg/kg/day By inhalation	90 days	Could not be determined due to lack of control group	**Haematology** Combi low+high, bud: eos↓, lymph↓ (f) Combi high, bud: neut↑, WBC↑ (f) Bud: thromb↑ (f) **Clinical chemistry** Combi low+high, bud: albumin↑, creatinin↓ Combi high, bud: ALP↑, GGT↑, Cl↓ (f) Combi high: Glucose↓, Na↑ (f) Sal: creatinin↑ **Histopathology** Combi low+high, bud: Adrenals atrophy zona fasciculata + reticularis, thymus lymphoid depletion, GALT + lymph nodes + spleen decreased germinal centre development, NALT depletion Combi high, bud: Liver glycogen↑

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (Mg/m^3)	Major findings
TNO V 9015	Dog 5/sex/gp from which 2/sex/gp for recovery	B/S: 268/0; 0/18; 60/4; 262/18 µg/kg/day By inhalation	14 days with 14 days recovery	Could not be determined due to lack of control group	**ECG** Combi high, sal: Tachycardia **Clinical chemistry** Combi low+high, bud: creatinin↓ Combi high, bud: ALP↑, GGT↑ Combi high, sal: K↓ **Organ weights** Combi low+high, bud compared to sal: lung↓ **Histopathology** Combi low+high, bud: Liver glycogen↑, thymus lymphoid depletion, lymph nodes decreased germinal centre development, adrenals vacuolation zona fasciculata (f)

B/S= budesonide/salmeterol; bw=body weight; bud=budesonide only; sal=salmeterol only; retic=reticulocytes; WBC=white blood cells; lymph=lymphocytes; mono=monocytes; neut=neutrophils; eos=eosinophils; thromb=thrombocytes; A/G=albumin/globulin; ALP=alkaline phosphatase; GGT=gamma glutamyl transferase; PALS=periarterial lymphoid sheeths; GALT=gut associated lymphoid tissue; NALT=nasal associated lymphoid tissue; * salmeterol base doses were originally intended as 18.72 and 3.74 µg/kg

28-day repeated dose toxicity study with the Fixed Dose Combination in rats through the inhalation route (study TNO #5452)

Budesonide and salmeterol xinafoate were administered to rats by inhalation once daily for 6 hours/day, 5 days/week for 28 days. Besides salmeterol and budesonide, the formulation contained Tween 80 as an emulsifier. Investigated parameters were clinical signs, body weight, food consumption, food conversion efficiency, haematology, clinical chemistry, gross necropsy, organ weights and histopathology. Blood samples for toxicokinetics were taken, but results were not given. It is explained in the study report that salmeterol exposure was too low to be measured with the methods available at the time of the study. However, results for budesonide were also not given. Exposure in rats was up to approximately 3 – 5 times the human exposure based on steady state parameters.

It was concluded that the effects observed at the high combi level were largely similar to the effects caused by budesonide alone and that addition of salmeterol did not enhance the effects induced by budesonide.

A 3-month repeated dose toxicity study by the inhalation route in dogs (study TNO#8141)

Budesonide and salmeterol xinafoate were administered to dogs by inhalation daily for 3 months. To generate the test atmosphere, two separate turn-table dust feeders were filled with Budesonide and Salmeterol Xinafoate, respectively. Dogs were exposed daily for 5 minutes (high dose groups) or 1 minute (low dose group) with target concentrations of 112 µg/m^3 budesonide and 10.4 µg/m^3 salmeterol xinafoate. The dose of salmeterol was inadvertently calculated as xinafoate. The doses of salmeterol base are therefore 69% of the originally intended target concentration. Investigated parameters were clinical observations, ophthalmoscopic examination, body weight, consumption, haematology, clinical chemistry, gross necropsy, organ weights, histopathology. Most of the observed budesonide effects are known to be related to glucocorticosteroid treatment, and are considered to be secondary pharmacological effects rather than toxicological effects. Decreased eosinophil and lymphocyte counts and effect on the spleen are associated with the anti-inflammatory activity of glucocorticosteroids. Effects on adrenals and electrolyte disbalance in blood are considered to be due to glucocorticosteroid-mediated inhibitory effects on the pituitary-adrenal axis. Inhibition of the pituitary gland function results in reduced ACTH release by the adrenals, and consequently, the electrolyte resorption by the kidneys is affected, leading to electrolyte disbalance in blood. Several other observed changes (i.e. increased liver weight, increased ALP and GGT levels, decreased glucose levels) are related to glucocorticosteroid-mediated effects on liver function. The effects observed in the high combi group were generally comparable to those observed in the animals treated with budesonide alone except for some minor differences.

A 14-day study in dogs with toxicokinetic, cardiac, glucose/potassium data and inclusion of a recovery period (study TNO#9015)

This study was a bridging study to provide additional data on electrocardiography and toxicokinetics. Budesonide and salmeterol xinafoate were administered to dogs by inhalation daily for 2 weeks. The target concentrations and exposure durations were chosen to be the same as in the preceding 3-month inhalation study. Investigated parameters were clinical observations, body weight, food consumption, toxicokinetics, electrocardiography, haematology, clinical chemistry, gross necropsy, organ weights, histopathology. A mild QT increase was observed in 2 dogs, 1 female from the budesonide group and 1 female from the salmeterol group. QT remained however within reference values. Of the effects observed, the following were still visible after 14 days recovery: in the thymus there was still lymphoid depletion, though there were signs of recovery and in the zona fasciculata in the adrenals, there was still vacuolation. It was concluded that no evidence was found of enhancement of toxic effects or onset of novel toxic effects after repetitive treatment of male and female dogs with a mixture of budesonide and salmeterol xinafoate for 2 weeks, in comparison with the effects observed after treatment with either budesonide or salmeterol xinafoate alone.

The maximum exposure to budesonide in combination with salmeterol was 11 and 16 times the human exposure to epimer A based on AUC and Cmax respectively and 12 and 19 times the human exposure to epimer B (for toxicokinetic values in the dog study see section 3.2; based on human steady state values AUC 1746 pg.h/ml and Cmax 879 pg/ml for epimer A and AUC 1430 pg.h/ml and Cmax 776 pg/ml for epimer B). The maximum exposure to salmeterol in combination with budesonide was 57 times human exposure based on AUC and 19 times human exposure based on Cmax (based on human values AUC 138 pg.h/ml and Cmax 138 pg/ml).

Interspecies comparison

No new pharmacokinetic studies were provided by the applicant for interspecies comparison. Therefore, only a brief summary on interspecies comparison can be made based on the pharmacokinetics of the separate compounds.

The plasma protein binding of salmeterol was independent of drug concentration and ~95% in all species. For budesonide, plasma protein binding was 85% in rabbits, 86% in mice and human, 89% in dogs and 92% in rats.

The metabolic pattern in the pre-clinical species and humans is different for salmeterol. In mouse, rat and rabbit the predominant metabolic route is via glucuronidation of the parent drug. The major metabolite in dogs was eventually identified as the 3-catechol sulphate of the benzoic acid derivative. This metabolite was shown to have very similar physicochemical properties to a major endogenous component of the bile. In humans, salmeterol undergoes extensive aliphatic oxidation to α-hydroxysalmeterol. For budesonide, the metabolic pattern is more comparable across the pre-clinical species mouse and rat and in humans, except that in rat two metabolites are formed via reductive metabolism which are not present in mouse and one metabolite not present in humans.

For salmeterol, excretion was predominantly via feces in all species both after oral and intravenous administration. Biliary excretion was found in rats and dogs after oral administration. After oral administration, budesonide was mainly excreted as metabolites in the bile and eliminated in the feces in rat and dog. After intravenous administration in rabbits, approximately the same was eliminated in urine and feces. In humans, after oral and inhalation administration, budesonide was mainly excreted in urine.

Genotoxicity

Salmeterol

Salmeterol was found devoid of genotoxic potential in the following in vitro and in vivo tests: in vitro chromosomal aberration test, Ames test, fluctuation test, a gene conversion assay using Saccharyomyces cerevisiae, Chinese hamster assay and in an in vivo micronucleus test.

Budesonide

Budesonide was found negative in the six following genotoxicity assays: Ames test, mouse lymphoma, unscheduled DNA synthesis, human lymphocyte chromosome aberration, mouse in vivo micronucleus and recessive lethal test in Drosophila.

Salmeterol / budesonide

No genotoxicity studies have been performed for the combination salmeterol/budesonide which is considered acceptable by the CHMP.

Carcinogenicity

Salmeterol

Long-term carcinogenity assays with salmeterol xinafoate were conducted in rats administered by inhalation (doses 0.06, 0.18 and 0.58 mg/kg/day) followed by gavage (doses (0.15, 0.5 and 2.0 mg/kg/day) for 104 weeks and in mice administered by gavage (doses 0, 0.1, 1 or 10 mg/kg/day) for 80 weeks. Treatment was associated with increased incidences of smooth muscle hyperplasia and benign smooth muscle tumours (leiomyomas) of the mesovarium in the rat and the uterus in the mouse. For both species the incidence of tumours was statistically significantly increased at the intermediate and high doses only. Three malignant smooth tumours were identified in salmeterol-treated mice. Significant increases were observed in the incidence of tumours of the pars anterior of the pituitary in the rat study in intermediate and high dose groups. The number of malignant smooth muscle tumours were not statistically significant compared to controls and were reported within the laboratory range. The greater number of pituitary adenomas noted correlated with a reduction in the proportion of rats with hyperplasia with the pars anterior suggesting that rather than initiating tumour formation, treatment with salmeterol had merely accelerated the progression from hyperplasia to adenoma formation that occurs as normal ageing process in rats. At the no effect doses, clear safety margins could be calculated (figures not given). Leiomyomas are believed to be an adaptive physiological response to continuous relaxation of the smooth muscle. Mouse uterus and rat mesovarium are described as uniquely sensitive to the pharmacological effects of β2-agonists and the tumours in these organs were considered not clinically relevant.

Budesonide

Long term studies were conducted in mice and rats using oral administration to evaluate the carcinogenic potential of budesonide. There was no evidence of a carcinogenic effect when budesonide was administered orally for 91 weeks to mice at doses up to 200 µg/kg/day. In a 104-week oral study in Sprague Dawley rats, a statistically significant increase in the incidence of gliomas was observed in male rats receiving an oral dose of 50 µg/kg/day. No such changes were seen in male rats receiving oral doses of 10 and 25 µg/kg/day, or in female rats at oral doses up to 50 µg/kg/day. Two additional 104-week carcinogenicity studies have been performed with oral budesonide at doses of 50 µg/kg/day in male Sprague-Dawley and Fischer rats. These studies did not demonstrate an increased glioma incidence in budesonide-treated animals, as compared with concurrent controls or reference corticosteroid-treated groups (prednisolone and triamcinolone acetonide) in these studies.

Salmeterol / budesonide

The fixed dose combination of salmeterol/budesonide contains two compounds assessed as non carcinogenic. The carcinogenic potential is thus fully assessed. Hence other studies assessing carcinogenic potential with the combination are not needed in accordance with the requirements of the “Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products “(EMEA/CHMP/SWP/258498/2005).

Reproduction Toxicity

Salmeterol

In reproductive toxicology studies, salmeterol xinafoate did not affect fertility in rats at doses of 0.15, 0.5 and 2.0 mg/kg per os. Salmeterol xinafoate was not teratogenic in rats at doses of 0.1, 1.0 and 10 mg per os. However, in rabbits administered 0.1 and 10.0 mg/kg per os, teratogenicity was seen at doses of 1.0 mg/kg and above per os. The malformations consisted of open eyelid and/or cleft palates. In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above, salmeterol exhibited foetal toxic effects characteristically resulting from β-adrenoreceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg. New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10.0 mg/kg In the peri- and post-natal development stage in rats 10 mg/kg per os was fetotoxic and decreased the fertility of the survivors. Salmeterol xinafoate crosses the placenta following oral administration of 10.0 mg/kg to mice and is excreted in the milk.

Budesonide

The effects of subcutaneous budesonide on fertility and general reproductive performance were studied in rats. At 20.0 µg/kg/day decreases in maternal body weight gain, prenatal viability and viability of the young at birth and during lactation were observed. No such effects were observed at 5 µg/kg/day. As with other glucocorticoids, budesonide produced fetal loss, decreased pup weight and skeletal abnormalities at subcutaneous doses of 25 µg/kg/day in rabbits and 500 µg/kg/day in rats. No teratogenic or embryocidal effects were observed in rats when budesonide was administered by inhalation at doses up to 250 µg/kg/day. Corticosteroids are secreted in human milk.

Salmeterol / budesonide

No fertility and early embryonic , embryo-foetal, pre-natal and post-natal development studies have been performed for the combination salmeterol/budesonide which is considered acceptable by the CHMP.

Local Tolerance

In the literature data provided with this application, no specific concerns appear for the local tolerance of either salmeterol or budesonide. During the repeat-dose toxicity studies performed in the rat and dog with the combination, a thorough examination of the respiratory tract i.e. trachea/bronchi and lungs was performed and did not reveal any particularity with the exception of slight inflammatory signs occasionally seen in the respiratory tract but not considered of importance.

Salmeterol / budesonide

No local toterance studies have been performed for the combination salmeterol/budesonide which is considered acceptable by the CHMP.

Other toxicity studies

Immunotoxicity

Salmeterol

A publication was provided describing a 28-day repeated dose toxicity test in which salmeterol was administered to Wistar rats. Several immunotoxicity screening parameters were incorporated in the study protocol to investigate the immunotoxic potential of the compound. Male rats were orally treated with 0, 0.2, 2 and 20 mg salmeterol/kg body weight/day. At the 20 mg/kg/day dose level, intubation errors occurred because the animals tried to resist intubation. Some of these animals died intercurrently. Therefore, the magnitude of the dose was lowered to 10 mg/kg/day at day 9 of treatment. Body weight and bone marrow cellularity were not affected. Hematological parameters were not altered either, except for platelet counts, that were decreased at all dose levels. Also liver weights were decreased at all dose levels tested. Absolute thymic weights were decreased at the 2 and 20/10 mg/kg/day dose levels. No treatment-related (histo)pathological lesions were seen in the (non)lymphoid organs. Serum IgM levels were increased at the 0.2, and IgG at the 2 and 20/10 mg/kg/day dose levels, respectively. B cell numbers in the spleen were decreased at all dose levels tested. It was concluded that salmeterol has weak immunotoxic properties, as can be expected based on its anti-inflammatory properties. Salmeterol-associated immune dysfunction is however considered unlikely because the dose levels in this study are extremely high compared to therapeutic dose levels used in asthma.

Budesonide

Immunotoxicity studies were not considered relevant since budesonide has strong anti-inflammatory properties which are dose-dependent as seen in all the repeated dose toxicity studies presented earlier. Those changes consist of lymphoid depletion in thymus and all lymphoid tissues, decreased cellularity in the bone marrow and decreased white blood cell counts (except for the apparent neutrophil increase).

Salmeterol / budesonide

No immunotoxicity studies have been performed for the combination salmeterol/budesonide which is considered acceptable by the CHMP.

2.3.5. Ecotoxicity / environmental risk assessment

The Environmental Risk Assessment (ERA) submitted for Labazenit was prepared in compliance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). The two active substances salmeterol and budesonide have been assessed separately.

Salmeterol

Phase I

Calculation of the Predicted Environment Concentration (PEC)

The environmental exposure assessment was estimated according to the formula for the calculation of the Predicted Environmental Concentration (PEC):

$$PEC_{\text{SURFACE WATER}} = \frac{DOSEai \cdot F_{pen}}{WASTEW_{inhab} \cdot DILUTION}$$

The following values were used for the calculation:

DOSEai = 0.100 mg (The maximum daily dose of salmeterol recommended for the treatment is 2 capsules of 50 µg)

Fpen = 1 % (default values proposed in the guideline)

WASTEWinhab = 200 (default values proposed in the guideline)

DILUTION = 10 (default values proposed in the guideline)

$PEC_{surfacewater}$ is 0.0005 µg/L.

$PEC_{surfacewater}$ is below 0.01 µg/L, and thus a phase II assessment is not necessary.

Octanol/Water Partition Coefficient

As stated earlier, salmeterol is also a well-known substance used as inhaled anti-inflammatory drug for respiratory affections. The Octanol/Water partition coefficient (LogKow) measured at 3 different pH conditions and 3 concentrations of the substance was found to be between 1.32 and 2.20 (Environmental Assessment, Serevent, NDA 20-692, Attachment 4). The value provided by the originator of salmeterol is LogKow = 2.2 at pH 7 (MSDS-2, Serevent Diskus). Also according to the ERA of salmeterol (Serevent) available on the website of the Swedish Medicine Agency (MPA) there is no significant bioaccumulation potential for salmeterol as its Octanol/Water partition coefficient was found to be 1.71 at pH 7, 2.06 at pH 5, 1.71 at pH 7, and 1.32 at pH 9. The compound undergoes degradation in the environment and has no potential to accumulate in aquatic organisms (FASS.se-salmeterol).

Action limits

As the PEC < 0.01 µg/l and the logKow <4.5, it can be assumed according to EMA guideline on the ERA of medicinal products for human use (CPMP/SWP/4447/00).that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

Table 3. Summary of main study results

Substance (INN/Invented Name): salmeterol			
CAS-number (if available): 94749-08-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	No study report provided.	Potential PBT (Y/N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	No study report provided	B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.0005	µg/L	> 0.01 threshold : No
Other concerns (e.g. chemical class)	No		

Budesonide

Phase I

Calculation of the Predicted Environment Concentration (PEC)

The environmental exposure assessment was estimated according to the formula for the calculation of the Predicted Environmental Concentration (PEC):

$$PEC_{\text{SURFACE WATER}} = \frac{DOSE\text{ai} \cdot F_{\text{pen}}}{WASTEW_{\text{inhab}} \cdot DILUTION}$$

The following values were used for the calculation:

*DOSE*ai = 0.600 (mg patient^{-1} d^{-1})

F_{pen} = 0.01 (patient inh^{-1})

*WASTEW*inhab = 200 (L inh^{-1} d^{-1})

DILUTION = 10 (–)

$PEC_{surfacewater}$ is 0.003 µg/L.

The PECsurfacewater is below 0.01 µg/L, and thus a phase II assessment is not necessary.

Octanol/Water Partition Coefficient

Budesonide is a well-known substance used as inhaled anti-inflammatory drug for respiratory affections, and as such ample information on its (physicochemical) properties is available. Experimentally measured values for the Octanol/Water partition coefficient (logKow) are less than 3.5. Values of 2.55 (Green J and Gommeren E, 2004) and 3.2 (Lin H et al., 2005, and Product Information, Pulmicort 2006) have been reported. Also according to the ERA of budesonide available on the Swedish

Medicine Agency (MPA) website (FASS.se-Budesonide), based on a number of study reports, the logKow = 3.3 (experimentally determined by "shake flask method" United States Pharmacopoeia (USP)).

Action limits

As the PEC <0.01 µg/l and the logKow <4.5, it can be assumed according to EMA guideline on the ERA of medicinal products for human use (CPMP/SWP/4447/00).that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

Table 4. Summary of main study results

Substance (INN/Invented Name): Budesonide			
CAS-number (if available):51333-22-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	No study report provided.	Potential PBT (Y/N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	No study report provided	B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.003	µg/L	> 0.01 threshold : No
Other concerns (e.g. chemical class)	Yes, endocrine disruptor, phase II testing required		

2.3.6. Discussion on non-clinical aspects

The combination of the ICS budesonide with the LABA salmeterol is in line with treatment guidelines for asthma treatment in patients with reversible airway obstruction who continue to experience symptoms despite treatment with an anti-inflammatory agent such as an ICS.

The pharmacology of budesonide and salmeterol is well-known hence no further pharmacology studies are deemed necessary.

One new inhalation toxicokinetic study in dogs has been provided by the Applicant with the fixed-dose combination of salmeterol and budesonide. Overall, T_{max} did not differ when budesonide and salmeterol were given as single compound and when they were given in combination. For maximum concentrations and systemic exposure, values were lower in the low concentration combination group compared to the budesonide and salmeterol only groups after both single and repeated dosing. This could be explained by the difference in exposure time (1 minute vs. 5 minutes). The C_{max} and AUC values were not a factor 5 lower in the low concentration combination group though, as would be expected by the assumption that exposure increases equally over time. Since clinical pharmacokinetic data do not indicate pharmacokinetic interactions between budesonide and salmeterol, overall it can be considered that the pharmacokinetic parameters of salmeterol and budesonide are not altered when given in combination.

Based on information provided for budesonide and salmeterol as single compounds, it is suggested that both compounds of Labazenit have a large volume of distribution since both salmeterol and budesonide are widely distributed when given alone. No new studies were submitted by the Applicant on the distribution of salmeterol and budesonide when both compounds are administered in combination. Based on the present knowledge on the pharmacokinetics of both compounds and considering the fact that systemic concentrations are low for both compounds, no influence is expected on the distribution when salmeterol and budesonide are given in combination compared to given alone.

Both compounds are metabolized by CYP3A4. As such, salmeterol and budesonide may interact with each other at the level of metabolizing enzymes. CYP3A4/5 is also present in lung tissue and as both compounds will reach the lungs first before entering the systemic circulation, metabolism of both compounds may occur in the lungs. Clinically, there are no indications that interactions between the two compounds occur.

The major excretion route for salmeterol and budesonide in human is different – respectively via faeces and urine - no major interactions are expected. Also, no differences are observed in kinetic parameters when given both compounds alone compared to given in combination by inhalation. Therefore, no clinically relevant alterations are expected regarding the excretion of salmeterol and budesonide.

Systemic exposure to budesonide and salmeterol will not be very high since both compounds will be inhaled (C_{max} was ~3 ng/mL for salmeterol and ~15 ng/mL for budesonide at dosages of 10.4 mg/m^3 salmeterol and 112 mg/m^3 budesonide for 5 minutes). CYP induction and inhibition potentials and other drug-drug interactions as found for both substances individually are also included in the proposed Labazenit SmPC in section 4.5.

Since all three toxicology studies indicate that toxic effects are not aggravated by the combination and toxicokinetics in dogs as well as pharmacokinetics in humans indicate no relevant interaction between budesonide and salmeterol, the present data can be regarded sufficient. In the combination studies, mainly effects were observed that could be ascribed to budesonide: decreased body weight gain (rat), decreased lymphocytes and depletion of lymphoid tissues, increases of transaminases (dog), increased glucose and triglycerides (rat) and atrophy of the zona fasciculata in the adrenals (dog). In the 2-week dog study, tachycardia and decreased potassium were observed as effects caused by salmeterol. Neither budesonide nor salmeterol effects were aggravated due to the combination. The maximum exposure to budesonide and salmeterol was sufficient.

Regarding interspecies comparison it was noted that plasma protein binding differed across species for budesonide (85-92%), with the free fraction in humans (86% plasma protein binding) approximately twice as large as in rats (92%). For salmeterol the plasma protein binding was approximately the same (~95%) across the non-clinical species and in humans. The metabolic patterns of salmeterol and budesonide are more (salmeterol) or less (budesonide) different across species, including the human situation. The 3-catechol sulphate metabolite found in dog bile after metabolism of salmeterol is expected to be a species-specific metabolite, and due to the resemblances with a major endogenous component in bile assumed to react with bile salts. The excretion of salmeterol occurs mainly via elimination in feces in all species. For budesonide however, excretion is via bile and faeces in rat and dog, via both urine and feces in rabbit, and via urine in humans.

There is considerable clinical experience with budesonide during pregnancy hence further peri- and postnatal development studies with budesonide seem not necessary.

Immunotoxicity of salmeterol can be considered not relevant at therapeutic dose levels. Effects of budesonide on the immune system were caused by its pharmacological actions and were not aggravated by the combination with salmeterol in combination studies in rats and dogs. Additional immunotoxicity studies were not necessary.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical developmental plan of the combination salmeterol/budesonide was limited to necessary studies. This is considered acceptable. The available non-clinical data including the results obtained from the repeat dose toxicity studies with the FDC salmeterol/budesonide and the environmental risk assessment did not identify any new safety issues. The non-clinical safety profile of salmeterol/budesonide appears to be consistent with those established for salmeterol and budesonide when used as monotherapy. Based on the available non-clinical safety data with the two monotherapy compounds, salmeterol and budesonide, it is concluded that the FDC should be well tolerated when used in human at the proposed dosage.

2.4. Clinical aspects

2.4.1. Introduction

The Applicant is seeking a Marketing Authorisation for salmeterol/budesonide inhalation powder in hard capsules for the regular treatment of asthma in adults where use of a fixed combination medicinal product (inhaled corticosteroid and long-acting β2-agonist) is appropriate: patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting β2-agonists or patients already adequately controlled on both inhaled corticosteroids and long-acting β2-agonists.

The recommended dose in adults patients is one inhalation of Labazenit 120 micrograms/20 micrograms twice daily, or one inhalation of Labazenit 240 micrograms /20 micrograms twice daily. No dose adjustment is required in patients with renal and/or hepatic impairment.

The clinical development program of Labazenit was designed to demonstrate the safety and efficacy of salmeterol/budesonide as FDC in patients with asthma. No dedicated studies with salmeterol or budesonide as monotherapy were conducted. The pharmacokinetics, safety, and efficacy profiles of salmeterol and budesonide as monotherapy are well known. The clinical development programs for salmeterol/budesonide is presented in the three tables below.

Scientific advice was provided by the CHMP in January 2010 on the non-clinical and clinical aspects of the development program. The CHMP highlighted that the clinical program as proposed by the Applicant might not be sufficient since the phase III studies faced issues with regard to the strengths and the lack of assay sensitivity in phase II and III studies.

GCP

According to the applicant the clinical trials were performed in accordance with GCP. The Applicant has provided a statement to the effect that clinical trials conducted outside the Union were carried out in accordance with the ethical standards provided for under Directive 2001/20/EC.

A triggered GCP inspection was requested by the CHMP in the light of concerns related to data reporting and analyses that were highlighted during the assessment. A GCP inspection was conducted which focused on studies BUSAL SS071 and BUSAL III-02-01. Critical findings concerning monitoring for study BUSAL SS071 were identified during the inspection but it was considered that these findings had no consequences for the reported data. In contrast, the conduct of trial BUSAL III-02-01 was not conducted in compliance with GCP due to deficiencies identified in data management of the secondary efficacy parameters FEV_1 and FVC. The integrated inspection report recommended the data for FVC and FEV_1 from all sites should not be accepted by the CHMP to support this initial MAA. It was highlifghted during the inspection that the data seems to have been well recorded in the CRF despite some issues about the position of the comma in the CRF that would also been in line with the study protocol. The deviation should not impact the overall results as the values used were derived from three reproducible spirometric measurement, which should not differ by > 5% or by 0.1 L, whichever is the greatest. The inspection's outcome recommended that the Applicant should perform a statistical reanalysis of the FVC and FEV_1 parameters with the highest values recorded in the CRF for study BUSAL-III-02-1. As requested, a statistical reanalysis of the highest FEV_1, and FVC for week 12 was submitted by the Applicant during the evaluation as were the spirometric values measured in the safety phase of the study from week 12 to week 24.The difference with the originally presented values were small. No statistically significant differences were seen for FEV1 and FEV1 % of predicted and FVC between the two strengths of Labazenit.

Table 5. Overview of pharmacokinetic studies (Busal =Labazenit)

Study N° (year)	N° of subjects	Design	Product Strengths (µg)	Aim
SMB-BUSAL-SD033 (2003)	24 healthy subjects	Single dose 3-way cross-over	BUSAL 300/25 BUSAL 15025 Pulmicort 2x200	- comparative budesonide exposure - dose proportionality
SMB-BUSAL-SS032 (2003)	24 healthy subjects	Multiple dose 3-way cross-over	BUSAL 1x300/25 Pulmicort 2x200 Serevent 1x50	comparative exposure budesonide and salmeterol
SMB-BUSAL-SS071 (2007)	36 healthy subjects	Multiple dose 2-way cross-over	BUSAL 150/25 Pulmicort+Serevent 200+50	comparative exposure budesonide and salmeterol
SMB-BUSAL-SD101 (2010)	40 healthy subjects	Single dose 4-way cross-over	BUSAL 2x300/25 SMB Budesonide* 2x300 SMB Salmeterol* 2x25 SMB Bud+Salm* 2x(300+25)	interaction
SMB-BUSAL-DP102 (2010)	40 asthma	Single dose 2-way cross-over + charcoal	BUSAL 300/25 BUSAL 150/25	dose proportionality
SMB-BUSAL-SD111 (2012 – submitted at Day 120)	40 asthma	Single dose 2-way cross-over + charcoal	BUSAL 150/25 Pulmicort 1x200	comparative lung deposition budesonide
SMB-BUSAL-SD121 (2012 – submitted at Day 120)	32 Healthy subjects	Single dose 2-way cross-over	BUSAL 2x150/25 Serevent 2x50	comparative exposure salmeterol

Table 6. Overview of the Phase II Clinical studies with BUSAL (=Labazenit)

Study Ref.	**BUSAL-II-03-1** *Supportive study*	**BUSAL-II-10-1** *Supportive study*	**BUSAL-II-10-2** *Supportive safety study*
Aim	Proof of substitution indication for salmeterol	Proof of substitution indication for salmeterol	Proof of safety of budesonide on HPA axis: both indications
Methods	Controlled single-blind	Controlled partially blinded	Controlled partially blinded
Population	Moderate persistent asthma	Moderate to severe persistent asthma	Mild persistent asthma
Duration	Single dose	Single dose	Four periods of 10 days
Treatment groups	BUSAL 150/25 µg vs. SEREVENT DISKUS 50 µg	BUSAL 150/25 µg vs. BUSAL 150/12.5 µg vs. BUSAL 150/6.25 µg vs. SEREVENT DISKUS 50 µg vs. SEREVENT EVOHALER 25 µg vs. SEREVENT EVOHALER 2x25 µg	BUSAL 300/25 µg BID vs. BUSAL 150/25 µg BID vs. PULMICORT TURBUHALER 400 µg BID and SEREVENT DISKUS 50 µg BID vs. Placebo BID

Total randomized patients (N=123)	35	48	40

Table 7. Overview of the Phase III Clinical studies with BUSAL (=Labazenit)

Study Ref.	**BUSAL-III-02-1** *Pivotal study*	**BUSAL-III-05-1** *Supportive study*	**BUSAL-III-06-1** *Extension supportive safety study*	**BUSAL-III-08-1** *Supportive study*
Aim	Proof of step-up indication, proof of substitution indication for budesonide	Proof of substitution indication	Proof of long term efficacy: both indications	Proof of substitution indication
Methods	Controlled partially blinded	Controlled open-label	Open-label	Controlled open-label
Population	Moderate persistent asthma	Moderate to severe persistent asthma	Moderate to severe persistent asthma	Moderate to severe persistent asthma
Duration	Run in period: 2 weeks Controlled PB period: 12 weeks Open-label period: 12 weeks	Run in period: 2 weeks Controlled open-label period: 12 weeks Open-label period: 12 weeks	Open-label: 28 additional weeks	Run in period: 2 weeks Controlled open-label period: 12 weeks
Treatment groups	Run in period: Placebo BID Controlled PB period: BUSAL 300/25 µg BID vs. BUSAL 150/25 µg BID vs. PULMICORT TURBUHALER 2x200 µg BID Open-label period: BUSAL 300/25 µg BID vs. BUSAL 150/25 µg BID	Run in period: QVAR 200 µg BID Controlled open-label period: BUSAL 300/25 µg BID vs. SERETIDE DISKUS 500/50 µg BID Open-label period: BUSAL 300/25 µg BID	BUSAL 300/25 µg BID	Run in period: PULMICORT TURBUHALER 2x200 µg BID Controlled open label period: BUSAL 150/25 µg BID vs. SYMBICORTTURBUHALER 200/12 µg BID
Total randomized patients (N=1206)	375	492	110	229

2.4.2. Pharmacokinetics

Only limited data on the pharmacokinetics of salmeterol are available. This lack of information is most likely due to the very low plasma concentration obtained after inhalation of therapeutic doses of salmeterol. Indeed, salmeterol is rapidly absorbed from the lung after inhalation and only a few part of the administered dose reached the systemic circulation. Furthermore, due to these low salmeterol plasma concentration, developing an analytical method that is sensitive enough to determine these low concentrations was difficult. Salmeterol exerts its therapeutic effects through local action on β2 receptors in the lung. Hence, plasma levels of the drug have no bearing on the therapeutic efficacy of salmeterol. Previous studies reviewed by Van Eenoo *et al*. have demonstrated that patients have a Cmax at the first sampling point (5 min). Therefore as most of the subsequent concentration values obtained were close to LOQ, no pharmacokinetic parameters were calculable due to assay limitations.

Budesonide consists of a one-to-one mixture of epimers with 22R and 22S configuration – also referred to as epimer A and B, respectively. Both epimers seem to have the same qualitative pharmacological effects. The fraction deposited in the oral cavity is relatively poorly absorbed into the systemic circulation. In addition, the amount of budesonide that penetrates the air/blood barrier is low.

Analytical methods

Concentrations of budesonide (epimers A and B) and salmeterol in human plasma were measured using specific LC/MS/MS method. The method was 4 times optimised but the LLOQ levels for the budesonide enantiomers 22.5-50 pg/ml and 15 pg/ml for salmeterol remained relatively high compared to the plasma concentrations of budesonide and salmeterol. For Labazenit 150/25 µg strength, C_{max} for budesonide and salmeterol were less than 10x the LLOQ in studies BUSAL-SS032, BUSAL-SD033, BUSAL-SS071 and busal-SD101. Therefore, AUC levels could not be determined accurately for budesonide when Labazenit or the respectively mono-products were administered at the lowest therapeutic dose in these studies. In study BUSAL-DP102 (dose proportionality) and study BUSAL-SD111 (lung deposition PK), submitted by the Applicant with the responses to the D120 LOQ, the analytical assay was improved and evaluation of the low strength of Labazenit was possible.

As many of the salmeterol data fell below the LLOQ, the Applicant omitted the salmeterol data from the study reports. This is an important omission as, arguably, the delivery of salmeterol is as important as that of budesonide in terms of clinical safety and efficacy. With the D120 LOQ responses, the Applicant submitted a new PK study, study BUSAL-SD121, with a more robust analytical method, comparing the bioavailability of salmeterol between Labazenit and Serevent Diskus following a higher than recommended dose to increase the salmeterol plasma concentrations. As a result, ccomparison of pharmacokinetics of salmeterol between Labazenit and salmeterol mono compound will only be based on the results from study BUSAL-SD121. There were some irregularities observed with the pharmacokinetic analysis. Subjects were excluded from PK and/or statistical analysis seemingly arbitrarily. Criteria for exclusion of subjects from PK or statistical analysis were not defined in the protocol and not adequately discussed in the study reports. In addition, in the multiple dose studies Cmin plasma concentrations above the LLOQ were calculated as being at the level of LLOQ. An additional correct analysis with plasma concentrations below the LLOQ treated as missing data was submitted by the Applicant with their responses to the D120 LOQ. In the studies initially submitted with this initial MAA, removal of subjects from pharmacokinetic analysis has not been adequately defined. This may have led to inconsistent removal of subjects from the analysis but this occurred mainly when budesonide plasma concentration curve could not be fully characterised when the low budesonide dose was administered. Therefore, AUC values from studies BUSAL-SS071 and BUSAL-

SD033 with the low Labazenit strength were considered very cautiously. Data on the high Labazenit strength were assessed using data from all studies. In studies BUSAL-SD111 and BUSAL-SD121 (submitted during the evaluation), removal from pharmacokinetic analysis has been adequately defined in the protocol. Sufficient data with respect to budesonide PK was obtained from remaining PK studies using the highest strength or using an improved analytical method to evaluate the pharmacokinetics of budesonide in Labazenit.

Absorption

In vitro comparison of Labazenit with reference products and between Labazenit strengths

Table 8. Overview of the main in vitro results

Product Name	Type of study	Objectives	Results
Budesonide	Comparative study	- To compare the unfiformity of the Delivered (UDD) of Labazenit Axahler and Pulmicort Turbohaler - To compare the reproducibility in the Fine Particle Dose (FPD) from Labazenit Axahaler and from Pulmicort Turbohaler	- The UDD is better for budesonide delivered from Labazenit Axahaler than from Pulmicort Turbohaler. - The reproducibility in the Fine Particle Dose (FPD) is better for budesonide delivered from Labazenit Axahlaer than from Pulmicort Turbohaler.
	Comparative study	- To compare the stage by stage deposition of budesonide from Labazenit 150/25 µg compared to reference products (via Turbohaler) at the optimal airflow rate - To determine the influence of the inhalation airflow on the FPD of budesonide from Labazenit (via Axahaler) compared to reference products (via Turbohaler).	- The budesonide deposition is comparable between the test and the reference products at the optimal airflow rate. - The budesonide desposition is very strongly dependent on the inhalation airflow with the Turbohaler whereas Labazenit shows a reproductibe FPD and stage by stage deposition at sub-optimal airflow (60 % to 80 % of optimal airflow).
	Dose-response study	- To evaluate the in vitro dose response between Labazenit 150/25 µg and Labazenit 300/25 µg.	- The dose linearity of particle size distribution profile of budesonide from Labazenit 150/25 µg and 300/25 µg is demonstrated.
Salmeterol	Comparative study	- To compare the stage by stage deposition of salmeterol from Labazenit 150/25 µg vs Serevent Diskus 50 µg at the optinal airflow rate - To determine the influence of the inhalation airflow on the stage by stage deposition of salmeterol from Labazenit (via Axahaler) compared to the reference product (via Diskus).	- Comparable FPD and deposition profile for salmeterol between the test and the reference product at the optinal airflow rate. - Comparable FPD and deposition profile for salmeterol between the test and the reference product at sub-optimal airflow (60 % to 80 % of the optimal airflow rate).

*The complete in-vitro data for budesonide are given in annex 4 of the present document.
** The complete in-vitro data for budesonide dose-response are given in annex 5 of the present document.
*** The complete in-vitro data for salmeterol are given in annex 6 of the present document.

In-vitro comparison of budesonide from Labazenit Axahaler 150/25 µg versus Pulmicort Turbuhaler 200 µg at optimal airflow

In order to allow a statistically reliable comparison between Labazenit Axahaler 150/25 µg and Pulmicort Turbuhaler 200 µg, 5 batches of Labazenit were used among which 4 batches used in clinical trials and one is an industrial batch. For Pulmicort Turbuhaler also 5 batches were used. All the batches of Pulmicort Turbuhaler used for the comparison were within the product specification for UDD and show approximately the expected and published value FPD (± 30 % of the nominal dose) for this marketed product.

Table 9. 90% confidence interval for the observed in vitro differences between LABAZENIT150/25 (TEST) and PULMICORT 200 (REF.)

Deposition (µg)	Budesonide				
	Test	Ref	Ratio	CI lower	CI upper
> 5 µg	61,98	69,37	0,89	0,83	0,96
4-5 µg	8.43	6,68	1,26	1,14	1,39
3-4 µg	12,33	11,05	1,12	1,02	1,21
2-3 µg	18,14	19,58	0,93	0,86	0,99
< 2 µg	20,55	24,45	0,84	0,74	0,94
Delivered Dose	121,14	131,37	0,92	0,87	0,98
FPD	59,16	62,00	0,95	0,89	1,02

The mean ratio of test/reference for the FPD is of 0,95 with a 90% CI of 0,89-1,02.

In-vitro comparison of budesonide from Labazenit AxahalerR 150/25 µg versus Symbicort Turbuhaler 160/4.5 µg at different airflows

Since most of the clinical and/or validation batches of test and reference products presented above were expired, and that the OIP guideline recommends three different batches for this comparison, it was decided to analyse and compare the following batches:

- For Labazenit a clinical batch and the first two industrial batches (Labazenit 150/25 g) and (Labazenit 300/25 g with a dose correction)
- For Symbicord Turbohaler the clinical batch used in the recent pharmacokinetic study SMB-BUSAL-SD-111 and 2 commercial batches recently purchased by the Applicant
- For Pulmicort Turbohaler three commercial batches recently purchased by the applicant

Table 10. 90% confidence interval for the observed in vitro differences between LABAZENIT 150/25 (TEST) and SYMBICORT (REF.) at 3 inhalation airflows

i. 100% (i.e. the optimal airflow)

Deposition (µg)	Budesonide				
	Test	Ref	Ratio	CI lower	CI upper
> 5 µg	69,32	64,80	1,07	0,95	1,19
4-5 µg	9,21	7,77	1,19	1,01	1,36
3-4 µg	13,26	12,75	1,04	0,91	1,17
2-3 µg	18,73	23,85	0,79	0,72	0,85
< 2 µg	17,63	22,93	0,77	0,59	0,94
FPD	55,83	67,29	0,87	0,79	0,96

ii. 80 % (of the optimal airflow)

Deposition (µg)	Budesonide				
	Test	Ref	Ratio	CI lower	CI upper
> 5 µg	68,50	66,14	1,04	0,97	1,10
4-5 µg	9,27	6,69	1,39	1,19	1,58
3-4 µg	13,14	12,26	1,07	0,96	1,18
2-3 µg	18,97	19,66	0,96	0,88	1,05
< 2 µg	14,55	17,07	0,85	0,68	1,03
FPD	55,75	55,68	1,00	0,91	1,09

iii. 60 % (of the optimal airflow)

Deposition (µg)	Budesonide				
	Test	Ref	Ratio	CI lower	CI upper
> 5 µg	69,32	66,48	1,04	0,93	1,15
4-5 µg	9,21	4,69	1,96	1,62	2,30
3-4 µg	12,97	8,34	1,55	1,37	1,74
2-3 µg	18,15	10,87	1,67	1,47	1,87
< 2 µg	10,99	9,12	1,21	0,80	1,61
FPD	51,32	33,02	1,55	1,34	1,76

In-vitro dose-response of budesonide between Labazenit Axahaler 150/25 µg and LabazenitT Axahaler 300/25 µg

In order to assess the dose-response of budesonide between the two proposed dosage strengths of LABAZENIT, in-vitro comparison were performed with the same methodology as previously described. 5 batches of LabazenitT 150/25 µg were compared (4 clinical batches and an industrial batch) to 5 batches of Labazenit 300/25 µg (4 clinical batches and an industrial batch).

Table 11. 90% confidence interval for the observed in vitro differences between LABAZENIT 150/25 and LABAZENIT 300/25 for budeseonide (MSLI)

Deposition (µg)	Budesonide				
	L150/25	L300/25	Ratio	CI lower	CI upper
> 5 µg	0,41	0,37	1,11	1,06	1,15
4-5 µg	0,06	0,05	1,05	0,97	1,13
3-4 µg	0,08	0,08	0,99	0,92	1,06
2-3 µg	0,12	0,14	0,90	0,85	0,94
< 2 µg	0,14	0,18	0,78	0,71	0,85
Delivered dose	0,81	0,82	0,99	0,96	1,02
FPD	0,39	0,44	0,89	0,84	0,93

* The amount of budesonide deposited on each group was divided by the nominal dose

If dose linearity is demonstrated *in-vitro* it may be sufficient to establish therapeutic equivalence clinically with only one strength of the active substance as per the OIP guideline (CPMP/QWP/EWP/1401/98 rev.1). Dose linearity was evaluated by comparison of the average delivered dose and FPD. Statistical analysis of the amounts of budesonide recovered from each stage of the MLI needs to be submitted. Furthermore, flow rate dependency of both strengths was compared at 100, 80, 60 and 30 L/min. As shown in the figures below, there is no significant influence of the airflow on the deposition of salmeterol and budesonide between 80 L/min and 100 L/min. Below 80L/min, the deposition decreases slightly, while it declines significantly at 30 L/min, reaching about half of the pulmonary deposition at the optimal flow. The flow rate dependency of FPD was comparable for Labazenit 300/25 µg and Labazenit 150/25 µg. Based on the provided FPD data and flow dependency the two strengths are dose proportional.

Figure 1. Influence of the airflow on the FPD of Labazenit 150/25 mcg, n=5

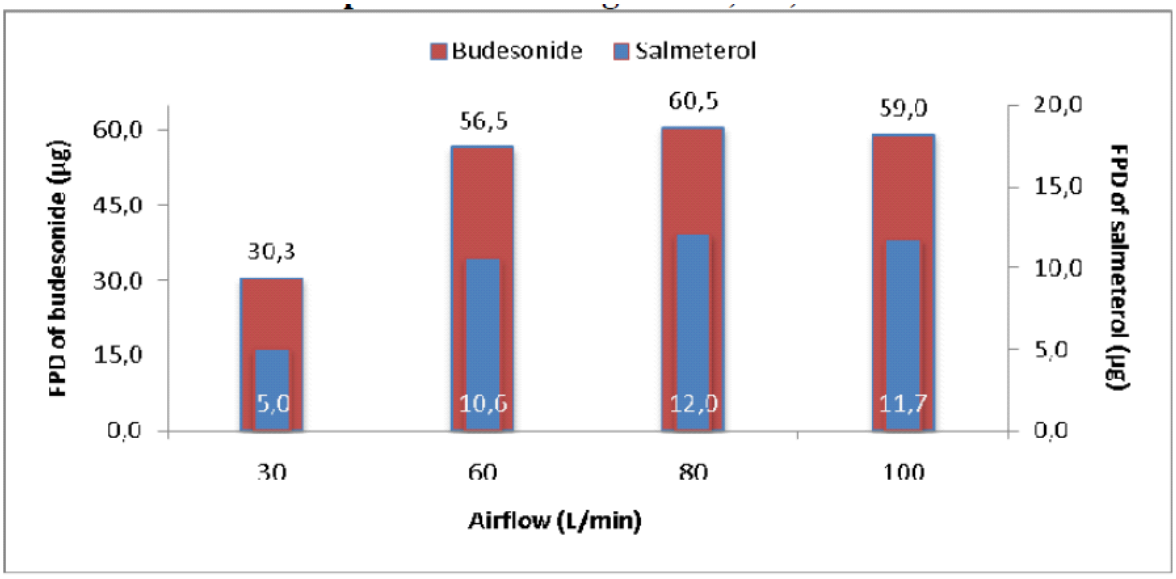
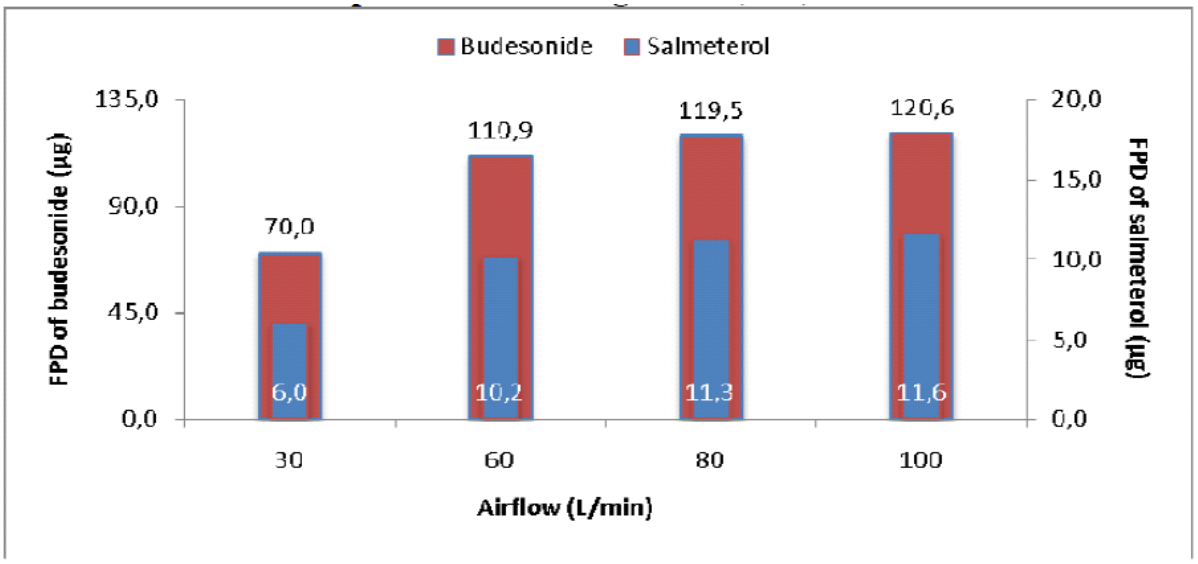


Figure 2. Influence of the airflow on the FPD of Labazenit 300/25 mcg, n=5



Bioavailability

Salmeterol

Salmeterol is rapidly absorbed after inhalation with Tmax 5 min in more than 80% of subjects. Salmeterol and its counter ion, xinaphoic acid, dissociate in solution and are absorbed, distributed, metabolised and eliminated separately. In patients with asthma receiving salmeterol 50 µg twice daily, peak salmeterol concentrations of 150 ng/l were detected in plasma 5 to 10 minutes after inhalation and a second peak concentration of 115 ng/l occurred in plasma approximately 45 minutes after inhalation, probably as the result of absorption of swallowed drug. Larger inhaled doses give approximately proportionally increased blood concentrations. Plasma salmeterol concentrations of 0.1 to 0.2 and 1 to 2 µg/L have been attained in healthy volunteers about 5 to 15 minutes after inhalation of a single dose of 50 and 400 µg, respectively.

Budesonide

The oral availability of budesonide is low. In the original review by Clissold SP and Heel RC, the systemic bioavailability of budesonide following oral administration was 10.7%. Since 73% of the dose reaching the lung was systemically available, extensive first-pass metabolism was suggested.

After oral administration of budesonide, peak plasma concentration was achieved in about 1 to 2 hours and the absolute systemic availability was 6-13%. In contrast, most of budesonide delivered to the lungs is systematically absorbed. In healthy subjects, 34% of the metered dose was deposited in the lungs as assessed by plasma concentration method and using a different budesonide delivered from Pulmicort Flexhaler in adults asthma (n=39) occurred at approximately 10 minutes post-dose and averaged 0.6 and 1.6 nmol/L at doses of 180µg once daily and 360µg twice daily, respectively.

Salmeterol/budesonide

In three studies (studies SMB-BUSAL-SS032, SMB-BUSAL-SS071 and SMB-BUSAL-SD033) bioavailability following Labazenit inhalation was compared with that of the reference products Pulmicort Turbuhaler and Serevent DiskusS. The first study, study SMB-Busal-SS032 was a multiple dose, steady state, 3 way, cross-over study to compare the bioavailability of budesonide and salmeterol of Labazenit 300/25 with the respective single agent reference products Pulmicort Turbuhaler and Serevent DiskusS. In the second study SMB-Busal-SS071, pharmacokinetics of Labazenit 150/25 µg was compared to the combination of Pulmicort Turbuhlaer and Serevent Diskus in a multiple dose, steady state, 2 way, cross-over study. The dose administration in the multiple dose studies is in line with the dose recommendation for Labazenit. Finally, in study SMB-Busal-SD033, a single dose of Labazenit 300/25 and Labazenit 150/25 were compared with one single dose of 2 puffs of Pulmicort Turbuhaler, no comparison with Serevent was made.

Study SMB-Busal-SS032 (300/25)

Study SMB-Busal-SS032 was a comparative multiple dose, three-treatments, three-periods, six-sequences, randomised, crossover study in 24 healthy volunteers, with at least 7 days wash-out between each period. This study was conducted in Poland in 2003.

The fixed dose combination of budesonide/salmeterol 300/25µg or the budesonide reference drug product (2 inhalations of PULMICORT 200µg) or salmeterol reference drug product (Serevent 50µg) were administered during the seven first days of each period twice a day.

Results

As demonstrated in the table and figure below, budesonide (epimer A and epimer B) of Labazenit 300/25µg and Pulmicort 2*200µg showed comparable bioavailability after multiple-dose administrations.

Due to the rapid elimination of budesonide and salmeterol, 12 h after the inhalation, most of plasma budesonide and salmeterol concentrations were below the limit of quantification. Therefore, no Cmin and swing could be determined for both agents.

Figure 3. Mean plasma concentration of budesonide (budesonide total) after oral administration of Budesonide/Salmeterol 300/25µg and Pulmicort 2*200 µg for seven days twice daily (study SMB-Busal-SS032).

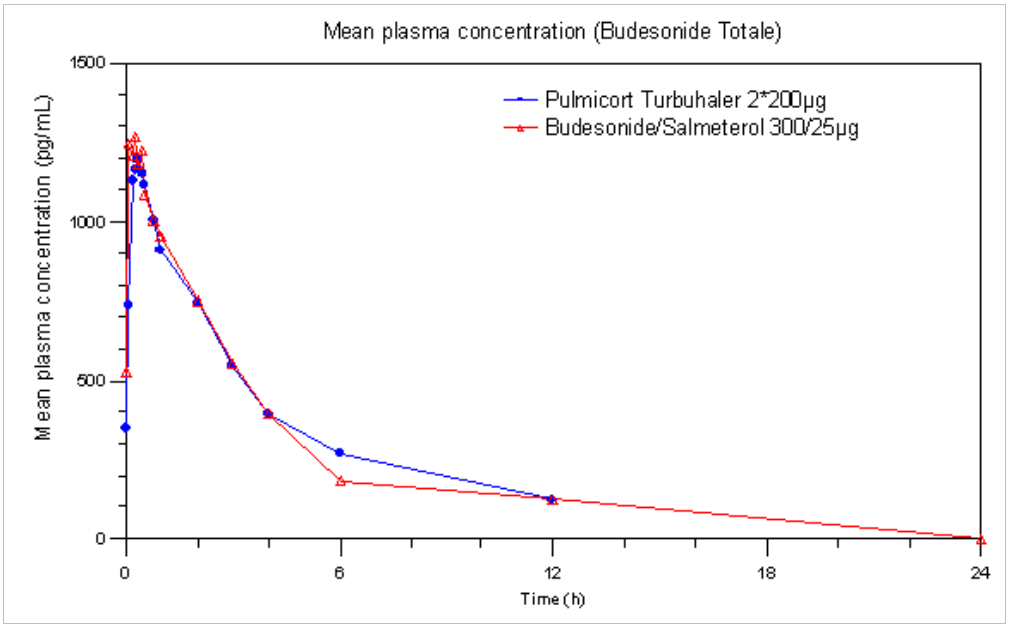


Table 12. Statistical comparison of pharmacokinetic parameters for budesonide and salmeterol following inhalation of Labazenit 300/25µg and Pulmicort 2*200 µg for seven days twice daily in 24 healthy volunteers (study SMB-Busal-SS032).

Budesonide –Epimer A				
Parameters	PULMICORT TURBOHALER 2 x 200 µg	LABAZENIT 1 x 300/25 µg	90 % CI Range	Point estimate
AUC_{τ} (pg.h/ml)	1994 ± 884	1746 ± 922	71-103	85.09
C_{max} (pg/ml)	897 ± 376	880 ± 436	85-107	95.48
t_{max} (h)	0.48 ± 0.42	0.51 ± 0.62	NS	-
Budesonide –Epimer B				
AUC_{τ} (pg.h/ml)	1138 ± 749	1430 ± 2151	83-136	106.6
C_{max} (pg/ml)	644 ± 253	776 ± 428	95-132	112.15
t_{max} (h)	0.43 ± 0.37	0.36 ± 0.45	NS	-
Budesonide total				
AUC_{τ} (pg.h/ml)	3249 ± 1550	3260 ± 2669	79-112	93.98
C_{max} (pg/ml)	1519 ± 615	1615 ± 831	90-115	101.77
t_{max} (h)	0.43 ± 0.38	0.38 ± 0.45	NS	-

Salmeterol (N=23)				
Parameters	Serevent Diskus 1x50 µg	LABAZENIT 1 x 300/25 µg	90 % CI Range	Point estimate
AUC_{τ} (pg.h/ml)	170 ± 313	262 ± 499		
C_{max} (pg/ml)	197 ± 189	255 ± 127		
t_{max} (h)	5 (0-10)	5 (5-10)		

The plasma levels of salmeterol were low for all the subjects and full characterization of the pharmacokinetic profile including 5 points in the absorption phase and 5 points in the elimination phase was not possible for most subjects. Therefore, the values given for the main pharmacokinetic parameters are aimed to roughly describe the pharmacokinetic profile of each product but no statistical analysis could be performed.

Study SMB-Busal-SS071 (150/25)

In study SMB-Busal-SS071, the pharmacokinetics of Labazenit 150/25 µg was compared to the combination of Pulmicort Turbuhaler and Serevent Diskus at steady state.

Day 1 to day 6: one capsule by inhalation twice a day containing 150 µg budesonide and 25 µg salmeterol or one inhalation twice a day containing 200 µg of budesonide followed immediately after by one inhalation containing 50 µg of salmeterol twice a day. On Day 7 one capsule by inhalation containing 150 µg budesonide and 25 µg salmeterol or one inhalation containing 200 µg of budesonide followed immediately after by one inhalation containing 50 µg of salmeterol were administered.

Venous blood samples for PK at Day 7 were collected at –00:35 pre-dose for steady state control and at the following timepoints: 00:05, 00:10, 00:15, 00:20, 00:25, 00:30, 00:45, 01:00, 01:30, 02:00, 02:30, 03:00, 04:00, 06:00, 12:00 and 24:00 hours post-dose.

Results

The bioavailability of budesonide in study SMB-Busal-SS071 was almost 2-fold higher for Labazenit 150/25µg than for the combination of Pulmicort Turbuhaler 200µg+ Serevent Diskus. It should be noted that the LLOQ for budesonide was ~40 pg/ml and as a result almost all samples were below the LLOQ 4-6 hours after inhalation.

According to the Applicant the higher bioavailability following Labazenit inhalation is most likely be explained by the very high variability of the delivery of budesonide from the Turbuhaler device. The Turbuhaler is a reservoir based device, and if the delivery of one dose is not complete, the following dose will deliver more drug than scheduled. In this study only 1 inhalation was taken, thus if the delivery of the dose was not complete, no compensation with a following dose could be achieved.

Table 13. Statistical comparison of pharmacokinetic parameters for budesonide following inhalation of Labazenit 150/25µg and Pulmicort 1*200 µg for seven days twice daily (study SMB-Busal-SS071).

Budesonide –Epimer A (N=36)				
Parameters	PULMICORT TURBOHALER 1 x 200 µg	LABAZENIT 1 x 150/25 µg	90 % CI Range	Point estimate
AUC_{τ} (pg.h/ml)	603 ± 510	956 ± 515	1.61-2.60	2.04
C_{max} (pg/ml)	275 ± 217	501 ± 282	1.67-2.31	1.97
t_{max} (min)	18 (5-45)	10 (5-60)		
Budesonide –Epimer B (N=34)				
AUC_{τ} (pg.h/ml)	366 ± 294	782 ± 422	2.43-3.53	2.93
C_{max} (pg/ml)	227 ± 175	543 ± 326	2.13-2.84	2.46
t_{max} (h)	15 (5-45)	7.5 (5-30)		

No results for salmeterol were reported.

Study SMB-Busal-SD033 (300/25 and 150/25)

Study SMB-Busal-SD033 was a cross-over bioequivalence study. One single dose of Labazenit 300/25µg was compared to one single dose of Labazenit 150/25µg and to one single dose of 2 puff Pulmicort Turbuhaler 200 µg.

This study was a comparative, single dose, three-treatment, three-period, six-sequence, randomized, crossover study in 24 healthy volunteers. This study was conducted in Poland in 2003.

Venous blood samples were collected at –0.35 pre-dose and at the following timepoints: 00:05, 00:10, 00:15, 00:20, 00:25, 00: 30, 00:45, 01:00, 02:00, 04:00, 06:00, 12:00 and 24:00 hours post-dose.

Results

The variability of the systemic absorption after inhalation was very high as demonstrated for budesonide by calculating the inter- and intra-variability of the pharmacokinetic parameters (CV >30%). The budesonide-epimer A showed a point estimate of 104.2 and 111.09 for AUC_t and C_{max} respectively and 90% CI of 84-130 and 92-134 respectively. Regarding the budesonide-epimer B, the point estimates were of 106.7 and 125.0 for AUC_t and C_{max} respectively. The statistical analyses performed on the total of the two epimers, point estimates were 1.08 (0.87-1.33) and 1.16 (0.94-1.42) for AUCt and Cmax, respectively. This demonstrates that administration of 1 dose of Labazenit 300/25 and 2 doses of Pulmicort 200 mg result in comparable budesonide exposure.

Table 14. Statistical comparison of pharmacokinetic parameters for budesonide after oral inhalation of Labazenit 300/25µg and PULMICORT® TURBOHALER 2*200µg administered to 24 healthy volunteers (study SMB-Busal-SD033)

Parameters	PULMICORT® 2 x 200 µg		LABAZENIT 300/25 µg		90 %CI Range (Point estimate)		
	Epimer A	Epimer B	Epimer A	Epimer B	Epimer A	Epimer B	Epimer A+B
AUC_t (pg.h/ml)	1606 ± 943	834 ± 375	1632 ± 804	928 ± 563	84-130 (104.2)	85-134 (106.7)	87-133 (107.7)
C_{max} (pg/ml)	575 ± 311	409 ± 215	624 ± 262	501 ± 231	92-134 (111.1)	100-157 (125.0)	94-142 (115.9)

fixed dose combination based on in-vitro studies and bronchodilating studies.

Bioequivalence

Salmeterol / budesonide

Dose proportionality of budesonide pharmacokinetics was assessed in two studies, studies SMB-Busal-SD033 and SMB-Busal-DP102.

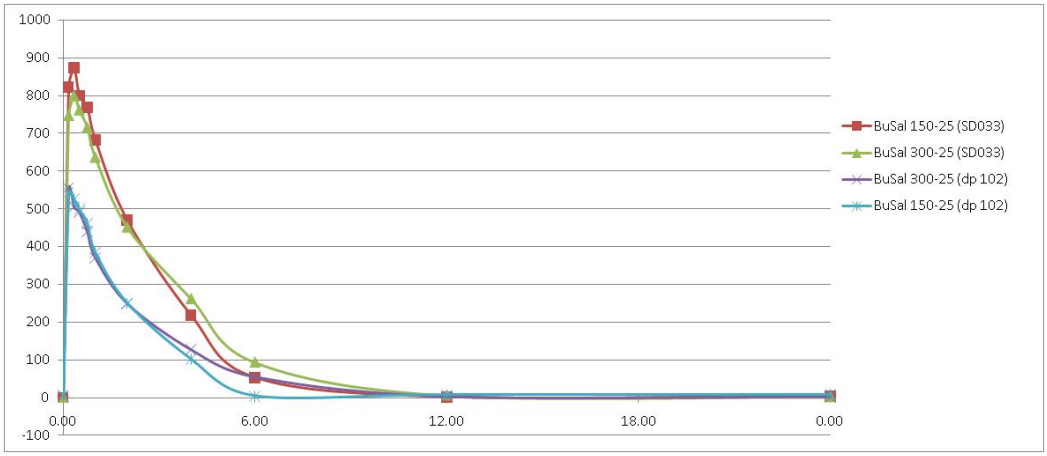
Study SMB-Busal-SD033 was a cross-over bioequivalence study. One single dose of Budesonide/Salmeterol 300/25µg fixed-dose combination was compared to one single dose of Budesonide-Salmeterol 150/25µg fixed-dose combination and to one single dose of 2 puff Pulmicort®Turbuhaler 200 µg. This study was a comparative, single dose, three-treatment, three-period, six-sequence, randomized, crossover study in 24 healthy volunteers (see also comparative bioavailability).

Study SMB-Busal-DP102 was a single dose, double-blind, 2-treatment, 2-period, 2-sequence, randomised, crossover study in 40 mild persistent asthmatic patients, with at least 3 days of wash-out to evaluate dose proportionality of Labazenit 300/25 and 150/50. This study was conducted in Bulgaria in 2010. Active charcoal was administered orally in order to prevent any gastro-intestinal absorption of the active ingredients. Venous blood samples were collected at day 1 and 5: at –00h35 for pre-dose sample and at the following timepoints: 00h10, 00h20, 00h30, 00h45, 01h00, 01h15, 01h30, 02h00, 02h30 03h00, 04h00, 05h00, 06h00, 08h00, 10h00, 12h00 and 24h00 hours post-dose.

Results

The pharmacokinetics was not dose proportional for budesonide in study SMB-Busal-DP102 since the AUC_t, and C_{max} of budesonide from Labazenit 300/25 µg were more than twice as high as the one of Labazenit 150/25 µg. The ratios were 1,43 / 1,33 for AUC t/dose and C_{max}/dose respectively for Epimer A, and 1,58 / 1,48 for Epimer B. This non-dose proportionality may at least in part be attributable to the relatively higher fraction of FPD in Labazenit 300/25 in comparison to Labazenit 150/25 143µg vs 57.5µg respectively. When corrected for FPD, the pharmacokinetics between Labazenit 300/25 and Labazenit 150/25 were comparable (see figure below).

Figure 4. Mean concentration values normalized to the dose of 300 µg and corrected with the FPD for studies SMB-Busal-SD033 and SMB-Busal-DP102.



Also in study SMB-Busal SD033, where the FPD for the used batches of Busal 300/25 and 150/25 were dose proportional, Cmax of budesonide increased dose proportional. Furthermore, the variability was higher for Labazenit 150/25 than for Labazenit 300/25 which may be due to the lower plasma concentrations of budesonide following Labazenit 150/25 inhalation. AUCt may be underestimated for Labazenit 150/25 as budesonide plasma concentrations were readily below the LLOQ of budesonide ~40 pg/ml.

Table 15. Summary of the pharmacokinetic parameters of budesonide and salmeterol for Labazenit 150/25 and Labazenit 300/25 in 40 mild to moderate asthmatic patients in presence of charcoal (study SMB-Busal-DP102) and in 24 healthy volunteers in study SMB-Busal-SD033.

Treatment	AUC_{0-t} pg/ml/h	C_{max} pg/ml	AUC_{0-t} pg/ml/h	C_{max} pg/ml	AUC_{0-t} pg/ml/h	C_{max} pg/ml
	Budesonide epimer A		Budesonide epimer B		Salmeterol	
Labazenit 150/25 study DP102	298 ± 145	139 ± 48	229 ± 143	132 ± 50	92 ± 58	97 ± 51
Labazenit 300/25 study DP102	851 ± 250	371 ± 116	720 ± 223	373 ± 195	133 ± 148	100 ± 56
Ratio (DP102) Labazenit150:Labazenit300 90% CI	0.66 0.60-0.73	0.74 0.69-0.80	0.58 0.51-0.65	0.68 0.59-0.77	not evaluated	not evaluated
Labazenit 150/25 study SD033	659 ± 369	303 ± 104	405 ± 310	274 ± 112	not evaluated	not evaluated
Labazenit 300/25 study SD033	1632 ± 804	624 ± 262	928 ± 563	501 ± 231	not evaluated	not evaluated
Ratio (SD033) Labazenit150:Labazenit300 90% CI	0.80 0.66-0.97	0.99 0.87-1.14	0.77 0.58-1.01	1.12 0.95-1.30	not evaluated	not evaluated

The plasma levels of salmeterol were low for most patients and the full characterization of the pharmacokinetic profile was not possible. Therefore, the values given for the main pharmacokinetic parameters are aimed to roughly describe the pharmacokinetic profile of each product but no statistical analysis could have been performed. Pharmacokinetics of salmeterol was comparable for Labazenit 150/25 and Labazenit 300/25 as can be expected as the amount of salmeterol and the FPD was the same in both strengths.

Two additional pharmacokinetic studies were submitted by the Applicant with their responses to the D120 LOQ to further establish the comparability of budesonide and salmeterol versus reference products Symbicort Turbuhaler 160/4.5 µg and Serevent Dislus 50 µg, respectively.

Study SMB-BUSAL-SD111

The objectives of this study was to compare the lung deposition of budesonide after a single-dose of Labazenit 150/25 µg versus a single dose of Symbicort Turbuhaler 160/4,5 µg.

The study was performed in 40 asthma patients as recommended by the OIP guideline (CPMP/QWP/EWP/1401/98 rev.1). Active charcoal was administered to patients to ensure that plasma levels of budesonide measured were due to lung deposition only.
Venous blood samples were collected at day 1 of each period: at –00h35 for pre-dose sample and at the following timepoints: 00h10, 00h20, 00h30, 00h45, 01h00, 01h15, 01h30, 02h00, 02h30, 03h00, 04h00, 05h00, 06h00, 08h00, 10h00, 12h00 and 24h00 hours post-dose.

Symbicort Turbuhlaer160/4,5 µg contains a fixed dose combination of budesonide and formoterol. The dose is expressed as the delivered dose and corresponds to nominal dose of 200 µg of budesonide and 6 µg of formoterol. Consequently, the product theoretically contains and delivers the same dose of budesonide than the Pulmicort Turbuhaler 200 µg. This comparator has been chosen instead of Pulmicort Turbuhaler 200 µg because the in vitro testing has demonstrated a lower intra and inter-batch variability of the delivered dose and the Fine Particle Dose (FPD) for Symbicort Turbuhaler. The decreased variability of Symbicort Turbuhaler versus Pulmicort Turbuhlaer is expected on the basis of the respective formulations.

Test product: Labazenit 150/25 µg Axahaler
FPD 58.5 µg budesonide (beginning PK study) and 51.9 µg (end PK study)
Reference product: Symbicort Turbuhlaer160/4.5
FPD 76.4 µg budesonide (beginning PK study) and 62.2 µg (end PK study)

Results:

Epimer A: Pharmacokinetic parametes of SMB-BUSAL-SD111

Parameters	Symbicort Turbohaler 160/4.5 µg (N = 40)	Budesonide – Salmeterol 150/25 µg (N = 40)	Bioequivalence 90 % CI	Point estimate
	Mean - SD	Mean - SD		
AUC∞ (pg.min/ml)	52025.45 – 61051.79	38718.94 – 46528.28	68.96-85.52	0.77
AUCt (pg.min/ml)	41214.17 – 41794.88	32049.84 – 43304.28	68.52-88.81	0.78
Cmax (pg/ml)	237.83 – 120.18	176.81 – 68.19	70.25-90.99	0.80
Tmax (min)	29.38 – 19.42	20.58 – 10.08	NS	-
T1/2 (min)	178.42 – 194.79	154.61 – 119.48	80.94 – 106.71	0.93

Epimer B: Pharmacokinetic parameters of SMB-BUSAL-DS-111

Parameters	Symbicort Turbohaler 160/4.5 µg (N = 39)	Budesonide – Salmeterol 150/25 µg (N = 39)	Bioequivalence 90 % CI	Point estimate
	Mean - SD	Mean - SD		
AUC∞ (pg.min/ml)	38685.75 – 38355.23	32387.92 – 34645.82	72.89 – 98.89	0.85
AUCt (pg.min/ml)	29074.14 – 31983.73	24395.18 – 31944.63	73.40 – 96.18	0.84
Cmax (pg/ml)	198.59 – 98.42	161.89 – 66.26	77.42 – 94.25	0.85
Tmax (min)	22.56 – 12.82	19.85 – 9.40	NS	-

T1/2 (min)	209.28 – 317.02	174.76 – 157.77	76.82 – 121.87	0.97

Results corrected by the FPD of budesonide in Labazent 150/25 and Symbicort 160/4.5

Epimer A: Pharmacokinetic parameters of SMB-BUSAL-SD111 (with correction by the FPD value at the beginning of the study)

Parameters	Symbicort Turbohaler 160/4.5 µg (N = 40)	Budesonide – Salmeterol 150/25 µg (N = 40)	Bioequivalence 90 % CI	Point estimate
	Mean - SD	Mean - SD		
AUC∞/FPD (pg.min/ml)	680.96 – 799.11	661.86 – 795.36	90.00 – 111.77	1.00
AUCt/FPD (pg.min/ml)	539.45 – 547.05	547.86 – 740.24	89.42 – 116.07	1.02
Cmax/FPD (pg/ml)	3.11 – 1.57	3.02 – 1.17	91.67 – 118.92	1.04
Tmax (min)	29.38 – 19.42	20.58 – 10.08	NS	-
T1/2 (min)	178.42 – 194.79	154.61 – 119.48	80.94 – 106.71	0.93

Epimer B: Pharmacokinetic parameters of SMB-BUSAL-SD111 (with correction by FPD value at the beginning of the study)

Parameters	Symbicort Turbohaler 160/4.5 µg (N = 40)	Budesonide – Salmeterol 150/25 µg (N = 40)	Bioequivalence 90 % CI	Point estimate
	Mean - SD	Mean - SD		
AUC∞/FPD (pg.min/ml)	506.36 – 502.03	553.64 – 592.24	95.15 – 129.20	1.11
AUCt/FPD (pg.min/ml)	380.55 – 418.64	417.01 – 546.06	95.79 – 125.70	1.10
Cmax/FPD (pg/ml)	2.60 – 1.29	2.77 – 1.13	101.05 – 123.18	1.12
Tmax (min)	22.56 – 12.82	19.85 – 9.40	NS	-
T1/2 (min)	209.28 – 317.02	174.76 – 157.77	76.82 – 121.87	0.97

Similar results were obtained when corrected for FPD at end of the PK study.

The bioavailability of budesonide was slightly higher following inhalation of Symbicort Turbuhaler compared to the bioavailability of budesonide following inhalation of Busal 150/25 µg. This difference is mainly due to the differences in in-vitro deposition profile (FPD values) of the bio-batches used which however are in the acceptable norms for both products.

When the pharmacokinetic parameters are corrected for the FPD values, the bioavailability is comparable and within the bioequivalence criteria between Labazenit 150/25 µg and Symbicort Turbuhaler 160/4.5 µg.

Study BUSAL-SD121

This study was a comparative study of the bioavailability of salmeterol after single inhalation in healthy volunteers: BUDESONIDE-SALMETEROL DPI Capsules 150/25 µg delivered by the Axahaler versus Serevent Diskus 50 µg. This was a randomised, single dose, 2-way, crossover study.

The goal of this study was to compare the plasma levels of salmeterol after a single-dose administration of two capsules of Labazenit 150/25 µg versus two puffs of Serevent Diskus 50 µg in 32 healthy volunteers.

Venous blood samples were collected at day 1 of each period: at pre-dose and at the following timepoints: 00:10, 00:15, 00:20, 00:30, 00:45, 01:00, 01:15, 01:30, 02:00, 02:30, 03:00, 04:00, 06:00, 08:00, 10:00, 12:00 post-dose.

Test product: Busal 150/25:
Delivered salmeterol dose: 20.2 µg, FPD: 10.9 µg
Reference product: Serevent Diskus
Delivered salmeterol dose: 44.1 µg, FPD 12.6 µg

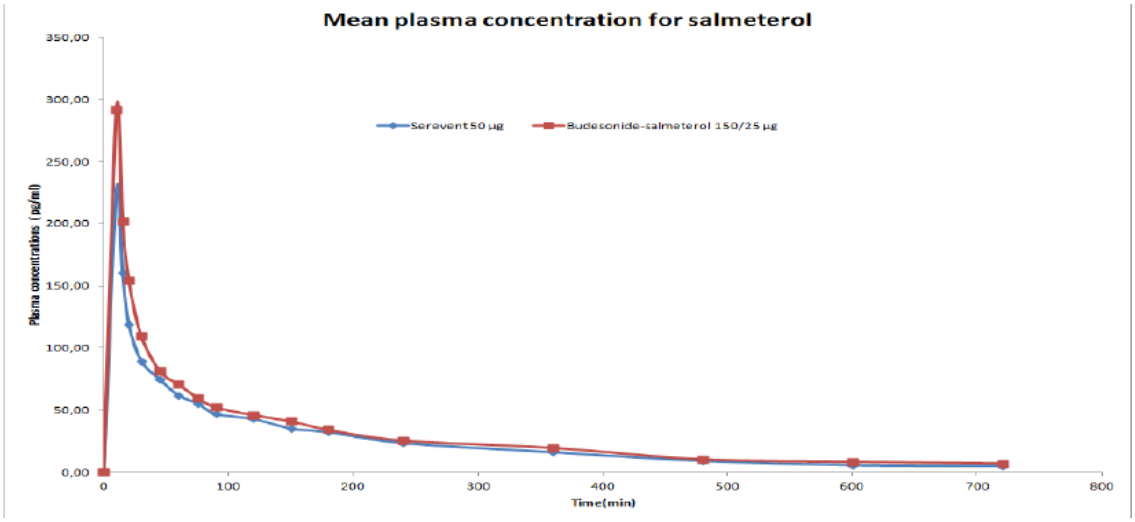
Results

The main pharmacokinetic findings for the study are summarized in the table and figure below.

Table 16. Pharmacokinetic parameters of salmeterol following inhalation of 2 puffs of Busal 150/25 µg and Serevent Diskus 50 µg in healthy volunteers (N=32, study SD121)

Parameters	SEREVENT® DISKUS® 50 µg (N=32)	BUDESONIDE-SALMETEROL 150/25µg (N=32)	Bioequivalence 90 %CI	Point estimate
	Mean ± SD	Mean ± SD		
AUC_{∞} (pg.min/ml)	27112.07 ± 18184.48	29976.47 ± 18415.20	[96.66 ; 132.59]	1.13
AUC_t (pg.min/ml)	18735.93 ± 13510.05	21493.89 ± 14396.18	[101.96 ; 135.29]	1.17
C_{max} (pg/ml)	231.04 ± 105.09	293.67 ± 108.23	[116.97 ; 147.11]	1.31
T_{max} (min)	10.47 ± 1.95	10.50 ± 1.95	NS	-
$t_{½}$ (min)	284.08 ± 277.70	287.60 ± 215.05	[88.29 ; 148.43]	1.14

Figure 5. Comparative curves of Salmeterol after single dose administration of SEREVENT DISKUS 50 µg and BUDESONIDE-SALMETEROL 150/25 µg in 32 healthy volunteers study SD121



Busal 150/25µg fixed-dose combination demonstrated similar pharmacokinetic profile as Serevent Diskus 50 µg for the analyte salmeterol.

However, the 90 % confidence interval for salmeterol was not in the predetermined norms of 80-125 % for AUC_t and C_{max}. Indeed, point estimates are respectively 1.17 and 1.31 for the following pharmacokinetic parameters: AUC_t and C_{max}. There was no significant difference between the T_{max} of both treatments.

The bioavailability (AUC and C_{max}) of salmeterol is somewhat higher for Busal 150/25 µg than for Sereven Diskus 50 µg.

Distribution

Salmeterol

Salmeterol is 94 to 98% bound to human plasma proteins in-vitro to both albumin and α- 9- acid glycoprotein. Salmeterol xinafoate, as an ionic salt, dissociates in solution to salmeterol and to 1-hydroxy-2-naphtoic acid (xinafoate) moiety. These two compounds are then absorbed, distributed, metabolised and excreted independently.

Budesonide

The volume of distribution of unchanged budesonide was reported as 301 L with distribution of the more hydrophobic epimer 22R (424L) being greater than of epimer 22S 245 L. Findings were similar in children with asthma: volume of distribution of epimers 22R and 22S was 4.8 and 3.1 L/lg, respectively. Budesonide is 88 % bound to plasma proteins, which is similar to other glucocorticoids.

Metabolism

Salmeterol

The cytochrome P450 (CYP) isoform 3A4 is responsible for aliphatic oxidation of salmeterol base, which is extensively metabolised by hydroxylation.

Budesonide

Budesonide is inactivated predominantly in the liver. Budesonide is not biotransformed in the lung or gastrointestinal tract. In the liver, budesonide is metabolised primarily via oxidative and, to a much lesser extent, via reductive pathways to six metabolites, primarily 16a-hydroxy-prednisolone and 6b-hydroxy-budesonide. These metabolites are products of the inducible form of cytochrome P450, CYP3A4, and have similar half-lives to the parent compound but are relatively inactive.

Metabolism of budesonide occurred 2 to 4 times faster than the metabolism of beclomethasone 17α-propionate (the active metabolite of beclomethasone 17α, 21 dipropionate) and 2 to 3 times faster than triamcinolone acetonide in human liver homogenate in vitro.

Additionally, the drug is pharmacokinetically characterised by a large volume of distribution and a high hepatic clearance. The extensive liver biotransformation contributes to the favourable ratio between local and systemic glucocorticoid effects shown for the compound.

In addition, formation of the budesonide metabolites was inhibited by antibodies against the CYP3A subfamily or control immunoglobulin G. The formation of 16- αhydroxyprednisolone and 6 β-hydroxybudesonide from budesonide is catalysed by isoenzymes within the CYP3A subfamily.

Elimination

Salmeterol

The major metabolite, alpha-hydroxysalmeterol, is predominantly eliminated in the faeces. It has been demonstrated that 57.4% of administered radioactivity is recovered in the faeces and 23% in the urine; most is recovered between 24 and 72 hours after administration. Unchanged salmeterol accounts for <5 % of the excreted dose in the urine.

Budesonide

The 22R form of budesonide was preferentially cleared by the liver with systemic clearance of 1.4L/min vs 1.0L/min for the 22S form. The terminal half-life, 2 to 3 hours, was the same for both epimers and was independent of dose. Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

Special populations

Salmeterol

Pharmacokinetics in patients with hepatic and renal failure

Since salmeterol is predominantly cleared by hepatic metabolism, liver function impairment may lead to accumulation of salmeterol in plasma. Patients with hepatic impairment receiving the drug should be closely monitored.

Unfortunately the pharmacokinetics of salmeterol base have not been studied in patients with hepatic impairment.

Similarly, information on the pharmacokinetics of salmeterol base in patients with renal dysfunction is limited. Following oral administration of a 500 µg (225 µg of 1-Hydroxy, 2-naphtoic acid) single dose of salmeterol xinafoate, AUC, t halfβ and total CLP were 11.4mg*h/L, 30 days and 10.8ml/h respectively, in patients with renal impairment. The same pharmacokinetic parameters were 4.4mg*h/L, 15 days and 18.6ml/h, respectively, in healthy volunteers. Plasma Cmax however, was lower in patients with impaired renal function than in healthy individuals.

Pharmacokinetics in elderly patients

To our knowledge the pharmacokinetics of salmeterol base have not been studied in elderly patients to date. Furthermore, no particular contraindication is suggested in the SmPC of the Serevent Diskus which states that “there is no need to adjust the dose of salmeterol in elderly patient”.

Budesonide

Pharmacokinetics in hepatic and renal failure

Compromised liver function may decrease the rate of glucocorticosteroid elimination.

Hepatic impairment increased the systematic availability of budesonide 2-fold after oral ingestion in adults with cirrhosis. However, after intravenous administration, the pharmacokinetic of budesonide was similar in patients with cirrhosis and healthy adults.

Pharmacokinetics in elderly patients

No differences in the pharmacokinetics of budesonide inhalation suspension related to race, gender, or advanced-age have been identified.

A subanalysis of the Symbicort Maintenance and Reliever Therapy (EuroSMART) showed that budesonide/formoterol maintenance and reliever therapy is effective and safe for elderly patients with asthma who are symptomatic despite daily use of ICS with or without LABAs.

Pharmacokinetic interaction studies

Salmeterol

When administered concurrently, inhaled glucocorticoids and cromolyn sodium did not alter the safety profile of salmeterol oral inhalation.

The effect of salmeterol on the vascular system may be potentiated in patients receiving concomitant therapy with monoamine oxidase inhibitors or tricyclic antidepressants.

Since the therapeutic dose of salmeterol is very low, it is unlikely that any clinically relevant interactions will be observed as a consequence of the coadministration of salmeterol and other drugs, such as fluticasone propionate, that are metabolised by CYP3A.

Budesonide

Ketoconazole has been found to bind to the glucocorticoid receptor and thereby to function as a glucocorticoid antagonist in cultured cell preparations. By that mechanism ketoconazole may reduce the pharmacological effect of budesonide.

When budesonide (10 µM) was incubated with human liver microsomes in the presence of compounds known to interact with different isoforms and subfamilies of CYP, ketonazole was found to be the strongest inhibitor of budesonide metabolism (IC50: approximately 0.1 µM) followed by troleandomycin (IC50: approximately 0.1 µM), erythromycin, and cyclosporin, all substances known to interact with CYP3A isoenzymes. Substances known to interact with CYP2C (sulfophenazole, mephetynoin, and tolbutalide) and with CYP2D6 (bufuralol and quinidine) did not specifically inhibit the metabolism of budesonide.

Furthermore, the proposed SmPC of the new Budesonide/Salmeterol fixed-dose combination states that the concomitant use of inhibitors of these CYP3A isoenzymes, e.g. ketoconazole and itraconazole, can increase systemic exposure to budesonide and are therefore not recommended.

Salmeterol / budesonide

Although both salmeterol and budesonide are primarily metabolised by CYP3A4, the low doses and low plasma concentrations make it is unlikely that any clinically relevant ginteractions following co-administration of salmeterol or budesonide occur. Nevertheless, a pharmacokinetic study following a single dose administration of the budesonide/salmeterol FDC, study SMB-BUSAL-SD101, was performed to assess whether any interaction occurs between the active ingredients of the combination versus each substance taken alone and versus the co-administration of both substances administered with the same pharmaceutical formulation and the same inhaler device. Inhouse Laboratoire SMB Budesonide 300 µg and SMB Salmeterol 25 µg products were used and compared to Labazenit 300/25.

This study was a comparative, single dose, 4-treatment, 4-period, 4-sequence, randomised, crossover study, with at least 3 days wash-out in 40 healthy volunteers following 2 puffs of each product (2x300/25, 2x300, 2x25, 2x(300+25).

Venous blood samples were collected at day 1: at –00:35 for pre-dose sample and at the following timepoints: 00:10, 00:20, 00:30, 00:45, 01:00, 01:15, 01:30, 02:00, 02:30, 03:00, 04:00, 05:00, 06:00, 08:00, 12:00 and 24:00 hours post-dose.

This study was conducted in Belgoium in 2010.

The results are summarised in the table below. The results showed that there is no evidence of pharmacokinetic interaction between budesonide and salmeterol and there is no difference between budesonide and salmeterol administered separately together and Labazenit 300/25µg FDC.

Table 17. Pharmacokinetic parameters of budesonide and salmeterol (non-transformed values; arithmetic mean ± SD) following inhalation of 2x300 µg budesonide and 2x25µg salmeterol separately and together to evaluate interaction between budesonide and salmeterol. Study SMB-BUSAL-SD101, N=40.

Treatment	AUC_{0-t} pg/ml/h	C_{max} pg/ml	AUC_{0-t} pg/ml/h	C_{max} pg/ml	AUC_{0-t} pg/ml/h	C_{max} pg/ml
	Budesonide epimer A		Budesonide epimer B		Salmeterol	
Labazenit 300/25	2281 ± 532	982 ± 289	1684 ± 424	897 ± 314	275 ± 114	276 ± 114
SMB Bud	2468 ± 903	968 ± 273	1913 ± 634	968 ± 317		
SMB Salm					271 ± 119	277 ± 100
SMB Bud + SMB Salm	2234 ± 535	927 ± 308	1587 ± 420	830 ± 319	305 ± 121	308 ± 122
***Ratio Labazenit vs SMB Bud 90% CI**	1.06 1.00-1.12	0.99 0.92-1.07	1.12 1.06-1.19	1.09 1.00-1.18	0.93 0.91-1.04	1.02 0.96-1.09
Ratio Labazenit vs SMB Salm 90% CI					0.93 0.91-1.04	1.02 0.96-1.09
Ratio Labazenit vs SMB Bud + SMB Salm 90% CI	0.98 0.94-1.05	0.93 0.88-1.00	0.94 0.87-1.00	0.91 0.84-0.99	1.12 1.03-1.20	1.14 1.04-1.24
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours					
C_{max}	maximum plasma concentration					

**ln-transformed values*

2.4.3. Pharmacodynamics

Mechanism of action

Salmeterol

β2-Adrenergic agonists produce their effects through interaction with specific β2-adrenergic receptors present in high concentration in lung tissue. All β2-agonists exert their biological and therapeutic effects through cell-surface β2-adrenoceptors, which are members of the 7-transmembrane, G-protein–coupled receptor family. The major adverse effects of β-adrenergic agonists occur as a result of excessive activation of β-adrenergic receptors.

Salmeterol is a selective long-acting β2-adrenoceptor agonist with a long side chain that reversibly binds to an active site on the β2-receptor and irreversibly to the exosite of the receptor. In vitro and in vivo pharmacologic studies indicate that the selectivity of salmeterol for β2- versus β1-adrenergic receptors is greater than that of other β-adrenergic agonists.

Salmeterol results from a modification of salbutamol to obtain a drug with much greater affinity for its receptors which translates in increased exoreceptor binding and a prolonged action (12 hours). The following figures show a chemical structure of salmeterol and salbutamol a close member of the β-adrenoceptors family.

Budesonide

Budesonide is a non-halogenated glucocorticosteroid structurally related to 16α- hydroxyprednisolone that possesses a strong local anti-inflammatory action, with a lower incidence and severity of adverse effects than those seen with oral corticosteroids.

Corticosteroids modulate the action of numerous inter- and intracellular mediators and influence the transcription of target genes that regulate the production of cytokines, receptors, and enzymes. Budesonide inhibits multiple airway inflammatory cells involved in the asthma response. After therapeutic use of orally inhaled budesonide delivered via dry powder inhaler, improvement in lung function has been shown to occur within 2 days of initiation of treatment, although maximum benefit may not be achieved after up to 4 weeks.

The pharmacodynamic properties of glucocorticosteroids can be described by the binding of the drug to its glucocorticoid receptor. Glucocorticoid receptors are very widely distributed outside the lungs, so systemic side effects on bone, growth, skin, skeletal muscles, and blood vessels are common; this provides the rationale for the use of inhaled glucocorticosteroids to reduce systemic exposure. Also budesonide possesses a good degree of topical potency (local anti-inflammatory activity) compared to systemic effects as discussed below.

Primary and Secondary pharmacology

Salmeterol

Bronchodilating effect

The principal action of β2-agonists is to relax airway smooth muscle by stimulating β2- adrenergic receptors. This increases the intracellular messenger cyclic adenosine monophosphate (cAMP) that is responsible for the control of smooth muscle tone. Thus, activation of the β2-adrenergic receptor results directly in bronchodilation. β2-agonists interact with β2 receptors (β2R) to activate coupling of the stimulatory G protein (Gs) with adenylcyclase (AC). This leads to enhanced production of cAMP which activates protein kinase A (PKA) and results in smooth muscle relaxation. β2-adrenergic receptor agonists may also attenuate cholinergic neurotransmission due to stimulation of β2-adrenergic receptors on parasympathetic ganglia.

Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than equipotent doses of a conventional short-acting β2-adrenoceptor agonist such as salbutamol with no differences in cardiovascular effect or skeletal muscle tremor. This represents a therapeutic advantage compared to salbutamol, particularly in patients with nocturnal asthma.

The delayed onset and prolonged duration of action of salmeterol may result from its slow cellular uptake and/or membrane translocation to the β2 receptor, lipophilicity, and protracted binding at the β2 receptor. Other groups suggest that the sustaining bronchodilating effect of salmeterol is related to slow dissociation from the receptor or to the turnover of the occupied β2-adrenergic receptor protein. The long duration of action of salmeterol may be of value in the treatment of asthma, particularly in those patients with nocturnal symptoms.

Anti-inflammatory effect

In addition to its bronchial smooth muscle relaxation, salmeterol inhibits the release of pro-inflammatory mediators including histamine, leukotrienes C4 and D4, and prostaglandin D2 associated with early phase inflammatory response to allergen challenge in human lung tissue and may thereby attenuate early-and late phase associated bronchoconstriction as observed in asthma.

Systemic effect

It has been demonstrated that the systemic effects of salmeterol are more likely to occur with higher doses, which lead to approximately proportionally increase blood concentrations (Cazzola M et al., 2002). Some of the major adverse effects of β- adrenergic agonists in the treatment of asthma are caused by stimulation of β-adrenergic receptors in the heart. The coexistence of β1 and β2-adrenoceptors in the heart clearly indicates that β2-agonists do have some effect on the heart, even when they are highly selective. It should also be taken into account that the β2-agonists utilised in clinical practice have differing selectivities and potencies. However at the recommended doses of salmeterol, systemic concentrations are low or even undetectable.

Effect on lung function

Salmeterol demonstrated significant improvement in lung function. A review by Tashkin DP and Fabbri LM (2010) found that improvements in pre-bronchodilator forced expiratory volume in 1 second (FEV1) ranged from 50-90 mL compared with placebo.

Those improvements in lung function were sustained in studies of 3 months to 3 years' duration when twice-daily LABAs were used as maintenance therapy. In the same review some studies suggested there may be a decline in bronchodilator efficacy over time with salmeterol as with salbutamol; over 6 months, significant declines in peak forced vital capacity (FVC) relative to placebo (-83 mL, $p < 0.05$), but not FEV1 (-12 mL), were observed with salmeterol. Other studies have also suggested a partial loss of bronchodilator efficacy of formoterol over time.

Budesonide

Topical and systemic glucocorticoid activity

In animals budesonide has a high ratio of topical to systematic activity compared with 5 reference corticosteroids including beclomethasone dipropionate, flunisolide and triamcinolone acetonide. Similar observation is made in human, where budesonide is shown to have 1.6 to 3 times greater local anti-inflammatory activity using a skin vasoconstriction assay, and between 2 and 4 times less systemic activity than beclomethasone dipropionate.

Trials in patients with asthma have not revealed any significant differences between conventional doses of budesonide and beclomethasone dipropionate.

The systemic glucocorticoid activity of budesonide, as determined by changes in plasma cortisol and total or differential white blood cell count in healthy volunteers, was 2-4 times less than that of beclomethasone dipropionate following oral administration, and it was also significantly less active after inhalation.

Effect on haematological parameters

Systemic prednisolone produces an increase in blood neutrophils and a decrease in blood basophils, eosinophils and lymphocytes within 4-8 hours of intravenous administration to healthy volunteers. These effects have generally returned to, or are returning to normal within 24 hours, and a similar transient lymphopenia has been noted following oral administration of prednisone to steroid-dependent asthmatic patients.

Likewise in healthy patients, single doses (200, 800 and 3200 µg) of inhaled budesonide and beclomethasone dipropionate decreased the number of lymphocytes and eosinophils and increased the number of neutrophils without significantly affecting the number of monocytes. When given orally, beclomethasone had a significantly greater effect on the white cell response than did budesonide.

However, in contrast to these findings in volunteers, treatment with aerosol budesonide (200 µg twice daily) for 4 weeks did not significantly alter any of the haematological parameters measured in patients with chronic asthma.

Effect on adrenal function

The potential for systemic effects of inhaled glucocorticosteroids is often evaluated using measurements of adrenal function. The two most sensitive methods involve the measurement of plasma cortisol concentrations at regular intervals over 20 to 24h or of free urinary cortisol over 24h. In practice, usual doses of inhaled or intranasal budesonide have caused only minimal changes in hypothalamic-pituitaryadrenal (HPA) function, although a dose response relationship with plasma cortisol concentrations have been documented. When inhaled therapy was substituted for oral prednisolone there was a gradual increase in plasma cortisol concentrations, highlighting the lower adrenal suppressive activity of budesonide compared with oral steroid. Literature data in most studies performed in patients with asthma show that suppression of the HPA axis did not occur as long as doses did not exceed 800 µg of budesonide twice daily.

Effect on antigen induced reactions

It has been noted that as long as pre-treatment was sufficiently long, inhaled budesonide inhibits both the immediate and late reactions provoked by bronchial allergen challenge.

Similarly, intranasal budesonide inhibits the type 1-mediated immediate nasal reaction and this may be related to suppression of histamine release in nasal biopsy sample in vitro.

Effect on bronchial and nasal mucosa

Long term application of potent topical corticosteroid on the skin may cause dermal atrophy and the question arises whether similar changes occur in respiratory mucosa following prolonged aerosol or intranasal administration of these substances. Following intranasal administration of budesonide for up to 1 year in patients with rhinitis, no adverse morphological changes in the nasal mucosa such as metaplasia or atrophy occurred. There is only little data on the histological characteristics of the bronchial mucosa after inhaled budesonide in asthma patients. In a prospective study, measurement of a 9.00 a.m. basal serum cortisol and biopsies of the inferior turbinate mucosa were taken from 40 patients using topical nasal corticosteroid (budesonide) continuously for months or years. No systemic adverse effects and no histopathological changes of significance were found. The authors concluded that these findings do not suggest that topically corticosteroids are harmful to the nasal mucosa and do not produce systemic effects. It should be noted that during the three repeat-dose toxicity studies performed in rat and dog with the salmeterol-budesonide combination, a thorough examination of the respiratory tract was performed and did not reveal any particularity with the exception of slight inflammatory signs occasionally seen in the respiratory tract but not considered of importance.

Acute dose-response studies

Inhaled budesonide has been shown to offer an effective alternative to oral ICS in the management of asthma and rhinitis. In studies performed by the Applicant with ICS (study BUSAL-III-02-1), no significant dose-response relationship was observed, which in agreement with recent report (GINA, 2010). However in a much earlier study comparing 3 doses of inhaled budesonide (100, 400 and 1600 µg) with oral budesonide (1600 µg) and oral prednisolone (40 mg) over a 12-hour period, all inhaled doses of budesonide produced a significantly greater increase in peak expiratory flow rate (PEFR) than did oral budesonide and when the areas under the PEFR times curves (AUCs) were calculated, a dose-response relationship was established.

Salmeterol/budesonide

An evaluation of the systemic effects on the HPA axis by the course of plasma cortisol and urine cortisol was performed as required in the OIP guideline (CPMP/QWP/EWP/1401/98 rev.1).

Study BUSAL II-10-2

This study was a Phase II , randomized, partially-blinded, cross over study to evaluate the systemic effect of two doses of the SMB BUDESONIDE-SALMETEROL DPI FIXEDDOSE combination capsule (300/25 µg BID AND 150/25 µg BID) delivered by the Axahaler versus Pulmicort Turbuhaler 400 µg BID + Serevent Diskus 50 µg BID versus PLACEBO in mild persistent asthmatic patients.

Methods

Design

BUSAL II-10-2 is randomized, cross-over, partially-blinded study. Patients received each treatment for 10 days separated by wash-out periods of at least 21 days.

In order to reach the steady state of the ICS systemic effects, the study treatments were administered during 10 days for each period. Maximal cortisol suppression occurs after 7 days of glucocorticosteroids treatment.

The duration of the wash-out period is based on the studies published in the literature.

All patients were from one Bulgarian centre, included between October 2010 and November 2010.

Objectives

The study's objectives were the following:

- To compare the systemic effect of two doses of SMB Budesonide-Salmeterol DPI capsule (300/25 µg BID and 150/25 µg BID) versus Pulmicort Turbohaler 400 µg BID + Serevent Diskus 50 µg BID versus placebo by the measurement of 24-hour plasma and urinary cortisol.

- To assess and compare the safety of the tests versus reference products.

Study participants

Male and female patients 18 to 70 years old, with a diagnosis of mild persistent asthma for a minimum of 3 months with FEV1 <80% predicted, at least 12% and 200 ml FEV1 reversibility to 4 puffs of Salbutamol 100 µg were recruited in the study. Patients should be corticosteroid naïve and should not have received oral, parenteral or inhaled steroids in the preceding 3 months.

The study was performed in mild persistent asthmatic corticosteroid naïve patients as they have to sustain a withdrawal of inhaled glucocorticosteroids during the run-in and wash-out periods.

Outcomes / endpoints

Primary endpoint:
Change from baseline in the area under the curve (AUC) of 24-hour plasma cortisol (mean change from baseline to day 11 of each period).

Plasma cortisol was collected over 24 hours on the 1st day (before administration of the study drug) and on the 11th day of each of the 4 periods. Blood were collected over 24 hours at 8h00, 9h00, 10h00, 12h00, 14h00, 16h00, 18h00, 20h00, 22h00, 24h00, 2h00, 4h00, 6h00, 7h00 and 8h00.

Other safety parameters:

- Change from baseline in the Cmax of 24-hour plasma cortisol (mean change from baseline to day 11 of each period)
- Change from baseline in the concentration of urinary cortisol over 24 hours (mean change from baseline to day 11 of each period), collected over 24 hours
- Adverse events (including asthma exacerbations)
- Physical examination
- Vital signs
- Laboratory data
- 12-lead ECG data
- Withdrawals or drop-out rate

Statistical methods

PRIMARY OUTCOME

The null hypothesis was that Labazenit 300/25 µg BID and Pulmicort Turbohaler 400 µg BID + with SereventDiskus 50 µg BID were not equivalent regarding the decrease in the 24-hour AUC of plasma cortisol after a 10-day treatment. If the difference in the decrease of 24-hour AUC of plasma cortisol between Labazenit 300/25 µg BID and Pulmicort Turbohaler 400 µg BID + with Serevent Diskus 50 µg BID was included in the range [-20%; + 20%] the two drugs were to be considered as equivalent regarding their impact of the 24-hour AUC of plasma cortisol.

AUC0–24h values were calculated using the trapezoidal rule for numerical integration using the actual recorded collection times. A mixed model with treatment, period and predosing baseline as fixed effects and patient as random effect was built. No interaction terms was added in the model. The carry over effect was not tested given that the wash out time between each treatment period was 21 days.

Contrasts were calculated between each treatment:

- Labazenit 300/25 µg vs. Pulmicort Turbohaler 400 µg + with Serevent Diskus 50 µg

- Labazenit 150/25 µg vs. Pulmicort Turbohaler 400 µg + with Serevent Diskus 50 µg

- Labazenit 300/25 µg vs. placebo

- Labazenit 150/25 µg vs. placebo

- Pulmicort Turbohaler 400 µg + with Serevent Diskus 50 µg vs. placebo

- Labazenit 300/25 µg vs. Labazenit 150/25 µg

Tests were two-sided. The global α risk was set at 0.05. To deal with the inflation of the risk due to multiple comparisons, the Bonferroni inequality was applied to adjust the α risk which was therefore reduced to 0.0085 for each of the 6 pair-wise comparisons. Pair-wise differences along with the 99.15% confidence interval were computed with the "estimate" function of the SAS mixed procedure. For the main analysis the limit of the 99.15% confidence interval (CI) was compared to the equivalence margins, concluding to equivalence if the bounds of the CI were included in the interval [-20%; +20%]. For secondary analyses of the main criterion, comparisons were computed the same way for descriptive purposes.

Results

Participant flow

49 patients were screened and 40 patients randomised.

Safety analysis set: all randomized patients who used the trial medication at least once were included in the safety analysis set: 40 patients in all groups

Intent-to-treat (ITT) analysis set: all randomized patients who used the trial medication at least once and who had a value of 24-hour plasma cortisol both at baseline and at day 11 for at least one period were included in the ITT analysis set: In Labazenit 300/25 µg 39 patients, in Labazenit 150/25 µg 39 patients, in placebo 38 patients and in Pulmicort Turbohaler + Serevent Diskus 39 patients.

Per protocol (PP) analysis set: all patients were included in the PP analysis set who were in the ITT analysis set and were not major protocol violators. In the PP subset, 2 patients were excluded from the analysis in the Labazenit 150/25 µg group and 1 patient was excluded in the placebo group.

Major protocol violations were no treatment dispensation on period 2.

Baseline data

Patients, all Caucasians, were aged 46.02±12.88 years, 61.22% of women and 38.78% of men. Patients were suffering from mild persistent asthma for 4.4±7.0 years. Mean FEV1 was 2.55±0.58 L/sec i.e. 83.80±2.89 % of predicted. FEV1 reversibility was 0.64±0.31 L i.e. 25.08±9.33% after inhalation of 4*100 µg salbutamol.

Outcomes and estimations

Primary endpoint: Mean change from baseline in AUC0-24h for plasma cortisol

All active treatments led to a decrease in the mean change from baseline to day 11 in the AUC of 24-hour plasma cortisol (see table below):

- Labazenit 300/25 µg: -13.67±3.05 % (Lsmeans±SE)

- Labazenit 150/25 µg: -6.49±3.09 % (Lsmeans±SE)

- Pulmicort Turbohaler 400 µg and Serevent Diskus 50 µg: -7.45±3.09 % (Lsmeans±SE).

Table 18. AUC0-24h for plasma cortisol - ITT population

		ITT population N=40				
		Labazenit 300/25 µg N=39	Labazenit 150/25 µg N=39	Placebo N=38	PUL Turbohaler 400 µg + SER Diskus 50 µg N=39	
AUC 0-24H FOR PLASMA CORTISOL						
	N	39	38**	38	38*	
AUC baseline (nmol/L*h)	m±SD	4239.70 ± 1011.66	4412.51 ± 1330.68	4424.30 ± 1011.23	4321.99 ± 1014.08	
AUC D11 (nmol/L*h)	m±SD	3648.37 ± 958.67	3968.88 ± 938.83	4422.02 ± 933.36	3919.04 ± 1104.54	
Absolute change AUC D11 - baseline (nmol/L*h)	m±SD	591.33 ± 804.51	-443.64 ± 1135.51	-2.28 ± 786.25	-402.94 ± 1059.65	
	Lsmeans ±SE	-658.02 ± 127.89	-385.63 ± 129.4	38.55 ± 129.48	-409.91 ± 129.34	0.0008
Relative change AUC D11 - baseline (%)	m±SD	-12.59 ± 19.20	-7.37 ± 19.20	2.45 ± 20.84	-7.30 ± 24.41	
	Lsmeans ±SE	-13.67 ± 3.05	-6.49 ± 3.09	2.99 ± 3.09	-7.45 ± 3.09	0.0015

** Missing values correspond to patient #34 who had no available values of plasma cortisol at D1 for the period under Pulmicort+Serevent*
*** Missing values correspond to patient #21 who had too many missing values of plasma cortisol at D1 to allow the calculation of a relevant AUC for the period under* Labazenit *150/25 µg.*

A higher decrease was observed with Labazenit 300/25 µg leading to a significant decrease from baseline to D11 when compared to placebo (p=0.0001). The comparison to placebo was not significant for the other treatments.

When comparing the active treatments together, Labazenit 300/25 µg and Labazenit 150/25 µg showed to be both equivalent to the association of Pulmicort Turbohaler 400 µg and Serevent Diskus 50 µg. Effect sizes were respectively -6.22±4.14 % (p=0.14) with a 99.15% confidence interval (CI) of [-17.31% ; 4.87%] included in the [-20% ; +20%] equivalence margin defined in the protocol for Labazenit 300/25 µg and 0.95±4.16% (p=0.82) with a CI of [-10.21% ; 12.11%] for Labazenit 150/25 µg.

Moreover, Labazenit 300/25 µg and Labazenit 150/25 µg were equivalent in decreasing the AUC of 24-hour plasma cortisol (effect size -7.17±4.14%, CI [-18.29%; 3.94%]) (see table below).

Table 19. Contrast between treatment groups on relative changes in AUC plasma cortisol (difference of LSmeans) – ITT population

Contrast	p	Effect size	99.15% two sided CI
Labazenit 300/25µg vs. Pulmicort 400µg + Serevent 50µg	0.1355	-6.22 ± 4.14	[-17.31 - 4.87]
Labazenit 300/25µg vs. Labazenit 150/25µg	0.0864	-7.17 ± 4.14	[-18.29 - 3.94]
Labazenit 300/25µg vs. placebo	0.0001	-16.66 ± 4.14	[-27.77 - -5.55]
Labazenit 150/25µg vs. placebo	0.0247	-9.49 ± 4.16	[-20.65 - 1.68]
Labazenit 150/25µg vs. Pulmicort 400µg + Serevent 50µg	0.8197	0.95 ± 4.16	[-10.21 - 12.11]
Pulmicort 400µg + Serevent 50µg vs. placebo	0.0137	-10.44 ± 4.16	[-21.6 - 0.72]

Secondary parameter: Mean change from baseline in 24-hour urinary cortisol

Level of 24-hour urinary cortisol was characterized by a wide dispersion and some outlier values were noticed.

Table 20. 24-hour urinary cortisol - ITT population

		ITT population N=40				
		BUSAL 300/25 µg N=39	BUSAL 150/25 µg N=39	Placebo N=38	PUL Turbohaler 400 µg + SER Diskus 50 µg N=39	
24-HOUR URINARY CORTISOL						
24h urinary cortisol baseline (µmol/mol)	N	39	38	37	39	
	m±SD	9.15 ± 6.61	11.06 ± 12.34	9.68 ± 6.91	9.25 ± 7.55	
	[min - max ; med]	[1.20 - 27.70 ; 6.70]	[2.30 - 69.10 ; 6.90]	[1.70 - 31.90 ; 7.40]	[2.70 - 44.70 ; 7.60]	
24h urinary cortisol D11 (µmol/mol)	N	39	39	38	39	
	m±SD	10.48 ± 19.10	8.97 ± 7.32	10.34 ± 8.07	7.05 ± 5.22	
	[min - max ; med]	[2.30 - 122.10 ; 6.10]	[1.90 - 31.30 ; 6.20]	[2.40 - 39.40 ; 7.20]	[2 - 30.50 ; 5.40]	
Absolute change D11-baseline (µmol/mol)	N	39	38	37	39	
	m±SD	1.33 ± 16.27	-1.97 ± 11.10	0.77 ± 5.94	-2.20 ± 4.76	
	[min - max ; med]	[-22.40 - 94.40 ; -0.60]	[-60.30 - 13.60 ; -1.10]	[-16.80 - 13.30 ; -0.10]	[-15.90 - 9.20 ; -1.90]	
	Lsmeans±SE	0.92 ± 2.72	1.46 ± 2.73	3.05 ± 2.73	-0.12 ± 2.73	0.0263
Relative change D11-baseline (%)	N	39	38	37	39	
	m±SD	10.25 ± 72.91	4.06 ± 56.45	18.86 ± 68.91	-15.66 ± 39.83	
	[min - max ; med]	[-86.31 - 340.79 ; -10.17]	[-87.26 - 157.14 ; -18.16]	[-68.02 - 254.05 ; -2.56]	[-69.33 - 121.05 ; -26.39]	
	Lsmeans±SE	8.75 ± 9.52	5.80 ± 9.66	18.14 ± 9.77	-16.48 ± 9.51	0.0777

Only the Pulmicort Turbohaler 400 µg+ Serevent Diskus µg treatment led to a decrease in the relative change versus baseline (-16.48±9.51 % (Lsmeans±SE)). This change was nevertheless not statistically significant (p=0.0125) when compared to the 0.0085 threshold due to the multiple comparisons.

Pair-wise comparisons of the treatments did not show any statistical difference between:

- Labazenit 300/25 µg (and 150/25 µg) and Pulmicort Turbohaler 400 µg+ SereventDiskus 50 µg,

- Labazenit 300/25 µg (and 150/25 µg) and the placebo treatment,

- Labazenit 300/25 µg and Labazenit 150/25 µg.

Table 21. Contrasts between treatment groups on relative changes (difference of LSmeans) - ITT population

Contrasts between treatment groups on relative changes (difference of LSmeans)			
Contrast	p	Effect size	99.15% two sided CI
Labazenit 300/25µg vs. Pulmicort 400µg + Serevent 50µg	0.0634	25.23 ± 13.45	[-10.84 - 61.29]
Labazenit 300/25µg vs. Labazenit 150/25µg	0.8286	2.95 ± 13.58	[-33.47 - 39.37]
Labazenit 300/25µg vs. placebo	0.4921	-9.4 ± 13.63	[-45.94 - 27.15]
Labazenit 150/25µg vs. placebo	0.3713	-12.34 ± 13.75	[-49.2 - 24.52]
Labazenit 150/25µg vs. Pulmicort 400µg + Serevent 50µg	0.1038	22.28 ± 13.58	[-14.13 - 58.69]
Pulmicort 400µg + Serevent 50µg vs. placebo	0.0125	-34.62 ± 13.63	[-71.18 - 1.94]

Secondary outcome: Mean change from baseline in Cmax for plasma cortisol

Cmax for plasma cortisol did not significantly evolve from baseline to D11 in any treatment group during the study. There was no difference on relative changes between groups.

Conclusion

24-hour AUC for plasma cortisol remained stable in the placebo group while it decreased in all active treatment groups. Effect size was significant for Labazenit 300/25 µg (p=0.0001). Equivalence in cortisol suppression has been demonstrated between all active treatments: the 99.15% CI was included in the [-20%;+20%] equivalence margin defined in the protocol for all three pair-wise comparisons. Equivalence was also demonstrated between the two doses of Labazenit (300/25 µg and 150/25 µg). 24-hour urinary cortisol decreased with Pulmicort Turbohaler 40 µg+Serevent Diskus 50 µg only but without reaching significance (p=0.0125) when compared to the 0.0085 threshold due to the multiple comparisons. Based on the evaluation of 24-hour urinary cortisol, no significant difference has been observed. Cortisol Cmax at D11 was unchanged in all groups when compared to baseline. All these results were confirmed by the PP analysis.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Labazenit is a new fixed combination of salmeterol/budesonide. As the fine particle dose (FPD) fraction is higher for Labazenit a lower nominal dose in both active ingredients is used than in the reference monotherapies Pulmicort and Serevent Diskus to obtain a similar lung deposition of each active ingredient. The Applicant conducted in total 7 pharmacokinetics study to evaluate the potential interaction between salmeterol and budesonide and to demonstrate the same anti-inflammatory effect of budesonide with Labazenit as with the reference product by establishing comparable exposure of budesonide following inhalation with Labazenit or Pulmicort/Symbicort. Support for the same bronchodilation effect of salmeterol in Labazenit as with Serevent was established in a phase II study (discussed under section Main studies).

Analytical methods

Concentrations of budesonide (epimers A and B) and salmeterol in human plasma were measured using LC/MS/MS methods. The method was 4 times optimised but the LLOQ levels for the budesonide enantiomers 22.5-50 pg/ml and 15 pg/ml for salmeterol remained relatively high compared to the plasma concentrations of budesonide and salmeterol. For Labazenit 150/25 µg strength, Cmax for budesonide and salmeterol were less than 10x the LLOQ. Therefore, AUC levels could not be determined accurately for budesonide and salmeterol when Labazenit or the respectively reference products were administered at the lowest therapeutic dose. Therefore, no reliable comparison of bioavailability between test and reference product could be made for the lowest strength.

There were some irregularities observed with the pharmacokinetic analysis. Subjects were excluded from PK and/or statistical analysis seemingly arbitrarily. Criteria for exclusion of subjects from PK or statistical analysis were not defined in the protocol and not adequately discussed in study reports. In addition, in the mulitple dose studies Cmin plasma concentrations< LLOQ were calculated as being at the level of LLOQ.

In vitro comparison of Labazenit with reference products and between Labazenit strengths

Because of higher lung deposition of fine particle dose with the use of a patented 75/25 mixture of lactose anhydrate (main carrier) and lactose monohydrate (carrier of small particles) in the formulation and because of the lower airflow resistance of the inhaler device Axahaler compared to the Diskus and Turbohaler devices (used for the reference products Serevent and Pulmicort), lower doses of salmeterol and budesonide were used in Labazenit. Development studies with the multistage liquid impinger demonstrated that Labazenit 25 µg salmeterol and 150 µg budesonide has a comparable fine particle dose deposition as 50 µg salmeterol of the reference product Serevent Diskus and as 200 µg budesonide of the reference product Pulmicort Turbohaler. However, the extent of the in-vitro data was considered too limited to demonstrate therapeutic equivalence by the CHMP.

The Applicant with their responses to the D120 LOQ argued that the mean ratio for FPD (test/reference) was of 0.95 with 90% confidence interval of 0.89–1.02. Furthermore, the mean ratio and 90% CI was calculated for each size range for the five following groups : <2 µm, 2-3 µm, 3-4 µm, 4-5 µm and > 5 µm and the results obtained support the overall similarity between the test and the reference products. Moreover, the influence of the inhalation airflow on the FPD of budesonide from Labazenit has been assessed and compared to the influence of airflow on FPD observed with the reference product. Globally, Labazenit shows a more reproducible FPD than TURBOHALER when the airflow is sub-optimal (60 to 80% of optimal airflow). In addition, the Applicant argued that a complete in-vitro comparison has been performed to definitely establish the dose linearity of the particle size distribution profile of budesonide from Labazenit 150/25 µg and 300/25 µg. The dose proportionality of budesonide in-vitro was demonstrated since the mean ratio for the FPD between both dosage strengths (corrected for the dose) is of 0.89 with a 90% CI of 0.84-0.93. The comparison of each particle size range, from the impactor (as described above) confirms this linearity of budesonide between Labazenit 150/25 µg and Labazenit 300/25µg. Furthermore, as expected, the deposition profile of salmeterol is the same for Labazenit 150/25 µg and 300/25 µg.

The CHMP concluded that the in vitro comparisons of Labazenit with the reference products and with the two strengths of Labazenit have been adequately performed by the Applicant in line with the OIP Guideline (CHMP/EWP/4151/00/rev. 1) and the method described in the Ph Eur Monograph. As explained above the two Labazenit strenghts contain less active substance to achieve fine particle doses comparable to the comparator products (salmeterol 25 µg versus 50 µg and budesonide 150 µg versus 200 µg). Except for the group < 2 µm, distribution of salmeterol fine particles is similar at 100% and 80% of optimal flow between test and reference product. The distribution of budesonide fine particles of the proposed product does not comply with the reference product at any flow. Except for the group <2 µm, the distribution of budesonide fine particles is dose proportional for both product strengths (150 µg versus 300 µg). The distribution of salmeterol fine particles is equivalent for both product strengths.

Bioavailability studies

In studies SMB-Busal-SS032 and SMB-Busal-SD033 not all PK parameters for budesonide fell within the 80-125% norm for comparison of Labazenit 300/25 µg with Pulmicort Turbohaler 2x200 µg but point estimate of all parameters were close to unity: at steady-state ratio and 90% CI for AUC_{τ} was 0.94 (0.79-1.12) and for Cmax 1.02 (0.90-1.15). Following single dose administration the variability of the systemic absorption after inhalation was high resulting in wide 90% confidence intervals AUCt 1.08 (0.87-1.33) and Cmax 1.16 (0.94-1.42). These results indicate that the systemic exposure to budesonide is comparable after single dose and multiple dose inhalation of the reference product Pulmicort Turbohaler 2x200 µg and the new Labazenit 300/25 µg combination. However, in studies SMB-Busal-SS032 (and also in study SMB-Busal-SS071), LLOQ values were reported as Cmin when plasma concentrations were below the LLOQ which is not acceptable.

In the multiple dose study SMB-Busal-SS071 the bioavailability of budesonide was almost 2-fold higher for Labazenit 150/25µg than for the combination of Pulmicort Turbuhaler 200µg+ Serevent Diskus. It should be noted that LLOQ for budesonide was ~40-50 pg/ml and as a result almost all samples were below LLOQ 4-6 hours after inhalation. The difference can not be explained by a difference in FPD between the 2 products. The Applicant discussed that the difference may be due to the Turbuhaler being a reservoir based device. If the delivery of one dose is not complete, the following dose will deliver more drug than scheduled. This may have contributed to a lower exposure following inhalation with the Turbuhaler. On the other hand the exposure following Labazenit 150/25 µg seemed higher compared to other studies. For epimer B, two subjects were not included in the analysis because for one subject all plasma concentrations were<LLOQ and the other subject had only two samples> LLOQ. For epimer A, one subject was included who had only one sample> LLOQ, this subject had sufficient samples of epimer B values> LLOQ.

Active charcoal to block the gastrointestinal absorption has not been used in the comparison between Labazenit with Pulmicort. The Applicant justified this by the low ±10% (Clissold et al., 1984) oral bioavailability of budesonide. Indeed, comparison of availability with/without charcoal following inhalation with the Turbuhaler, indicated that intestinal absorption of budesonide contributed ~15% to the systemic availability after inhalation. As the initial budesonide plasma concentrations are mainly due to absorption through the lung and no remarkable differences were observed in plasma ct curves between Labazenit and Pulmicort, no additional studies with charcoal are required.

In study SMB-Busal-SS032, no analysis for salmeterol was made because many of the plasma levels of salmeterol were below LLOQ and the full characterization of the pharmacokinetic profile including 5 points in the absorption phase and 5 points in the elimination phase was not possible for most subjects. It is unfortunate that in study SMB-Busal-SS071 a single puff was administered of test and reference products while knowing that salmeterol and budesonide evaluation was limited by the analytical method.

In conclusion, results from studies SMB-Busal SS032 and SMB-Busal-SD033 suggest that the systemic exposure to budesonide is comparable following inhalation of the reference product Pulmicort Turbohaler 2x200 µg and the new combination Labazenit 300/25 µg.

For salmeterol, no comparative data are available as the LLOQ of the analytical method was not low enough to estimate systemic exposure reliably. Instead, the Applicant aimed to show equivalence of the salmeterol compound of the new fixed dose combination based on in-vitro studies and bronchodilating studies.

Bioequivalence studies

In study SMB-BUSAL-DP102, FPD of salmeterol were comparable for batches of Labazenit 300/25 µg and 125/25 µg: 13.4 and 13.1 µg, respectively, whereas the FPD for budesonide was relatively higher for the 300/25 µg strength 143 µg vs 57.5 µg for the 125/25 µg strength. Although the precise relation between FPD and PK is not well-defined, the difference in FPD of the batches was reflected in the pharmacokinetics of budesonide and salmeterol. Salmeterol pharmacokinetics was comparable for the 300/25 µg and the 150/25 µg strengths whereas the budesonide exposure was relatively higher in the 300/25 µg strength compared to the 150/25 µg strength. Taking into account the difference in FPD between Labazenit 300/25 µg and Labazenit 150/25 µg and considering that AUCt may be underestimated for Labazenit 150/25 µg as more budesonide plasma concentrations were < LLOQ, there is no indication for non-dose proportionality. This is also supported by the dose proportional increase in Cmax of budesonide in study SMB-BUSAL-SD033. AUC values seemed to increase more than proportional in this study but this is probably due to the higher LLOQ of budesonide 40-50 pg/ml in this study resulting in an underestimation of AUC in the lower strength.

Budesonide exposure was considerably higher in study SMB-BUSAL-SD033 compared to SMB-BUSAL-DP102. This may be due to difference in population studied healthy volunteers vs asthmatic patients. In study SMB-Busal-DP102 intestinal absorption of budesonide was blocked by charcoal administration. However, as the difference in exposure was already apparent immediately following inhalation, it is unlikely that the difference in exposure is due to intestinal absorption of budesonide. Moreover literature data indicate that oral absorption contributes only for 10-15% to the overall systemic exposure following inhalation. For the two strengths the quantity and quality of the excipients are the same, the active substances constituent <5% of the formulation. The specifications of delivered dose and FPD are dose proportional and the flow rate dependency of both strengths is similar. Therefore, results obtained with Labazenit 300/25 µg can be extrapolated to Labazenit 150/25 µg.

In study SMB-BUSAL-SD111, charcoal was administered to evaluate the lung deposition of budesonide. The first sample was taken 10 min following inhalation and several subjects had C_{max} of budesonide at the first time point. Although the addition of an earlier time point would have been preferred to determine C_{max} more optimally, based on previous studies with median T_{max} of 10-20 min, the determination of C_{max} at 10 min is acceptable. The low budesonide plasma concentrations compared to the LLOQ may have contributed to the high variability in AUC determination.

Budesonide lung deposition was 15-23% lower following Labazenit 150/25 µg compared to Symbicort 160/4.5 µg. Lung deposition is dependent on the FPD although the precise relation between FPD and PK is not well-defined, in general the higher the FPD fraction, the higher the lung deposition is for an orally inhaled product. FPD of both batches were within the acceptable specification range of the products but there was a more than 20% difference in FPD of the Labazenit batch (58.5 µg) and the Symbicort batch (76.4 µg) used in the PK study. When the PK parameters were corrected for FPD, the lung deposition of Labazenit and Symbicort was comparable. However this is not acceptable as the correction based on FPD was not pre-specified in the study protocol and adjustment/correction by FPD of the PK parameters cannot be accepted unless a clear in vitro/in vivo correlation has been established. The test and reference products batches should be as similar as possible in all their in vitro parameters to avoid the need for correction by FPD.

In study BSM-BUSAL-SD121, 2 inhalations of Labazenit 150/25 and Serevent Diskus were administered to increase the salmeterol plasma concentration and the analytical method was modified to reduce the matrix effect. Here plasma concentrations of salmeterol could be adequately determined over the time period of 12 hours and salmeterol plasma concentrations following inhalation of Labazenit and Serevent Diskus could be compared. LLOQ salmeterol 15 pg/ml. PK and statistical evaluation were standard. Both test and reference products were acceptable, DD and FPD was within specification range of the products. Although the addition of an earlier time point than 10 min would have been preferred to determine C_{max} more optimally, the plasma ct curves could be determine adequately. The bioavailability (AUC and C_{max}) of salmeterol is higher for Labazenit 150/25 µg than for Serevent Diskus 50 µg: point estimates are respectively 1.17 and 1. 31. Differences in FPD fraction of both products can not explain the difference in PK parameters of the two products.

Therefore based on the submitted studies, bioequivalence of budesonide between Labazenit and the comparator Pulmicort and of salmeterol between Labazenit and the comparator Serevent have not been demonstrated.

ADME

Plasma protein binding is approximately 90% and the volume of distribution is 3 L/kg for budesonide. Budesonide undergoes an extensive degree (approx. 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-beta-hydroxy-budesonide and 16-alfa-hydroxy-prednisolone, is less than 1% of that of budesonide. There are no indications of any metabolic interactions or any displacement reactions between salmeterol and budesonide.

Budesonide is eliminated via metabolism mainly catalysed by the enzyme CYP3A4. The metabolites of budesonide are eliminated in urine as such or in conjugated form. Only negligible amounts of unchanged budesonide have been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 L/min) and the plasma elimination half-life after intravenous dosing averages 4 hours.

Salmeterol acts locally in the lung. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the active substance in plasma due to the very low plasma concentrations (approximately 200 pg/ml or less) achieved after inhaled dosing.

The pharmacokinetics of budesonide or salmeterol in patients with renal failure is unknown. The exposure to budesonide and salmeterol may be increased in patients with liver disease.

Interaction study

Study SMB-BUSAL-SD101 was conducted to assess whether any interaction occurs between the two active substances of the FDC versus each substance administered alone and versus both active substances administered with the same device. In house SMB salmeterol and SMB budesonide products were used in order to be able to use the same inhaler device as is being used for the Labazenit FDC. FPD for budesonide and salmeterol of the SMB in house products was comparable to the FPD of Labazenit 300/25 µg. The study design was in line with the guideline on fixed combination medicinal product (CHMP/EWP/240/95/Rev. 1).

As the first sample was taken 10 min following inhalation, almost all subjects had Cmax of salmeterol at the first time point. As a result Cmax could not be determined accurately but time course of pharmacokinetics of salmeterol and budesonide could be determined sufficiently accurately. The first evaluation showed that there is no difference in pharmacokinetics of budesonide and salmeterol when administered separately compared to Labazenit 300/25 FDC. The latter evaluation showed that there is no difference when the two substances are administered together compared to after each other. These results indicate that there is no pharmacokinetic interaction between salmeterol and budesonide.

Pharmacodynamics

The mechanism of action, primary and secondary pharmacology of both salmeterol and budesonide are well known.

As required in the OIP guideline, a safety pharmacodynamics study, study BUSAL II-10-2, was conducted to evaluate the systemic effect on the HPA-axis by the course of plasma cortisol and urine cortisol in Labazenit DPI 300/25 µg BID and 150/25 µg BID compared to Pulmicort Turbuhaler 400 µg BID and Serevent Diskus 50 µg BID and compared to placebo in mild persistent asthmatic patients. The highest recommended dose was used. The primary endpoint considering, 24-hour AUC for plasma cortisol remained stable in the placebo group while it decreased in all active treatment groups. Labazenit 300/25 µg appeared to decrease serum cortisol (AUC0-12 h) more than Labazenit 150/25 µg and Pulmicort Turbohaler 400 µg+ Serevent Diskus 50 µg. However, when assessing equivalence between the different treatment groups cortisol suppression could be considered being equivalent because the 99.15% CI was included in the predefined [-20%;+20%] equivalence margin, which was supported by bibliographical data. The 24-hour urinary cortisol observations supported the finding of the primary endpoint.

2.4.5. Conclusions on clinical pharmacology

The mechanism of action, primary and secondary pharmacology of both salmeterol and budesonide are well known. Evaluating the systemic effect on the HPA-axis it was shown that the 24-hour AUC for plasma cortisol remained stable in the placebo group while it decreased in all active treatment groups. Labazenit 300/25 µg appeared to decrease serum cortisol (AUC0-12 h) more than Labazenit 150/25 µg and the active comparator, but the difference is within the predefined equivalence margins. These findings were supported by the 24-hour urinary cortisol observations. Pharmacokinetic data and in vitro data support the dose proportionality with respect to budesonide between Labazenit 300/25 µg and Labazenit 150/25 µg. The pharmacokinetic profile of salmeterol was the same for Labazenit 150/25 µg and 300/25 µg in study BUSAL-DP102. The absence of a pharmacokinetic interaction between budesonide and salmeterol was confirmed by results from study SMB-BUSAL-SD101.

In three pharmacokinetic studies budesonide exposure following inhalation of Labazenit was compared with a budesonide active comparator (either Pulmicort or Symbicort). Two studies (SMB-BUSAL-SD032, SMB-BUSAL-SD033) showed point estimates for C_{max} and AUC that were reasonably close to unity but the individual studies did not formally demonstrate bioequivalence for both parameters of budesonide based on a 90% confidence interval of 80-125%. The third study (SMB-BUSAL- SD111) showed around 20% lower lung deposition for budesonide when comparing Labazenit with Pulmicort. The difference in Fine particle Dose (FPD) has potentially contributed to the differences observed in the pharmacokinetic parameters. By adjusting for FPD, the results fell within the bioequivalence margins. However this is not considered appropriate since the FPD correction was not pre-specified in the study protocol and such correction of the pharmacokinetic parameters cannot be accepted unless a clear in vitro/in vivo correlation has been established. Therefore the pharmacokinetic data do not sufficiently support a comparable anti-inflammatory control by budesonide between Labazenit and the anti-inflammatory control of budesonide has to be established in the clinical studies.

The pharmacokinetic study BUSAL-SD21 in healthy volunteers showed that systemic bioavailability (Cmax and AUC) of salmeterol was higher following inhalation of Labazenit 150/25 µg compared to Serevent Diskus 50 µg (salmeterol). The higher systemic exposure to salmeterol did not result in more severe extra pulmonary side effects. Comparative efficacy and safety of salmeterol is to be established in the clinical studies.

2.5. Clinical efficacy

Two phase II studies and four phase III studies were submitted to provide evidence regarding the efficacy and safety. The aim of the clinical development program to support the two claimed indications (step up and substitution) was the following:

- To demonstrate a higher efficacy of Labazenit compared with budesonide monotherapy (step-up indication)
- To demonstrate similar efficacy and safety of salmeterol in Labazenit as compared with the reference salmeterol product (substitution indication)
- To demonstrate similar efficacy and safety of budesonide in Labazenit as compared with the reference budesonide product (substitution indication)
- To demonstrate a dose response between the two strengths of Labazenit
- To compare the efficacy and safety of Labazenit with other FDC of an ICS and a LABA

2.5.1. Dose response studies

No dose responses study has been performed and this is justified since the efficacy for both substances is well established.

2.5.2. Main studies

Demonstration of the bronchodilation effect of salmeterol

The Applicant conducted two phase II bronchodilation studies (BUSAL II-03-1 and BUSAL II-10-1) after single dose. These two phase II studies intend to provide evidence for efficacy and safety with respect to the salmeterol component.

Table 22. Overview of the Phase II Clinical efficacy studies with Labazenit

Study Ref.	**BUSAL-II-03-1** ***Supportive study***	**BUSAL-II-10-1** ***Supportive study***
Methods	Controlled single-blind	Controlled partially blinded
Population	Moderate persistent asthma	Moderate to severe persistent asthma
Duration	Single dose	Single dose
Treatment groups	Labazenit 150/25 µg vs. SEREVENT DISKUS 50 µg	Labazenit 150/25 µg vs. Labazenit 150/12.5 µg vs. Labazenit 150/6.25 µg vs. SEREVENT DISKUS 50 µg vs. SEREVENT EVOHALER 25 µg vs. SEREVENT EVOHALER 2x25 µg
Total randomized patients (N=123)	35	48

Study SMB-BUSAL II-10-1 is a randomized, single dose, cross-over, partially blinded study to compare the efficacy of a fixed-dose combination of budesonide-salmeterol DPI capsule 150/25 µg, budesonide-salmeterol DPI capsule 150/12.5 µg, budesonide-salmeterol dpi capsule 150/6.25 µg delivered by the Axahaler versus Serevent Diskus 50 µg, versus Serevent Evohaler 25 µg, versus Serevent Evohaler 25 µg (2 doses) in moderate to severe persistent asthmatic patients.

Study BUSAL II-03-1 is a randomised, single-blind, cross-over study to compare the efficacy and safety of Budesonide-Salmeterol DPI capsule 150-25 µg delivered by the Miat Monodose Inhaler and Serevent Diskus 50 µg in chronic moderate asthmatic patients.

Studies BUSAL-II-10-1 and BUSAL-II-03-1

Methods

Study Participants

Main inclusion criteria

- Male and female patients aged between 18 and 70 years, with a diagnosis of moderate to severe persistent asthma for a minimum of 3 months duration with FEV1 range of 50-80% predicted, reversibility of at least 12% in FEV1 and 200 ml following inhalation of 100 µg or 200 µg of salbutamol with a total increase of at least 17% in FEV1 after a maximum total dose of 400 µg of salbutamol and having asthma symptoms partly controlled or uncontrolled according to the GINA guidelines.
- Patients needed to be on the same regular asthma treatment for at least 4 weeks.

Main exclusion criteria

- Severe, life-threatening asthma or hospitalization for asthmatic exacerbation within 3 months prior to the screening visit and hospitalization for a related disorder in the past 6 months.
- Presence or history of any significant cardiac arrhythmia or diagnosed cardiac disease including coronary artery disease, congestive heart failure and uncontrolled hypertension (classed as a diastolic blood pressure of 95 mmHg or above and a systolic blood pressure of 140 mmHg or above).

- Respiratory tract infection requiring treatment with antibiotics within 4 weeks prior to the screening visit.
- Any significant respiratory disorder other than asthma.
- Smoker more than 10 cigarettes/day (or equivalent) or a smoking history of more than 10 pack years (number packs smoked per day times number of years smoked).
- Pure seasonal asthma and/or a history of seasonal exacerbation of asthma.

Patients were permitted to take their current medications for asthma provided the doses are kept constant during 4 weeks prior to and throughout the study except the following treatments:

- Inhaled Short-acting ß2 agonists at least 6 hours
- Inhaled cromoglycate and nedocromil at least 48 hours
- Xanthines taken 2 times daily at least 24 hours or taken daily at least 48 hours
- Aspirin and non-steroidal antiinflammatory drugs at least 48 hours
- Anticholinergics at least 12 hours
- Antileukotrienes at least 48 hours

The long-acting beta-2 agonist intake is forbidden during the whole study period and at least 72 hours before the screening visit.

Below are described aspects that were study specific:

Study BUSAL-II-10-1

This study was a randomized, single dose, cross-over, partially blinded study to compare the efficacy of a fixed-dose combination of budesonide-salmeterol DPI capsule 150/25 µg, budesonide-salmeterol DPI capsule 150/12.5 µg, budesonide-salmeterol dpi capsule 150/6.25 µg delivered by the Axahaler versus Serevent Diskus 50 µg, versus Serevent Evohaler 25 µg, versus Serevent Evohaler 25 µg (2 doses) in moderate to severe persistent asthmatic patients.

Patients were treated in 4 centers in Macedonia. The study period was from the 25th of September 2010 to the 22nd of November 2010.

Methods

Design

This was a cross-over, single dose, partially blinded, 6-treatment study with a washout period of at least 3 days and up to 5 days between each visit. Equal numbers of patients were randomly assigned to each sequence.

Table 23. Basic design of the cross-over study BUSAL II-10-1

	N=48					
Visit 1 (screening)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
N=68	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	Treatment 6
	Treatment 2	Treatment 3	Treatment 4	Treatment 5	Treatment 6	Treatment 1
	Treatment 3	Treatment 4	Treatment 5	Treatment 6	Treatment 1	Treatment 2
	Treatment 4	Treatment 5	Treatment 6	Treatment 1	Treatment 2	Treatment 3
	Treatment 5	Treatment 6	Treatment 1	Treatment 2	Treatment 3	Treatment 4
	Treatment 6	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5

A wash-out period of 3 days was enough because salmeterol, a selective beta-2 agonist, has a duration of action of up to 12 hours following a single dose inhalation of 50 µg.

Baseline of FEV1 measured at each visit was to be within -20% and +10% of the baseline value obtained at randomisation visit. Furthermore, FEV1 was to be no more than 15% higher than the baseline FEV1 of the preceding study visit. If this criterion was not met, the patients were allowed to return for another attempt the day after (only one retest per visit was allowed by the protocol).

Patients were required to visit the clinic 7 times.

Visit 1 was the screening visit performed within 2 weeks prior to the randomization visit (Visit 2).

From Visit 2 to Visit 7, there were 6 periods of one day during which the patients inhaled a single dose of either Labazenit 150/25 µg or Labazenit 150/12.5 µg or Labazenit 150/6.25 µg or Serevent Diskus 50 µg or Serevent Evohaler 25 µg or Serevent Evohaler 2x25 µg. Each of the 6 periods was separated by a wash-out period of at least 3 days and the last period was followed up by a phone call one week after the final study visit.

Treatments

Test product:

- BUDESONIDE-SALMETEROL DPI 150/25 µg, one capsule via the Axahaler,
- BUDESONIDE-SALMETEROL DPI 150/12.5 µg, one capsule via the Axahaler
- BUDESONIDE-SALMETEROL DPI 150/6.25 µg, one capsule via the Axahaler

Reference product:

- Serevent Diskus 50µg, one inhalation via the Diskus
- Serevent Evohaler 25µg, one inhalation via the Evohaler
- Serevent Evohaler 50µg, two inhalations via the Evohaler

Objectives

The primary objective was to assess the dose-response of the 3 doses (150/25 µg, 150/12.5 µg and 150/6.25 µg) of the fixed dose combination (FDC) of Budesonide-Salmeterol dry powder inhaler (DPI) by measuring the bronchodilatating effect.

Outcomes/endpoints

Primary efficacy endpoint: mean change from baseline in FEV1 max.

Secondary efficacy endpoint: secondary efficacy variables were the mean changes from baseline in:

- FEV1 at 12 hours post dose (L/sec and %), FEV1 max (%),
- PEFR max (L/sec), PEFR at 12 hours post-dose (L/sec),
- FVC max (L), FVC at 12 hours post-dose (L).

Other secondary efficacy variables included: area under the curve (AUC) of FEV1 (L/sec and %), PEFR and FVC (%) respectively from 0 to 12 hours post-dose (L/sec and %), Tmax for FEV1 and safety parameters: adverse events, physical examination, vital signs, 12-lead ECG data, tremor assessment.

Sample size

Calculation was based on the equivalence design of analysis that required a larger sample size than the superiority one. Moreover in a William's design the number of patients must be a multiple of the number of tested treatments (and therefore of the number of periods). The required number of patients was the maximum value of 14, 24, and 38.

Therefore 42 patients were to be treated over the 6 periods of the cross over study to obtain 38 completed patients with a drop-out rate of 10%.

Randomisation

At the baseline/randomization visit (visit 2), after confirmation that the patient met all eligibility criteria for the study, the patient was randomized and assigned a randomization number.

Blinding (masking)

This was a partly blinded study. Indeed, as the double blind was not feasible due to the impossibility to obtain placebo from the reference products, the blind was maintained only for the three doses of the salmeterol/budesonide combination. The randomization procedure was applied in the study design to minimize bias possibility as the investigator was not able to predict the next treatment option for the sequential patient randomization in the trial.

Statistical methods

The main criteria of analysis are known to be normally distributed. The normality of the distribution has not been tested.

Change from baseline has been calculated for each period. The analysis has been made using a mixed model for the serially balanced complete block cross-over design. Terms of the model were period, treatment and baseline of each period as fixed-effect. No interaction term was added in the model. The main criteria for efficacy involved both dose response for Budesonide-Salmeterol and equivalence testing between Budesonide-Salmeterol 150/25 µg and Serevent Diskus 50 µg (and respectively Serevent Evohaler 2*25 µg). The analyses were conducted independently.

Contrasts were calculated between the 3 dosages of Budesonide-Salmeterol. To deal with inflation of type I error risk due to multiple comparisons, the α-risk was reduced to 0.0167 according to the Bonferroni inequality. The two-sided 98.33% confidence interval (CI) of the difference of LSmeans (least squares adjusted means derived from mixed model) was calculated.

In addition a contrast between Budesonide-Salmeterol 150/25 µg and Serevent Diskus 50 µg (and respectively with Serevent Evohaler 2*25 µg) was calculated using the same model as above. As these factors were face to face comparisons of two pairs of products, the Bonferroni correction was not applied. The two-sided 95% CI of the difference of LSmeans was calculated. The limit of the 95% CI was compared to the equivalence margin.

Analyses of secondary criteria were conducted as for the main criterion. Descriptive statistics were used for the safety analysis.

Results

Participant flow

Twenty-two (22) out of the 70 selected patients (31.43%) were screening failures and were not randomized in the trial: 16 patient did not met inclusion criteria, 1 patient did not met exclusion criteria, I patents was patients decision, and 4 patients had other reasons.

Each of the 48 randomised patients received each of the 6 treatments of the cross-over study.

Conduct of the study

There were no protocol amendments to the original clinical trial protocol.

Baseline data

All patients, were of Caucasian race, were aged 47.1±11.3 years with no patient aged more than 70 years at enrolment. Women were in a majority (54.17%).

At the screening visit, patients were suffering from moderate to severe persistent asthma for 3.2±3.6 years. In reference to GINA criteria for asthma control, all patients were partly controlled or uncontrolled.

Table 24. GINA level of asthma control at screening (ITT population)

		ITT population N=48
Daytime symptoms of asthma	N (%)	42 (87.50%)
Limitation of activities	N (%)	31 (64.58%)
Nocturnal symptoms of asthma/awakening	N (%)	39 (81.25%)
Need for reliever / rescue medication	N (%)	45 (93.75%)
Lung function < 80% of predicted or personal best	N (%)	48 (100%)
Exacerbation	N (%)	27 (56.25%)

All patients had a FEV1% between 50% and 80% (66.37 ± 8.04) and all patients demonstrated reversibility (0.56 ± 0.35 L, 26.31±12.82%) and dose-response as per the inclusion criteria.

93.75% of the patients have never smoked while 6.25% were current smokers. Smokers' tobacco consumption was 4.3±1.2 cigarettes per day.

ECG was normal for all patients at screening visit. At randomization visit, one patient presented with left axis deviation and one patient presented with a mild sinus bradycardia. Both abnormalities were judged not clinically significant by the investigator. QTc measurements (msec): (N=48): m ± SD 398.50 ± 23.16 msec; min – max- 360 – 446 msec; med 400.50 msec.

Numbers analysed

All randomised patients received at least one treatment intake and had one assessable FEV1 max for at least one study period after having taken study medication (safety set, Intent-To-Treat (ITT) analysis set):

- 48 patients were included in the safety analysis subset and in the ITT analysis subset

- 48 patients were included in the PP subset analysis

    - 46 patients in the Labazenit 150/12.5 µg period,
    - 47 patients in the Labazenit 150/25 µg period,
    - 47 patients in the Labazenit 150/6.25 µg period,
    - 48 patients in the SER Diskus 50 µg period
    - 47 patients in the SER Evohaler 25 µg period
    - 47 patients in the SER Evohaler 2*25 µg period

Major protocol deviations were: baseline of FEV1 out of range (4), delay last intake of short beta agonist and spirometry (1).

Outcomes and estimation

Primary endpoint: mean change in FEV1max

Mean maximum FEV1 value was 2.68±0.86 L/sec for Labazenit 150/25 µg and 2.66±0.70 L/sec for Serevent Diskus 50 µg . There was no statistically significant difference between treatments (p=0.780) but the related 95% CI (-0.16; 0.12) was marginally outside the predefined equivalence limits (-0.15; +0.15L) (see table below).

Table 25. Post dose FEV1 max- ITT population

		Labazenit 150/25 µg N = 48	Labazenit 150/12.5 µg N = 48	Labazenit 150/6.25 µg N = 48	SER DISKUS 50 µg N=48	SER Evohaler 25 µg N = 48	SER Evohaler 2*25 µg N = 48
FEV1 baseline (L/s)	m ± SD	2.02±0.56	2.02±0.55	2.03±0.54	2.00±0.52	2.03±0.52	2.05±0.56
Post-dose FEV1 max (L/s)	m ± SD LS means ± SD	2.58±0.73 2.59±0.06	2.76±0.79 2.77±0.06	2.68±0.86 2.67±0.06	2.66±0.70 2.69±0.06	2.66±0.75 2.65±0.06	2.65±0.85 2.62±0.06
Mean change in FEV1max (L/s)	m ± SD LS means ± SE	0.56±0.40 0.56±0.06	0.75±0.52 0.75±0.06	0.64±0.46 0.64±0.06	0.66±0.39 0.66±0.06	0.63±0.38 0.63±0.06	0.60±0.48 0.60±0.06

Table 26. Statistical comparisons for changes FEV1 max

FEV_1 max post-dose changes - Contrasts between the 3 BUSAL formulations*			
Contrast	p	Effect size	98.33% two sided CI
6.25 vs 12.5 µg	0.2479	0.06 ± 0.05	[-0.04 - 0.17]
12.5 vs 25 µg	0.8796	-0.01 ± 0.05	[-0.11 - 0.10]
6.25 vs 25 µg	0.3152	0.05 ± 0.05	[-0.05 - 0.16]

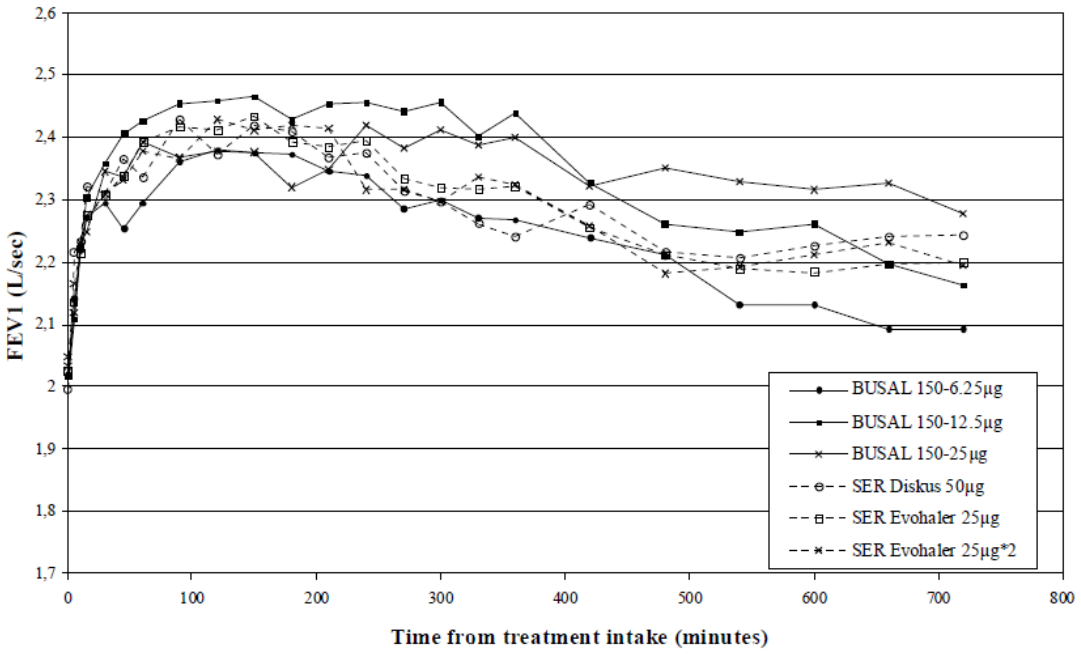
FEV_1 max post-dose changes - Contrasts between BUSAL 150/25 µg and Serevent formulations**			
Contrast	p	Effect size	95% two sided CI
BUSAL 150/25 µg vs SER Diskus 50 µg	0.7796	-0.02 ± 0.07	[-0.16 - 0.12]
BUSAL 150/25 µg vs SER Evohaler 2*25 µg	0.5284	0.05 ± 0.07	[-0.10 - 0.19]
BUSAL 150/25 µg vs SER Evohaler 25 µg	0.8661	0.01 ± 0.07	[-0.13 - 0.15]

FEV_1 max post-dose changes - Contrasts between BUSAL 150/12.5 µg and Serevent Evohaler 25 µg**			
Contrast	p	Effect size	95% two sided CI
BUSAL 150/12.5 µg vs SER Evohaler 25 µg	0.1125	0.11 ± 0.07	[-0.03 - 0.25]

**mixed model with period, treatment, baseline for each period as fixed effects; α risk set at 0.05 for each contrast between the 3 Labazenit formulations; Effect size calculated as the difference between LS means (two-sided 95% CI)

It appeared that results were robust but that the great variability in bronchodilatory response resulted in a 95% CI of the effect size that was larger than expected.

Figure 6. Evolution of FEV1 from 0 to 12 hours post-dose by treatment group



There was no clear dose-response relationship between the 3 doses of Labazenit concerning the post-dose FEV1 max. From a statistical point of view, Labazenit 150/12.5 µg gave better improvement of FEV1 than Labazenit 150/6.25 µg (p=0.01), however there was no significant difference between Labazenit 150/12.5 µg and Labazenit 150/25 µg (see table below).

Table 27. Statistical comparisons of post dose FEV1max between 3 Labazenit formulations

FEV_1 max post-dose changes - Contrasts between the 3 BUSAL formulations*			
Contrast	p	Effect size	98.33% two sided CI
6.25 vs 12.5 µg	0.0113	0.18 ± 0.07	[0.04 - 0.32]
12.5 vs 25 µg	0.1558	-0.10 ± 0.07	[-0.24 - 0.04]
6.25 vs 25 µg	0.2599	0.08 ± 0.07	[-0.06 - 0.22]

The absence of a dose-response relationship between the two different dosages of budesonide and salmeterol was also observed with the reference product. Indeed, no significant difference was observed between the two dosages of Serevent Evohaler (p=0.64) (see table below).

Table 28. Statistical comparisons of post dose FEV1max between 2 Serevent Evohaler formulations

FEV_1 max (%) 12-hour post-dose changes - Contrasts between the 2 Serevent Evohaler doses*			
Contrast	p	Effect size	95% two sided CI
SER Evohaler 2*25 µg vs SER Evohaler 25 µg	0.8402	-0.57 ± 2.81	[-6.10 - 4.97]

Secondary endpoint: FEV1AUC

The AUC of FEV1 over 12 hours were 26.92±7.54 L/sec*h in the Labazenit 150/6.25 µg group, 28.16±7.71 L/sec*h in the Labazenit 150/12.5 µg and 28.20±8.65 L/sec*h in the Labazenit 150/25 µg group (see table below).

Table 29. Statistical comparisons FEV1AUC T0-T12h

		ITT population N=48					
		BUSAL 150/6.25 µg N=48	BUSAL 150/12.5 µg N=48	BUSAL 150/25 µg N=48	SER Diskus 50 µg N=48	SER Evohaler 25 µg N=48	SER Evohaler 2*25 µg N=48
FEV_1 AUC T0-T12h (L/sec*h)	N	48	48	48	48	48	48
	m±SD	26.92 ± 7.54	28.16 ± 7.71	28.20 ± 8.65	27.52 ± 6.85	27.50 ± 8.43	27.47 ± 7.87
	[min - max ; med]	[13.27 - 47.06 ; 26.00]	[14.12 - 47.58 ; 27.42]	[16.63 - 52.89 ; 26.56]	[15.01 - 43.71 ; 27.23]	[11.02 - 57.23 ; 25.68]	[15.08 - 49.10 ; 26.92]
	Lsmeans±SE	26.92 ± 1.09	28.16 ± 1.09	28.20 ± 1.09	27.52 ± 1.09	27.50 ± 1.09	27.47 ± 1.09

The differences between Labazenit 150/6.25 µg and each superior dosages of Labazenit were both at the limit of statistical significance: p=0.064 for the comparison with Labazenit 150/12.5 µg and p=0.057 for the comparison with Labazenit 150/25 µg. No difference was found between Labazenit 150/12.5 µg and Labazenit 150/25 µg (p=0.96).

The AUC tended to increase with the dose of the three Labazenit combinations. This trend was at the limit of statistical significance (see table below).

Table 30. Statistical comparisons of FEV1AUC T0-T12h between 3 Labazenit formulations

FEV_1 AUC 0-12 hours - Contrasts between the 3 BUSAL formulations*			
Contrast	p	Effect size	95% two sided CI
6.25 vs 12.5 µg	0.0637	1.25 ± 0.67	[-0.07 - 2.56]
12.5 vs 25 µg	0.9600	0.03 ± 0.67	[-1.28 - 1.35]
6.25 vs 25 µg	0.0569	1.28 ± 0.67	[-0.04 - 2.60]

No statistical difference was noted for the AUC of FEV1 over 12 hours between Labazenit 150/25 µg and Serevent Diskus 50 µg (p=0.31) (see table below).

Furthermore, no statistical difference was demonstrated between Labazenit 150/25 µg and the two dosages of Serevent Evohaler 25 µg and 50 µg (p=0.30 and p=0.28 respectively).

Table 31. Statistical comparisons of post dose FEV1 AUC 0-12 h between Labazenit 150/25 µg and Serevent formulations

FEV_1 AUC 0-12 hours - Contrasts between BUSAL 150/25 µg and Serevent formulations*			
Contrast	p	Effect size	95% two sided CI
BUSAL 150/25 µg vs SER Diskus 50 µg	0.3127	0.68 ± 0.67	[-0.64 - 1.99]
BUSAL 150/25 µg vs SER Evohaler 2*25 µg	0.2773	0.73 ± 0.67	[-0.59 - 2.05]
BUSAL 150/25 µg vs SER Evohaler 25 µg	0.2980	0.70 ± 0.67	[-0.62 - 2.02]

In addition, no dose-response was observed between the two dosages of Serevent Evohaler (p=0.96).

A trend for the higher doses to have longer duration of action was outlined.

This was confirmed in a post-hoc analysis of AUC between 8 and 12 hours post-dose (AUC8-12) which demonstrated a significant dose-response between Labazenit 150/25 µg and Labazenit 150/6.25 µg (p = 0.008) (see tables below).

Table 32. FEV1 - AUC between 8-hour post-dose and 12-hour post-dose - ITT population

		ITT population N=48						
		BUSAL 150/6.25 µg N=48	BUSAL 150/12.5 µg N=48	BUSAL 150/25 µg N=48	SER Diskus 50 µg N=48	SER Evohaler 25 µg N=48	SER Evohaler 2*25 µg N=48	
FEV_1 AUC T8-T12h (L/sec*h)	N	48	48	48	48	48	48	
	m±SD	8.50 ± 2.49	8.92 ± 2.58	9.29 ± 3.32	8.91 ± 2.38	8.78 ± 3.07	8.82 ± 2.75	
	[min - max ; med]	[4.08 - 15.70 ; 8.23]	[4.08 - 15.82 ; 8.56]	[5.15 - 20.26 ; 8.46]	[4.84 - 14.90 ; 8.63]	[3 - 18.93 ; 7.98]	[4.10 - 16.62 ; 8.63]	
	Lsmeans±SE	8.50 ± 0.39	8.92 ± 0.39	9.29 ± 0.39	8.91 ± 0.39	8.78 ± 0.39	8.82 ± 0.39	0.18*

Table 33. Statistical comparisons FEV1AUC T8-T12h between 3 Labazenit formulations

FEV_1 AUC 8-12 hours - Contrasts between the 3 BUSAL formulations*			
Contrast	p	Effect size	95% two sided CI
6.25 vs 12.5 µg	0.158	0.42 ± 0.29	[-0.16 - 0.99]
12.5 vs 25 µg	0.2023	0.37 ± 0.29	[-0.20 - 0.95]
6.25 vs 25 µg	0.0076	0.79 ± 0.29	[0.21 - 1.37]

Table 34. Statistical comparisons of FEV1AUC T8-T12h between Labazenit and Serevent formulations

FEV_1 AUC 8-12 hours - Contrasts between BUSAL 150/25 µg and Serevent formulations*			
Contrast	p	Effect size	95% two sided CI
BUSAL 150/25 µg vs SER Diskus 50 µg	0.1938	0.38 ± 0.29	[-0.20 - 0.96]
BUSAL 150/25 µg vs SER Evohaler 2*25 µg	0.1067	0.47 ± 0.29	[-0.10 - 1.05]
BUSAL 150/25 µg vs SER Evohaler 25 µg	0.0806	0.51 ± 0.29	[-0.06 - 1.09]

Difficulties in establishing dose-response have been encountered also in other well-controlled studies. Indeed, dose-response assessments of topical bronchodilatators are challenging due to the variability and to the low signal to noise ratio in FEV1, the standard measure of bronchodilatation.

Other secondary endpoints

Overview of key secondary efficacy results - ITT population displays the key secondary efficacy results.

Table 35. Overview of key secondary efficacy results - ITT population

	Labazenit 150/25 µg (N = 48) (A)	Labazenit 150/12.5 µg (N = 48) (B)	Labazenit 50/6.25 µg (N = 48) (C)	SEREVENTDISKUS 50 µg (N=48) (D)	Comparisons between treatments			
					p-value A/B	p-value A/C	p-value A/D	p-value B/C
Tmax (min)	209.06 ± 109.15	192.08 ± 109.38	183.54 ± 95.78	159.79 ± 101.02	0.388	0.195	0.013	0.66
FEV1 at 12h post dose (L/s)	2.28 ± 0.95	2.16 ± 0.68	2.09 ± 0.68	2.24 ± 0.69	0.301	0.073	0.978	0.445
FVC max (L)	3.61 ± 0.90	3.75 ± 0.89	3.58 ± 0.90	3.66 ± 0.84	0.104	0.485	0.387	0.021
PEFR max (L/s)	7.38 ± 2.11	7.52 ± 2.06	7.02 ± 1.97	7.28 ± 1.93	0.291	0.325	0.990	0.042
PEFR at 12h (L/s) post dose	6.05 ± 2.55	5.82 ± 2.30	5.44 ± 1.80	5.77 ± 1.69	0.719	0.171	0.624	0.311
AUC= Area Under the Curve; FEV= Forced Expiratory Volume; FVC= Forced Vital Capacity; PEFR= Peak Expiratory Flow Rate								

Study BUSAL II-03-1

This study was a randomised, single-blind, cross-over study to compare the efficacy and safety of BUDESONIDE-SALMETEROL DPI capsule 150-25 µg delivered by the Miat Monodose Inhaler and Serevent Diskus 50 µg in chronic moderate asthmatic patients.

Patients were treated in once centre in Poland. The study period was from 19th of May 2004 to 26th of July 2004.

Methods

Treatments

Placebo: the placebo capsules were used at the screening to check the ability of the patient to use the Miat Monodose Inhaler. 5 inhalations were made at the screening.

Test product: BUDESONIDE-SALMETEROL 150-25 µg DPI inhaled via the Miat Monodose Inhaler. Each capsule contains 150 µg of budesonide and 25 µg of salmeterol.

Reference product: Serevent 50 µg Diskus. 1 inhalation via the Diskus contains 50 µg of salmeterol.

Objectives

The primary objective was to determine the equivalence of a single dose of BUDESONIDE-SALMETEROL DPI capsule 150-25 g with a single dose of Serevent Diskus.

Outcomes/endpoints

Primary efficacy endpoint: Peak bronchodilatory effect (FEV1 max)

Secondary efficacy endpoint:

- Area under the curve (AUC) of FEV1 from 0 to 12 hours post dosing
- Tmax of FEV1
- FEV1 at 12 hours post dose
- PEFR (peak expiratory flow rate) max
- FVC (forced vital capacity) max
- PEFR at 12 hours post dose
- PEFR (peak expiratory flow rate) at the different time points
- FVC (forced vital capacity) at the different time points
- Number of bronchodilator (salbutamol) rescue inhalations.

Safety variables:

- adverse event profiles
- tremor
- serum glucose and potassium measurements
- 12-lead ECG measurements

Sample size

For the sample size calculation a true difference of zero was used. Using an estimate of within patient standard deviation of the treatment difference of 0.277 and 80% power, 32 evaluable patients were needed to show the equivalence of BUDESONIDESALMETEROL DPI and Serevent Diskus.

Randomisation

Patients received a randomisation number and were assigned to the treatment sequence according to the randomisation list.

Blinding (masking)

The patients were aware that they had been taking either the reference treatment or the test treatment but they were instructed not to discuss or reveal their study medications at any time with the person conducting their pulmonary function tests, as that person was blind to the treatment arm to which the patient was assigned.

Statistical methods

Summaries and analyses of secondary efficacy parameters were performed on the ITT and on the PP analysis sets.

The primary efficacy parameter was the maximum FEV1 attained post dosing (peak bronchodilatory effect). The statistical comparison was based on a 95% confidence interval for the difference between treatments (BUDESONIDE-SALMETEROL DPI-Serevent Diskus), concluding equivalence if the lower bound of the confidence interval was not lower than -0.15 L and the upper bound were not greater than +0.15 L. The 95% confidence interval was calculated as the difference in least squares means between the two treatment groups using an analysis of variance (ANOVA) model.

Results

Participant flow

Thirty-seven patients were screened for the study and thirty-five were randomized. Three patients were randomized being treated by a prohibited drug were replaced by three other patients (105, 106, and 107). These patients were considered in the ITT analysis but excluded from the per protocol analysis.

Conduct of the study

There were no protocol amendments to the original clinical trial protocol.

Baseline data

23 females and 12 males were enrolled in the study. They were white Caucasians from 21 to 68 years old. 4 males were smokers. These patients were not used to smoke and did not smoke not more than 10 cigarettes per day. No female was smoking.

Table 36. Demographic data (safety analysis set)

	Female (n=23)					Male (n=12)					Total (n=35)				
Parameter	mean	SD	min	med	max	mean	SD	min	med	max	mean	SD	min	med	max
Age (y)	42,6	12,5	22	43	68	38,3	14,6	21	38	60	41,1	13,2	21	41	68
Height (cm)	162,2	6,1	152	163	172	178,4	6,3	168	175	193	167,7	9,9	152	168	193
Weight (kg)	70,2	14,2	50	71,3	100	89,0	15,1	60	87,5	112	76,6	16,9	50	72,6	112

Table 37. Smokers and non-smokers (safety analysis set)

Smoking	Female	Male	Total
yes	n=0	n=4	n=4
no	n=23	n=8	n=31

The 35 patients included in the study had a history of chronic moderate asthma for at least 3 months prior to the screening visit.

Descriptive statistics on lung function tests measured at screening are given in the table below. All patient enrolled into the clinical trial had at minimum 3 month history of chronic moderate asthma prior to the screening visit.

All the patients had reversibility of at least 12 % in FEV1 following inhalation of 400 µg salbutamol at screening. All patients had FEV1 values of more than 50% and lower than 85% of predicted at screening.

All the values reported in the table below completely satisfied with the inclusion criteria regarding the spirometry testing.

Table 38. Pulmonary function test at screening (safety analysis set)

Parameter	N	Mean	SD	Minimum	Median	Maximum	CV (%)
Highest value of FEV1(L/sec.)	35	2,35	0,70	1,31	2,17	3,70	29,6
Predicted value FEV1 (L/sec)	35	3,19	0,80	2,02	2,99	4,79	25,1
FEV% of predicted normal	35	73,26	7,40	56,00	74,00	83,00	10,3
FVC (L)	35	3,20	0,78	1,90	3,01	4,74	23,8
PEFR (L/sec)	35	6,00	1,38	3,76	5,90	8,66	21,8
% reversibility	35	17,03	4,44	12,00	15,00	29,00	25,7

Numbers analysed

Thirty seven patients (37) were screened based on established inclusion and exlusion criteria.

Two patients (S10 and S36) were not enrolled into the study.

Patient (S10) was not included into the study because he presented at the screening visit the following findings: ALT = 137 U/l (UNL=31), AST = 147 U/l (UNL=32) and a positive HCV Ab test. As these values and findings were considered as clinically significant by the investigator, the patient was not randomised.

Patient (S36) was screened but not randomized because the clinical site had already randomized the 32 scheduled patients.

Thirty-five (35) patients were randomised into the study and were included in the intent-to treat analysis set.

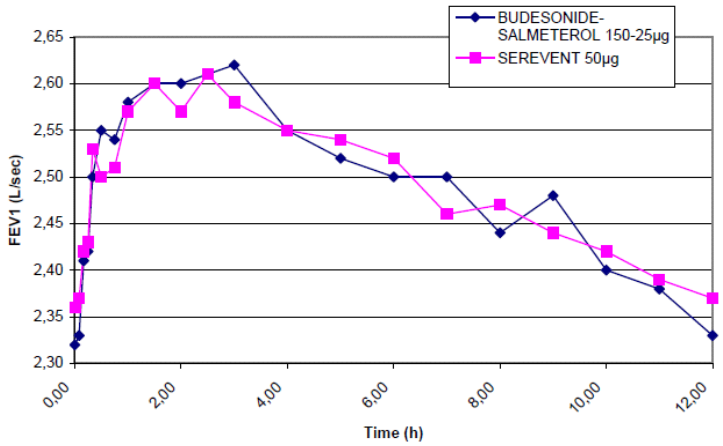
Outcomes and estimation

Primary endpoint: Peak bronchodilatory effect of FEV1

Mean FEV1 max values reached 2,72 ±0,79 l/sec (mean ±SD) and 2,69±0,81 l/sec after administration of BUDESONIDE-SALMETEROL and Serevent Diskus respectively (see figure below).

The difference of 0,03 l/sec between test and reference treatments was not statistically significant (p=0.8650). The related 95% CI (-0.0339: 0.1025) was entirely inside the predefined equivalence limits (-0.15: +0.15 l), demonstrating equivalence between the two treatments with respect to the peak of bronchodilatory effect of FEV1 for the ITT population.

Figure 8. Average FEV1 (l/sec) versus time (ITT analysis set).



Secondary efficacy parameter: area under the curve of FEV1

The mean (±SD) AUC0-12h of FEV1 values were 29.93±8.85 L.h for Labazenit 150/25 µg and 29.87±9.25 L.h for Serevent Diskus 50 µg, with no statistically significant difference between treatments (p=0.865).

Other secondary efficacy parameter

Also several other efficacy secondary parameters were included a.o. FEV1 at 12h post dose, number of bronchodilator (salbutamol) rescue medication. These secondary parameters showed no statistically significant difference between treatments.

Demonstration of the anti-inflammatory effect of budesonide

Study BUSAL-III-02-1

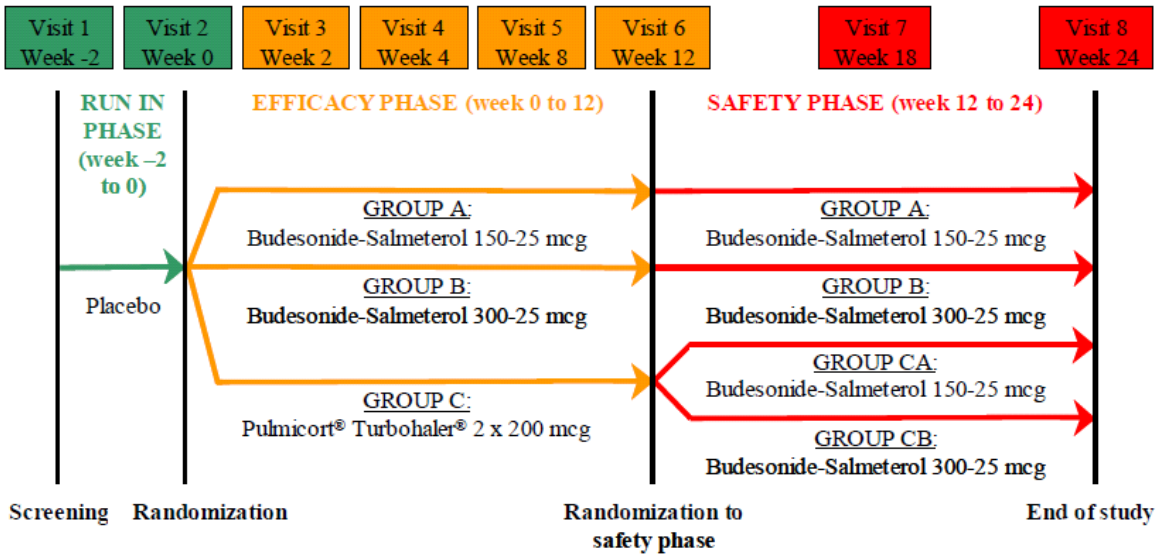
Methods

Study design

This was a phase III, randomized, 24-week parallel study to determine the therapeutic efficacy and safety of BUDESONIDE-SALMETEROL DPI capsule 150-25 µg b.i.d. versus BUDESONIDE-SALMETEROL DPI capsule 300-25 µg b.i.d. delivered by the Monodose Inhaler versus Pulmicort Turbuhaler 2x200 µg b.i.d. in chronic moderate asthma patients.

The study was performed in 18 centres in Poland and in 3 centres in Ukraine. The study period was from the 6th of April 2003 to the 24th of November 2004.

Figure 9. Study design diagram



Study participants

Inclusion criteria

Patients had to satisfy the following criteria before entering the study:

1. Male or female, aged between 18 and 70 years inclusive;
2. History of moderate asthma for at least 3 months prior to the screening visit;
3. Reversibility of at least 12% in FEV1, following inhalation of 400 mcg of Salbutamol at screening;
4. FEV1 of more than or equal to 50% (upper limit 85% inclusive) of predicted at screening and baseline (prior to dosing with study medication);
5. Able to comply with all study procedures, including the use of study inhalers, spirometer and peak flow meter;
6. Willing to withhold the use of short acting β-agonists for at least 6 hours prior to each clinic visit;
7. Provided written, informed consent to participate in the study, indicated by a personal signature and date on the patient consent form;
8. If the patient was female and of childbearing potential, she had to be using an efficient means of birth control, as determined by the investigator and had to provide a negative blood pregnancy test at the screening visit and negative urine test at visit 2.

Exclusion criteria

Patients who met any of the following criteria were excluded from participating in the study:

1. Severe, life-threatening asthma or hospitalisation for asthmatic exacerbation within 3 months prior to the screening visit and hospitalisation for a related disorder in the past 6 months;

2. Evidence of any unstable or untreated clinically significant immunological, neoplastic, endocrine, haematological, hepatic, renal, gastrointestinal, neurological or psychiatric abnormalities or medical disease;

3. Presence or history of any significant cardiac arrhythmia or diagnosed cardiac disease including coronary artery disease, congestive heart failure and uncontrolled hypertension (classed as a diastolic blood pressure of 95 mmHg or above);

4. Respiratory tract infection requiring treatment with antibiotics within 8 weeks prior to the screening visit;

5. Any significant respiratory disorder other than asthma;

6. Patients who smoked more than 10 cigarettes/day (or equivalent) or a smoking history of more than 10 pack years;

7. Pure seasonal asthma and/or a history of seasonal exacerbation of asthma;

8. Use of any of the prohibited medication;

9. Participation in any other clinical study within 3 months prior to the screening visit;

10. Presence of any other condition or illness, which, in the opinion of the investigator would interfere with optimal participation in the study;

11. Patients with any sensitivity or allergy to any of the products used within this clinical study;

12. Patients with diabetes mellitus;

13. Incompliance to PEF tests and study medication (more than 20% of PEF tests or study medication intake missing);

14. Patients who received oral or parenteral steroids in the preceding 8 weeks.

Treatments

Run in period: Placebo.

Controlled PB period:

Labazenit 300/25 µg BID vs. Labazenit 150/25 µg BID vs. Pulmicort Turbuhaler 2x200 µg BID

Open-label period:

Labazenit 300/25 µg BID vs. Labazenit 150/25 µg BID

A. BUDESONIDE-SALMETEROL DPI 150-25 µg inhaled with the MIAT Monodose Inhaler.

B. BUDESONIDE-SALMETEROL DPI 300-25 µg inhaled with the MIAT Monodose Inhaler.

C. PULMICORT Turbuhaler 2x200 µg Multi-dose DPI inhaled with the Turbuhaler.

Ventolin 100 µg (GSK) was offered to all enrolled patients to be used p.r.n. as rescue medication.

Concomitant therapies

Therapy restrictions

There was a wash out period prior to the screening for restricted pulmonary medications (see table below).

Table 39. Wash out periods for restricted pulmonary medications

Not allowed pulmonary medication	Wash-out period
Inhaled nasal corticosteroids >400 µg /day	At least 4 weeks
Inhaled short-acting β-agonists	At least 6 hours *
Inhaled long-acting β-agonists	At least 48 hours
Inhaled anticholinergics	At least 8 hours
Oral β-agonists	At least 24 hours
Xanthines, short acting	At least 24 hours
Sustained release xanthines	At least 48 hours
Oral anticholinergics	At least 7 days
Nebulised β-agonists	At least 24 hours
Nebulised anticholinergics	At least 24 hours
Ephedrine	At least 72 hours
Nebulised corticosteroids	At least 4 weeks
Antihistamines (ketotifen, astemizole, etc.)	At least 4 weeks
Nedocromil, Sodium Cromoglycate	At least 4 weeks
Leukotriene antagonists	At least 4 weeks
β-blockers including eye-drops	At least 4 weeks
Oral, intravenous/ intramuscular corticosteroids	At least 8 weeks

* The above washout period also applies for MDI 100µg on all study visits.

Permitted therapy: Salbutamol, taken by inhalation (rescue medication) to a maximum daily dose of 1600 µg.

Objectives

The primary objective was to determine the therapeutic efficacy of BUDESONIDE-SALMETEROL 150-25 µg b.i.d. versus BUDESONIDE-SALMETEROL 300-25 µg b.i.d. versus Pulmicort Turbuhaler 2 x 200 µg b.i.d. (reference), in patients with chronic moderate asthma.

The secondary objectives were to evaluate the safety of BUDESONIDE-SALMETEROL b.i.d. and to compare it to the safety profile of the reference product (PulmicortTurbuhaler 2 x 200 µg).

The safety variables were adverse events (AEs), withdrawals or drop-out rate, physical examination, vital signs, laboratory data, pulmonary function test and 24h urinary and morning plasma cortisol levels in subgroup of 45 patients (15 patients per study arm).

Outcomes/endpoints

The primary efficacy variable was the mean change from baseline in morning PEF (mean change over the weeks from 0 to 12).

The secondary efficacy variables were the mean change from baseline in evening PEF, FEV1, asthma symptoms score change from baseline averaged over the weeks from 0 to 12, sleep disturbance score (subset of the asthma symptom score) change from baseline averaged over the weeks from 0 to 12, change from baseline in FVC and the number of bronchodilator rescue inhalations.

Data for PM PEF, asthma symptom score/total asthma symptoms score, sleep disturbance score, number of bronchodilator (*β 2*-agonist) rescue inhalations were collected from the diary cards.

Sample size

With 100 evaluable patients per treatment group, and the standard deviation of 50 L/min in morning PEF, it is estimated that a difference in change in morning PEF of 15 L/min could be found with 80% power at the 5% significance level using pair-wise comparison.

Assuming a 20% screening failure rate and a 20% withdrawal rate a total of 432 patients will be required in order to achieve 100 evaluable per group.

Randomisation

Patients received a randomization number and were assigned to the treatment sequence according to the randomization list. The patients were selected from 21 centers in two countries. The numbers were allocated sequentially in the order in which the patients were enrolled independently of the study centre where they were randomized.

Blinding (masking)

The efficacy phase was an open-label part preceded by a single blind screening run-in phase where patients received a placebo.

The efficacy phase could not have been blinded because of the significant difference in the appearance of the investigational and reference devices while a double-dummy design could not be performed because of the technical impossibility to manufacture placebo devices of the reference product.

At visit 6 (end of the efficacy phase), all patients treated with the reference product underwent a second randomization and were assigned to either treatment with BUDESONIDE-SALMETEROL DPI 150-25 µg or BUDESONIDE-SALMETEROL 300-25 µg for the rest of the study (safety phase). A complete double-blind scheme was used as to which treatment they were receiving.

The patient and doctor were instructed to not speak about their treatments to the technician responsible of the measurement of the pulmonary function tests. Furthermore, a complete double-blind design was maintained between both investigational drugs during the efficacy and safety phase.

Statistical methods

The primary analysis was an intent-to-treat analysis, including all randomized patients who received at least one dose of study medication except for patients withdrawn after few days of treatment. Such patients could be withdrawn from the final analysis and the reason had to be reported. The primary efficacy variable was morning PEF as recorded by the patients in diary cards. Averages of existing values were calculated for morning PEF for the last 5 days of the run-in period and for the whole of the treatment period. All hypothesis testing was made using two-sided alternatives.

The level of statistical significance was set at 0.05.

During the efficacy phase:

The changes from baseline of the mean weekly values and of the endpoint were analyzed with an ANCOVA model using as co-variable the baseline value. Superiority was addressed by calculating the 95% CIs for the mean difference between each formulation and was concluded if the two-sided 95 % CI for the treatment difference measured using the morning PEF (l/min) exceeded 0 L/min. A test to demonstrate if the difference exceeded 15 L/min was also performed. All 3 pair-wise comparisons between the 3 groups ("Labazenit 150/25 µg", "Labazenit 300/25 µg" and "Pulmicort 2x200 µg") were done.

Within-group comparisons were done per timepoint and per treatment group by means of a paired t-test.

During the safety phase:

Between-group comparisons were done for the efficacy variables by means of an ANCOVA model with baseline as covariate on the *changes* from baseline for "Labazenit 150-25 µg after reference" versus "Labazenit 300-25 µg after reference". Between-group comparisons by means of an ANCOVA model with baseline as covariate were done on the *actual* values for "Labazenit 150-25 µg" at baseline week 12 versus "Labazenit 150-25 µg after reference" at endpoint week 24 and for "Labazenit 150-25 µg" versus "Labazenit 150-25 µg after reference" at endpoint week 24 (similar for "Labazenit 300-25 µg"). *Within-group* comparisons were done for the efficacy variables by means of paired t-tests for "Labazenit 150-25 µg after reference" on the changes from baseline (similar for "Labazenit 300-25 µg after reference"); and for "Labazenit 150-25 µg" from week 12 till week 24 and at endpoint week 24 on the changes from baseline week 12 (similar for "Labazenit 300-25 µg").

During the whole treatment period:

Between-group comparison was done for the groups "Labazenit 150-25 µg" and "Labazenit 300-25 µg" on the changes from initial baseline by means of an ANCOVA model with baseline value as covariate. *Within-group* comparison was done on the changes from initial baseline over the whole 24 weeks by means of a paired t-test for the groups "Labazenit 150-25 µg" and "Labazenit 300-25 µg". The secondary variables evening PEF, PFTs, asthma symptoms score, *β2*-agonist use and sleep disturbance score were analyzed in a manner similar to that for the primary variable, without the test if the difference between treatments exceeded 15L/min.

Results

Participant flow

The actual number of patients selected was 478 screened, 375 randomized and 342 terminated.

Table 40. Analyzed populations

	Labazenit 150-25 µg	Labazenit 300-25 µg	Reference group
Safety: All patients (375)	126	125	124
Efficacy:			
ITT (374)	126	124	124
Per Protocol (331)	111	113	107

One patient assigned to BUDESONIDE-SALMETEROL 300-25 µg b.i.d. treatment was excluded from the ITT population (374 patients) as recorded FEV1 values after screening were missing for this patient. Major protocol deviations were reported for 43 patients, resulting in a PP population of 331 patients (see table below).

Discontinuation

Table 41. Reasons for discontinuation – study BUSAL III-02-1

	Efficacy phase			Safety phase		Safety phase for patients on reference treatment during the efficacy	
	Labazenit 150/25 N= 126	Labazenit 300/25 N=125	Reference N=124	Labazenit 150/25 N=123	Labazenit 300/25 N=117	Labazenit 150/25 N=60	Labazenit 300/25 N=56
Total discontinued	3 (2)	8 (6)	8 (7)	5 (4)	2 (2)	4 (7)	3 (5)
Adverse event	0	1 (1)	1 (1)	2 (2)	1(1)	0	1 (2)
Insufficient response	0	1 (1)	2 (2)				
Patient not compliant	0	2 (2)	2 (2)	1 (1)	0	2 (3)	0
Patient lost to follow up				1 (1)	0	1 (2)	1 (2)
Asthma exacerbation	0	0	1 (1)	1 (1)	0		
Withdrawal consent	1 (1)	0	1 (1)				
ineligible	1 (1)	0	0				
Other	1 (1)	4 (3)	1 (1)	1 (1)	0	1 (2)	1 (2)

Compliance based on the mean number of inhalations and the mean number of PEF tests performed was at least 97% in any analysis phase for any treatment group.

Conduct of the study

There was one protocol amendment to the original clinical trial protocol: the highest FEV1 and FVC do not need to come from the same curve. As both parameters are secondary efficacy variables the highest values of both parameters revealed during spirometry should be recorded for analysis. In previous version those two values must come from the same curve.

Other protocol amendments were made (of editorial nature) and were in relation to the addition of sites in Ukraine.These amendments were considered not influencing the study results.

Baseline demographics

At baseline, demographic parameters and severity of the disease were similar between treatment groups (see table below).

Table 42. Demographic data (Safety 'all patients' population)

Characteristic		BUSAL 150-25 mcg N = 126	BUSAL 300-25 mcg N = 125	Reference N = 124
Age (years)	Mean ± SE	45.3 ± 1.19	43.7 ± 1.17	45.9 ± 1.22
	Median (range)	49.0 (18-69)	45.0 (18-71)	48.0 (18-67)
Sex, n (%)	Female	63 (50)	72 (58)	76 (61)
	Male	63 (50)	53 (42)	48 (39)
Smoking habits, n (%)				
Patient ever smoked	No	97 (77)	85 (68)	103 (83)
	Yes	29 (23)	40 (32)	21 (17)
≥ 10 cigarettes/day	Not applicable	97 (77)	83 (66)	102 (82)
	No	28 (22)	40 (32)	21 (17)
	Unknown	1 (1)	2 (2)	1 (1)
History of >10 pack years	Not applicable	96 (76)	84 (67)	103 (83)
	No	30 (24)	41 (33)	21 (17)
Asthma severity, n (%)	Moderate	126 (100)	125 (100)	124 (100)
Years from first diagnosis of asthma[a]	Mean ± SE	9.2 ± 0.83	8.4 ± 0.74	10.5 ± 1.06
	Median (range)	6.5 (0-48)	7.0 (0-42)	6.3 (0-53)
Asthma medication during last 3 months, n (%)	No	5 (4)	6 (5)	6 (5)
	Yes	121 (96)	119 (95)	118 (95)

Baseline disease characteristics

Over the last 5 days of the run-in phase, mean (± SE) morning and evening PEF measurements were 363.2 (± 4.98) L/min and 373.1 (± 4.94) L/min, respectively.

Mean FEV1% (± SE) was 65.3% (± 0.48%) of the patients' predicted normal. Mean (± SE) values FEV1 and FVC at baseline were 2.07 (± 0.031) L/s and 3.03 (± 0.047) L, respectively.

Table 43. Disease characteristics

Characteristic	Labazenit 150-25 µg	Labazenit 150-25 µg	Reference
Reversibility test at visit 1			
Reversibility (%)	23.51 ± 1.069	25.16 ± 1.205	27.88 ± 1.449
PFT during run-in phase			
Morning PEF (L/min)	370.23 ± 8.017	364.22 ± 9.214	354.82 ± 8.633
Evening PEF (L/min)	380.97 ± 7.907	370.82 ± 9.165	367.38 ± 8.603
PFT at visit 2			
FEV1 % of predicted Normal	65.21 ± 0.951	65.72 ± 0.747	64.97 ± 0.754
FEV1 (L/s)	2.11 ± 0.052	2.11 ± 0.056	2.00 ± 0.053
FVC (L)	3.08 ± 0.082	3.10 ± 0.085	2.91 ± 0.079
Asthma symptoms (mean of last 5 days) during run-in phase			
Asthma symptom: Cough score#	0.95 ± 0.064	0.90 ± 0.066	0.97 ± 0.066
Asthma symptom: Shortness of breath score#	1.23 ± 0.064	1.16 ± 0.067	1.22 ± 0.065
Asthma symptom: Wheezing score#	1.05 ± 0.066	0.95 ± 0.068	1.10 ± 0.063
Total asthma symptom score	3.22 ± 0.170	3.00 ± 0.177	3.27 ± 0.172
Sleep disturbance	1.77 ± 0.060	1.81 ± 0.068	1.74 ± 0.061

score§			
Use of rescue medication (mean of last 5 days) during run-in phase			
Use of rescue medication (no. of puffs/day)	3.12 ± 0.313	3.21 ± 0.335	3.12 ± 0.313

0 = absent, 1 = mild, 2 = moderate and 3 = severe
§ 0 = absent, 1 = waking once, 2 = waking twice or more, 3 = awake most of night and 4 = no sleep at all
N = number of patients in the treatment group; n = number of patients with that observation

Homogeneous distribution of patients over the three treatments groups was demonstrated for morning PEF, evening PEF, FEV1 and FVC, as no statistically significant differences were seen for these parameters. Statistically significant difference was noted for reversibility after inhalation of 400 µg Salbutamol at screening (p=0.045); mean (± SE) reversibility at screening was 23.5, 25.2 and 27.9 %, in the BUDESONIDE-SALMETEROL 150-25 µg, BUDESONIDE-SALMETEROL 300-25 µg and reference groups, respectively. Overall, patients had a mean reversibility (± SE) at screening of 25.5% (± 0.73%).

At week 12, the start of the safety phase, no differences between the subdivision of patients who were on reference treatment during the efficacy phase were noted with respect to morning PEF, evening PEF, FEV1 and FVC.

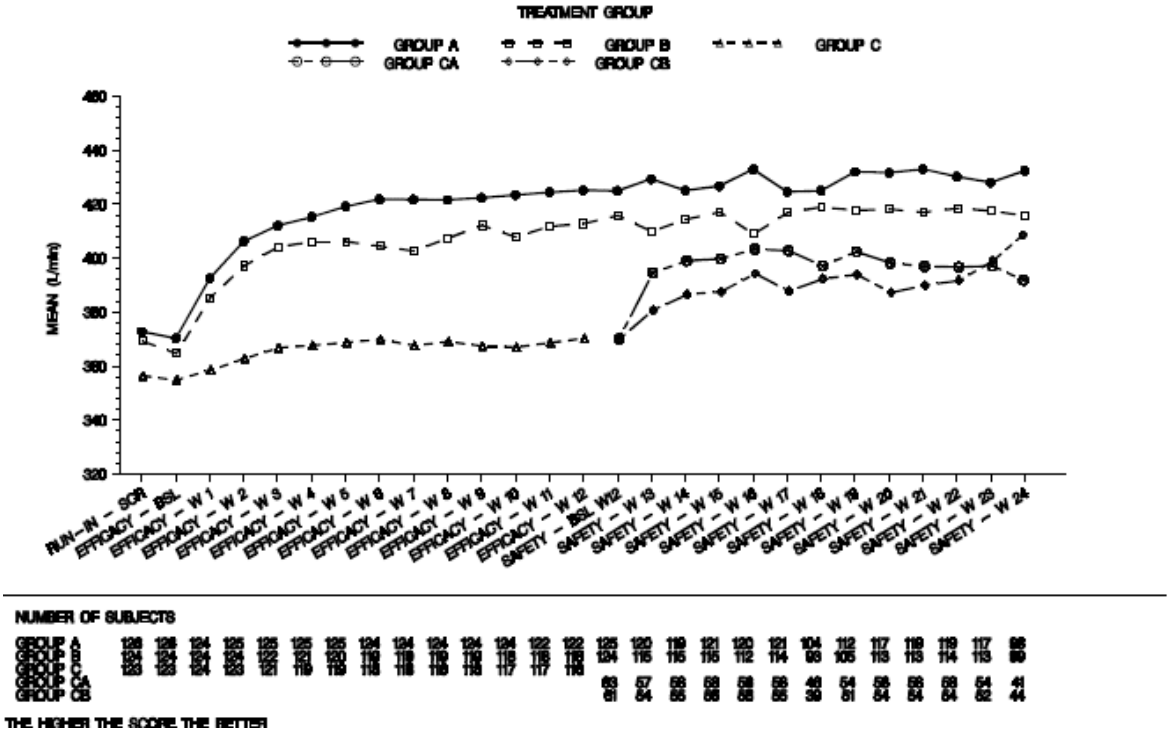
Baseline disease characteristics for the PP and ITT populations were similar as for the Safety 'all patients' population.

Outcomes and estimation

Primary efficacy variable: morning PEF

A graphical presentation of the actual mean morning PEF values, for the 4 treatment groups during the 24-week treatment period, is shown in the figure below for the ITT population

Figure 10. Actual mean morning PEF values – Whole study period



Mean change in morning PEF during the efficacy phase

The mean change ±SD in morning PEF (primary endpoint) from baseline to Week 12 was 54.37±66.25 L/min for the Labazenit 150/25 µg group, 51.37±61.00 L/min for the Labazenit 300/25 µg group and 15.64±47.92 L/min for the PulmicortTurbuhaler 400 µg group. These increases were statistically significant within the 3 treatment groups (p<0.001). The results are displayed in the table below.

Table 44. Mean change in morning PEF

	Labazenit 150-25 µg (A)		Labazenit 150-25 µg (A)		Reference (C)				
	n	mean ± SE	n	mean ± SE	n	mean ± SE	PA/B*	PA/C*	PB/C*
Week 2	125	35.1±4.12	124	32.5±4.22	122	8.5±2.88	0.534	<0.001	<0.001
Week4	125	44.2±4.80	121	41.3±5.24	118	14.9±3.62	0.536	<0.001	<0.001
Week8	124	51.1±5.39	119	45.8±5.92	117	15.0±4.31	0.321	<0.001	<0.001
Week12	**122**	**54.4±6.00**	**118**	**51.4±5.62**	**115**	**15.6±4.47**	**0.522**	**<0.001**	**<0.001**
Endpoint	125	53.8±5.78	124	51.1±5.52	123	15.0±4.22	0.584	<0.001	<0.001

N = number of patients with data; Endpoint: the last non-missing 7 days of the efficacy period
* Significance in the difference in efficacy between treatments (ANCOVA model with factor baseline value as continuous parameter)

Both Labazenit 150/25 µg and Labazenit 300/25 µg treatments were shown to be superior to Pulmicort Turbuhaler 400 µg treatment at Week 2, 4, 6, 8, 10 and 12 since the two-sided 95% CIs for the treatment difference did not contain 0 L/min (p<0.001).

It was demonstrated that both BUDESONIDE-SALMETEROL 150-25 µg and 300-25 µg treatments were superior to reference treatment after 12 weeks of treatment (BUDESONIDE-SALMETEROL 150-25 µg vs. reference: p<0.001; BUDESONIDE-SALMETEROL 300-25 µg vs. reference: p=0.004).

Table 45. Superiority test with 95% CIs of the difference in LSmeans* for morning PEF between treatment groups - Efficacy phase

Mean change in morning PEF between:	BUSAL 150-25 mcg (A) vs. BUSAL 300-25 mcg (B)	BUSAL 150-25 mcg (A) vs. Reference (C)	BUSAL 300-25 mcg (B) vs. Reference (C)
Week 2 and baseline	-7.04; 13.55	17.88; 38.60	14.62; 35.35
Week 4 and baseline	-8.37; 16.08	19.70; 44.38	15.77; 40.60
Week 8 and baseline	-6.86; 20.87	25.21; 53.10	18.09; 46.21
Week 12 and baseline	-9.69; 19.04	27.18; 56.15	22.42; 51.57

* LSmeans estimated from ANCOVA model for mean values in the phase with factor baseline value as continuous parameter
BUSAL 150-25 mcg: BUDESONIDE-SALMETEROL 150-25 mcg b.i.d.
BUSAL 300-25 mcg: BUDESONIDE-SALMETEROL 300-25 mcg b.i.d.
Reference: PULMICORT® TURBOHALER® 2 x 200 mcg b.i.d.

Mean change in morning PEF during the safety phase

The switch from reference treatment to treatment with BUDESONIDE-SALMETEROL 150-25 µg or BUDESONIDE-SALMETEROL 300-25 µg resulted in statistically significant increases in morning PEF values from week 12 to week 18 and 24 within both treatment groups receiving BUDESONIDE-SALMETEROL after 12 weeks of reference treatment (p<0.001; see table below).

Table 46. Mean change in morning PEF (L/min) and ANCOVA test results for BUDESONIDE-SALMETEROL 150-25 µg or 300-25 µg treatment after reference – Safety phase

Mean change in morning PEF between:	BUSAL 150-25 mcg after reference (CA)			BUSAL 300-25 mcg after reference (CB)			$P_{CA/CB}$##
	N	mean±SE	p#	N	mean±SE	p#	
Week 18 and week 12	46	24.6±4.95	<0.001	39	15.9±4.41	<0.001	0.207
Week 24 and week 12	41	22.1±5.04	<0.001	44	30.9±6.47	<0.001	0.255

N = number of patients with data
# Significance in the difference in efficacy of the treatment between week 12 and week x (two-sided paired t-test)
Significance in the difference in efficacy between treatments (ANCOVA model with factor baseline value as continuous parameter)
BUSAL 150-25 mcg: BUDESONIDE-SALMETEROL 150-25 mcg b.i.d.
BUSAL 300-25 mcg: BUDESONIDE-SALMETEROL 300-25 mcg b.i.d.
Reference: PULMICORT® TURBOHALER® 2 x 200 mcg b.i.d.

The results of the test on superiority revealed that treatment with BUDESONIDE-SALMETEROL 150-25 µg after reference was similar to treatment with BUDESONIDE-SALMETEROL 300-25 µg after reference, with respect to the mean changes from week 12 in morning PEF values to week18 and 24 (p=0.207 and 0.255 at weeks 18 and 24, respectively.

Mean change in morning PEF during the whole study period

Statistically significant increases from baseline to week 2, 4, 8, 12, 18 and 24 in mean morning PEF values were observed within both test treatment groups (p<0.001).

Under BUDESONIDE-SALMETEROL 150-25 µg and 300-25 µg treatments, mean morning PEF values increased after baseline and had increased by 55.1 ± 6.35 L/min and 60.4 ± 6.21 L/min, respectively, after 24 weeks of treatment.

24-week treatment with BUDESONIDE-SALMETEROL 150-25 µg was similar to 24-week treatment with BUDESONIDE-SALMETEROL 300-25 µg, with respect to the change from baseline in morning PEF (p<0.321). Indeed, the two-sided 95% CIs for the treatment difference contained 0 L/min at week 2, 4, 8, 12, 18 and 24.

Secondary parameters

FEV1: Mean change in FEV1 during the efficacy phase

Statistically significant increases from baseline to week 2, 4, 8 and 12 in mean FEV1 values were observed within the 3 treatment groups (p<0.001; see table below).

Across the 3 treatment groups, mean FEV1 values increased from baseline to week 2 and remained stable thereafter. At week 12, mean increases from baseline in FEV1 were 0.42 ± 0.043 L/s, 0.41 ± 0.039 L/s and 0.29 ± 0.044 L/s in the BUDESONIDE-SALMETEROL 150-25 µg, BUDESONIDE-SALMETEROL 300-25 µg and reference treatment groups, respectively.

Table 47. Mean change in FEV1 (L/s) and ANCOVA test results - Efficacy phase

Mean change in FEV_1 between:	BUSAL 150-25 mcg (A)			BUSAL 300-25 mcg (B)			Reference (C)			$P_{A/B}$##	$P_{A/C}$##	$P_{B/C}$##
	N	mean±SE	p#	N	mean±SE	p#	N	mean±SE	p#			
Week 2 and baseline	122	0.34±0.040	<0.001	123	0.39±0.035	<0.001	119	0.20±0.032	<0.001	0.322	0.009	<0.001
Week 4 and baseline	122	0.41±0.042	<0.001	119	0.39±0.047	<0.001	118	0.25±0.040	<0.001	0.762	0.015	0.034
Week 8 and baseline	122	0.43±0.041	<0.001	118	0.42±0.044	<0.001	118	0.28±0.041	<0.001	0.888	0.017	0.026
Week 12 and baseline	122	0.42±0.043	<0.001	117	0.41±0.039	<0.001	113	0.29±0.044	<0.001	0.795	0.036	0.068

N = number of patients with data
# Significance in the difference in efficacy of the treatment between baseline and week x (two-sided paired t-test)
Significance in the difference in efficacy between treatments (ANCOVA model with factor baseline value as continuous parameter)

At week 12, only BUDESONIDE-SALMETEROL 150-25 µg treatment was found to be superior to reference treatment regarding mean changes from baseline FEV1 (BUDESONIDE-SALMETEROL 150-25 µg vs. reference: p=0.036; BUDESONIDE-SALMETEROL 300-25 µg vs. reference: p=0.068).

Both BUDESONIDE-SALMETEROL 150-25 µg and BUDESONIDE-SALMETEROL 300-25 µg treatments were shown to be superior to reference treatment regarding mean changes from baseline FEV1 at week 2, 4 and 8; the two-sided 95% CIs for the treatment difference did not include 0 L/s (p≤0.034; see table below).

Table 48. Superiority test with 95% CIs of the difference in LSmeans* for FEV1 between treatment groups - Efficacy phase

Mean change in FEV_1 between:	BUSAL 150-25 mcg (A) vs. BUSAL 300-25 mcg (B)	BUSAL 150-25 mcg (A) vs. Reference (C)	BUSAL 300-25 mcg (B) vs. Reference (C)
Week 2 and baseline	-0.15; 0.05	0.03; 0.23	0.08; 0.28
Week 4 and baseline	-0.10; 0.14	0.03; 0.27	0.01; 0.25
Week 8 and baseline	-0.11; 0.12	0.03; 0.26	0.02; 0.25
Week 12 and baseline	-0.10; 0.13	0.01; 0.24	-0.01; 0.23

* LSmeans estimated from ANCOVA model for mean values in the phase with factor baseline value as continuous parameter

Mean change in FEV1 during the safety phase

Statistically significant increases in FEV1 from week 12 to week 18 and 24 were observed within the group receiving BUDESONIDE-SALMETEROL 150-25 µg after 12-week reference treatment (p≤0.030). No statistically significant changes in mean FEV1 values from week 12 to week 18 and 24 on the other hand, were observed in the group treated with BUDESONIDE-SALMETEROL 300-25 µg after 12-week reference treatment (p≥0.067). These results indicate that the switch from reference treatment to BUDESONIDE-SALMETEROL 150-25 µg or 300-25 µg treatment did not notably affect FEV1 values.

The results of the superiority test revealed that treatment with BUDESONIDE-SALMETEROL 150-25 µg after reference was similar to treatment with BUDESONIDE-SALMETEROL 300-25 µg after reference with respect to the mean changes in FEV1 from baseline to week 18 and 24 (p=0.790 and 0.984 at week 18 and 24, respectively) (see table below).

Table 49. Mean change in FEV1 (L/s) and ANCOVA test results for BUDESONIDE-SALMETEROL 150-25 µg or 300-25 µg treatment after reference - Safety phase

Mean change in FEV_1 between:	BUSAL 150-25 mcg after reference (CA)			BUSAL 300-25 mcg after reference (CB)			$P_{CA/CB}$##
	N	mean±SE	p#	N	mean±SE	p#	
Week 18 and week 12	59	0.09±0.038	0.026	55	0.09±0.050	0.091	0.790
Week 24 and week 12	57	0.08±0.034	0.030	54	0.08±0.045	0.067	0.984

N = number of patients with data
# Significance in the difference in efficacy of the treatment between week 12 and week x (two-sided paired t-test)
Significance in the difference in efficacy between treatments (ANCOVA model with factor baseline value as continuous parameter)

Mean change in FEV1 during the whole study

Statistically significant increases from baseline to week 2, 4, 8, 12, 18 and 24 in mean FEV1 values were observed within the both test treatment groups (p<0.001). In the BUDESONIDE-SALMETEROL 150-25 µg and 300-25 µg treatment groups, mean FEV1 values increased from baseline to week 2 and remained stable thereafter. At week 24, a mean increase in FEV1 versus baseline of 0.40 ± 0.043 and 0.43 ± 0.041 L/s was observed in the BUDESONIDE-SALMETEROL 150-25 µg and the BUDESONIDE-SALMETEROL 300-25 µg treatment groups, respectively.

24-week treatment with BUDESONIDE-SALMETEROL 150-25 µg was similar to 24-week treatment with BUDESONIDE-SALMETEROL 300-25 µg with respect to change in FEV1 from baseline (p≥0.322). The two-sided 95% CIs for the treatment difference contained 0 L/s at week 2, 4, 8, 12, 18 and 24.

A graphical presentation of the actual mean FEV1 values, for the 4 treatment groups during the 24-week treatment period, is shown in the figure below for the ITT population.

Figure 11. Actual mean FEV1 values (L/s) - Whole study period

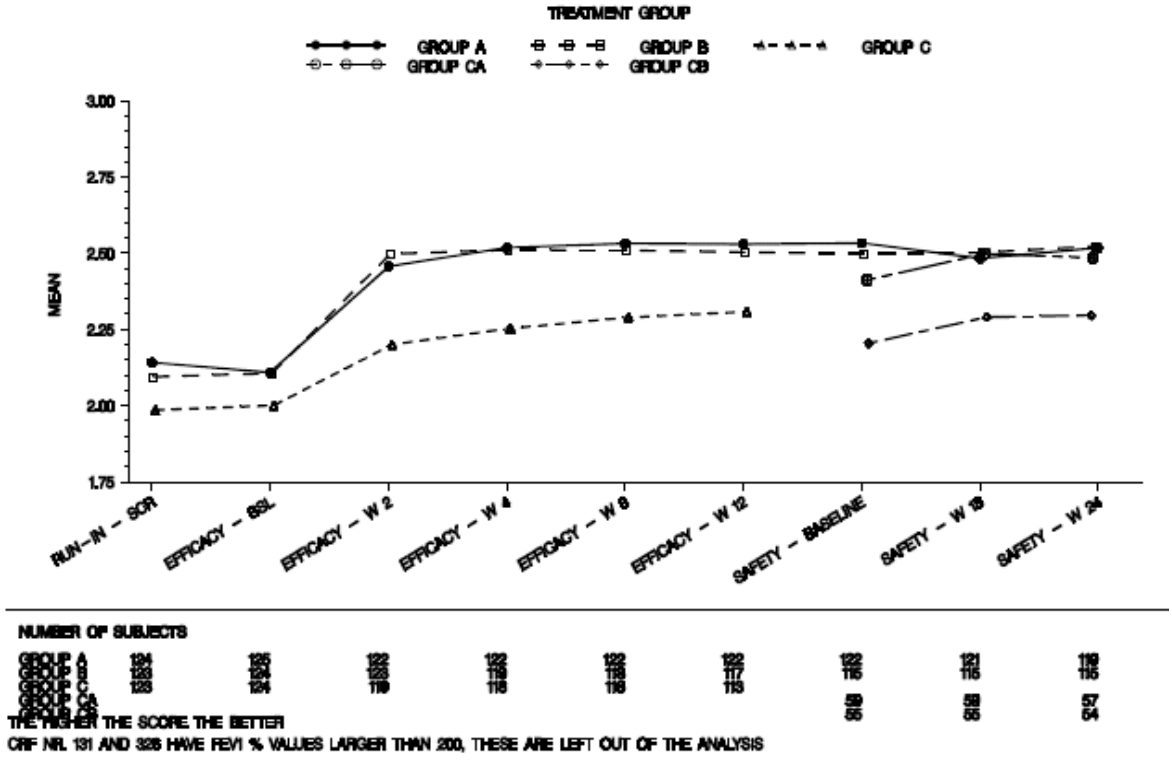


Table 50. Increase in pre-dose FEV1 at week 12 and week 24

	Labazenit 150/25 µg (A)	*Labazenit 300/25 µg (B)*	*Pulmicort (C)*	
FEV1 baseline (L/s)	*2.11*	*2.11*	*2.00*	
FEV1 at 12 wks (L/s)	*2.54**	*2.52*	*2.27*	
Increase FEV1	*0.42±0.043*	*0.41±0.039*	*0.29±0.044*	
	Labazenit 150/25 µg	*Labazenit 300/25 µg*	*Switch to Labazenit 150/25 µg (CA)*	*Switch to Labazenit 300/25 µg (CB)*
FEV1 baseline safety period	*2.53*	*2.50*	*2.41*	*2.20*
FEV1 at 24 wks(L/s)	*2.50*	*2.52*	*2.50*	*2.29*
Increase FEV1 (L/s)	*0.43±0.041*	*0.40±0.043*	*0.08±0.034*	*0.08±0.045**

** statistically significant (note: without Bonferroni correction)*

Other secondary parameters

As for the primary efficacy parameter, no significant differences were found between both BUDESONIDE-SALMETEROL dose regimens regarding the secondary efficacy parameters.

Similar results were obtained regarding increases from baseline in evening PEF and PFT measurements (FEV1 and FEV1% of predicted normal) and regarding decreases from baseline in asthma symptoms (cough, wheezing, shortness of breath, worst and total symptom scores), sleep disturbance score and the use of rescue medication (daily number of inhalations and number of days with rescue treatment).

Table 51. Secondary Efficacy analysis

Efficacy Results – Short Term Efficacy Period of Study BUSAL III-02-1 (Week 0 to Week 12)									
Analyses (ITT population)	Labazenit 150/25 µg (N = 126) (A)		Labazenit 300/25 µg (N = 124) (B)		PULMICORT TURBUHALER 2x200 µg (N = 124) (C)		Comparisons between treatments		
Secondary Efficacy analysis	Mean change Week 12 versus baseline (Week 0) (Mean ± SD)	p-value	Mean change Week 12 versus baseline (Week 0) (Mean ± SD)	p-value	Mean change Week 12 versus baseline (Week 0) (Mean ± SD)	p-value	p-value A/B	p-value A/C	p-value B/C
Evening PEF (L/min)	47.01 ± 58.31	<0.001	48.89 ± 53.30	<0.001	11.52 ± 42.21	0.004	0.962	<0.001	<0.001
FEV_1 of predicted (%)	13.66 ± 15.09	<0.001	13.20 ± 13.02	<0.001	8.92 ± 13.81	<0.001	0.920	0.005	0.007
FVC (L)	0.43 ± 0.60	<0.001	0.33 ± 0.55	<0.001	0.30 ± 0.52	<0.001	0.181	0.061	0.585
Asthma symptoms score *	-1.65 ± 1.85	<0.001	-1.49 ± 1.95	<0.001	-0.76 ± 1.69	<0.001	0.693	<0.001	<0.001
Cough	-0.45 ± 0.73	<0.001	-0.42 ± 0.69	<0.001	-0.27 ± 0.63	<0.001	0.684	0.008	0.026
Wheezing	-0.58 ± 0.73	<0.001	-0.50 ± 0.78	<0.001	-0.28 ± 0.71	<0.001	0.694	<0.001	<0.001
Shortness of breath	-0.62 ± 0.69	<0.001	-0.59 ± 0.72	<0.001	-0.23 ± 0.64	<0.001	1.000	<0.001	<0.001
Sleep disturbance score	-0.45 ± 0.66	<0.001	-0.50 ± 0.78	<0.001	-0.24 ± 0.50	<0.001	0.721	0.007	0.003
Number of rescue inhalations (daily doses)	-2.16 ± 3.09	<0.001	-2.55 ± 3.53	<0.001	-1.22 ± 2.74	<0.001	0.166	<0.001	<0.001
*Asthma symptoms score: defined as the sum of cough, wheezing and shortness of breath symptoms scores. PEF= Peak Expiratory Flow; FVC= Forced Vital Capacity; FEV= Forced Expiratory Volume									

Exacerbations

Exacerbations were defined as a safety parameter where it was recorded as an AE when the patient presented clinical features of an exacerbation. During the efficacy phase, 1 patient in the reference group experienced a asthma exacerbation.

Summary of main efficacy results

Table 52. Summary of efficacy for trial Labazenit II-10-1

Title: pharmacodynamic, randomised, single dose, cross-over, partially blinded study to compare the efficacy of a fixed-dose combination of BUDESONIDE-SALMETEROL DPI capsule 150/25 µg, BUDESONIDE-SALMETEROL DPI capsule 150/12.5 µg, BUDESONIDE-SALMETEROL DPI capsule 150/6.25 µg delivered by the Axahaler versus Serevent Diskus 50 µg, versus Serevent Evohaler 25 µg, versus Serevent Evohaler 25 µg (2 doses) in moderate to severe persistent asthmatic patients.						
Study identifier	BUSAL II-10-1					
Design	randomised, single dose, cross-over, partially blinded, 6-treatment study with a wash-out period of at least 3 days and up to 5 days					
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 h 2 weeks between screening and randomization not applicable				
Hypothesis	Equivalence: equivalence margins -150 ml/sec ; +150 ml/sec					
Treatments groups	Labazenit	150/25 µg, 150/12.5 µg, 150/6.25 µg 1 single dose				
	Serevent Diskus	50 µg, 1 single dose				
	Serevent Evohaler	50 µg, 25 µg, 1 single dose				
Endpoints and definitions	FEV1max	l/sec				
	FEV1AUC	l/sec* h				
	FEV1AUC8-12 h	l/sec* h				
Database lock	No information on date of database lock					
Results and Analysis						
Analysis description	**Primary Analysis**					
Analysis population and time point description	Intent to treat					
Descriptive statistics and estimate variability	Treatment group	Labazenit 150/25 µg	Labazenit 150/12.5 µg	Labazenit 150/6.25 µg	Serevent Diskus 50 µg	
	Number of subject	48	48	48	48	
	Change of FEV1max LSmeans±SE	0.56±0.06	0.75±0.06	0.64±0.06	0.66±0.06	
	Change of FEV1AUC LSmeans±SE	28.20±1.09	28.16±1.09	26.92±1.09	27.52±1.09	
	Change of FEV1AUC8-12 h	9.29±0.39	8.92±0.39	8.50±0.39	8.91±0.39	

Effect estimate per comparison	Change of FEV1max	Comparison groups Labazenit 150/25 (A) Labazenit 150/12.5 (B) Labazenit 150/6.25 (A Serevent Diskus 50 (D)	 A B C D
		Differences A vs B A vs C A vs D	 -0.01±0.05 0.05±0.05 -0.02±0.07
		95% CI A vs B A vs C A vs D	 -0.11,0.10 -0.05,0.16 -0.16,012
		P-value A vs B A vs C A vs D	 0.8796 0.3152 0.7796
	Change of FEV1AUC	Comparison groups Labazenit 150/25 (A) Labazenit 150/12.5 (B) Labazenit 150/6.25 (A Serevent Diskus 50 (D)	 A B C D
		Differences A vs B A vs C A vs D	 0.03±0.67 1.28±0.67 0.68±0.67
		95% CI A vs B A vs C A vs D	 -1.28;1.35 -0.04;2.60 -0.64;1.99
		P-value A vs B A vs C A vs D	 0.9600 0.0569 0.3127
	Change of FEV1AUC8-12 h	Comparison groups Labazenit 150/25 (A) Labazenit 150/12.5 (B) Labazenit 150/6.25 (A Serevent Diskus 50 (D)	 A B C D
		Differences A vs B A vs C A vs D	 0.37±0.29 0.79±0.29 0.38±0.29
		95% CI A vs B A vs C A vs D	 -0.20,0.95 0.21,1.37 -0.20,0.96
		P-value A vs B A vs C A vs D	 0.2023 **0.0076** 0.193

Table 53. Summary of efficacy for trial BUSAL III-02-1

Title: A phase III, randomised, 24-week parallel study to determine the therapeutic efficacy and safety of BUDESONIDE-SALMETEROL DPI capsule 150-25 µg b.i.d. versus BUDESONIDE-SALMETEROL DPI capsule 300-25 µg b.i.d. delivered by the Monodose Inhaler versus PULMICORT TURBOHALER 2x200 µg b.i.d. in chronic moderate asthma patients.				
Study identifier	BUSAL III-02-1			
Design	multicenter, randomized, partly blinded , 3-arm, parallel study that compared the safety and efficacy of Labazenit 300/25 µg and Labazenit 150/25 µg with Pulmicort 200 µg in patients with moderate to severe persistent asthma.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks 2 weeks 12 weeks		
Hypothesis	Superiority compared to Pulmicort			
Treatments groups	BUDESONIDE-SALMETEROL DPI 150-25 µg b.i.d.	12 weeks randomized: 126; ITT 126; PP: 111		
	BUDESONIDE-SALMETEROL DPI 300-25 µg b.i.d.	12 weeks randomized 125; ITT: 124; PP: 113		
	PULMICORTTURBOHALER 2x200 µg Multi-dose DPI	12 weeks, randomized 124; ITT 124; PP: 107		
Endpoints and definitions	Primary endpoint:	Δ AM PEF 0-12 weeks	mean change in morning PEF (mean change over the weeks from 0 to 12)	
	Secondary endpoints	Efficacy	mean change in FEV1 (mean change over the weeks from 0 to 12) and evening PEF	
	Other secondary	Efficacy	asthma symptoms score change from baseline averaged over the weeks from 0 to 12, sleep disturbance score (subset of the asthma symptom score) change from baseline averaged over the weeks from 0 to 12, change from baseline in FVC and the number of bronchodilator rescue inhalations	
Database lock				
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat Efficacy phase 12 weeks, safety phase 24 weeks			
Descriptive statistics and estimate variability	Treatment group	BUDESONIDE-SALMETEROL DPI 150-25 µg	BUDESONIDE-SALMETEROL DPI 300-25 µg	PULMICORT TURBOHALER 2x200 µg Multi-dose DPI
	Number of subject	126	124	124
	Change of AM PEF	54.4	51.4	15.6
	Change of FEV1	0.42	0.41	0.29

	Asthma symptom score	-1.65	-1.49	-0.76
Effect estimate per comparison	AM PEF	Labazenit 150/25 (A) Labazenit 300/25 (B) PULMICORT 400 (C)	A B C	
		95% CI A vs B A vs C B vs C	 -9.69; 19.04 27.18; 56.15 22.42; 51.57	
		P-value A vs B A vs C B vs C	 0.522 <0.001 < 0.001	
	FEV1	Labazenit 150/25 (A) Labazenit 300/25 (B) PULMICORT 400 (C)	A B C	
		95% CI A vs B A vs C B vs C	 -0.10;0.13 0.01; 0.24 -0.01; 023	
		P-value A vs B A vs C B vs C	 0.795 0.036 0.068	
	Asthma symptom score	Labazenit 150/25 (A) Labazenit 300/25 (B) PULMICORT 400 (C)	A B C	
		P-value A vs B A vs C B vs C	 0.166 < 0.001 < 0.001	

Clinical studies in special populations

No clinical studies in special populations were performed with the FDC salmeterol/budesonide. This was considered acceptable by the CHMP based on the well know efficacy of salmeterol and budesonide monocompounds.

Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analysis or meta-analysis was performed with the FDC salmeterol/budesonide which was considered acceptable by the CHMP.

Supportive studies

Study BUSAL III-05-1

This was a phase III, randomized, parallel group study to compare the therapeutic efficacy of Labazenit 300/25 µg BID delivered by the AxahalerR versus Seretide Diskus 500/50 µg (Fluticasone Propionate 500 µg/Salmeterol 50 µg) BID over 12 weeks and to evaluate the safety of Labazenit 300/25 µg over an additional period of 12 weeks in moderate to severe persistent asthmatic patients.

This was a randomized, non-inferiority, parallel group, open-label, multicenter study with 2-week run-in phase with inhaled beclometasone dipropionate 200 µg twice daily plus placebo, 12-weeks active treatment: Labazenit 300/25 µg (75% of patients), or Seretide Diskus 500/50 µg (25% of patients).

Patients attended the clinic for interim visits after 3 weeks (Visit 3) and 6 weeks (Visit 4) of treatment.

Patients in the Seretide Diskus 500/50 µg group completed the study at Week 12. Patients in the Labazenit 300/25 µg group continued the study for a further 12 weeks treatment and safety assessments. They attended the clinic for an interim visit 18 weeks after randomization (Visit 6) and completed the study after 24 weeks treatment (Visit 7).

Methods

Study participants

Diagnosis and main criteria for inclusion:

Male and female patients aged 18 to 70 years, with a diagnosis of moderate to severe persistent asthma for a minimum of 3 months duration, with forced expiratory volume in 1 second (FEV1) range of 50-80% of predicted, at least 12% FEV1 reversibility to 4 puffs of salbutamol 100 µg. Patients were excluded if they received oral or parenteral steroids in the previous 8 weeks or were hospitalized for a related disorder in the previous 3 months.

Objectives

The objectives of the study were the following:

- to compare the therapeutic efficacy, in a non-inferiority model, of a 12-week course of Labazenit 300/25 µg, taken twice daily, versus Seretide Diskus 500/50 µg taken twice daily by inhalation, in patients with moderate to severe persistent asthma.

- to compare the safety of Labazenit 300/25 µg taken twice daily by inhalation versus SeretideDiskus 500/50 µg taken twice daily by inhalation in patients with moderate to severe persistent asthma over 12 weeks.

- to evaluate the safety of a 24-week course of Labazenit 300/25 µg taken twice daily by inhalation, in patients with moderate to severe persistent asthma.

Outcomes / endpoints

Primary efficacy variable:

- Mean change from baseline to Week 12 in morning peak expiratory flow (PEF).

Secondary efficacy variables:

- Mean change over the weeks from baseline to Week 12 in LFO: evening PEF, FEV1, FEV1% of predicted and FVC.
- Change from baseline in symptomatic parameters averaged over the weeks from baseline to Week 12: asthma symptoms score, sleep disturbance score (subset of the asthma symptom score)
- Number of asthma exacerbations.
- Number of doses (inhalations) of bronchodilator rescue medication.

Safety variables:

- Adverse events
- Physical examination, Vital signs.
- Laboratory data.
- Withdrawals or drop-out rate.

Statistical methods: randomisation, blinding and statistical plan

For the primary efficacy variable, mean change in morning PEF from baseline to Week 12 was analyzed using analysis of covariance (ANCOVA) with fixed factors of treatment, center within country, age and gender and using baseline mean morning PEF as covariates. To estimate the treatment effect, the mean difference between treatments and 95% confidence interval (CI) was calculated. Non-inferiority could be concluded if the lower limit of the 95% CI was greater than –15 L/min for both the PP and ITT populations.

FEV1 (highest FEV1 and FEV1 percent of predicted normal), and FVC values were log-transformed at each visit and analyzed by ANCOVA with the log-transformed baseline value used as covariate.

Weekly asthma symptoms score and weekly sleep disturbance score from baseline to Week 12 were analyzed using Cochran-Mantel-Haenszel [CMH] statistic with rank-scores and center as stratification factor.

Other efficacy variables and safety data were summarized using appropriate summary statistics. All data were listed.

Results

Participant flow

Run In: 584 patients

Randomized: 372 patients in the Labazenit 300/25 µg group and 117 patients in the Seretide Diskus 500/50 µg group were randomized and took study medication:

Competed 12-week efficacy phase: 351 (94.4%) patients in the Labazenit 300/25 µg group and 109 (94.0%) patients

Conduct of the study

The following amendments were made to the initial study protocol:

- Change of the inclusion criterion wit respect to FEV1: one measure of more than or equal to 50% (upper limit 80%) is acceptable (the best achievable value) in stead of all.
- Change of dates of Visit 6 and Visit 7 to allow the patients randomised to Labazenit 300/25µg arm to continue in the study for two more weeks in order to arrange smooth shift and enrolment of hundred and twenty patients in Poland to continue in the extension protocol (BUSAL III-06-1)
- a definition of PEF compliance is added
- a description for representative selection of FEV1 is added.

Baseline data

Mean age was approximately 46.5 years and ranged between 18 and 69 years in both groups. There were more females than males: 220 (61.6%) females in the Labazenit 300/25 µg group and 75 (64.7%) females in the Seretide Diskus 500/50 µg group. All patients were Caucasian.

Outcomes

Primary efficacy parameter

The mean change (± SD) in morning PEF from baseline to Week 12 was 39.0 ± 52.4 L/min in the Labazenit 300/25 µg group and 40.4± 56.5 L/min in the Seretide Diskus 500/50 µg group. These increases were statistically significant within the 2 treatment groups ($p<0.001$) (see table below).

Table 54. Change of Morning PEF - Short Term Efficacy Period of Study BUSAL III-05-1 - ITT population

Analyses (ITT population)	Labazenit 300/25 µg (N = 357) (A)			SERETIDE DISKUS 500/50 µg (N = 116) (B)			Compari-sons between treatments
Primary Efficacy Analysis	Mean change Week 12 versus baseline (Week 0)		p-value*	Mean change Week 12 versus baseline (Week 0)		p-value*	p-value A/B
	Mean ± SD	Median		Mean ± SD	Median		
Morning PEF (L/min)	39.0 ± 52.4	28	<0.001	40.4 ± 56.5	30	<0.001	0.660

* difference between baseline and week 12

The mean difference between the groups at Week 12 was –2.5 L/min and the 95% CI was [–13.4; 8.5] L/min (p=0.660). The lower limit of the 95% CI was greater than –15 L/min, therefore non-inferiority was demonstrated between Labazenit 300/25 µg and Seretide Diskus 500/50 µg.

The lower limit of the 95% CI for the mean difference between the groups in mean morning PEF values was above -15 L/min at each post-baseline visit. Moreover, the mean morning PEF values were similar in both treatment groups between baseline and each post-baseline visit.

Secondary efficacy variables

Table 55. Short Term Efficacy Period of Study BUSAL III-05-1 (Week 0 to Week 12)

Analyses (ITT population)	Labazenit 300/25 µg (N = 357) (A)			SERETIDE DISKUS 500/50 µg (N = 116) (B)			Comparison between treatments
	Mean change Week 12 versus baseline (Week 0)		p-value	Mean change Week 12 versus baseline (Week 0)		p-value	p-value A/B
	Mean ± SD	Median		Mean ± SD	Median		
Evening PEF (L/min)	35.2 ± 48.8	28	<0.001	35.8 ± 51.8	23	<0.001	0.775
FEV_1 (L/s)	0.44 ± 0.45	0.36	<0.001	0.50 ± 0.50	0.42	<0.001	0.259
FEV_1 of predicted (%)	14.49 ± 13.79	12.30	<0.001	16.63 ± 15.15	15.95	<0.001	0.273
FVC (L)	0.42 ± 0.54	0.33	<0.001	0.40 ± 0.59	0.32	<0.001	0.854
Asthma symptoms score *	-0.70 ± 1.28	-0.50	<0.001	-0.67 ± 1.45	-0.58	<0.001	0.528
Cough	-0.22 ± 0.56	-0.10	<0.001	-0.15 ± 0.66	-0.10	<0.001	0.423
Wheezing	-0.22 ± 0.49	0.00	<0.001	-0.22 ± 0.51	-0.10	<0.001	0.705
Shortness of breath	-0.29 ± 0.54	-0.20	<0.001	-0.29 ± 0.57	-0.20	<0.001	0.363
Sleep disturbance score	-0.18 ± 0.49	0.00	<0.001	-0.13 ± 0.54	0.00	0.004	0.151
Number of rescue inhalations (weekly doses)	-5.3 ± 10.6	-2.0	-	-5.3 ± 9.8	-3.0	-	0.191

*Asthma symptoms score: defined as the sum of cough, wheezing and shortness of breath symptoms scores.

The mean change (±SD) in FEV_1 from baseline to Week 12 was 0.44±0.45 L/s for the Labazenit 300/25 µg group and 0.50±0.50 L/s for the Seretide Diskus 500/50 µg group. These increases were similar and statistically significant within the 2 treatment groups (p<0.001). The ratio of means was 0.98 (95% CI: [0.95;1.02]) and the mean difference between the groups was –0.02 (95%CI: [-0.06 ; 0.01]). This was not statistically significant (p=0.259).

No significant differences were found between Labazenit 300/25 µg and Seretide Diskus 500/50 µg regarding the primary and the secondary efficacy parameters.

For almost all secondary parameters for both Labazenit 300/25 µg and Seretide Diskus 500/50 µg the changes compared to baseline were statistically significant.

Sleep disturbance score values were lower on treatment compared with baseline, and were significantly (p<0.001) lower than baseline in both treatment groups at every post-baseline visit in the Labazenit 300/25 µg group only. In the Seretide Diskus 500/50 µg group, mean sleep disturbance scores were not statistically significantly different from baseline at Weeks 1–5 and 8 (p>0.05) but were statistically significantly different at Weeks 6, 7 and 9–12 (p<0.05).

Use of rescue medication at baseline was (median [range]) 5.0 (0–64) inhalations/week in the Labazenit 300/25 .g group and 5.0 (0–59) inhalations/week in the Seretide DikusS 500/50 µg group. Use of rescue medication was lower on treatment compared with baseline throughout the study. The median (range) change from baseline to Week 12 in number of puffs of rescue medication was –2.0 (-54–23) inhalations/week in the Labazenit 300/25 µg group and –3.0 (-40–19) inhalations/week in the Seretide Diskus 500/50 µg group. The medians (distribution free CIs) for the differences were 0.0 [0.0;1.0] in both treatment groups and was not statistically significant (p=0.191).

Exacerbations

Exacerbations were defined as an efficacy parameter and recorded as when the patient presented clinical features of an exacerbation.

8 patients reported asthma exacerbations during the efficacy phase of the study: 7 (2.0%) patients in the Labazenit 300/25 µg group and 1 (0.9%) patient in the Seretide Diskus 500/50 µg group. Six (1.7%) additional patients in the Labazenit 300/25 µg group reported asthma exacerbations during the safety phase of the study.

The results of the PP population were similar to the results of the ITT population for the above parameters.

Labazenit 300/25 µg is non-inferior to Seretide Diskus 500/50 µg in terms of morning PEF in patients with moderate to severe persistent asthma.

For the secondary efficacy variables: evening PEF, FEV1, FEV1 percent of predicted, FVC, asthma symptoms scores and use of rescue medication, treatment with Labazenit 300/25 µg and Seretide Diskus 500/50 µg both similarly improved the symptoms of asthma throughout the study. There were no statistically significant differences between the two treatments for any of the secondary efficacy variables.

Study BUSAL III-08-1

This was a phase III, randomized, parallel group, open study to compare the therapeutic efficacy and safety of SMB Budesonide-Salmeterol DPI capsule 150/25 µg BID delivered by the Axahaler versus Symbicort Turbuhaler 200/12 µg BID over 12 weeks in moderate to severe persistent asthmatic patients.

The planned duration was 14 weeks:

- a 2-week screening/run-in period during which patients were all treated with Budesonide (Pulmicort Turbuhaler, 800 µg/d) and placebo via Axahaler
- a 12-week open-label treatment period during which patients were treated either with SMB Budesonide-Salmeterol DPI capsule 150/25 µg BID or Symbicort Turbuhaler 200/12 µg BID.

Inhaled Salbutamol (max. 1600 µg/d) was permitted as rescue medication at any time of the study but at least 6 hours prior to performing the pulmonary function test.

26 out of the 26 centres were active and selected at least one patient (7 in Bulgaria, 9 in Romania, 4 in Macedonia and 6 in Serbia). 24 of these 26 centres enrolled at least one patient: 7 in Bulgaria, 7 in Romania, 4 in Macedonia and 6 in Serbia.

5 visits were planned for each patient:

V1 - Screening visit (W-2)

V2 - Randomization (W1±2 days)

V3 - 3 weeks (21 days) after randomization (±3 days)

V4 - 6 weeks (42 days) after randomization (±3 days)

V5 - Final visit, 12 weeks (84 days) after randomization (±3 days)

Methods

Study participants

Men or women, aged from 18 to 65 years old, with a diagnosis of moderate to severe persistent asthma for a minimum of 6 months duration with FEV1 range of 50-80 % predicted at screening and baseline, at least 12 % in FEV1 and 200 ml reversibility to 4 puffs of Salbutamol 100 µg and having asthma symptoms partly controlled or uncontrolled according to the GINA guidelines.

Patients were excluded from participating in the study if they received oral or parental corticosteroids in the past 8 weeks or were hospitalized for an asthma exacerbation or a related disorder in the past 3 months beore screening visit.

Treatment

2-week run-in period: Budesonide (Pulmicort Turbuhaler, 800 µg/day) and placebo (Axahaler).

12-week open-label treatment period: Budesonide-Salmeterol DPI 150/25 µg BID or Symbicort Turbuhaler 200/12 µg BID.

Objectives

The study objectives were the following:

- to compare the therapeutic efficacy in a non-inferiority model of 12 weeks course of SMB Budesonide-Salmeterol DPI capsule 150/25 µg delivered by Axahaler, taken BID, versus Symbicort Turbuhaler 200/12 µg BID, taken by inhalation, in patients with moderate to severe persistent asthma.
- to compare the safety of SMB Budesonide-Salmeterol DPI capsule 150/25 µg taken BID versus Symbicort Turbuhaler 200/12 µg BID taken by inhalation, in patients with moderate to severe persistent asthma over 12 weeks.

Outcomes / endpoints

Primary efficacy assessment: Mean change over the weeks from baseline to W12 in morning pre-dose peak expiratory flow (PEF).

Secondary efficacy assessment: (Note: Pulmonary Function Test was performed at each visit before study drug intake at least 12 hours after the previous dose):

- Mean change over the weeks from baseline to W12 in evening pre-dose PEF, FEV1, FEV1 % of predicted, and FVC

Symptomatic parameters

- Mean change over the weeks from baseline to W12 in asthma symptoms score, sleep disturbance score (subset of the asthma symptom score),
- Number of asthma exacerbations
- Number of bronchodilator rescue inhalations

Safety assessment:

- Adverse events (AEs) and withdrawals or drop-out rate due to AEs
- Physical examination and vital signs
- 12-lead ECG
- Laboratory data

Statistical methods: randomisation, blinding and statistical plan

Handling of missing data: missing efficacy data were replaced using the LOCF method

Definitions:

Baseline value: for parameters assessed every day, baseline was defined as the mean of the 5 last days with available results within 10 days before randomization; for FEV1, FEV1% of predicted and FVC parameters, the baseline was defined as the value at randomization visit (V2).

Endpoint value: for parameters assessed every day, week 12 was defined as the mean of the 5 last days with available results within 10 days before Visit 5 (week12); for FEV1, FEV1% of predicted and FVC parameters, the endpoint value was defined as the value at Visit 5 (week12). Same rules were applied for calculation of W3 and W6 values.

Efficacy analysis:

Given the non-inferiority design, both the PP and the ITT sets were used for a robust interpretation of the efficacy analysis.

The analysis of covariance (ANCOVA) with factors for treatment, site within country, age, sex, and baseline value was used on efficacy parameters to compare the two treatments (Budesonide-Salmeterol 150/25 µg vs. Symbicort 100/6 µg, significance level $p<0.05$). Two-sided 95% adjusted confidence interval (CI) was calculated for the mean difference of LSmeans between treatments for each efficacy parameter between baseline and W12. To demonstrate the non-inferiority, CI had to be above the non-inferiority margin, - 20 L/min, for both the PP and the ITT analysis set.

Safety analysis:

The number and frequency of patients experiencing a specific adverse event and the number of AEs were tabulated by group, system organ class, and preferred term.

Evolution of vital signs and ECGs during the efficacy period (from V2 to V5) was analyzed by ANOVA for repeated measurements.

Laboratory data were described at V1, V3, V4 and V5 per treatment group. For each parameter and for each treatment group, change from baseline to V5 was provided. A Student's t-test for paired series was performed in order to test if the change observed between V5 and baseline was significantly different from 0 (= no change) in each treatment group. Moreover, an analysis of covariance adjusted on baseline was performed to test the difference at V5 between treatment groups.

Results

Participant flow

One hundred (100) out of the 329 selected patients (30.40 %) were screening failures, mostly referring to non-compliance with inclusion criteria, non compliance with the protocol, or referred to patient's decision.

229 patients were randomized: 115 patients in the SMB Budesonide-Salmeterol 150/25 µg group and 114 patients in the Symbicort Turbuhaler 200/12 µg group.

Safety analysis (treated patients): 229 patients (115 patients in the SMB Budesonide-Salmeterol 150/25 µg group and 114 patients in the Symbicort Turbuhaler 200/12 µg group).

ITT efficacy analysis: 222 patients (113 patients in the SMB Budesonide-Salmeterol 150/25 µg group and 109 patients in the Symbicort Turbuhaler 200/12 µg group).

In this ITT population 6 patients presented a major protocol violation and/or did not complete the study (from ITT) (** 5 patients with 2 major deviations*):

- FEV1<50% or >80% at V1: N=1

- Forbidden concomitant therapy: N=1

- Compliance V2-V5<70% on e-PEF diary: N=5

- Compliance V2-V5<70% on study drug: N=4

PP analysis: 216 patients (109 patients in the SMB Budesonide-Salmeterol 150/25 µg group and 107 patients in the Symbicort Turbuhaler 200/12 µg group).

Conduct of the study

One amendment (dated 19th of December 2008) was made to the initial study protocol. The purpose of the amendment was neither to enter new procedures nor to amend the protocol selection criteria but to clarify few protocol text sections. This amendment performed during the study is not considered as influencing the study results.

Demographics and disease characteristics

Treated patients, all of Caucasian race, were aged 45.2±11.6 years with no patient aged more than 65 years at enrolment. Women were in a majority (62.01%).

No difference was observed between groups neither in demographics nor in biometrics.

ITT: Asthma was diagnosed 8.14±8.47 years before entry in the study. In reference to GINA criteria for asthma control, all patients presented with a partly controlled or uncontrolled asthma despite being treated with inhaled corticosteroids. 95.95% of patients reported symptoms of asthma during daytime and 75.68% during nighttime. 89.64% required rescue medications. 44.14% reported exacerbations of asthma.

At baseline (W0), mean peak expiratory flow (PEF) measurement was 342.96±121.32 L/min in the morning and 350.98±125.41 L/min in the evening. The spirometry test performed at W0 showed a mean FVC of 3.19±0.92 L, a mean FEV1 of 2.09±0.54 L/sec and reversibility in FEV1 (measured 15 minutes after inhalation of 4*100µg Salbutamol) of 570±337 ml or 28.50±16.51%. No difference was observed at baseline between the randomization groups.

Outcomes

No significant differences were found between Labazenit 150/25 µg and Symbicort Turbuhaler 200/12 µg regarding the primary and the secondary efficacy parameters.

Primary efficacy parameter

The mean change (± SD) in morning PEF from baseline to Week 12 was 36.03±54.55 L/min in the Labazenit 150/25 µg group and 20.99±66.38 L/min in the Symbicort Turbuhaler 200/12 µg group; these increases were statistically significant within the 2 treatment groups (p<0.001) (see table below).

Table 56. Primary efficacy variable Short Term Efficacy Period of Study BUSAL III-08-1 (Week 0 to Week 12)

Analyses (ITT population)	Labazenit 150/25 µg (N = 113) (A)		SYMBICORT TURBUHALER 200/12 µg (N = 109) (B)		Comparisons between treatments
Primary Efficacy Analysis	Mean change Week 12 versus baseline (Week 0)	p-value*	Mean change Week 12 versus baseline (Week 0)	p-value*	p-value A/B
	Mean ± SD		Mean ± SD		
Morning PEF (L/min)	36.03 ± 54.55	<0.0001	20.99 ± 66.38	0.001	0.11

* difference between baseline and week 12

The mean difference between the groups for morning PEF at Week 12 was 12.19 L/min and the 95% CI was [–2.93; 27.32] L/min (p=0.11). The lower limit of the 95% CI was greater than 20 L/min; therefore non-inferiority was demonstrated between Labazenit 150/25 µg and Symbicort Turbuhaler 200/12 µg.

The lower limit of the 95% CI for the mean difference between both groups in mean morning PEF values was above -20 L/min at each post-baseline visit. However, the mean morning PEF values of the Labazenit 150/25 µg group significantly increased after 3 weeks of treatment (mean change of 32.02±51.98 L/min at W3, p<0.0001) while 6 weeks of treatment were necessary in patients treated with Symbicort Turbuhaler 200/12 µg to observe a significant increase in morning PEF (mean change of 24.62±60.95 L/min at W6, p<0.0001).

Therefore, the between groups difference was significant at W3 with an effect size of 22.84 L/min in favour of Budesonide-Salmeterol (p=0.001).

Results obtained with the PP subset confirmed those observed with the ITT subset. The lower bound of the 95% two-sided confidence interval was -3.21 L/min far upper of the no inferiority limit defined by the protocol as -20 L/min.

Therefore as ITT analysis and PP analysis give consistent results, Budesonide-Salmeterol 150/25 µg can be regarded as non inferior to Symbicort 200/12 µg regarding the mean change from baseline in morning PEF.

Secondary efficacy variables

Spirometry variables

No differences between both treatments were observed regarding increases from baseline in evening PEF and other PFT measurements (FEV_1, FEV_1% of predicted and FVC).

Table 57. Secondary efficacy variables Short Term Efficacy Period of Study BUSAL III-08-1 (Week 0 to Week 12)

Analyses (ITT population)	Labazenit 150/25 µg (N = 113) **(A)**		SYMBICORT TURBUHALER 200/12 µg (N = 109) **(B)**		Comparisons between treatments
	Mean change Week 12 versus baseline (Week 0) Mean ± SD	p-value*	Mean change Week 12 versus baseline (Week 0) Mean ± SD	p-value*	p-value A/B
Evening PEF (L/min)	27.30 ± 60.27	<0.0001	17.23 ± 58.61	0.003	0.27
FEV_1 (L/s)	0.28 ± 0.34	<0.0001	0.26 ± 0.39	<0.0001	0.72
FEV_1 of predicted (%)	9.04 ± 11.62	<0.0001	8.38 ± 12.23	<0.0001	0.46
FVC (L)	0.31 ± 0.46	<0.0001	0.22 ± 0.51	<0.0001	0.24
Asthma symptoms score **	-0.86 ± 1.61	<0.0001	-0.73 ± 1.51	<0.0001	0.34
Cough	-0.34 ± 0.59	<0.0001	-0.27 ± 0.50	<0.0001	0.27
Wheezing	-0.22 ± 0.60	0.0001	-0.20 ± 0.54	0.0003	0.49
Shortness of breath	-0.32 ± 0.57	<0.0001	-0.23 ± 0.54	<0.0001	0.13
Sleep disturbance score	-0.34 ± 0.60	<0.0001	-0.26 ± 0.51	<0.0001	0.30
Number of rescue inhalations (daily doses)	-1.23 ± 2.30	<0.0001	-0.90 ± 2.07	<0.0001	0.91

* difference between baseline and week 12
**Asthma symptoms score: defined as the sum of cough, wheezing and shortness of breath symptoms scores.

All these increases were statistically significant within the 2 treatment groups ($p<0.0001$).

Other secondary efficacy parameters

No differences between both treatments were observed regarding decreases from baseline in asthma symptoms (cough, wheezing, shortness of breath and total symptom scores), sleep disturbance score and the use of rescue medication.

Exacerbations

Exacerbations were defined as an efficacy parameter: in addition to the clinical features of an exacerbation, the protocol definition also took into account decreases in asthma control (20% decrease in morning PEF versus baseline or an additional need for rescue medication on two consecutive days).

Fifty-five asthma exacerbations occurred during the treatment period: 10 patients treated with Labazenit 150/25 µg reported 17 exacerbations -all of mild intensity- and 15 patients treated with Symbicort reported 38 exacerbations -36 of mild intensity and 2 of moderate intensity.

Conclusions

The results of this study demonstrate that a 12-week administration of Labazenit 150/25 µg is non-inferior to Symbicort Turbuhaler 200/12 µg in terms of morning PEF in patients with moderate to severe persistent asthma. Both treatments similarly improved the PFTs (PEF, FEV1, FEV1% of predicted, FVC), the asthma symptoms and the use of rescue medications.

Study BUSAL III-06-1

This was an open-label phase III extension study to evaluate the safety of BUDESONIDE-SALMETEROL DPI capsule 300/25 µg BID delivered by the Axahaler over 28 weeks in moderate to severe persistent asthmatic patients selected from the BUSAL III-05-1 study and already taking BUDESONIDE-SALMETEROL DPI capsule 300/25 µg BID for 24 weeks.

Methods

Study participants

Male and female patients, 18-75 years, who presented with moderate to severe persistent asthma, and selected from the BUSAL III-05-1 study and already taking Labazenit 300/25µg BID for 24 weeks and willing to continue in the new one were included.

Patients should not have received oral or parenteral steroids in the preceding 8 weeks or being hospitalized for a related disorder in the past 3 months.

Objectives

The objectives of the study were to evaluate the safety of an additional 28 weeks course of Labazenit 300/25 µg twice daily (BID), taken by inhalation, in patients with moderate to severe persistent asthma selected from the BUSAL III-05-1 study and having taken BUDESONIDE-SALMETEROL DPI capsule 300/25 µg BID for 24 weeks in order to obtain, by combining the data from the both studies, the assessment of safety over 1 year.

Outcomes / endpoints

Safety Assessments

- Adverse events (AEs) and Withdrawals or drop-out rate.
- Physical examination and Vital signs.
- Laboratory data.

Efficacy Assessments:

- Mean change from initial baseline (run-in period in BUSAL III-05-1) in morning PEF, in evening PEF.
- Mean change from initial baseline (Visit 2 in BUSAL III-05-1) in FEV1, FVC
- Mean change from initial baseline (run-in period in BUSAL III-05-1) in asthma symptoms score, in sleep disturbance score (subset of the asthma symptom score).
- Number of asthma exacerbations.
- Number of doses (inhalations) of bronchodilator rescue medication.

Results

Participant flow

3 patients were screening failures. All of these patients had respiratory tract infections requiring treatment with antibiotics within 8 weeks of the screening visit.

110 patients were enrolled in the study. Of these, 108 (98.2%) patients completed the study.

Table 58. End of study information: Safety analysis set

	BUSAL 300/25 µg (N=110)	
	n	(%)
Completed the study	108	(98.2%)
Completed the study as planned in the protocol	96	(87.3%)
Did not complete the study as planned in the protocol	14	(12.7%)
Reason for not completing the study as planned in the protocol		
Protocol deviation	12	(10.9%)
Lost to follow-up	1	(0.9%)
Other	1	(0.9%)

For 2 patients the deviation was considered to be major. Since the primary objective of this extension study was to collect long-term safety data, the data from all patients enrolled, including patients with major protocol deviations, were included in the Safety Analysis Set.

The patients will visit the clinic 3 times according to the following: V7 in BUSAL III-05-1, 98 days (14 weeks) and 196 days (28 weeks)

Conduct of the study

The following changes from the analyses planned in the protocol (dated 15 February 2007) were made:

- In addition to 95% CIs for efficacy parameters (mean of morning PEF, mean of evening PEF, FEV1, highest FEV1 and FEV1 % of predicted normal, FVC, wheezing, cough, shortness of breath, weekly asthma symptoms score, weekly sleep disturbance score and weekly total asthma symptoms score), baseline was compared to other timepoints using paired t-test or Wilcoxon Signed Rank-test.

- In the protocol, efficacy parameters were planned to be derived using 4-week intervals.

This was modified for use of the same principles as were used in the initial study (BUSAL III-05-1). Derivation in the initial study was based on the last 5 days within each diary week (i.e. Day 3, Day 4, Day 5, Day 6 and Day 7). Derivation was done at each visit over the two studies (combined).

Baseline data

Demography

Mean age of the study population at the start of this extension study was 44.8 years and ranged between 18 and 69 years. There were more females 66 (versus 60.0). All patients were Caucasian.

Medical history

Medical history was recorded for 76 (69.1%) patients.

39 [35.5%] patients had allergic rhinitis (undefined allergic rhinitis, SAR, PAR, nasal polyps) and 28 [25.5%] patients) had vascular disorders of which hypertension (21 [19.1%] patients).

90.9% of patients had moderate persistent asthma. The remainder had severe persistent asthma. No patients had mild asthma, in accordance with the protocol. Mean duration of asthma was 117.6 months. The minimum duration of asthma (4 months) was also in accordance with the inclusion criteria for study BUSAL III-05-1.

Two (1.8%) patients were current smokers at the start of this extension study and 25 (22.7%) patients were previous smokers. The remaining patients were non-smokers.

Measurement of treatment compliance

Overall, patients were compliant both with the study medication and with PEF measurements. Over the combined study periods of 52 weeks, mean (SD) compliance with study medication was 99.5 (2.0)% and mean (SD) compliance with PEF was 99.3 (1.9)%.

107 (97.3%) patients were compliant with study medication, i.e. 80-120% (inclusive) compliant throughout the combined 52-week study periods.

Outcomes and estimation

Table 59. Overview of key efficacy results in study BUSAL III-06-1 (Extension Period – W52)

	Labazenit 300/25 µg (N = 110)					
Primary Efficacy Analysis	Mean change Week 12 versus baseline (Week 0) (Mean ± SD)	p-value difference week 12-baseline	Mean change Week 24 versus baseline (Week 0) (Mean ± SD)	p-value difference week 24-baseline	Mean change Week 52 versus baseline (Week 0) (Mean ± SD)	p-value difference week 52-baseline
Morning PEF (L/min)	38.2 ± 53.0	<0.001	38.0 ± 55.3	<0.001	44.8 ± 65.3	<0.001
Key secondary Efficacy analysis						
Evening PEF (L/min)	34.8 ± 46.0	<0.001	32.1 ± 50.6	<0.001	40.4 ± 65.1	<0.001
FEV_1 (L/s)	0.44 ± 0.50	<0.001	0.43 ± 0.51	<0.001	0.41 ± 0.51	<0.001
FEV_1 of predicted (%)	13.44 ± 13.60	<0.001	13.08 ± 14.30	<0.001	12.62 ± 14.12	<0.001
FVC (L)	0.44 ± 0.57	<0.001	0.45 ± 0.62	<0.001	0.42 ± 0.64	<0.001
Weekly asthma symptoms score*	-0.79 ± 1.41	<0.001	-0.76 ± 1.78	<0.001	-0.87 ± 1.64	<0.001
Cough	-0.23 ± 0.54	<0.001	-0.14 ± 0.70	0.023	-0.22 ± 0.60	<0.001
Wheezing	-0.23 ± 0.48	<0.001	-0.29 ± 0.64	<0.001	-0.29 ± 0.57	<0.001
Shortness of breath	-0.31 ± 0.55	<0.001	-0.31 ± 0.69	<0.001	-0.34 ± 0.70	<0.001
Sleep disturbance score	-0.12 ± 0.53	<0.001	-0.11 ± 0.56	0.066	-0.15 ± 0.62	0.003
Number of rescue inhalations (daily doses)	-6.4 ± 11.7	<0.001	-6.1 ± 13.0	<0.001	-6.9 ± 13.2	<0.001
1. Weekly asthma symptoms score*: calculated as average scores for each week separately, except that sleep disturbance score is not included in the score.						

Efficacy conclusions

The improvements in pulmonary functions and in asthma symptoms that were measured during study BUSAL III-05-1 were sustained throughout this 6-month extension study.

PFT

- mean morning PEF values at week s 38 and 52 were 44.4 L/min and 44.8 L/min, resp., higher than the baseline value of 341.5 L/min (p<0.001 for the changes from baseline).

- Median highest FEV1 values at weeks 38 and 52 were 0.30 L/sec and 0.28 L/sec, resp., higher than the baseline value of 2.06 L/sec. Similarly, median FEV1 percent of predicted normal values were 11.30% at week 38 and 10.00% at week 52 higher than the baseline value of 65.70%. Median highest FVC values at weeks 38 and 52 were 0.33 L and 0.32 L, resp., higher than the baseline value of 2.97 L. The changes from baseline were statistically significant ($p<0.001$).

Symptomatic endpoints

- Median weekly asthma symptom scores at Weeks 38 and 52 were 0.3 points and 0.4 points, respectively, lower than the baseline value of 1.6 points ($p<0.001$ for the changes from baseline).

- Median sleep disturbance score was zero at baseline. Statistically significant reductions in sleep disturbance scores occurred at Week 52 ($p=0.003$) but not at Week 38 ($p=0.271$).

- Median weekly total scores were 1.8 points at baseline. At Weeks 38 and 52, median weekly total scores were 0.3 points and 0.5 points, respectively, lower than at baseline.

Median weekly wheezing scores were 0.0 points and 0.1 points at Weeks 38 and 52, resp., different from the baseline value of 0.3 points. Median weekly shortness of breath scores were both 0.1 points lower at Weeks 38 and 52 than the baseline value of 0.8 points. The differences were statistically significant ($p<0.001$). Median weekly cough scores were 0.4 points at baseline. At Weeks 38 and 52, median weekly cough scores were 0.0 points and 0.1 points, respectively, lower than at baseline and the differences were statistically significant ($p=0.019$ at Week 38; $p<0.001$ at Week 52).

- At Weeks 38 and 52, median weekly inhalations of rescue medication were 2 inhalations and 4 inhalations, respectively lower than the baseline value of 7 inhalations ($p<0.001$ for the changes from baseline).

Asthma exacerbations

A total of 13 (11.8%) patients reported asthma exacerbations over the entire 12-month study period. 8 (7.3%) patients each reported one exacerbation during months 6–9 and 3 (2.7%) patients each reported one exacerbation during months 9–12. 3 patients had exacerbations of asthma both during the first 6-month period and during the second 6-month period.

2.5.3. Discussion on clinical efficacy

Step-up indication

Demonstration that both strengths of Labazenit result in a higher efficacy of budesonide than an ICS monotherapy i.e. Pulmicort, is needed to support the step-up indication.

In the pivotal phase III study BUSAL III-02-1, three study arms were included: Labazenit 150 µg/25 µg bid, Labazebit 300 µg/25 µg bid and Pulmicort 400 µg bid. The study design makes a comparison of a FDC with a considered lower dose of ICS dose (Labazenit 150 µg/25 µg) with a doubled dose of ICS (Pulmicort 400 µg). For the primary endpoint, PEF, both Labazenit 150/25 µg and Labazenit 300/25 µg treatments were superior to Pulmicort 400 µg after 12 weeks of treatment (Labazenit 150/25 µg vs. Pulmicort: $p<0.001$; Labazenit 300/25 µg vs. Pulmicort: $p=0.004$). Even, when adjusting for performing 3 comparisons, the (non)-significance of the comparisons would remain the same i.e. the Labazenit formulations are still superior to Pulmicort by at least 15 L/min. It was also demonstrated that the switch from Pulmicort, the reference treatment, after 12 weeks to Labazenit 150 µg/25 µg or Labazenit 300/25 µg resulted in statistically significant increases in morning PEF values from week 12 to week 18 and 24 within both treatment groups ($p<0.001$). For PEF neither at week 12 nor at week 24 the difference between the two Labazenit strengths (150/25 µg and 300/25 µg) was statistically significant. Therefore, a dose response was not demonstrated between the two doses of Labazenit.

Dose response inhaled corticosteroids

In study BUSAL III-02-1, as only a comparison with one dose of reference ICS budesonide (Pulmicort 400 µg) was made, the study design is not sensitive to conclusively demonstrate the equivalence/non-inferiority regarding inflammatory control. The results of this study therefore do not provide evidence regarding the therapeutic equivalence regarding the ICS doses. As no difference between the two strengths of Labazenit were observed (no dose response), the CHMP raised that the study design was not sensitive to conclusively assess comparability of the anti-inflammatory control.

Comparable anti-inflammatory treatment

FEV1 also increased after 12 weeks with both Labazenit 150/25 µg and Labazenit 300/25 µg with differences in increases in FEV1 compared to Pulmicort of 130 ml and 120 ml respectively. The As per CHMP's request the Applicant provided post-hoc analysis regarding the primary and secondary endpoints conducted with a Bonferroni correction as 3 simultaneous comparisons were made. The superiority of the two strengths of Labazenit over the comparator Pulmicort was demonstrated for the primary endpoint PEF even after the Bonferroni correction.

Between the end of the efficacy phase and the start of the safety phase in the group Pulmicort-Labazenit 150/25 µg, FEV1 already improved and in the group Pulmicort-Labazenit 300/25 µg, FEV1 already decreased explaining that after the switch a similar improvement was found and explaining that no statistical difference was found in difference of improvement at 24 weeks while at week 24 the FEV1 differs. According to the Applicant, an almost significant difference at the end of the 24 weeks treatment was demonstrated in patients receiving Labazenit 300/25 µg continuously and those previously on Pulmicort. However the Applicant did not discuss why patients switched to Labazenit 300/25 µg and did not demonstrate the same PEF improvement as observed at week 12.

Actual mean FEV1 values at the end of the study (week 24) were higher after 24-week treatment with Labazenit 150/25 µg or Labazenit 300/25 µg treatment compared to 12-week treatment with Labazenit 150/25 µg or Labazenit 300/25 µg preceded by 12-week reference treatment. The Applicant explained that the mean FEV1 value for the patient group receiving Pulmicort during the first 12 weeks and who switched to Labazenit 150/25 µg was higher than for the patients group who switched to Labazenit 300/25 µg (2.41 versus 2.20) because the randomization did not balance treatment groups among the covariate levels. This explanation was considered acceptable by the CHMP.

During the GCP inspection, it was noticed that the secondary parameter spirometric values (FEV1, FEV1 % predicted and FVC) were not analyzed as specified in the study protocol. The protocol specified to use the highest spirometric values of three satisfactory and reproducible spirometry maneuvers, while in the database and in the clinical study report as filed, the lowest values of three satisfactory and reproducible spirometry maneuvers have been used. Therefore it is not know whether the highest of the lowest of the three reproducible measurements were being used. The Applicant provided as requested re-analysis for the two secondary efficacy parameters with the highest values recorded in the CRF. The difference with the originally presented values were small.

The fact that in the clinical studies the results of PEF and FEV1, after only 12 hours withdrawal of study treatment, and the symptom scores, are influenced by both budesonide and salmeterol was raised by the CHMP during the evaluation. A difference in anti-inflammattory effect of budesonide could be masked by the broncholidation effect of salmeterol. The Applicant justified that PEF and FEV1 can be used to demonstrate the same anti inflammatory effect between treatments in line with the asthma guidelines and this was considered acceptable by the CHMP. However, the obtained results must be univocal and represent the underlying pathophysiological mechanism of what is being studied: the same anti-inflammatory effect. The design of the study BUSAL-III-02-1 can not be used to demonstrate that Labazenit provides a similar anti-inflammatory control than the reference product PulmicortThe Applicant was requested to provide further proof for similar inflammation control. Exacerbation numbers or rates, especially of severe exacerbations could have been used as the parameter to demonstrated equivalent anti-inflammatory control between Labazenit and Pulmicort, provided that the numbers are large enough. However, in the Phase III studies , this was not the case: the numbers of exacerbations were too small to detect a potential statistically significant difference. Moreover, exacerbations were not homogeneously defined in the different Phase III studies: in study BUSAL III-02-1 as a safety parameter and in studies BUSAL III-05-1, BUSAL III-08-1 and BUSAL III-06-1 as an efficacy parameter. In the study BUSAL III-08-1 the definition of exacerbation was more strict. The Applicant acknowledged that the Phase III studies were not designed to demonstrate differences in exacerbations and that longer studies duration would have been needed.

The open label study BUSAL III-06-1 evaluated the long term effect of Labazenit 300/25 µg BID on the improvement of lung function and asthma control symptoms. In this one dose study, improvements obtained during the blind part of the study were sustained during the extension phase . For the primary efficacy parameter at weeks 38 and 52, morning PEF was 44.4 L/min and 44.8 L/min, respectively, higher than the baseline value of 341.5 L/min ($p<0.001$ for the changes from baseline) compare to 382.9 and 377.7 at week 12 and 24 respectively. For FEV1 a small, clinically not relevant difference is seen with the end of the blind phase. All asthma symptoms were more improved at the end of study BUSAL III-06-1. However, for this study patients were recruited from the one way blind study BUSAL III-05-1. Therefore, selection bias might be present assuming that the patient with best efficacy and/or best safety would be more willing to continue than others. As a consequence the Applicant was requested to include exacerbations as an important identified risk in the proposed RMP.

Substitution indication

Demonstration of similar bronchodilation, asthma control and asthma inflammation with the reference need to be established.

Salmeterol

Study BUSAL II-10-1 is the main study to demonstrate similar bronchodilation of salmeterol between Labazenit and the reference product Serevent. BUSAL II-10-1 was a single dose, cross-over bronchodilation studiy in 48 patients with persistent asthma with a lung function limitation with reversibility. Study BUSAL II-10-1 was designed to prove bronchodilation equivalence between Labazenit and Serevent: patients were symptomatic according to GINA criteria and different dosages of Labazenit with respect to salmeterol were used (25, 12.5 and 6.25 µg) and compared to different dosages of Serevent administered as DPI or MDI.

The primary efficacy variable was the mean change in $FEV_{1,max}$ (L) the mean change for Labazenit 150/25 µg was 0.64 ± 0.46 L, while this was 0.66 ± 0.39 L for Seretide Diskus. The p value between treatments is 0.776 and the 98.33 % CI is -0.16 – 0.12 just outside the predefined limit of equivalence (0.15). With a wider margin set at 0.2L, therapeutical equivalence would have been demonstrated (the 98.33% CI would have been within the acceptance range). As no clinically relevant differences in safety parametes was observed in this study, the CHMP was able to conclude on the non-inferiority of the salmeterol component based on the totality of evidence available despite the CI found. The mean change FEV1 over 12 h was comparable between the two groups: Labazenit 150/25 µg 7.03 ± 18.28 L, Serevent Discus 8.30 ± 16.31, difference -0.92 ± 2.81 95% CI -6.46 – 4.62 p=0.74. Also various other secondary efficacy endpoints, FEV1 AUC 8-12 h, PEF and FVC, were not statistically different.

Only one dose of the reference salmeterol was included because lower doses of salmeterol are not commercially available. No comparisons between doses of Labazenit could be made. However, as the study had a cross over design, the observed differences are corrected for differences between patients and reflect the differences within patients. Therefore, the observed differences are most likely to be attributed to the different dosages.

In the clinical study BUSAL-II-10-1, no clinically relevant differences were seen in clinically important parameters, like heart rate, blood pressure and potassium. Additional safety information with respect to potassium and blood glucose was provided by the Applicant during the evaluation which was re-assuring. The safety of Labazenit was further confirmed in the phase III studies including the extension study BUSAL-III-06-1 and the long term safety study. No unexpected adverse events were reported (see clinical safety section).

The Applicant submitted during the evaluation extensive literature data to support the dose related duration of salmeterol's bronchodilating effect observed in study BUSAL-II-10-1. As demonstrated in the BUSAL –II-10-1 study and in the literature, the peak response is similar in the range of 25-50 µg salmeterol. However, differences of the duration of bronchodilation effect between doses become apparent after 6 h of dosing, especially after the 12 h observation period. The 12 h observation period was not included in the BUSAL II-10-1 study. In the literature, the bronchodilating effect and its duration with the 6.25 mcg salmeterol dose, the lowest dose used in the BUSAL II-10-I study, have not been described.

The dose related duration of bronchodilation is not specific for salmeterol. The dose related duration of bronchodilation is also described for salmeterol´s main comparator, formoterol. Formoterol showed a dose related duration of response, with formoterol 6 µg being the lowest effective dose. Bronchodilation is observed for at least 8 hours after formoterol 6 µg, and for 12 hours after formoterol 12 µg and 24 µg. The time course of bronchodilation observed with formoterol 6 µg is most variable, with sustained bronchodilation being observed for periods varying from 8-12 hours. The observed dose related duration of bronchodilation seems therefore being a class characteristic, which supports the observed difference in AUC FEV1 8-12 h between the different doses of salmeterol in study BUSAL-II-10-1.

All together the data provide evidence that the bronchodilatory effect of BUSAL 150/25 µg is comparable to Serevent Diskus 50 µg and no clinically important differences are apparent.

In study BUSAL II-03-1, administration of a single dose of Labazenit and Serevent Diskus resulted in similar broncholilator effects of salmeterol and the difference was within the predefine equivalence range. The study design is not sensitive to conclusively assess comparability of the bronchodilation effect of salmeterol because only one dose of the test and the comparator was used, comparability cannot be claimed as it is not known whether the studies were sensitive enough to pick up differences if present. A conclusion on equivalence of broncholilation effect between Labazenit and Serevent therefore cannot be drawn from this study.

Budesonide

The same results and conclusions are applicable as for the step-up indication (see above). Equivalence with regards to the number of exacerbations has not been demonstrated.

Comparison of Labazenit with other approved LABA / ICS fixed combinations

For this purpose two supportive studies, studies BUSAL III-08-1 and BUSAL III-05-1, were performed. In study BUSAL III-05-1 the higher Labazenit dose (300/25 µg) showed a similar improvement in morning PEF as Seretide Diskus 500/50 µg. Fluticasone is a stronger ICS and for a comparable dose less fluticasone was expected to be used. For both morning PEF and FEV1, and the symptomatic secondary efficacy variables treatment with Labazenit 300/25 µg and Seretide Diskus 500/50 µg did not show statistically significant differences. The improvements in PEF and FEV1 are clinically relevant. However, only one dose of both Labazenit (300/50 µg) and Seretide (500/50 µg) was used and the study design not sensitive to conclusively asses comparability of the anti-inflammatory control. Non-inferiority was therefore not proven. In study BUSAL III-08-1, the lower Labazenit dose (150/25 µg) was compared with Symbicort Turbuhaler 200/12 µg BID. Both treatments similarly improved PEF and FEv1, the asthma symptoms and the use of rescue medications. The improvements in PEF and FEV1 are clinically relevant, although morning PEF improvement is marginally above clinical relevant difference of 20 L/min as defined for the non-inferiority margin. The improvement in FEV1 is clinically relevant. However, also in this study only one dose of both Labazenit (300/50 µg) and Symbicort (300/25 µg) was tested hence employing a design not sensitive to conclusively assess comparability of the anti-inflammatory effect of budesonide.

Persistence of efficacy

For demonstration of the long term safety and efficacy of Labazenit, study BUSAL III-05-01 was continued open label for up to 24 weeks as study BUSAL III-06-01. This extension phase could support the step up and substitution indication.

Post hoc analyses demonstrated that there was no difference between groups in demographics, FEV1, PEF asthma control and adverse events. The amount of treatment related events was higher for those patients who were not included. An important inclusion criterion for study BUSAL III-06-01 was that patients had not experienced a moderate to severe asthma exacerbation in the preceding 8 weeks. It was shown that an experienced exacerbation did not introduce a bias. The results of the long term safety/efficacy regarding the exacerbation rate are difficult to interpret. Also, study BUSAL III-06-01 lacks a comparison with a currently approved comparable asthma treatment, which makes it difficult determine the comparative benefit. This is an issue considering The observed higher incidence of exacerbations with Labazenit in study BUSAL III-05-01 questions the long term anti-inflammatory effect of budesonide.

2.5.4. Conclusions on the clinical efficacy

Step-up indication

The results of study BUSAL III-02-01 demonstrated superiority of both doses of Labazenit versus the budesonide active comparator alone (Pulmicort 400 µg) for the primary efficacy variable morning PEF, and for FEV1 % predicted. However, a dose response between the two different strengths of Labazenit was not shown. For this reason study BUSAL III-02-1 is not considered sensitive to demonstrate comparable anti-inflammatory control of budesonide between Labazenit and the comparator.

Substitution indication

The PD study BUSAL II-10-1 was designed to prove bronchodilation comparability between Labazenit and the salmeterol active comparator alone (Serevent).The primary efficacy variable was the mean change in $FEV_{1,max}$ (L). The 98.33% confidence interval is -0.16 – 0.12 just outside the predefined limit of equivalence (150mL). As no clinically relevant differences in safety parameters was observed in this study, the CHMP was able to conclude on the non-inferiority of the salmeterol component based on the totality of evidence available despite the CI found. A dose response for Labazenit was seen for the duration of the response as expressed with $FEV1AUC_{8-12h}$.

As for the step-up indication a comparable anti-inflammatory effect of budesonide between Labazenit and the budesonide active comparator would have needed to be established which is not the case.

In the supportive studies BUSAL III-05-1 and BUSAL III-08-1 comparing Labazenit with other fixed combinations of a LABA and an ICS (budesonide), the responses of the lung function parameters and the clinical parameters were comparable to the responses in the pivotal study BUSAL III-02-1. However, only one dose of both Labazenit and the budesonide active comparator was used in both studies and therefore the study design was not sensitive to conclusively assess comparability of the budesonide anti-inflammatory control.

2.6. Clinical safety

One of the key safety objectives of the phase III clinical development program for the Labazenit 300/25 and 150/25 µg fixed combination was to assess the safety and tolerability by evaluating the incidence of AEs and laboratory abnormalities and to identify any potential new AEs.

The main safety concerns for ICS/LABA combinations include local AEs such as cough, dysphonia and oral candidiasis, systemic AEs including adrenal suppression, decreased bone mineral density, growth suppression, cataract and glaucoma, hypokalemia, hyperglycemia and also tachycardia as well as possible paradoxical bronchospasm.

The safety of Labazenit was compared to the budesonide monotherapy group and to the two marketed ICS-LABA combinations, fluticasone/salmeterol and budesonide/formoterol, over 12 weeks in Phase III studies. The safety of the two doses of the Labazenit was compared across the controlled and medium term exposed cohorts. The long term safety was assessed in the long-term exposed cohort with 1 year exposure to the study drug. According to these objectives, the analysis of adverse events (AEs) of Labazenit from the 4 phase III clinical trials has been performed on the pooled safety data and is presented separately for the three defined cohorts.

Data from phase III clinical trials were pooled in three different analysis cohorts:

- The "controlled cohort" included all data from patients exposed to the study treatment for 12 weeks. This applied to the 12-week efficacy controlled phases of studies BUSAL III-02-1, BUSAL III-05-1 and BUSAL III-08-1. Data collected from week 12 to week 24 with the Labazenit combination after the efficacy period under Budesonide in study BUSAL III-02-1 were also included in this cohort.
- The "medium-term exposed cohort" included all data from patients exposed for 24 weeks (6 months) to the two dosages (300/25 µg and 150/25 µg) of the Labazenit combination (study BUSAL III-02-1 and BUSAL III-05-1).
- The "long-term exposed cohort" included all data from patients exposed for 52 weeks (1 year) to the highest dosage (300/25 µg) of the Labazenit combination (study BUSAL III-06-1).

The presentation of the pooled safety data rather than the results of each individual study is justified since the phase III have similar designs.

A fourth population comes from subjects or patients exposed in phase I and II studies that were not included in the pooled analysis. Data from these studies will be presented when appropriate to underline specific safety issues.

Patient exposure

During phase III:

- 301 patients were exposed to at least one dose of Labazenit 150/25µg, 109 (36%) of them being exposed for at least 24 weeks
- 553 patients were exposed to at least one dose of Labazenit 300/25µg, 406 (73%) patients were exposed for 24 weeks and 101 (18%) patients were exposed for 1 year

Table 60. Extent of exposure – Phase III studies

Extent of exposure	Labazenit 300/25µg N=553		Labazenit 150/25µg N=301		Pulmicort 400µg N=124		Seretide 500/50µg N=117		Symbicort 200/12µg N=114	
	N	%	N	%	N	%	N	%	N	%
1 day	0	0.00	0	0.00	0	0.00	0	0.00	1	0.88
2 days to 1 week	1	0.18	0	0.00	0	0.00	0	0.00	2	1.75
1 w to 4 weeks	13	2.39	5	1.68	4	3.23	4	3.42	4	3.51
4 w to 12 weeks	23	4.22	60	20.13	12	9.68	15	12.82	40	35.09
12 weeks to 24 weeks	102	18.72	124	41.61	108	87.10	98	83.76	67	58.77
24 weeks to 1 year	305	55.96	109	36.58						
> 1 year*	101	18.53								
Number of days (m±SD)	192.87 ± 93.94		117.31 ± 44.40		82.05 ± 14.67		80.50 ± 14.40		78.89 ± 17.31	

Labazenit= Fixed-dose combination Budesonide/Salmeterol.
**One year was computed as 360 days.
Source: Integrated Summary of Safety / Section 1.1.5

The exposure during phase II is shown in the table below.

Table 61. Extent of exposure – Phase I and II studies

Extent of exposure	Labazenit 300/25µg N=167		Labazenit 150/25µg N=222	
	N	%	N	%
In healthy volunteers				
1 day	64	38.32	24	10.81
2 days to 1 week	24	14.37	36	16.22
1 week to 10 days	0	0.00	0	0.00
In mild asthmatic patients				
1 day	40	23.95	40	18.02
2 days to 1 week	0	0.00	0	0.00
1 week to 10 days	39	23.35	39	17.57
In moderate to severe asthmatic patients				
1 day	0	0.00	83	37.39
2 days to 1 week	0	0.00	0	0.00
1 week to 10 days	0	0.00	0	0.00
Total				
1 day	**104**	**62.28**	**147**	**66.22**
2 days to 1 week	**24**	**14.37**	**36**	**16.22**
1 week to 10 days	**39**	**23.35**	**39**	**17.57**
Labazenit= Fixed-dose combination Budesonide/Salmeterol. Sources: SMB-BUSAL-SD033, SMB-BUSAL-SS032, SMB-BUSAL-SS071, SMB-BUSAL-SD101, SMB-BUSAL-DP102, BUSAL II-03-1, BUSAL II-10-1 and BUSAL II-10-2 CSRs.				

Both salmeterol and budesonide are well known substances and have been used for a long and extensive way. The Applicant performed three studies wherein 406 patients were exposed for 24 weeks to the highest dose and a long-term study wherein 101 patients were exposed for more than one year. This is considered sufficient by the CHMP.

Adverse events

Phase III studies

In the 12-week controlled cohort, 283 (23.41%) patients reported 465 treatment emergent adverse events (TEAEs). Across the treatment groups, the percentage of patients with a TEAE in the controlled cohort was around 20% except in the Symbicort group with 46.49% of TEAEs.

In BUSAL III-08-1 a higher rate of patients had TEAEs both with Symbicort and with Labazenit 150/25 µg. This rate of TEAEs nevertheless did not result in a higher percentage of drug-related TEAEs in this group (4.39%).

Table 62. Overview of Adverse Events - Controlled cohort

Categories	Labazenit 300/25µg		Labazenit 150/25µg		Pulmicort 400µg		Seretide 500/50µg		Symbicort 200/12µg		Total	
	N=553		N=301		N=124		N=117		N=114		N=1209	
	N (%)*	*n***	N (%)*	*n***	N (%)*	*n***	N (%)*	*n***	N (%)*	*n***	N (%)*	*n***
TEAEs	109 (19.71)	*144*	67 (22.26)	*111*	24 (19.35)	*39*	30 (25.64)	*38*	53 (46.49)	*133*	283 (23.41)	*465*
Drug-related TEAEs	17 (3.07)	*23*	13 (4.32)	*15*	12 (9.68)	*15*	8 (6.84)	*8*	5 (4.39)	*5*	55 (4.55)	*66*
Severe TEAEs	6 (1.08)	*7*	0 (0)	*0*	1 (0.81)	*2*	0 (0)	*0*	0 (0)	*0*	7 (0.58)	*9*
Severe drug-related TEAEs	2 (0.36)	*2*	0 (0)	*0*	0 (0)	*0*	0 (0)	*0*	0 (0)	*0*	2 (0.17)	*2*

* Number (and percentage) of patients with at least one TEAE in the respective category
** number of TEAE in the respective category

Table 63. Overview of Adverse Events – Medium and long term exposed cohorts

Medium term exposed cohort					**Long term exposed cohort**	
Categories	Labazenit 300/25µg		Labazenit 150/25µg		Labazenit 300/25	
	N=497		N=126		N=110	
	N (%)*	*n***	N (%)*	*n***	N (%)*	*n***
TEAEs	141 (28.37)	*204*	27 (21.43)	*49*	48 (43.64)	*89*
Drug-related TEAEs	23 (4.63)	*30*	10 (7.94)	*10*	4 (3.64)	*6*
Severe TEAEs	9 (1.81)	*11*	4 (3.17)	*4*	1 (0.91)	*1*
Severe drug-related TEAEs	2 (0.40)	*2*	1 (0.79)	*1*	0 (0)	*0*

* Number (and percentage) of patients with at least one TEAE in the respective category
** number of TEAE in the respective category

Across all treatment groups, most events were considered mild or moderate in intensity.

Controlled cohort

The most frequently reported TEAEs with both Labazenit doses (300/25µg and 150/25µg) irrespective of causality were nasopharyngitis (16 patients, 2.89% and 8 patients, 2.66% respectively), viral infection (7 patients, 1.27% and 5 patients, 1.66% respectively) and dysphonia (6 patients, 1.08% and 4 patients, 1.33% respectively).

The other most frequently reported TEAEs with:

- Labazenit 300/25µg were pharyngitis (13 patients, 2.35%) and upper respiratory tract infection (6 patients, 1.08%)

- Labazenit 150/25µg were headache (8 patients, 2.66%) and asthma exacerbation (6 patients, 1.99%). These two AEs were the most commonly reported with Symbicort (13.16% and 11.40% respectively) in study BUSAL III-08-1 comparing both treatments. The incidence of those AEs with Labazenit 150/25µg was lower than with Symbicort.

The most frequently reported AE with Labazenit (300/25µg and 150/25µg) assessed by the investigator as having at least a possible relationship to Labazenit (>1% MedDRA preferred term) was dysphonia (1.08% and 1.33% respectively).

Overall, the incidence of AEs was generally low (<3% in the Labazenit groups) and no significant difference in intensity and/or frequency was observed between the new fixed combination and the reference groups, except for the incidence of headache (13.16%) and asthma exacerbation (11.40%) which was higher in the Symbicort group.

Medium-term exposed cohort

The most common TEAEs experienced by patients were in the same main classes as in the controlled cohort (12-week exposure).

The most frequently reported AEs with Labazenit irrespective of causality were:

- nasopharyngitis and pharyngitis (23 patients (4.63%)) with Labazenit 300/25µg

- nasopharyngitis, viral infection and cough (4 patients (3.17%)) with Labazenit 150/25µg.

No difference between the two doses of the Labazenit could be noted from the incidence of the most common TEAEs after 24-week exposure to the treatment.

The most frequently reported TEAE assessed by the investigator as having at least a possible relationship to Labazenit (>1% MedDRA preferred term) was dysphonia (2.01% and 1.59% with Labazenit 300/25µg and 150/25µg respectively).

The results observed in the controlled cohort (over 12 weeks of treatment) were confirmed in the medium-term exposed cohort (up to 24 weeks of treatment). The incidence of AEs remains generally low (<5%) and no significant difference in intensity and/or frequency was observed between the two doses of the Labazenit.

Long-term exposed cohort

The data over long-term exposure (up to 52 weeks) to the highest dosage of Labazenit (300/25µg BID) confirmed the data observed over shorter periods (12 and 24-weeks): the more frequently reported AE was nasopharyngitis (14 patients, 12.73%). Pharyngitis (6 patients, 5.45%), viral infection (6 patients, 5.45%) and bronchitis (5 patients, 4.55%) complete the picture of the most commonly reported events.

No drug-related AE was reported with an incidence over 1% after 52 weeks of exposure to Labazenit 300/25 µg.

The incidence of AEs in the long-term exposed cohort was higher than in the two other cohorts (see table below).

Table 64. Expected AE - Controlled and long term exposed cohorts

Controlled cohort							**Long term exposed cohort**
Expected AE		**Labazenit 300/25µg**	**Labazenit 150/25µg**	**Pulmicort 400µg**	**Seretide 500/50 µg**	**Symbicort 200/12 µg**	**Labazenit 300/25 µg**
SOC	AE (group) denomination	N=553	N=301	N=124	N=117	N=114	N=110
Cardiac disorders	Cardiac arrhythmias	2 (0.36%)	**4 (1.33%)**	1 (0.81%)	1 (0.85%)	0 (0%)	0 (0%)
Gastrointestinal disorders	Gastrointestinal disorders	1 (0.18%)	1 (0.33%)	**3 (2.42%)**	0 (0%)	**4 (3.51%)**	1 (0.91%)
Immune system disorders	Hypersensitivity	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Infections and infestations	Gastroenteritis viral	3 (0.54%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Oral candidiasis	2 (0.36%)	2 (0.66%)	1 (0.81%)	**2 (1.71%)**	0 (0%)	**3 (2.73%)**
	Respiratory tract infection	**48 (8.68%)**	**10 (3.32%)**	**8 (6.45%)**	**14 (11.97%)**	**7 (6.14%)**	**32 (29.09%)**
Metabolism and nutrition disorders	Hyperglycaemia	1 (0.18%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Hypokalemia	0 (0%)	**3 (1.00%)**	1 (0.81%)	0 (0%)	1 (0.88%)	0 (0%)
Musculoskeletal and connective tissue disorders	Back pain	3 (0.54%)	1 (0.33%)	0 (0%)	0 (0%)	**3 (2.63%)**	**2 (1.82%)**
	Muscle cramps	4 (0.72%)	2 (0.66%)	0 (0%)	0 (0%)	1 (0.88%)	**2 (1.82%)**
	Traumatic fracture	2 (0.36%)	0 (0%)	0 (0%)	1 (0.85%)	0 (0%)	**2 (1.82%)**
Nervous system disorders	Headache	4 (0.72%)	**8 (2.66%)**	0 (0%)	0 (0%)	**15 (13.16%)**	1 (0.91%)
	Tremor	0 (0%)	2 (0.66%)	0 (0%)	0 (0%)	0 (0%)	1 (0.91%)
Psychiatric disorders	Psychiatric disorders	1 (0.18%)	**3 (1.00%)**	1 (0.81%)	0 (0%)	**2 (1.75%)**	0 (0%)
Respiratory, thoracic and mediastinal disorders	Bronchospasm paradoxical	0 (0%)	0 (0%)	**3 (2.42%)**	0 (0%)	0 (0%)	0 (0%)
	Dyspnoea	0 (0%)	**4 (1.33%)**	1 (0.81%)	0 (0%)	0 (0%)	0 (0%)
	Oropharyngeal (respiratory) disorders	**9 (1.63%)**	**9 (2.99%)**	**5 (4.03%)**	**5 (4.27%)**	1 (0.88%)	**2 (1.82%)**
	Rhinitis allergic	0 (0%)	1 (0.33%)	0 (0%)	0 (0%)	0 (0%)	1 (0.91%)
	Sinus congestion	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin and subcutaneous tissue disorders	Contusions	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.91%)
Incidences over 1% are in bold characters. Any event with occurrence over 1% in any treatment group is reported.							

Phase I and phase II studies

No new AEs were identified in the phase I and II trials and the frequency and intensity of AEs observed was comparable to those of the reference products.

In BUSAL II-03-1 a total of 17 adverse events were reported during the whole study. After intake of BUDESONIDE-SALMETEROL, 9 patients reported 14 adverse events and 3 patients reported 3 adverse events after intake of Serevent Diskus.

The most common adverse events reported were cough and hoarseness. They were related to the study medication at possible or probable grade. They have been resolved spontaneously without any medication or therapy.

In BUSAL II-10-1 twenty-five (25) emergent adverse events (AEs) were reported. All emergent AEs were of mild to moderate intensity.

The most frequent adverse event reported was headache. Eight (8) episodes were reported, 1 in the Labazenit 150/6.25 µg group, 2 in the Labazenit 150/12.5 µg group, 1 in the Serevent Diskus 50 µg group and 4 in the Serevent Evohaler 2*25 µg group. 5 out of them were of mild intensity and 3 were of moderate intensity.

Two AEs were judged related to the study treatment: one episode of moderate tremor which occurred during the Labazenit 150/12.5 µg treatment period and one episode of hypokaliemia (mild intensity) which occurred during the Serevent Evohaler 2*25 µg treatment periods. Other emergent AEs were infrequent and unspecific, all of mild to moderate intensity.

In BUSAL II-10-2 the most frequently reported adverse events were hypertension (19 episodes, 42.22% of emergent events) and headache (16 episodes, 35.56% of emergent AEs).

Hypertension and headache were also the most frequently reported AE assessed as related to the study treatment (respectively 18 episodes and 10 episodes).

One AE not related to study treatment led to patient withdrawal in the Labazenit 300/25 µg group (acute viral infection). All emergent AEs were of mild to moderate intensity.

Adverse events of special interest

Asthma exacerbations

The information collected in the different studies on asthma exacerbation was not homogeneous.

Table 65. Overview of exacerbations

Categories	Labazenit 300/25µg		Labazenit 150/25µg		Pulmicort 400µg		Seretide 500/50µg		Symbicort 200/12µg	
	N=553		N=301		N=124		N=117		N=114	
	n	%	N (%)*	%	n	%	n	%	n	%
Controlled cohort										
exacerbations	10	*1.81*	10	*3.32*	4	*3.23*	1	*0.85*	15	*13.16*
withdrawal due to exacerbation	1				2				2	
treated for exacerbation	5				3				2	
Medium-term exposed cohort										
exacerbation	15	*3.02*	1	*0.79*						
withdrawal due to exacerbation	1		1							
treated for exacerbation	5									
Long-term exposed cohort (110 patients)										
exacerbation	13									
withdrawal due to exacerbation	0									
treated for exacerbation	3									

None of the exacerbations was considered to be SAEs and none led to withdrawal of the patient.

The definition of asthma exacerbation was not homogeneous in the different studies. Moreover, severity of asthma exacerbation was not defined besides in BUSAL III-08-1. Asthma exacerbations are considered as an parameter of asthma control i.e. inflammation control and are therefore discussed under efficacy. In the medium term exposed cohort and long-term exposed cohort patientns only received Labazenit.

Cardiac AEs and ECG abnormalities

Cardiac AEs

Controlled cohort

Eight patients had cardiac arrhythmias during the first 12 weeks of treatment. Half of them were taking Labazenit 150/25µg.

All events were of mild intensity. All were assessed as treatment related except an episode of palpitations reported by a patient taking Labazenit 300/25 µg.

None of these events were serious or led to withdrawal of a patient. All patients recovered without requiring any treatment.

Medium exposed cohort

In addition to the events reported in the controlled cohort, a patient taking Labazenit 300/25 µg had an episode of atrial fibrillation of moderate intensity. This event was assessed as unrelated to the treatment, not serious and did not require any corrective treatment.

Long term exposed cohort

There were no reports of cardiac arrhythmia in patients exposed to Labazenit 300/25 µg for up to one year of treatment.

ECG abnormalities

The incidence of ECG abnormalities was low in every treatment group (see table below). All events were of mild intensity. All patients recovered from these events and none resulted in permanent discontinuation of treatment. All events except the ECG T-wave inversion were reported as related to the study treatment.

Table 66. ECG abnormalities in the controlled cohort (from W0 to W12)

Appearance of ECG	**Labazenit 300/25µg**	**Labazenit 150/25µg**	**Pulmicort 400µg**	**Seretide 500/50µg**	**Symbicort 200/12µg**
	N=553	N=301	N=124	N=117	N=114
Abnormalities (N (%))	13 (2.35%)	9 (2.99%)	2 (1.61%)	0 (0%)	6 (5.26%)
CS abnormalities (N (%))	1 (0.18%) - T-wave inversion	1 (0.33%) - tachycardia	2 (1.61%) - tachycardia - 1e degree AV-block	0 (0%)	0 (0%)
CS = Clinically Significant					

In the medium exposed group, the incidence of ECG abnormalities was still low with a slightly higher percentage of abnormalities for longer duration of exposure to the treatment.

Four AEs were reported by 4 patients. Two events came from the controlled cohort. In addition, myocardial infarction and atrial fibrillation were reported with Labazenit 300/25µg.

The event of atrial fibrillation of moderate intensity was considered as not related to the study treatment.

The heart rate corrected QTc intervals, using Bazett's correction method, were analysed. The number and percentages of significant delta QTc versus baseline values and of borderline and prolonged QTc values are presented in the table below. None of these findings were considered as clinically significant by the investigator and no AEs were reported in relation to these QTc values. No patients with such QTc values (or without) reported torsade de pointe during the Labazenit development.

Table 67. Significant QTc interval observations

Significant QTc interval observations versus pre-treatment values	**Labazenit 300/25µg**	**Labazenit 150/25µg**	**Symbicort 200/12µg**	**Serevent 50µg***
	N=39	N=237	N=114	N=83
30 msec < Delta QTc < 60 msec	0 (0%)	13 (5.49%)	4 (3.51%)	6 (7.23%)
Delta QTc > 60 msec	0 (0%)	4 (1.69%)	5 (4.39%)	0 (0%)
Borderline QTc	0 (0%)	12 (5.06%)	0 (0%)	10 (12.05%)
Prolonged QTc	0 (0%)	2 (0.84%)	1 (0.88%)	1 (1.20%)
Labazenit = Budesonide-Salmeterol Fixed-dose combination. * Serevent 50µg taken with the Diskus or the Evohaler Source: BUSAL II-03-1, BUSAL II-10-1, BUSAL II-10-2 and BUSAL III-08-1 CSRs				

In BUSAL II-03-1 it seems that the two drugs are comparable regarding the ECG results and do not raise significant concerns. This is quite expected after a single dose. Indeed, previous data on salmeterol indicate that only large doses of inhaled salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias.

In BUSAL II-10-1 ECGs were taken at 60 minutes and 12 hours post dosing. QTc, QRS, RR and PQ levels remained unchanged in all groups within 12 hours after treatment intake (respectively: p=0.26, 0.11, 0.49 and 0.56).

In BUSAL II-10-2 QTc, QRS, RR and PQ remained unchanged during the study. No patients presented delta QTc > 30 msec (between baseline and D14 of each period) or borderline or prolonged QTc.

Some patients presented non clinically significant findings on their ECG: all cases were either judged as normal or as clinically irrelevant by the investigator:

No unexpected safety signals were present. All cardiac events (ECG) were in line of expectation (BUSAL II-10-1, BUSAL II-10-2, BUSAL III-08-1).

Paradoxical bronchospasms

There were no reports of paradoxical bronchospasm in patients with Labazenit at all.

Serious adverse events / deaths / other significant events

Deaths

No patients died during the course of any clinical trial performed with Labazenit.

Serious AEs in the controlled cohort

A total of 5 patients had at least one SAE: 2 (0.36%) patients in the Labazenit 300/25 µg group and 1 (0.8%) patient in each reference group. No patient in the Labazenit 150/25µg group had a SAE.

None of these SAEs was considered related to treatment by the investigator.

Table 68. Overview of Serious Adverse Events - Controlled cohort

Categories	Labazenit 300/25µg	Labazenit 150/25µg	Pulmicort 400µg	Seretide 500/50µg	Symbicort 200/12µg
	N=553	N=301	N=124	N=117	N=114
	N (%)* /n**	N (%)*/n**	N (%)*/n**	N (%)*/n**	N (%)*/n**
SAEs	2 (0.36) - Peritonsilitis - Aseptictic necrosis bone	0	1 (0.81) - metrorrhagia	1 (0.85) - Foot fracture - Humerus fracture	1 (0.88) - Pregnancy
Drug-related SAEs	0	0	0	0	0

Serious AEs in the medium-term exposed cohort

Seven (1.12%) patients had at least one SAE: 4 patients with the higher dose and 3 patients with the lower dose of the fixed combination.

Serious AEs in the long-term exposed cohort

Two (1.82%) patients had one SAE after long-term treatment with Labazenit 300/25µg. None was related to the treatment.

Table 69. Overview of Serious Adverse Events – Medium and long term exposed cohorts

Medium term exposed cohort			**Long term exposed cohort**
Categories	Labazenit 300/25µg	Labazenit 150/25µg	Labazenit 300/25
	N=497	N=126	N=110
	N (%)*/*n***	N (%)*/*n***	N (%)*/*n***
SAEs	4 (0.80)/5 - Myocardial infarction - Vertigo - Peritonsillitis - Viral infection - Syncope	3 (2.38)/4 - Bronchitis - CVA - Renal failure - Asthma	2 (1.82)/2 - Toe deformity - Cervical conisation
Drug-related SAEs	0	1 (0.79) - Bronchitis (possibly)	0 (0)

No SAEs were experienced by more than 1 patient in any treatment group in any cohort. A review of the frequency and types of events, as well as an assessment of potential relationships between the events and study medication, suggested that there was no trend for any SAE in any treatment group that could raise a particular new safety concern.

Phase I and phase II studies

Only 1 SAE was observed with Labazenit 300/25 µg during the phase I and II trials, i.e. pyelonephritis in study SMB-BUSAL-DP102. This event was considered as not related to the study treatment by the investigator.

No trend for any SAE in any treatment group is observed that could raise a particular new safety concern. Only bronchitis in Labazenit 150/25µg group is been assessed as possibly related to treatment.

Laboratory findings

Cortisol

Cortisol was measured in two studies:

- Study BUSAL III-02-1 with the assessment of morning plasma cortisol and 24h urinary cortisol in 15 patients per group after 12 and 24 weeks of treatment in a parallel design
- Study BUSAL II-10-2 with the assessment of both plasma and urinary cortisol over 24h in 40 patients in a cross-over design

In the BUSAL III-02-1, no statistically significant changes from baseline to week 12 were observed in serum or urine cortisol levels within any of the treatment groups.

Table 70. Within-group comparisons of changes in serum cortisol levels – BUSAL III-02-1

Serum cortisol (nmol/l) Treatment group	N	Mean ± SE	95% CI	p-value
Changes from baseline to week 12 (Efficacy phase)				
BUSAL 150-25 mcg	14	6.4 ± 35.20	-69.61; 82.47	0.858
BUSAL 300-25 mcg	14	-23.5 ± 30.38	-89.13; 42.13	0.453
Reference	15	17.4 ± 57.54	-106.01; 140.81	0.767
Changes from baseline to week 24 (Whole study)				
BUSAL 150-25 mcg	13	16.2 ± 40.50	-72.10; 140.40	0.697
BUSAL 300-25 mcg	14	-17.6 ± 37.55	-98.77; 63.49	0.646

Over the whole study, from baseline to week 24, urinary cortisol levels were significantly increased during treatment with Labazenit 300/25µg (p=0.005) (see table below).

Table 71. Within-group comparisons of changes in urine cortisol levels

Urine cortisol (nmol/24h) Treatment group	N	Mean ± SE	95% CI	p-value
Changes from baseline to week 12 (Efficacy phase)				
BUSAL 150-25 mcg	14	66.9 ± 46.55	-33.70; 167.42	0.175
BUSAL 300-25 mcg	15	114.4 ± 55.94	-5.57; 234.37	0.060
Reference	15	-57.3 ± 83.16	-235.62; 121.09	0.502
Changes from baseline to week 24 (Whole study)				
BUSAL 150-25 mcg	13	109.3 ± 50.39	-0.48; 219.09	0.051
BUSAL 300-25 mcg	15	115.4 ± 35.12	40.07; 190.73	0.005

However, no definite conclusions can be drawn due to the low sample size of the groups in this study.

BUSAL II-10-2 was specifically designed and had more power to detect an effect of the Labazenit combination on cortisol levels. As a conclusion, the cortisol suppression observed with Labazenit 150/25µg and 300/25µg is similar to Pulmicort 400µg and is weak on a clinical point of view. The values in plasma and urinary cortisol are in line with the literature data available for inhaled Budesonide.

Potassium

Hypokalemia is a metabolic side effect expected with an ICS-LABA combination.

In the pharmacodynamic single dose study BUSAL II-10-01 potassium is measured properly: recommended dose is one capsule containing 25 µg salmeterol BID.
At the clinically important time T60 minutes no difference is been seen between Labazenit 150/25 µg and Serevent Diskus. The difference with baseline was for Labazenit 150/25 µg 0.03±0.30 and for Serevent Diskus 0.11±0.38. No clinical difference was noted between baseline and 12-hour post-dose measurement.
In conclusion no differences are seen between Labazenit and Serevent Diskus. The level of potassium remained steady within 12 hours of study drug intake in all treatment groups (p=0.20 at 60-minute post-dose and p=0.88 at 12-hour post-dose measurement).

No clinical difference was noted between baseline and 60 minutes or 12-hour post-dose measurement.

There were very few patients with clinically significant potassium values during the Labazenit clinical development: 2 patients with Labazenit 300/25µg, 3 patients with Labazenit 150/25µg, 1 with Pulmicort, 1 with Symbicort and 1 patient with Serevent 50µg.

In all patients, these events were of mild intensity and related to the study drug intake (see table below).

Table 72. Number and percentage of patients with clinically significant abnormal values in Potassium

Potassium						
	Labazenit 300/25µg	**Labazenit 150/25µg**	**Pulmicort 400µg**	**Seretide 500/50µg**	**Symbicort 200/12µg**	**Serevent 50µg***
Controlled cohort (N)	553	301	124	117	114	
CS Abnormal values (N (%))	2 (0.36%)	3 (1.00%)	1 (0.81%)	0 (0%)	1 (0.88%)	
Medium term exposed cohort (N)	497	126				
CS Abnormal values (N (%))	2 (0.40%)	2 (1.59%)				
Long term exposed cohort (N)	110					
CS Abnormal values (N (%))	0 (0%)					
Phase I and II studies (N)	167	222	123			182
CS Abnormal values (N (%))	0 (0%)	0 (0%)	0 (0%)			1 (0.55%)
CS = clinically significant, N = Number of patients, SD = Standard deviation. * Serevent 50µg taken with the Diskus or the Evohaler						

Glucose

Hyperglycemia is a metabolic side effect expected with an ICS-LABA combination.

There were no significant changes in the controlled cohort with no noticeable differences between the different treatment groups.

The changes observed over 12 weeks in the Labazenit groups remained the same over longer periods (24 and 52 weeks).

In all studies there were very few patients with clinically significant (CS) increase of glucose values during treatment with Labazenit: 4 patients with Labazenit 300/25µg and 2 patients with Labazenit 150/25µg and 2 patients with Serevent 50µg (see table below).

Three of the five patients from the phase III studies had diabetes mellitus, which would explain their high glucose levels.

Table 73. Number and percentage of patients with clinically significant abnormal values in glucose

Glucose	Labazenit 300/25µg	Labazenit 150/25µg	Pulmicort® 400µg	Seretide® 500/50µg	Symbicort200/12µg	Serevent® 50µg*
Controlled cohort (N)	553	301	124	117	114	
CS Abnormal values (N (%))	2 (0.36%)	1 (0.33%)	0 (0%)	0 (0%)	0 (0%)	
Medium term exposed cohort (N)	497	126				
CS Abnormal values (N (%))	4 (0.80%)	0 (0%)				
Long term exposed cohort (N)	110					
CS Abnormal values (N (%))	0 (0%)					
Phase I and II studies (N)	167	222	123			182
CS Abnormal values (N (%))	0 (0%)	1 (0.45%)	0 (0%)			2 (1.10%)

CS = clinically significant, N = Number of patients,
* Serevent® 50µg taken with the Diskus® or the Evohaler®

Study BUSAL II-10-1

In study BUSAL II-10-1 evolution of glucose level at 60-minute post-dose was significantly different between groups (p=0.005).

The increase in glucose levels observed at 60 minutes was transient as no more differences were present at 12-hour post-dose.

Glucose level remained steady between baseline and 12-hour post-dose measurement, without difference between groups (p=0.92).

No clinical difference was noted between baseline and 12-hour post-dose measurement.

Table 74. Glucose- safety population

		Labazenit 150/25 µg (N = 48)	Labazenit 150/12.5 µg (N = 48)	Labazenit 50/6.25 µg (N = 48)	SER DISKUS 50 µg (N=48)	SER Evohaler 25 µg (N = 48)	SER Evohaler 2*25 µg (N = 48)
Glucose baseline	m ± SD	5.43±0.77	5.49±0.77	5.41±1.02	5.40±0.69	5.40±0.69	5.40±0.65
Glucose delta T0-T60[1]	m ± SD LS means ± SD	-0.04±0.37 -0.04±0.05	-0.04±0.34 0.05±0.05	0.15±0.39 0.15±0.05	0.04±0.34 0.04±0.05	-0.01±0.37 -0.01±0.05	0.20±0.41 0.19±0.05
Glucose delta T0-T12h	m ± SD LS means ± SD	-0.03±0.96 -0.14±0.14	-0.07±0.71 -0.16±0.14	0.08±0.76 -0.04±0.14	0.00±0.84 -0.13±0.14	-0.10±0.82 -0.22±0.14	-0.05±1.07 -0.18±0.14

* mixed model with period, treatment, baseline for each period as fixed effect.

Study BUSAL II-10-2

In study BUSAL II-10-2 the evolution of glucose level appeared to be statistically different between the treatment groups. However, the most important change in glucose level from baseline to D11 was observed during treatment with placebo (LSmeans 0.41±0.15 mmol/L). The statistical difference between the treatment groups was therefore not clinically relevant.

Safety in special populations

The global safety profile has additionally been assessed in several sub-populations of patients: according to demographic data: gender (male and female), age (≤55 years of age, >55 and ≤65 years of age, and >65 years of age) and Body Mass Index (BMI) (>18 and ≤25 kg/m^2, >25 and ≤30 kg/m^2 and > 30 kg/m^2 at baseline), or at higher risk for an AE related to their asthma severity (FEV_1% ≤60%, >60 and ≤80% and > 80%)) and their smoking status (smoking or not).The two tables below give an overview of AEs in each subgroup versus the global population of patients for the medium term exposed cohort. This provides indication of the AE onset, causality, intensity and seriousness in the subgroups compared to the global population. The results show that there are no notable differences between the subgroups and the global population.

Table 75. Overview of AE profile in subgroups population, with respect to age, gender and BMI, analysed – Medium term exposed cohort

N (%) of patients with at least one	**All patients** N= 497	**Age subgroups**			**Gender**		**BMI subgroups**		
		≤55 years N= 372	**>55-≤65 year** N= 104	**> 65 years** N=21	**Males** N=197	**Females** N=300	**>18-≤25 kg/m²** N=194	**>25-≤30 kg/m²** N=189	**> 30 kg/m²** N=114
TEAEs	141 (28.37%)	108 (29.03%)	30 (28.85%)	3 (14.29%)	55 (27.92%)	86 (28.67%)	56 (28.87%)	56 (29.63%)	29 (25.44%)
Drug-related TEAEs	23 (4.63%)	18 (4.84%)	4 (3.85%)	1 (4.76%)	7 (3.55%)	16 (5.33%)	11 (5.67%)	7 (3.70%)	5 (4.39%)
Severe TEAEs	9 (1.81%)	8 (2.15%)	1 (0.96%)	0 (0%)	4 (2.03%)	5 (1.67%)	2 (1.03%)	5 (2.65%)	2 (1.75%)
Severe drug-related TEAEs	2 (0.40%)	2 (0.54%)	0 (0%)	0 (0%)	0 (0%)	2 (0.67%)	1 (0.52%)	1 (0.53%)	0 (0%)
Deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SAEs	4 (0.80%)	2 (0.54%)	2 (1.92%)	0 (0%)	1 (0.51%)	3 (1.00%)	2 (1.03%)	2 (1.06%)	0 (0%)
Drug-related SAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinuation due to AEs	6 (1.21%)	4 (1.08%)	2 (1.92%)	0 (0%)	1 (0.51%)	5 (1.67%)	2 (1.03%)	1 (0.53%)	3 (2.63%)
Discontinuation due to drug-related AEs	2 (0.40%)	1 (0.27%)	1 (0.96%)	0 (0%)	0 (0%)	2 (0.67%)	0 (0%)	1 (0.53%)	1 (0.88%)

Table 76. Overview of AE profile in all subgroups population with respect to asthma severity and smoking status analysed – Medium term exposed cohort

N (%) of patients with at least one	**All patients**	**Asthma severity based on FEV_1%**			**Smoking status**	
		≤60%	**>60-≤80%**	**>80%**	**Smoker**	**Non-smoker**
	N= 497	N=114	N=377	N=6	N=116	N=381
TEAEs	141 (28.37%)	39 (34.21%)	101 (26.79%)	1 (16.67%)	35 (30.17%)	106 (27.82%)
Drug-related TEAEs	23 (4.63%)	5 (4.39%)	18 (4.77%)	0 (0%)	5 (4.31%)	18 (4.72%)
Severe TEAEs	9 (1.81%)	3 (2.63%)	6 (1.59%)	0 (0%)	3 (2.59%)	6 (1.57%)
Severe drug-related TEAEs	2 (0.40%)	1 (0.88%)	1 (0.27%)	0 (0%)	0 (0%)	2 (0.52%)
Deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SAEs	4 (0.80%)	0 (0%)	4 (1.06%)	0 (0%)	2 (1.72%)	2 (0.52%)
Drug-related SAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinuation due to AEs	6 (1.21%)	4 (3.51%)	2 (0.53%)	0 (0%)	0 (0%)	6 (1.57%)
Discontinuation due to drug-related AEs	2 (0.40%)	2 (1.75%)	0 (0%)	0 (0%)	0 (0%)	2 (0.52%)

No specific AE appears to be significantly increased in any age subpopulation.

No difference in the most commonly reported AEs was observed between males and females. It was also the same as in the global population of patients.

The frequency of TEAEs increases with asthma severity; from 26.79% in patients with baseline FEV_1% between 60 and 80% to 34.21% in patients with baseline FEV_1% below 60%. No difference was observed on drug-related TEAEs (4.39% and 4.77% respectively).

The population of patients with FEV_1% above 80% is not representative as there are only 6 patients. This is expected because of the study inclusion criteria.

Nasopharyngitis was most commonly reported in patients with baseline FEV_1% between 60% and 80%, which is the largest population of patients. On the other side, viral infections were most commonly reported in patients with baseline FEV_1% below 60%.

No specific AEs appear to be significantly increased in any subpopulation based on the patient's smoking status.

Safety related drug-drug interactions and other interactions

Drug interactions of Labazenit are the same as for the marketed forms of budesonide and salmeterol.

Interactions with Cytochrome P (CYP)3A4 inhibitors (like ketoconazole, itraconazole, ritonavir) is described. In addition, the following drugs may interact with the salmeterol component: β-adrenergic blockers, xanthine derivatives, steroids and diuretics, quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors and tricyclic anti-depressants, L-Dopa, L-thyroxine, oxytocin, halogenated hydrocarbons and digitalis glycosides.

Discontinuation due to adverse events

In total, 13 (1.08%) patients discontinued the study due to an AE in the controlled cohort: 7 (1.27%) in the Labazenit 300/25µg group, 1 (0.33%) in the Labazenit 150/25µg group, 2 (1.61%) in the Pulmicort group and 3 (2.63%) in the Symbicort group.

Four (4) patients had AEs considered related to study medication by the investigators: 3 (0.54%) patients in the Labazenit 300/25µg group and 1 (0.88%) patient in the Symbicort group.

Table 77. Overview of Withdrawals to Adverse Events - Controlled cohort

Categories	Labazenit 300/25µg	Labazenit 150/25µg	Pulmicort 400µg	Seretide 500/50µg	Symbicort 200/12µg
	N=553	N=301	N=124	N=117	N=114
Withdrawal AEs not drug related	- viral infection - Hepatitis C Ab pos - Hepatitis C virus - Diabetes mellitus	- viral infection	- Asthma (2)	0	- Pregnancy - asthma
Withdrawal - Drug-related AE	- Dysphonia - Pharyngolaryngeal pain - neurosis	0	0	0	angiooedema

Table 78. Overview of Overview of Withdrawals to Adverse Events – Medium and long term exposed cohorts

Medium term exposed cohort			Long term exposed cohort
Categories	Labazenit 300/25µg	Labazenit 150/25µg	Labazenit 300/25
	N=497	N=126	N=110
Withdrawal AEs not drug related	- viral infection - Hepatitis C Ab pos - Hepatitis C virus - Diabetes mellitus	- Asthma - viral infection	0
Withdrawal - Drug-related AE	Dysphonia - Pharyngolaryngeal	- Bronchitis (possibly)	0 (0)

	pain		

The AEs reported during Labazenit intake are expected following treatment with an ICS and/or LABA. There is therefore no particular safety concern raised from data on AEs leading to discontinuation in the controlled cohort.

2.6.1. Discussion on clinical safety

Budesonide and salmeterol have been in therapeutic use, alone, and in combination for many years. Moreover they are recognized as high uptake products to treat a common disease and their safety profile is well known. Although not currently approved as fixed combination the separate components are readily available and have presumably been used in combination by co-administration.

During the phase III studies, 301patients, of which 109 (36%) exposed for at least 24 weeks were exposed to Labazenit 150/25µg and 553 patients, of which 406 (73%) were exposed for 24 weeks and 101 (18%) exposed for 1 year to Labazenit 300/25µg. However, no long term safety data (52 weeks) of the lower dose of Labazenit 150/25 were provided. According to the ICH E1A guideline "Population exposure: the extent of population exposure to assess clinical safety", the Applicant provided 12 months safety data for the highest strength of Labazenit (300 µg/25 µg) which is considered sufficient. Long term use is included as important missing information in the proposed RMP.

One of the specific AEs of interest is asthma exacerbation. The exacerbations were similar with the active comparators in study BUSAL III-05-1, whereas more patients using Labazenit 300/25 µg (n=7, 2%) than using Seretide (n=1, 0.9%) experienced an exacerbation. The number of observed exacerbations is small, and the observation period is too short to be conclusive. Asthma exacerbations is included in section 4.4 of the proposed SmPC and as an important identified risk in the proposed RMP.

Other specific AEs of interest regarding the LABA component are the cardiac events, regarding which no unexpected safety signals were present. All cardiac events (i.e ECG deviations) were in line with the expectations. Also no increased cases of hypokalaemia or hyperglycaemia were noticed, although muscle cramps and headache were more frequently reported. However, the reported number of events is low. No trend for any SAE in any treatment group is observed that could raise a particular new safety concern. None of these SAEs was considered related to treatment. No trends for withdrawals were observed. The majority have been assessed as unrelated or unlikely to be related to treatment. Hypokaliema, hyperglycaemia, QTc prolongation and adrenergic cardiac effects are included in sections 4.4 and 4.8 of the proposed SmPC and as important identified risks in the proposed RMP.

It is known that cortisol can be suppressed by a synthetic glucocorticosteroid like budesonide, even when inhaled. Labazenit 300/25 µg appears to decrease serum cortisol (AUC0-12 h) stronger than Labazenit 150/25 µg and Pulmicort Turbohaler 400 µg+ Serevent Diskus 50 µg. According to the predefined equivalence margin (-20% ; 20% of 99.15 CI of the difference in relative change serum cortisol (AUC0-12 h)) equivalence is established. The observed results are in line with previous results published in literature and the 20 % safety margin is justified by bibliographical data. Systemic effects of glucocorticosteroid treatment are included in sections 4.4 and 4.8 of the proposed SmPC and as important identified risk in the proposed RMP.

The number of elderly patients included in the clinical development program was quite low (67 patients in total so less than 5 % and no patient over 75 years of age was included). A statement recommending caution when treating elederly patients due to the limited data available has been included in section 4.2 of the proposed SmPC and use in patients over 65 years old is included as important missing information in the proposed RMP.

2.6.2. Conclusions on the clinical safety

Budesonide and salmeterol are well known substances used in the treatment of asthma. Although not currently approved as fixed combination the separate components are licensed and have presumably been used in combination by co-administration of LABA and ICS according to treatment guidelines.

In the clinical studies, both Labazenit 300/25 µg and Labazenit 300/25 µg were safe and well tolerated over a treatment period of up to one year.There were no differences in adverse events after short-term exposure and longterm exposure. The treatment emergent adverse events are comparable with comparator products. No new safety issue emerged. No specific AE appears to be significantly increased in any subpopulation.

In the PK studies a higher C_{max} was observed for salmeterol. A high C_{max} can be related to an increase of AEs like tremor, increased glucose, hypokalaemia or muscle cramps. The observed incidence of these events was low in the controlled cohort and long term cohort, indicating that the clinical relevance of the findings is probably limited.

For cardiac events, no unexpected safety signals were present. All cardiac events and ECG abnormalities were in line with expectation. Regarding the effect on serum cortisol Labazenit 300/25 µg appears to induce a stronger decrease than Labazenit 150/25 µg and the active comparator (budesonide+salmeterol), but the difference is within the predefined equivalence margins.

Overall, the safety profile of Labazenit is considered as sufficiently characterized and can be satisfactorily managed in clinical practice.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The Applicant submitted a risk management plan

Table 79. Summary of the risk management plan

IMPORTANT IDENTIFIED RISKS		
Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
Asthma exacerbation	• Routine pharmacovigilance	Labelling EU SmPC • 4.4. Special warnings and precaution for use. • Listed as adverse reaction (section 4.8) Communicated in the PIL
Paradoxical bronchospasm	• Routine pharmacovigilance	Labelling EU SmPC • 4.4. Special warnings and precaution for use. • Listed as adverse reaction (section 4.8) with the experience of other combinations of the same pharmacological class. Communicated in the PIL
Adrenergic cardiac effects	• Routine pharmacovigilance	Labelling EU SmPC • 4.4. Special warnings and precaution for use. • 4.5. Interaction with other medicinal products and other forms of interaction. • Listed as adverse reaction (section 4.8) with the experience of the combination. Communicated in the PIL
Respiratory disorders	• Routine pharmacovigilance	Labelling EU SmPC • 4.4. Special warnings and precaution for use. • Listed as adverse reaction (section 4.8) with the experience of the combination. Communicated in the PIL

IMPORTANT IDENTIFIED RISKS		
Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
Hyperglycaemia	• Routine pharmacovigilance	Labelling EU SmPC • 4.4. Special warnings and precaution for use. • Listed as adverse reaction (section 4.8) with the experience of other combinations of the same pharmacological class. Communicated in the PIL
Hypokalemia	• Routine pharmacovigilance	Labelling EU SmPC • 4.4. Special warnings and precaution for use. • 4.5. Interaction with other medicinal products and other forms of interaction. • Listed as adverse reaction (section 4.8) with the experience of the combination. Communicated in the PIL
QTc prolongation	• Routine pharmacovigilance	Labelling EU SmPC • 4.4. Special warnings and precaution for use. • 4.5. Interaction with other medicinal products and other forms of interaction. • Listed as adverse reaction (section 4.8) with the experience of other combinations of the same pharmacological class. Communicated in the PIL
Adrenal Suppression	• Routine pharmacovigilance	Labelling EU SmPC • 4.4. Special warnings and precaution for use. • Listed as adverse reaction (section 4.8) with the experience of other combinations of the same pharmacological class. Communicated in the PIL
Growth retardation	• Routine pharmacovigilance	Labelling EU SmPC • 4.4. Special warnings and precaution for use. • Listed as adverse reaction (section 4.8) with the experience of other combinations of the same pharmacological class. Communicated in the PIL

IMPORTANT IDENTIFIED RISKS		
Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
Cataracts	• Routine pharmacovigilance	Labelling EU SmPC • 4.4. Special warnings and precaution for use. • Listed as adverse reaction (section 4.8) with the experience of other combinations of the same pharmacological class. Communicated in the PIL
Glaucoma	• Routine pharmacovigilance	Labelling EU SmPC • 4.4. Special warnings and precaution for use. • Listed as adverse reaction (section 4.8) with the experience of other combinations of the same pharmacological class. Communicated in the PIL
Bone density decreased	• Routine pharmacovigilance	Labelling EU SmPC • 4.4. Special warnings and precaution for use. • Listed as adverse reaction (section 4.8) with the experience of other combinations of the same pharmacological class. Communicated in the PIL
Hypersensitivity	• Routine pharmacovigilance	Labelling EU SmPC • Contraindication in section 4.3 of the SmPC. Communicated in the PIL

IMPORTANT POTENTIAL RISKS		
Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
Off-Label Use	• Routine pharmacovigilance	No risk minimisation activity is considered necessary for the time being.

IMPORTANT MISSING INFORMATION		
Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
Use by children (Age < 18 years)	• Routine pharmacovigilance	Labelling EU SmPC • In Section 4.2 of the SmPC (Posology and method of administration), *Paediatric population* it is stated that "LABAZENIT is not recommended in children and adolescents". • Also mentioned in section 5.1. Communicated in the PIL
Use by elderly (Age > 65 years)	• Routine pharmacovigilance	Labelling EU SmPC: • In section 4.2 of the SmPC (Posology and method of administration), *Elderly patients (> 65 years)* it is stated that there is no need to adjust the dose in elderly patients. No risk minimisation activity is considered necessary for the time being.
COPD	• Routine Pharmacovigilance	No risk minimisation activity is considered necessary for the time being.
Other ethnical subgroup population than Caucasian	• Routine pharmacovigilance	Labelling EU SmPC • In Section 4.4 of the SmPC (Data from a large clinical trial (the Salmeterol Multi-Center Asthma Research Trial, SMART) suggested African-American patients were at increased risk of serious respiratory-related events or deaths when using salmeterol compared with placebo.
Long term use	• Routine pharmacovigilance	Labelling EU SmPC • In section 4.4 of the SmPC (Special warnings and precautions for use)), it is stated that the prolonged use of inhaled corticosteroids, particularly at high doses prescribed for prolonged periods may cause systemic side effects.

IMPORTANT MISSING INFORMATION		
Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
Use in patients with hepatic pathology	• Routine pharmacovigilance	Labelling EU SmPC: • In section 4.2 (Posology and methods of administration) of the SmPC it is stated that there are no data available for use of LABAZENIT in patients with hepatic disease. As budesonide and salmeterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis. Communicated in the PIL that patients with liver problems should take special care with LABAZENIT and are advised to tell their doctors before starting treatment with LABAZENIT.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The absence of a pharmacokinetic interaction between budesonide and salmeterol was confirmed by results from study BUSAL-SD101.

Comparable budesonide exposure following inhalation of Labazenit 300/25 µg and Pulmicort Turbohaler 2x200 µg was shown in studies BUSAL-SS032 and BUSAL SS033 in healthy volunteers. The lung deposition of budesonide in asthma patients was demonstrated to be ~20% lower for Labazenit 150/25 µg than for Symbicort Turbohaler 160/4.5 µg in study SD111 but the FPD of the batches used in the PK study differed significantly. After correction for FPD, the exposure to budesonide was comparable for Labazenit and Symbicort/Turbohaler..However this is not acceptable as the correction based on FPD was not pre-specified in the study protocol and adjustment/correction by FPD of the PK parameters cannot be accepted unless a clear in vitro/in vivo correlation has been established.

PK data and *in vitro* data support the dose proportionality with respect to budesonide between Labazenit 300/25 and Labazenit 150/25. The pharmacokinetic profile of salmeterol was the same for Labazenit 150/25 µg and 300/25 µg in study BUSAL-DP102.

Based on the results in study BUSAL-SD121 in healthy volunteers, systemic bioavailability of salmeterol was higher following inhalation of Labazenit 150/25 µg compared to Serevent Diskus 50 µg.

Pharmacodynamic

In Study BUSAL II-3-1 no significant difference was observed in the mean change in FEV1max between Labazenit 150/25 µg and Serevent 25 µg. Labazenit 150/25 had a 2.72 ± 0.79 L (mean ±SD) abd Serevent 2.69 ± 0.81 L, resulting in that the 95 % CI (-0.0339: 0.1025) was within the range of equivalence (-0.15: 0.15).

In Study BUSAL II-10-1 several strengths of Labazenit, i.e. 150/6.25 µg, 150/6.25 µg, 150/12.5 µg and 150/25 µg respectively, were compared with the comparators Salmeterol Diskus 50 µg, Serevent Evohaler 25 µg and Serevent Evohaler 50 µg. The mean increase in FEV1max was comparable between Labazenit 150/25 µg (mean ± sd) (2.68 ± 0.86 L) and Serevent Diskus 50 µg (2.66 ± 0.70 L). A dose response regarding the duration of the bronchodilatory AUC FEV1 8-12 h effect was observed for Labazenit 150/6.25 µg (LS mean ± SE 8,50 ± 2,49 L/s*h) and 150/25 µg (8,92 ± 0,93 L/s*h) (p=0.01). This effect is supported by a dose response of glucose and potassium after 60 minutes post dose.

Cortisol

In study BUSAL II-10-2 both strengths of Labazenit were compared to Pulmicort Turbohaler + Serevent Diskus and Placebo. The decrease in plasma cortisol was highest in Labazenit 300/25 µg, but the 95% CI for the difference was within the prespecified margin of ± 20%. The chosen limits were justified by literature. Equivalence with respect to cortisol influence is established.

Clinical studies

Step up indication

In study BUSAL III-02-1, three study arms were included: Labazenit 150/25 µg bid, Labazenit 300/25 µg bid and Pulmicort 400 µg bid. The study demonstrated a significantly higher increase of the primary efficacy parameter morning PEF of both doses of Labazenit over Pulmicort at week 12. This was supported by FEV1 % predicted (Labazenit 150/25 µg 12,51 ±13,33%, Labazenit 300/25 12,49 ±12,10 µg %, Pulmicort 400 µg 8,45±13,26%) and improvement in asthma symptom scores.

Substitution indication

Besides comparability of bronchodilation by salmeterol (pharmacodynamics) and inflammatory control/asthma control by budesonide (step-up indication) clinical studies comparing Labazenit with other fixed dose combinations were also performed (BUSAL III-05-01 and Study BUSAL III-08-01).

In order to support the substitution indication the Applicant provided two studies comparing Labazenit 150/25 µg with Symbicort 200/12 µg (BUSAL III-08-1) and the high dose of Labazenit 300/25 µg with Seretide 500/50 µg (BUSAL III-05-1). Both studies demonstrated no difference in morning PEF, FEV1 and symptomatic asthma control between treatments supporting comparability of other fixed combination with Labazenit.

Persistence of efficacy

In study BUSAL III-02-1 persistence of efficacy was demonstrated for Labazenit 300/25 µg and Labazenit 150/25 µg, which was confirmed by the results from study BUSAL III-06-01 for Labazenit 300/25 µg. The improvements in pulmonary functions and in asthma symptoms that were measured during study BUSAL III-05-1 were sustained throughout this 6-month extension study BUSAL III-06-1.

Uncertainty in the knowledge about the beneficial effects

Pharmacokinetics

Comparable exposure of budesonide for the highest Labazenit strength (300/25 µg) and the comparator product Pulmicort Turbohaler 2x200 µg was indicated by results from studies SMB-BUSAL-SS033 and SMB-BUSAL-SD032 following single and multiple dose inhalation. However, the variability was high and the 90% CI fell outside the 80-125% range. For the lowest strength, budesonide lung deposition was 15-23% lower following Labazenit 150/25 µg as compared to Symbicort 160/4.5 µg in study BUSAL-SD111.

In vitro comparison of several batches demonstrated a similar mean FPD for Labazenit as for Pulmicort. FDP fraction correlates linearly with whole-lung deposition. When correcting the PK parameters by FPD of the Labazenit and Symbicort batches used, the lung deposition of Labazenit 150/25 µg and Symbicort Turbuhaler 160/4.5 µg was comparable. However this is not acceptable as the correction based on FPD was not pre-specified in the study protocol and adjustment/correction by FPD of the PK parameters cannot be accepted unless a clear in vitro/in vivo correlation has been established. The test and reference products batches should be as similar as possible in all their in vitro parameters to avoid the need for correction by FPD. Combining all 3 PK studies together, a comparable inflammation control by budesonide in Labazenit as with the reference product can be expected but has not been demonstrated.

For salmeterol bioavailability between Labazenit 150/25 µg and Serevent Diskus 50 µg was only compared in one study with adequate salmeterol bioanalysis. In this study comparable bioavailability could not be demonstrated. Dose proportionality of budesonide was demonstrated *in vitro* for FPD between both dosage strengths but the size range of particles <2 µm was slightly higher for Labazenit 300/25 compared to Labazenit 150/25. PK data showed dose proportionality with respect to budesonide between Labazenit 300/25 and Labazenit 150/25 when correction for FPD was applied. However this is not acceptable as the correction based on FPD was not pre-specified in the study protocol and adjustment/correction by FPD of the PK parameters cannot be accepted unless a clear in vitro/in vivo correlation has been established. . The plasma profile of salmeterol was the same for Labazenit 150/25 µg and 300/25 µg in study DP102.

Pharmacodynamics

Substitution indication

In study BUSAL II-03-1 only one dose of Labazenit and Serevent were tested. Therefore, no conclusions regarding comparability can be drawn as the design was not sensitive to conclusively assess comparability. In Study BUSAL II-10-1 the mean increase in FEV1max was comparable between Labazenit 150/25 and Serevent Diskus 50, but the 95% CI (-0.16: 0.12 L) was just outside the predefined margin of (-0.15: 0.15 L). With a wider equivalence limit of 0.2 L, the 98.33 % CI would have been within acceptance. The CHMP was able to conclude on the non-inferiority of the salmeterol component based on the totality of evidence available despite the CI found. Therefore, comparability of broncholidation effect between salmeterol in Labazenit and salmeterol in Serevent Diskus is considered to be established. Furthermore, in this study a dose response between Labazenit 150/25 µg and Serevent Diskus was not observed in the primary efficacy variable mean change from FEV1 max. However, a post hoc analysis demonstrated a dose response in the AUC FEV1 8-12 h for Labazenit that was further substantiated with literature. No predefined margins for equivalence for the 95% CI were set. No dose response was observed for the comparator, probably because the higher doses of Serevent were used (Labazenit 6.25-25 µg vs. Serevent 25-50 µg). The dose response was confirmed in the extra pulmonary side effects, but no margins for equivalence for the 95% confidence intervals were defined.

Clinical

Step-up indication

In studies BUSAL III-02-01, the morning PEF was used as primary parameter A clinical significant improvement in mean change in FEV1 at week 12 was achieved for all treatments: Labazenit 150/25 mcg (mean ± SD) 0.40 ± 0.44 L, Labazenit 300/25 mcg 0.39 ± 0.38 L, Pulmicort 400 mcg 0.28 ±0.44 L but with no statistical difference between treatments. A statistically significant effect in FEV1 % predicted was observed. The FEV1 % predicted is a more precise measurement as this is corrected for age, gender and height. The difference between the two doses of Labazenit was statistically significant with Pulmicort ($p \leq 0.03$, both doses)), but the numerical difference was not provided. The estimated difference was less than the clinically relevant difference (5% -8%). With FEV1 a clinical relevant difference is seen, but which was not statistically significant.

The spirometric data (FEV1, FEV % predicted, FVC) were reanalysed following a GCP inspection. The above data are based on the highest of three producible values.

The study design used was not sensitive to conlusively assess comparability of the budesonide anti-inflammatory control in Labazenit and in Pulmicort. This was the result of the absence of a dose response between the two strengths of Labazenit. i.e. the difference in FEV1 between Labazenit 150/25 and Labazenit 300/25 mcg was 0.01 L (p-value = 1.000).

Furthermore, FEV1 and PEF were measured 12 h after inhalation, when salmeterol provides still a bronchodilatory effect. Therefore, a combined effect of budesonide and salmeterol can not be excluded. Under these conditions, a sound comparison between the budesonide components of Labazenit and Pulmicort is not possible.

Substitution indication

In the supportive studies BUSAL III-05-1 and BUSAL III-08-1 the repsonses of the lung function parameters and the clinical parameters were comparable to the responses in the pivotal study BUSAL III-02-1. However, as only one dose of both Labazenit and of the comparator was tested the study design was not sensitive to conclusively assess comparability of te budesonide anti-inflammatory control. Also in these studies FEV1 and PEF were measured 12 h after inhalation.

Long term efficacy

In study BUSAL III-06-01 patients were recruited from study BUSAL III-05-01. An analysis of the characteristics of the included patients compared to the patients who were not, revealed similar demographics, lung function parameters and asthma control. Also the experience of a moderate or severe exacerbation in the preceding eight weeks did not lead to bias. Less treatment related adverse related events were observed in the patients participating in study BUSAL III-06-01, although the amount of adverse events was similar. No active comparator was included. Also no long term data of the lower dose of Labazenit 150/25 µg has been provided. The long term (1 year) efficacy data have been obtained from a limited number of patients (n=110). Long term use is included as important missing information in the proposed RMP.

Risks

Unfavourable effects

Budesonide and salmeterol are well known substances used in the treatment of asthma. A lower nominal dose is applied in Labazenit. Comparable efficacy and safety should be demonstrated for the new fixed combination compared with already existing products. The clinical studies were not sensitive to demonstrate that the anti-inflammatory control provided by the ICS compound of the fixed dose combination was comparable to current asthma treatment. The demonstration of equivalence regarding the anti-inflammatory control has to be derived from the PK studies. Dose proportionality between the two strengths is considered demonstrated. In the lung deposition study exposure to budesonide was ~20 % lower following inhalation of Labazenit compared to Symbicort, while in two other PK studies budesonide exposure was comparable for Labazenit and Pulmicort. Based on the lung deposition study only, a slightly lower anti-inflammatory control provided by budesonide in the Labazenit fixed combination comparable to current asthma treatment can not be excluded. Furthermore, comparable exposure of salmeterol between Labazenit and Serevent Diskus was only demonstrated if a wider margein set a 0.2L was used.As no clinically relevant differences in afety parameters was observed in this study, the CHMP was able to conclude on the non-inferiority of the salmeterol component based on the totality of evidence available despite the CI found.

Pharmacodynamic

In the pharmacodynamics studies the observed differences in extra pulmonary side effects , such as glucose and potassium were small, but a formal predefined 95% CI limits for demonstrating equivalence was not provided. However, the 95% CI and the potency ratio's were reassuring.

Clinical

During the observation period no new safety effects become apparent. Nasopharyngitis and viral infections were most commonly reported. In study BUSAL III-05-01 more exacerbations were observed with Labazenit (n=7; 2%) compared with Seretide (n=1; 0.9%). Exacerbations is included in the proposed SmPC and as important identified risk in the RMP.

Known adverse events related to exposure to salmeterol are tremor, hypokalaemia and hyperglycaemia. These AEs were more frequently (3 patients versus 1 patient) reported with Labazenit although the incidence was <1%. Hypokaliema and hyperglycaemia are included in the proposed SmPC and as important identified risk in the RMP.

All cardiac events (including ECG) as observed in the studies BUSAL II-10-1, BUSAL II-10-2, BUSAL III-08-1were in line expectations. QTc prolongation and adrenergic cardiac effects are included in the proposed SmPC and as important identified risk in the RMP.

The safety and efficacy data in elderly patients is limited (n=110). This has been reflected in the proposed SmPC and use in patients over 65 is included as important missing information in the RMP.

Uncertainty in the knowledge about the unfavourable effects

For measuring inflammation control by exacerbations, the phase III studies were relatively short (12 weeks). This study duration is usually considered to be too short to demonstrate differences in exacerbation rate. More exacerbations were observed with Labazenit (n=7; 2%) compared with Seretide (n=1; 0.9%) in study BUSAL III-05-1. However, the observed numbers are low and a imbalance may have occurred due to the short duration of the study.

More side effects related to the use of β_2-agonists were observed with the use of Labazenit compared with the salmeterol active comparator. However, more patients were exposed to Labazenit (Labazenit 300/25 µg 553 patients; Labazenit 150/25 µg 301 patients), than to the comparators (Pulmicort 400 µg 124 patients, Seretide 500/50 µg 117 patients and Symbicort 200/12 µg 114 patients), making the AEs more likely to occur. Also the incidence of these events between the doses of Labazenit differs, although they harbour the same amount of salmeterol. No head to head comparison with Seretide was performed and this makes it more difficult to assess a reliable comparison in AE incidence.

Benefit-risk balance

Importance of favourable and unfavourable effects

Labazenit contains a lower nominal dose to achieve comparable FDP with the comparator products.

Therefore, comparability regarding the bronchodilatory effects of salmeterol and the anti-inflammatory control by budesonide between Labazenit and the respective reference products needs to be demonstrated.

The comparability of the broncholidation effect of salmeterol in Labazenit and Serevent Diskus is established in the clinical studies. The 98.33% CI (-0.16: 0.12) was just outside the predefined margin of (-0.15: 0.15 L), but with a wider limit of 0.2 L, bioequivalence would be demonstrated. As no clinically relevant differences in safety parameters was observed in this study, the CHMP was able to conclude on the non-inferiority margin of the salmeterol component based on the totality of evidence available despite the CI found.

The comparability of the broncholidation effect of salmeterol is supported by study BUSAL II-03-1 and the small differences seen in the responses. A dose response was seen with FEV1AUC8-12 hours and confirmed with the extra pulmonary parameters potassium and glucose.

The small differences in the extra pulmonary parameters, i.e. potassium and glucose were small. For the safety of salmeterol this is considered to be assuring, since the 95% CI of the differences and potency ratio's were assuring

For the step-up indication, superiority of Labazenit versus budesonide alone is proven with PEF and FEV1% in the pivotal study. However, for both the substitution indication and the step-up indication comparability in inflammation control should also be established. As a dose response was not observed between the two different strengths of Labazenit the comparability of inflammation control is not established. Support for the two strengths was obtained from *in vitro* and PK data. Pharmacokinetics showed a 20% lower lung deposition of budesonide for Labazenit compared to Symbicort.

Benefit-risk balance

Step-up indication

Evidence for equivalence of anti-inflammatory effect (inhaled corticosteroids)

The clinical studies demonstrated soundly that the addition of a LABA to an ICS provided more clinical control of asthma and improved lung function than ICS alone, even with a lower amount of ICS (Labazenit 150/25 µg compared with Pulmicort 400 µg). However, due to the known flat dose response curve of ICS the pivotal study design was not sensitive to demonstate a dose response between the two strengths. Therefore, the study did no allow for a conclusion on comparability of budesonide anti-inflammatory effect between Labazenit and the budesonide active comparator (Pulmicort).

Further evidence for comparability could not be derived form exacerbations> In study BUSAL III-05-1 slightly more exacerbations were observed with Labazenit (n=7; 2%) than with Seretide (n=1; 0.9%). However, the numbers are small and the study duration was too short to be conclusive.

To support the comparability of anti-inflammatory control, bioavailability of budesonide was compared in three PK studies between Labazenit and Pulmicort/Symbicort. Formal bioequivalence with 90%CI between 80-125% could not be demonstrated considering the three PK studies individually. Of concern is the ~20 % lower lung deposition following inhalation of Labazenit compared to Symbicort. FPD fraction correlates linear with whole-lung deposition. Therefore, the FPD of the batches used in PK studies at time of the PK study should be taken into consideration when interpreting the PK data.

The uniformity of delivered dose release specifications are set between 75 to 125% for Labazenit, which is in accordance with the European pharmacopoeia (instead of the usual specifications seen with oral dosage forms usually between 95% to 105%), the variability in the results of the PK studies is in the same range as the product specifications.

Overall, Labazenit demonstrated superiority over Pulmicort even with a lower dose of budesonide. However, the data was not compelling to prove comparability for budesonide between Labazenit and Pulmicort. Based on the pharmacokinetic and clinical data, comparability for budesonide between Labazenit and Pulmicort was not demonstrated.

Substitution indication

Evidence for equivalence of bronchodilatory effect (salmeterol)

In the pharmacodynamic study to support the equivalence of salmeterol between Labazenit 150/25 µg and Serevent Diskus 50 µg, the 95% CI of the primary efficacy variable was just outside the predefined margin. However, with a wider limit of 0.2 L, equivalence would be demonstrated. The CHMP was able to conclude on the non-inferiority of the salmeterol component based on the totality of evidence available despite the CI found.

A dose response regarding the duration of bronchodilatory response with FEV1,AUC8-12 h was only observed between Labazenit 150/6.25 and 150/25 µg.

Pharmacokinetic data comparing salmeterol pharmacokinetics of Labazenit with Serevent Diskus indicated a 31% higher C_{max} and 17% higher AUC of salmeterol for Labazenit. This may have implications on the safety of salmeterol. In the pharmacodynamics studies the differences between the extra pulmonary side effects of Labazenit 150/25 µg and Serevent Diskus 50 µg were small and the 95% CI reassuring. In the clinical safety data obtained from the clinical studies, the data do not provide evidence of an increased incidence of AEs related to LABA use, but the incidence is low and long term-data are sparse.

Altogether, the pharmacodynamic study BUSAL 10-02-1 demonstrated similar bronchodilation for salmeterol between Labazenit and Serevent Diskus. The measurement of a higher systemic exposure in the PK study did not give rise to differences in the clinical safety.

As for the step-up indication, evidence of comparable anti-inflammatory effect of budesonide should be demonstrated.

Discussion on the benefit-risk balance

Step-up indication

The results of study BUSAL III-02-01 demonstrated that the addition ofa LABA to an ICS increased lung function and decreased asthma symptoms, even with a lower dose of ICS as compared to ICS given alone, supporting the step up indication. However, besides superiority, comparability of inflammation control as efficacy of budesonide still remains to be established. As there was no dose response between the two different doses of Labazenit, the study design was not sensitive enough to conclusively assess comparability.

To overcome the clinical conclusion that comparability was not demonstrated, PK studies could have been an alternative for showing comparability. With the three PK studies individually, formal bioequivalence with a 90%CI between 80-125% could not be demonstrated. However, the results together showed no indication for a relevant difference in lung deposition. The variability in the results was in the same range as the product specifications for the delivered dose and the FPD. Based on these data, a comparable inflammation control by budesonide in Labazenit as with the reference product can be expected but has not been demonstrated.

Furthermore, dose proportionality of budesonide could be established with pharmacokinetic data together with in vitro data.

Altogether, the pharmacokinetic and clinical data are showing results that comparability for budesonide between Labazenit and Pulmicort is likely but has not been demonstrated. Additionally, dose proportionality is demonstrated.

Substitution indication

Evidence of comparability of salmeterol broncholidation effect between Labazenit and Serevent Diskus is established based on the pharmacodynamic study. The CHMP was able to conclude on the non-inferiority of the salmeterol component based on the totality of evidence available despite the CI found L. A dose response for Labazenit was seen for the duration of the response as expressed with $FEV_1AUC_{8\text{-}12\ h}$The higher systemic exposure to salmeterol did not result in more severe extra pulmonary side effects. The differences between Labazenit 150/25 µg and Seretide Discus 50 µg were small, while the 95% CI and the potency ratio's were assuring. In the clinical safety data obtained from the clinical studies, the data do not provide evidence of an increased incidence of adverse events related LABA, but the incidence is low.

As for the step-up indication comparability of budesonide anti-inflammatory control in Labazenit and Pulmicort should be established.

The overall benefit/risk balance of Labazenit is at present negative for both proposed indication i.e. step-up and substitution indication, because comparability of the budesonide anti-inflammatory effect between Labazenit and the comparator has not been demonstrated in the pharmacokinetic and clinical studies.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Labazenit in the treatment of asthma in adults where use of a combination product (inhaled corticosteroid and long-acting β2-agonist) is appropriate (patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting β2-agonists or patients already adequately controlled on both inhaled corticosteroids and long-acting β2-agonists), the CHMP considers by consensus that the efficacy of the above mentioned medicinal product is not sufficiently demonstrated. Therefore the CHMP, in accordance with Article 12(1) of Regulation 726/2004, recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product.

The CHMP considers that:

- The comparability of anti-inflammatory control by budesonide has not been adequately demonstrated between Labazenit and the comparator in clinical studies. Study BUSAL III-02-1 is not considered sensitive to demonstrate comparable anti-inflammatory control of budesonide between Labazenit and the comparator as there is no difference in effect between the two Labazenit doses investigated in the study. The supportive studies BUSAL III-05-1 and BUSAL III-08-1 had the limitation that only one dose of both, Labazenit and the comparator, was tested hence employing a design not sensitive to conclusively assess comparability.
- The available pharmacokinetic data does not support comparable anti-inflammatory control by budesonide between Labazenit and the reference product as it showed a lower bioavailability of budesonide from Labazenit, indicating lower deposition of budesonide in the lungs. Only by correcting for Fine Particle Dose (FPD) was it possible to demonstrate comparable bioavailability, but this is not considered appropriate since the FPD correction was not pre-specified and such correction is not acceptable unless specific requirements are met (e.g. clear in vitro/in vivo correlation has to be established).

Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation for Labazenit.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, Pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns cannot be agreed at this stage.

Re-examination of the CHMP opinion of 21 Match 2013

Following the CHMP conclusion that Labazenit was not approvable for the following indication:

Labazenit is indicated in the regular treatment of asthma in adults where use of a combination medicinal product (inhaled corticosteroid and long-acting β_2-agonist) is appropriate:

- *Patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting β_2-agonists.*

  or

- *Patients already adequately controlled on both inhaled corticosteroids and long-acting β_2-agonists.*

the applicant submitted detailed grounds for the re-examination of the above mentioned grounds for refusal, on 28 April 2013.

Following a request from the Applicant at the time of the re-examination, the CHMP convened an ad-hoc expert group meeting inviting the experts, including patient representatives, to provide their views on the questions posed by the CHMP, taking into account the Applicant's responses to the grounds for refusal.

The Applicant presented their details grounds for re-examination in writing on 28 April 2013 and at an oral explanation on 24 June 2013.

Detailed grounds for re-examination submitted by the applicant

Summary of the Applicant's detailed grounds for re-examination

According to the CHMP, comparability of asthma control and anti-inflammatory control by budesonide has not been adequately demonstrated between Labazenit and the comparators in clinical trials. However, Labazenit is a novel FDC and according to the Applicant it is therefore not appropriate to consider this in terms of bioequivalence with comparator FDCs. The primary purpose of the Labazenit development programme was to demonstrate superiority and not comparability over the ICS alone in asthmatic patients, in line with the guideline on FDC (CHMP/EWP/240/95), the OIP guideline (new fixed-dose combination product with no approved fixed combination reference product) and GINA guidelines. The fact that the Labazenit dossier was primarily based on the superiority versus an ICS monotherapy has been consistent throughout the development programme and was clearly explained to CHMP at all times throughout the development of this new medicine.

The goal of the PK studies for a new FDC is to support the clinical data. This has been the case in the Labazenit dossier as PK data demonstrated that the delivery of the active ingredients in Labazenit compared with the reference mono-products resulted in a similar bioavailability. Without correction for FPD only one of four studies comparing the budesonide exposure showed results slightly inferior to the lower bound of the pre-defined accepted margins (0.8 point estimate in budesonide). The other studies did not highlight any inferior exposure to budesonide contained in the Labazenit product compared to budesonide containing reference products. Furthermore, since the variability of the reference product, in particular the Pulmicort Turbohaler has been extensively demonstrated (on 16 batches) as extremely variable from one puff to another, it seems very challenging to obtain bioequivalence with Labazenit each time. Importantly the lower variability and airflow dependency of the drug delivery and lung deposition resulting from the efficiency of administration of Labazenit via the Axahaler versus existing device. The development of this new FDC with a device offering a significant advantage over existing delivery devices is considered by the Applicant as a significant advantage of Labazenit Axahaler versus the marketed products.

The dose-response issue discussed during Scientific Advice (SA) and addressed according to CHMP/SAWP recommendations (EMA/CHMP/SAWP/14715/2010) came up as unaddressed throughout the assessment of the Labazenit dossier. The additional PK and in-vitro testing recommended by the SA were performed and clearly demonstrated the dose-response of budesonide. In the CHMP assessment report it is clearly noted that the recommendations from the SA were followed.

The particular benefit of Labazenit's formulation over similar existing products has not been sufficiently appreciated during the assessment. The lower resistance of the Axahaler device versus marketed devices has been mentioned as a clear advantage for patients with lower inhalation airflow rates by the CHMP during the evaluation, but this advantage does not appear in the assessment of the benefit/risk ratio, while, according to the Applicant, this advantage is of clinical relevance for moderate to severe asthma patients.

The Applicant addresses specifically the CHMP's initial grounds for refusal:

GROUND 1: The comparability of anti-inflammatory control by budesonide has not been adequately demonstrated between Labazenit and the comparator in clinical studies. Study BUSAL III-02-1 is not considered sensitive to demonstrate comparable anti-inflammatory control of budesonide between Labazenit and the comparator as there is no difference in effect between the two Labazenit doses investigated in the study. The supportive studies BUSAL III-05-1 and BUSAL III-08-1 had the limitation that only one dose of both, Labazenit and the comparator, was tested hence employing a design not sensitive to conclusively assess comparability.

Applicant's position

1. Introduction

All of the studies presented in the dossier have been performed in accordance with the available regulations at the time when the studies were carried out.

The pivotal study BUSAL-III-02-1, was designed in accordance with the "guideline on clinical development of an FDC" (CHMP/EWP/240/95) and the note for "guidance on the clinical investigation of medicinal products in the treatment of asthma" (CPMP/EWP/2922/01), and even with the OIP guideline (page 18/26) :"new fixed-dose combination product with no approved fixed combination reference product" in order to demonstrate the superiority of the FDC as compared to the active substance alone (budesonide in Pulmicort 400 µg bid).

The development strategy of the Applicant aimed to demonstrate this superiority in the pivotal study has been consistent throughout the development programme.

The main goals of the global clinical development plan were to establish clearly the efficacy and safety of Labazenit, in agreement with the recommendations of the guideline in force, by demonstrating the following:

Major efficacy objective: Demonstrate that both dosage strengths of Labazenit result in a higher efficacy than an ICS monotherapy (even at a higher dose) in the intended population of asthmatic patients.

This objective corresponds to the requirement of:

- the guideline on fixed-dose combination which stipulates that an adequate justification of the development of a FDC should implicate an improvement of the benefit/risk ratio, due to a level of efficacy above the one achievable by a single substance (in the present case, the ICS), with an acceptable safety profile.

- the OIP guideline which stipulates that for fixed-dose combination with no approved fixed combination reference product, the combination should be compared to an ICS alone at the same dose, or alternatively at a higher dose.

- the GINA guidelines which recommend the use of ICS/LABA combinations in asthmatic patients not adequately controlled with an ICS alone.

The clinical endpoints (PEF and FEV1 for lung function assessment, asthma symptom score and the need for rescue medication for the control of asthma), the timing of assessment (12 hours post dose for a twice daily inhaled product and assessment in the morning and evening to deal with diurnal variations) and the duration of the trial (12 weeks) were also in accordance with relevant guidances, bibliography and CHMP's recent opinion on a similar product for the treatment of asthma.

2. Demonstration of superiority

Study BUSAL III-02-1 was designed to demonstrate the superiority of Labazenit, a novel FDC, by comparing the higher dose (Labazenit 300/25 µg bid) to the comparator ICS (Pulmicort 400 µg bid) in chronic moderate asthmatic patients. Two doses of the FDC were studied, with a dose of ICS in the lower strength of the FDC (Labazenit 150/25 µg bid) corresponding to half the dose dispensed in the reference product (Pulmicort 400 µg bid).

It was demonstrated for the primary parameter PEF that both Labazenit 150/25µg and Labazenit 300/25 µg treatments were superior to Pulmicort 400 µg (budesonide) after 12 weeks of treatment ($p<0.001$ for both active vs reference comparisons). This was supported by the results for FEV1% predicted (Labazenit 150/25 µg vs. Pulmicort 400 µg: $p=0.029$; Labazenit 300/25 µg vs. Pulmicort 400 µg: $p=0.021$).

The superiority of both dosages of Labazenit over Pulmicort was not only demonstrated on lung function, but also on the parameters assessing asthma control (asthma symptom scores and use of rescue medication) as required by the guidance for assessing the treatment of asthma (CPMP/EWP/2922/01). These data on PEF are supported by the data for FEV1% predicted and symptomatic asthma control which provide further evidence that Labazenit will provide better asthma control than monotherapy with ICS.

No statistical difference was observed between the two dosages of Labazenit over the 6-months treatment period, on any parameter.

The superiority of the FDC over an ICS alone was furthermore confirmed on each efficacy endpoint (lung function tests and asthma control parameters) in the following situations:

- After the switch from 3 months of treatment with Pulmicort to both doses of Labazenit in study BUSAL-III-02-1;

- In study BUSAL III-05-1 where a significant improvement in all parameters was recorded after the run-in period under an ICS monotherapy (beclomethasone (Qvar 200 µg bid) alone);

- In study BUSAL III-08-1 where a significant improvement in all parameters was also noted after the run-in period under an ICS monotherapy (budesonide, Pulmicort 400 µg bid) alone.

3. Issues raised by the CHMP on the Labazenit clinical dossier

The questions raised by the CHMP following the review of the clinical efficacy data were:

- PEF and FEV1 values were measured after only 12 hours withdrawal of study treatment when the LABA might still have some effect;
- The study duration was considered too short (12 weeks) to detect any differences in exacerbation rates.
- The studies lack of assay sensitivity as only one dose of budesonide was used.

3.1. Measurements 12 hours post dose

With regards to the comment on 12-hour post dose measurements: PEF and FEV1 were indeed measured 12 hours post dose, as expected for a product to be inhaled twice daily in accordance to the study protocol and the requirements laid out in the SmPC: PEF and FEV1 parameters were measured before the intake of the next dose in order to record the improvements in those parameters after administration. The choice of this endpoint was made in line with the Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Asthma – (CPMP/EWP/2922/01). It is accepted as an appropriate endpoint to measure the effect of an ICS according to the CHMP OIP Guideline (CPMP/EWP/4151/00 Rev.1) and it is advocated as an essential endpoint in asthma studies by a joint expert committee of the American Thoracic Society and European Respiratory Society (ATS/ERS).

The use of the same surrogate endpoint pre-dose FEV1 is then justified to establish the efficacy of the FDC. Furthermore, the results observed on lung function tests (notably pre-bronchodilation FEV1) over this period of time are a strong independent predictor of risk for future exacerbations, according to CHMP during the assessment of a similar FDC, Flutiform).

3.2. Study duration

With regards to the study duration, a 12-week duration is considered as an adequate period according to literature data and in the opinion of CHMP raised in the Flutiform Assessment Report, namely that treatment effects upon asthma control variables are maximal within 3 months and sustained thereafter.

The results observed on lung function tests (notably pre-bronchodilation FEV1) over this period of time are a strong independent predictor of risk for future exacerbations. The effects observed during the 12-week comparative periods in the three clinical phase III studies are therefore considered supportive of the effect of the FDC in the treatment of asthma.

In addition, the duration of the trials is in line with the guidance on treatments for asthma and with the literature data. Lasserson et al, 2009 indeed reviewed trials longer than 3 months for the comparison between two FDCs, and concluded that the 12-week period is an adequate time to assess treatment.

In study BUSAL-III-02-1, the persistence of the efficacy up to 6 months was assessed in the two arms of patients taking Labazenit 150/25 µg bid and 300/25 µg bid. The primary and secondary efficacy parameters were similar after 3 and 6 months of treatment, confirming that 3 months treatment time is an adequate duration of study in asthma patients (for pulmonary function tests, asthma symptom score and use of rescue medications). In other words, 6 month duration studies do not provide additional results compared to 3-month trials and the Applicant considers the duration of the studies performed with Labazenit to be appropriate.

3.3. Lack of assay sensitivity

With regards to the lack of assay sensitivity, two doses of Labazenit were initially compared in the pivotal study for up to 6 months and no difference was recorded for either strength used. During the evaluation, the CHMP stated that “Superiority of both strengths of Labazenit over Pulmicort is established in the pivotal study BUSAL III-02-1, but comparable asthma control by comparability of budesonide is not established in the pivotal trial. A dose response between the two strengths of Labazenit was lacking. Therefore, the study did not show assay sensitivity”. The Applicant questions this statement. Lack of assay sensitivity is the inability to pick up differences in treatment effects at non-placebo dose levels. When the CHMP acknowledges that Labazenit was superior at both strengths to Pulmicort then sensitivity has been proven.

The lack of any clinical ICS dose response relationship is well described in the literature with all ICS, including budesonide. Large trials including up to 4-fold difference in ICS administered doses failed to show significant differences in the efficacy parameters measured. Therefore, the Applicant is of the opinion that the demonstration of a clinical dose response is impossible with Labazenit or indeed any other ICS, including budesonide. In the case of budesonide, it has been shown that 80% of the maximum effect is achieved at a dose range of 200-400 µg. Theoretically, clinically significant differences in the effectiveness could be observed in the range of 50 - 200 µg/day only when the effect would be not mask by adding a LABA. The Rapporteurs also pointed out in their D180 clinical JAR that: "it is agreed that budesonide and other ICS show a flat dose response at the doses recommended, a doubling dose of budesonide does not readily show an improved asthma control".

This issue was already discussed during a Scientific Advice meeting (EMEA/H/SA/1462/1/2009/SME/III) requested by the Applicant in 2009/2010. During this meeting it was advised that the assay sensitivity and dose response relationship between the different ICS doses be indirectly supported with pharmacokinetic and in-vitro studies.

Those recommendations were followed by the Applicant and results - endorsed by the CHMP – demonstrated that "dose proportionality was already established between Labazenit 300/25µg and Labazenit 150/25µg with combination of pharmacokinetic data and in vitro data. Support for the two strengths of Labazenit is based on dose proportional pharmacokinetic data, and the short term studies providing evidence that a comparable asthma control has been achieved."

The CHMP endorsed the claimed step-up indication based on a demonstrated superiority over the mono ICS component with an acceptable safety profile for Labazenit. The flat dose response curve for efficacy parameters when assessing ICS, such as FEV1 and PEF and clinical parameters like asthma exacerbations and asthma control is also acknowledged.

The ICS in Labazenit FDC was proposed at two different dosage strengths (Budesonide 150µg and 300µg) in order to allow prescribers flexibility in achieving and maintaining adequate control of asthma. Furthermore, the GINA recommendations state that when a patient is stabilized with a high ICS dose, the dose should be decreased to the minimum that maintains optimal asthma control (GINA).

4. Demonstration of anti-inflammatory control

The clinical studies were not deemed sensitive enough to demonstrate that the anti-inflammatory control provided by the ICS compound is sufficient to support either indication. The demonstration of equivalence regarding the anti-inflammatory control should have been supported by the PK and in vitro data.

Exposure to budesonide following inhalation of Labazenit was compared in four PK studies. The comparator was either Pulmicort or Symbicort which both contain budesonide as the active ICS.

Two studies (SMB-BUSAL-SS032 and SMB-BUSAL-SD033) showed point estimates for Cmax and AUC close to unity, but the individual studies did not formally demonstrate bioequivalence for both parameters of budesonide based on a 90% confidence interval of 80-125%. The third study (SMB-BUSAL-SS071) showed around 100% higher lung deposition for budesonide when comparing Labazenit with Pulmicort and the fourth study (SMBBUSAL-SD111) showed around 20% lower lung deposition for budesonide when comparing Labazenit 150/25 µg with Symbicort 160/4.5 µg.

The above results show that it is not appropriate to use bioequivalence for a new FDC which is delivered with a different device and using different doses of the comparator ICS (i.e. a capsule-based device versus a reservoir device and a low-resistance device versus a high-resistance device).

However, it important to stress that the relative lower bioavailability observed in the single dose study BUSAL-SD111 should be weighed up in perspective with the results of the non inferiority phase III study BUSAL III-08-1 comparing Labazenit 150/25 µg with Symbicort 200/12 µg over 12 weeks . Indeed, the results of the BUSAL III-08-1 study showed that Labazenit 150/25 µg is non inferior to Symbicort 200/12 µg, but also demonstrated that the improvement recorded in lung functions and asthma control is numerically higher with Labazenit. The lower bioavailability obtained with budesonide delivered via the Axahaler as Labazenit, whilst maintain similar clinical effectiveness to the comparator product shows the overall improved therapeutic window for Labazenit.

Additionally, more exacerbations were reported with Symbicort compared with Labazenit. The data are in favour of Labazenit compared with Symbicort.

The relevance of the relatively lower bioavailability of Labazenit versus Symbicort recorded in study BUSAL-SD111 after a single dose of each product should be weighed up in light of the clinical efficacy results of a twice daily intake of the same products over 12 weeks PK data represent a post-event contrary to the results obtained in the daily observations of the clinical effect in the phase III studies.

5. Dose-response issue

5.1. Clinical dose-response – Literature review

An exhaustive review of the literature on ICS-LABA FDCs has failed to demonstrate a significant dose-response effect for any marketed and investigated ICS, alone or in an FDC.

Therefore as recommended during the scientific advice the dose response relationship for budesonide exposure between the two proposed dosage strengths was studied in in-vitro and PK studies.

5.2. In-vitro dose response of budesonide between Labazenit 150/25 µg and 300/25 µg

In order to assess the dose-response of budesonide between the two proposed dosage strengths of Labazenit, in-vitro comparisons were performed according to the recent OIP guideline. 5 batches of Labazenit 150/25 µg were compared (4 clinical batches and an industrial batch) to 5 batches of Labazenit 300/25 µg (4 clinical batches and an industrial batch).

The results clearly demonstrate the dose proportionality of the particle size distribution profile of budesonide between Labazenit 300/25 µg and 150/25 µg since:

- The mean ratio of the FPD between both dosage strengths (corrected for the dose) is of 0.89 with a 90% CI of 0.84 - 0.93.
- The mean ratio for the non respirable fraction (> 5 µm) is of 1.11 with a 90% CI of 1.06 - 1.15.
- The mean ratio of size groups of 4-5 µm, 3-4 µm and 2-3 µm are between 0.90 and 1.05 with all 90% CI lying between 80 - 125%. The mean ratio for the size range inferior to 2 µm is of 0.78 with a 90% CI of 0.71 – 0. 85.

For supportive information, these tests also confirm, as expected, that the deposition of salmeterol on the different stages of the MSLI is equivalent for both product strengths.

3. Pharmacokinetic dose response assessment of budesonide between Labazenit 150/25 µg and 300/25 µg

Two PK studies (BUSAL-SD033 and BUSAL-DP102) specifically addressed the linearity of budesonide plasma levels between the two proposed dosage strengths of Labazenit. The first study performed in 2003, BUSAL SD033, was a single-dose cross-over bioequivalence study, Labazenit 300/25 µg was compared to budesonide-salmeterol 150/25 µg and to one single dose of Pulmicort Turbuhaler 2x200 µg budesonide. One of the objectives of this study was to assess the dose proportionality between the two different dosages of Labazenit (300/25 µg vs. 150/25 µg) in 24 healthy volunteers after a single dose administration.

The comparison between Labazenit 300/25 µg and Labazenit 150/25 µg demonstrated a comparable rate and extent of absorption when the comparison was performed with a dose correction, which means that the absorption of budesonide is almost dose proportional. The point estimates were 102.7; 80.3 and 99.4 for AUC∞, AUCt and Cmax for epimer A and of 91.7; 76.7 and 111.5 for epimer B.

An important reason for the high variability of the PK parameters in this study is the low budesonide plasma concentrations obtained compared to the relative high LOQ. Indeed, the PK profile of budesonide could not be fully characterised following inhalation of the lowest dose of Labazenit as Cmax < 10x LLOQ. Therefore, AUC values from study BUSAL SD033 with the low BUSAL strength (150/25µg) should be considered very cautiously.

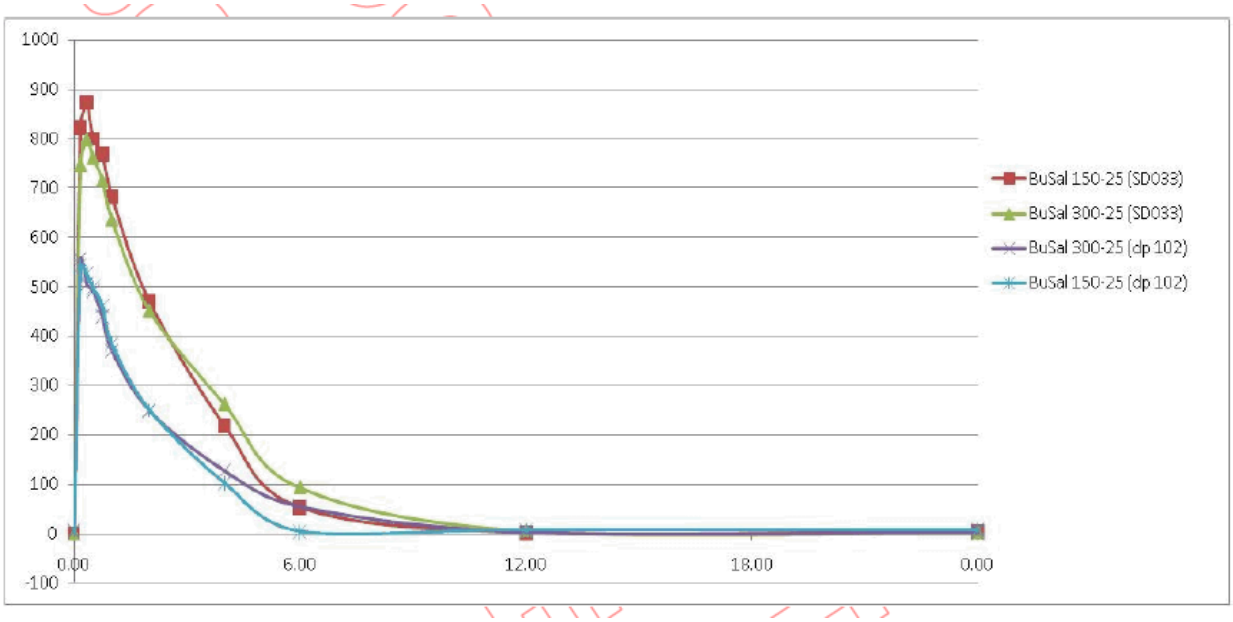
Therefore, following the recommendations of a scientific advice obtained from the CHMP (EMEA/H/SA/1462/1/2009/SME/III) where the Applicant was asked to characterize the dose-response relationship between budesonide-salmeterol 300/25 µg and budesonide-salmeterol 150/25 µg, another PK study was performed in order to assess the bioavailability of budesonide and salmeterol in 40 asthmatic patients after a single dose of either Labazenit 300 µg/25 µg or Labazenit 150 µg/25 µg delivered by the Axahaler.

The design of the study was a comparative single dose, two-treatment, two-period, two sequence, randomised, crossover study, with at least 3 days wash-out. The present study was performed using a blocker of the gastrointestinal absorption of the active substance (Active charcoal) to compare the amount of study drugs which reaches the plasma via the lung and with asthmatic patients to be in line with the CHMP OIP guideline (CPMP/EWP/4151/00 Rev.1).

Study BUSAL-DP102 demonstrates a clear dose response relationship in the PK of inhaled budesonide. When the inhaled dose increases from 150 to 300 µg, the budesonide plasma levels also increases. As previously mentioned, patients in the present study did take active charcoal, which means that the increase in bioavailability observed reflects an increase in the lung deposition of the drug. Nevertheless, budesonide exposure was slightly higher for Labazenit 300/25 µg than for 150/25 µg. Indeed, the 90% CI for all the PK parameters normalised by the dose are out of the acceptable margin of 80-125 and the point estimate are from 0.58 to 0.77 in favour to Labazenit 300/25µg. Additionally, as expected, the deposition profile of salmeterol was the same for Labazenit 150/25 µg and 300/25 µg in study DP102.

Given the wide specification limits for the FPD of OIPs and the differences observed between the FPD of the batches used in this study (143 µg for Labazenit 300/25 µg and 57.5 µg for Labazenit 150/25 µg; ratio=0.40), a correction of the raw PK data by the FPD was performed and the corrected results indicated a dose proportionality between the two test products (see the figure below below).

Figure 1. Mean concentration values normalized to the dose of 300 µg and corrected with the FPD



As already discussed, the dose proportionality was fully described and demonstrated in the in-vitro studies.

Therefore, it was concluded that after a single-dose inhalation (with active charcoal) by asthmatic patients of Labazenit 300/25 µg and Labazenit 150/25 µg, the bioavailability of budesonide increases in a linear manner, taking into account the in-vitro deposition data of the batches tested. These results are in good agreement with bibliographic data available for budesonide which usually shows a linear dose-response of budesonide through inhalation even if the variability is usually high.

6. Precedent CHMP opinion on Flutiform (fluticasone/formoterol FDC) Article 29 Referral procedure

The Applicant requests that the Labazenit dossier be assessed based on the same scientific reasoning as the ICS/LABA FDC Flutiform since similar objections, in particular with regards to the pharmacokinetic data, were raised in the case of Flutiform and were recently (28th June 2012) considered without any clinical relevance during CHMP arbitration.

A recent Assessment Report was published on the EMA website on June 28th, 2012 with regards to Flutiform (EMA/399193/2012, procedure EMEA/H/A-29-1326), another FDC containing fluticasone propionate as the ICS and formoterol fumarate as the LABA to be administered by the inhalation route and for which many similarities with the candidate product Labazenit have been noted.

On day 210 of the Decentralised Procedure which started in March 2010, the same issues on efficacy and bioequivalence were raised by the CHMP, namely that a lower bioavailability measured for the ICS between the candidate product and a reference could impair the asthma control in patients and additionally that the bronchodilating effects of the LABA component 12 hours post dose could mask those deficient corticosteroid effects. Those concerns triggered the referral procedure to the CMD(h) and eventually the CHMP arbitration at the end of 2011.

This assessment report is of particular interest as to CHMP views on similar objections raised again in the Labazenit dossier i.e. that based on pharmacokinetic data, comparable inflammation control by budesonide delivered by Labazenit with the reference product could be expected but is not proven.

GROUND 2: The available pharmacokinetic data does not support comparable anti-inflammatory control by budesonide between Labazenit and the reference product as it showed a lower bioavailability of budesonide from Labazenit, indicating lower deposition of budesonide in the lungs. Only by correcting for Fine Particle Dose (FPD) was it possible to demonstrate comparable bioavailability, but this is not considered appropriate since the FPD correction was not pre-specified and such correction is not acceptable unless specific requirements are met (e.g. clear in vitro/in vivo correlation has to be established).

Applicant's position

1. Background on the variability of OIPs

It should be highlighted that it is very challenging to demonstrate a comparable bioavailability between two OIPs because it is well known that the systemic exposure of OIPs is highly variable. This variability is dependent on several factors:

- Variability from different inhalers and between each inhalation from the same device. A high variability in the systemic exposure is expected when two inhaled products administered via two different devices are compared. Further evidence that the nature of the device is important for obtaining reproducible plasma levels comes from the results of the interaction study (BUSAL-SD101) where all treatments were administered with the same low resistance to airflow inhaler device (Axahaler).

Study BUSAL-SD101 is a single dose, 4-treatment, crossover study where four treatments administered by the AXAHALER device were compared: Labazenit 300/25 µg, an inhouse SMB formulation of budesonide 300 µg, an in-house SMB formulation of salmeterol 25 µg and the co-administration of the budesonide and salmeterol. The bioequivalence between each treatment has been demonstrated with a 90 % confidence interval for budesonide within the predetermined norms of 80-125 % for all relevant PK parameters. This study demonstrates that the bioequivalence between orally inhaled products might be demonstrated when the same reliable and robust inhaler (i.e. presenting a low inter and intrabatches variability device (e.g. the Axahaler) is used in all study arms. However, the fact is that the PK data remain a post-event measurement and are not directly representative of either the residence time or of the activity of the drug in the lungs.

Also the variability between each inhalation from the same device should be considered with this kind of product. Considerable variability was observed and fully described with the Turbuhaler, the device used in the medicine Pulmicort, which is strongly dependent on the inhalation airflow. This was confirmed by Ball et al., 2002 who compared the lung deposition (by gamma scintigraphy) and systemic resorption of budesonide from the Pulmicort Turbuhaler 200 µg at two peak inspiratory flow rates (optimal and half of optimal flow rates) versus the same measurements from a formulation of budesonide administered from the Axahaler device (called MIAT Monodose Inhaler at that time). In that study, the observed lung deposition dramatically decreases with the Turbuhaler when the airflow decreased, whereas it was non dependent on the airflow when using the Axahaler device used to administer Labazenit.

The lung deposition from the Turbohaler decreased from 25.1 ± 6.1% to 18.5 ± 6.5% of the nominal dose of budesonide when inhaled at 60 L/minute (optimal airflow) and 30 L/minute respectively. While with the Axahaler, the percentage of budesonide reaching the lungs was similar at the optimal flow (90 L/minute) and even with suboptimal flow (45 L/min) with respectively 21.4 ± 4.3% and 21.4 ± 7.5% of the nominal dose of budesonide quantified in the lungs by gamma scintigraphy.

The impact of the peak inspiratory flow rate (PIFR) on the deposition of budesonide from the Pulmicort Turbuhaler was also previously reported by Borgström et al., 1994, who observed that the lung deposition fell from 27% of the dose at a PIFR of 60 L/min to 14% at a PIFR of 30 L/min.

This variability of the Turbohaler device is clearly acknowledged by regulatory authorities as stated in the US labelling of Pulmicort.

Importantly the Labazenit Axahaler is less dependent on different airflows. In-vitro analysis performed at an optimal airflow showed similar FPD of budesonide between Labazenit Axahaler and the Pulmicort Turbohaler or the Symbicort Turbohaler while at lower airflows, Labazenit Axahaler demonstrated less variability of the FPD. The weak flow dependency of the aerodynamic properties of inhaled particles from the Labazenit Axahaler represents a real advantage for the patient, especially for patients with a significant decrease in their pulmonary function.

- Inter and intra subject variability

The variability of the OIPs can be increased in relation to the population included in a study. Indeed, the results of the systemic exposure of an OIP can be influenced by the age, and by health status of the subjects included in a study (e.g. healthy volunteers, mild, moderate or severe asthmatic patients....), by the inhalation airflow of a subject (see previous paragraph) or by the difference from one inhalation to another by the same subject (see previous paragraph).

In conclusion, even with an adequate monitoring and instruction for the adequate use of a device, there is an inter- and intra- patient variability in the handling of the device to obtain an optimal lung deposition, after a single-dose administration of orally inhaled drugs.

- Inter and intra-batch variability:

The high variability of OIP is well recognized by the European pharmacopoeia, in which the uniformity of delivered dose release specifications are set between 75 to 125%, instead of the usual specifications seen with oral dosage forms which are usually set between 95 to 105% (up to a maximum of 90% to 110%).

The inter and intra-batch variability of budesonide delivered with the Turbohaler (Pulmicort and Symbicort) is particularly high as already demonstrated in in-vitro studies by the Applicant where several of the batches tested were out of specification. Furthermore, variability is usually observed for the same batch budesonide when different devices are used and differences in drug delivery, even from the same device between different actuations, are also observed confirming the high variability of Pulmicort Turbohaler. This variability might be explained by the incomplete disaggregation and possible accumulation of the pelletized micronized particles in the spiral-shaped channels of the mouthpiece of the Turbohaler device, something that cannot happen with the Axahaler.

- Justification of the Fine Particle Dose (FPD) correction

It is very challenging to find a PK/PD correlation for locally acting OIPs. One reason for this is related to the fact that the site of action in the respiratory tract and the drug residence time in the lungs are not directly correlated with the absorption of the drug from the lungs. PK parameters are “post events” and therefore do not necessarily constitute a suitable surrogate marker of the efficacy and safety of the inhaled drug. Furthermore, each class of pharmacological agents considered has its specific targets located at different levels in the respiratory tract, which makes establishment of general and reliable PK/PD correlations very difficult for OIPs. However, for both ICS and LABA, systemic bioavailability should be as low as possible to minimise unwanted side effects.

Like other ICS, budesonide is believed to act by binding to glucocorticoid receptors distributed throughout the airways, with highest receptor concentrations found in the alveoli and bronchial smooth muscle. However, there is still controversy surrounding the site within the lungs to which inhaled corticosteroids should be delivered with opinion differing as to whether central airway deposition or peripheral airway deposition is more important.

As mentioned above, the PK results are also dependent on the variability between batches of the two products used in any study. This variability is easy to quantify using in-vitro tests and is defined by a key parameter for OIPs: the Fine Particle Dose or Fraction (FPD/FPF). It is defined in the European Pharmacopoeia as the proportion of aerosolised drug particles that are less than a 5 µm aerodynamic diameter and therefore deemed respirable and capable of reaching the lower part of the respiratory tract.

The particle size of inhaled drugs has been identified as one of the critical determinants of both the total lung dose and their regional pulmonary deposition pattern. According to the literature, studies have attempted to correlate the aerodynamic particle size distribution (APSD) data obtained by cascade impaction with lung deposition data measured using gamma scintigraphy. Whole-lung deposition correlated significantly with fine particle dose across a range of inhaler devices. FPF defined in terms of particles <3 µm showed closer numerical equivalence to the lung deposition, whereas FPF defined in terms of aerosol <5.8 µm somewhat overestimated the lung deposition. [The FPF of <3 µm and <5.8 µm were (arbitrarily) chosen because they represent stages in the Andersen cascade impactor routinely used for such in vitro studies].

As a benchmark product, Pulmicort Turbohaler has been widely studied and evaluated in numerous in vivo studies where lung deposition was quantified by gamma scintigraphy, a non invasive radionuclide imaging technique.

The pulmonary fraction of the Pulmicort Turbohaler is about 27% which is in agreement with the in vitro fine particle assessment in which the FPD (expressed in %) of budesonide from the Turbohaler device was about 31%.

In another study, Thorsson et al. assessed the pulmonary availability of budesonide through two PK methods (with or without blocking the gastrointestinal absorption by administration of charcoal). An intravenous infusion of budesonide was used as a reference. The pulmonary availability of budesonide from the Turbohaler device, calculated relative to metered-doses, was 32%.

This supports the results observed from in vivo scintigraphic deposition studies, as well as the in vitro FPD evaluations.

Furthermore, plasma levels of budesonide observed after inhalation mainly result from the absorption through the lung, since the contribution from deposition in the oropharynx and subsequent absorption from the gastrointestinal tract is negligible due to extensive first pass metabolism (85-95%). As a consequence, all the PK studies performed can be considered as an indirect measurement of the lung deposition of budesonide, despite all the uncertainties mentioned above (e.g. high variability of inhaled products, inter and intra-batches variability of the products, flow dependence of the reference product etc.).

As discussed above, literature data confirm that the FPD is an acceptable surrogate marker of the amounts of budesonide reaching the lungs as it allows the inter-batch variability to be taken into account. As a consequence, the correction by FPD of the PK values provides for more precise and reliable data.

Dose proportionality of Labazenit 300/25 µg and Labazenit 150/25 µg was also evaluated in PK studies SD033 and DP102. In study SD033, the plasma concentration curves for Labazenit were similar when normalised to dose. In study DP-102, exposure to budesonide was relatively higher for Labazenit 300/25. However, the FPD fraction between the Labazenit batches was different 143 µg vs 115 µg. When corrected for FPD, the budesonide pharmacokinetics between Labazenit 300/25 and Labazenit 150/25 were dose proportional in studies SD033 and DP102. Furthermore, as expected in light of the equal amounts present in the two strengths, the deposition profile of salmeterol was the same for LABAZENIT 150/25 µg and 300/25 µg in study DP102.

In conclusion, PK studies performed with OIPs are very challenging because of numerous variable parameters which must be considered important when interpreting PK study results.

2. Discussion on the PK study results

In the Labazenit dossier, the submitted PK studies (Five single dose and two steady-state studies) are in agreement with the guidelines on FDCs CHMP/EWP/240/95, with the guidelines on the investigation of bioequivalence (CPMP/QWP/EWP/1401/98 Rev.1) and with the guidelines on OIPs (for the studies performed from 2010 onwards). However the Applicant would like to emphasize that in this dossier, the goal of the PK studies for a new FDC is not to demonstrate bioequivalence, but to support the clinical data and to demonstrate that the delivery of the active ingredients versus the reference mono-products results in a similar or at least non-lower bioavailability.

The budesonide exposure following inhalation of Labazenit and Pulmicort/Symbicort has been assessed and compared in 4 of the 7 studies performed from 2003 to 2011:

- 1 single dose study BUSAL-SD-033, Labazenit 300/25 compared with Pulmicort Turbohaler 2x200 µg

- 2 multiple-dose studies BUSAL-SS-032 using the highest strength 300/25 and study BUSAL-SS071 using the lowest strength 150/25 versus Pulmicort 2*200µg and Pulmicort 200µg respectively.

These three studies were conducted in healthy volunteers without administration of charcoal (but this is without significant effect with budesonide since the gastro-intestinal absorption of the drug is very low and does not impact the overall PK parameters).

- 1 study BUSAL-SD-111, Labazenit 150/25 µg was compared with a less variable product, Symbicort 160/4.5 µg in mild persistent asthmatic patients using charcoal to compare only lung deposition of budesonide. This study was in line with the OIP guideline.

In study BUSAL-SD033 using the highest strength, not all PK parameters for budesonide fell within the 80-125% interval in the comparison of Labazenit 300/25 µg with Pulmicort Turbohaler 2x200 µg, but the point estimate of all parameters were close to unity (0.85 and 1.07 for AUC and 0.95 and 1.12 for Cmax):

The same trend was observed for the multiple dose study, BUSAL SS032. Indeed, point estimate of all parameters were close to unity at steady-state (0.94 and 1.02 for AUC and Cmax respectively) with a 90% CI obtained for the total budesonide was [0.79-1.12] for AUC and [0.90-1.15] for Cmax. To support the results of these two studies (BUSAL SD033 and BUSAL SS032), an appropriate the FPD was performed and the corrected results indicated a bioequivalence between the two test products. As already discussed, the bibliography data confirm that the FPD is an acceptable surrogate marker of the amounts of budesonide reaching the lungs since it takes into account the inter-batch variability. As a consequence, the correction by FPD of the PK values provide for more precise and reliable data. Furthermore, the PK profile of budesonide could not be fully characterised following inhalation as Cmax was < 10x LLOQ. Therefore, AUC values from this study should be considered very cautiously and the low plasma concentration observed can be explained by the high variability of the different batches.

The Applicant also states that the 20% of systemic exposure difference observed in this PK study does not have any relevant clinical consequence, particularly regarding the control of asthma. Indeed, it should be kept in mind that budesonide like all ICS have very flat efficacy dose response curves and it is generally considered that doubling the dose of budesonide does not significantly improve asthma control, nor does it significantly provide further reductions in asthma exacerbations , whilst a four-fold increase in the dose of budesonide slightly improved asthma control, but results in significantly more adverse events.

The absence of any relevant clinical consequence of a lower bioavailability of budesonide delivered as Labazenit was confirmed by the results obtained in the 12-week phase III study comparing Labazenit 150/25 µg and Symbicort 160/4.5 µg.

Furthermore, in the fourth study comparing budesonide bioavailability, BUSAL SS071, the budesonide exposure was almost twice to three times as high following Labazenit 150/25µg compared to Pulmicort Turbohaler 200 µg. The point estimates were 1.97 and 2.46 for the Cmax for the two epimers of budesonide.

However, in this study, the PK profile of budesonide could not be fully characterised following inhalation of the lowest dose as Cmax was < 10x LLOQ. Therefore, AUC values from study BUSAL SS071 should be considered very cautiously. Based on this statement, the following discussion regarding the results from this study will be based only on the Cmax data.

The results obtained in the BUSAL SS071 study reflect the high variability observed with OIP from one study to another. Indeed, in some studies the inter-subject variability of PK parameters is higher for Labazenit and in other studies for Pulmicort. An important reason for the high variability in PK parameters in study BUSAL-SS071 is the low budesonide plasma concentrations obtained compared to the relative high LOQ.

Based on the results from these four studies, the applicant maintains that Labazenit presents a comparable budesonide exposure to the reference products (Pulmicort or Symbicort).

Additionally to support the comparability of budesonide systemic exposure between Labazenit and the reference products (Pulmicort and Symbicort), the data from the four studies, SMB-BUSAL SD033, SMB-BUSAL SS032, SMB-BUSAL SS071 and SMBBUSAL SD111 were pooled and an ANOVA analysis was performed. The Applicant is well aware that such a pooling of between different PK studies is not usually recommended, but given the previously explained problems of variability of OIP, this pooling of the full PK data set in the present case allows for an overall idea of the bioavailability of budesonide delivered as Labazenit compared with the reference products (n=125).

Pooled data showed a slightly higher exposure to budesonide delivered from Labazenit than from the reference products. Indeed, not all the PK parameters fell within the 80-125 acceptable margins, but the point estimate are close to unity (1.12 for AUC and 1.18 for Cmax). The data confirm that the budesonide exposure is comparable and at least non-inferior for Labazenit versus reference products.

3. Conclusion

Considering all 4 PK studies together (SMB-BUSAL SD033, SMB-BUSAL SS032, SMBBUSAL SS071 and SMB-BUSAL SD111) and considering the known high variability of OIP, the Applicant maintains that Labazenit delivers a comparable and at least a non inferior budesonide exposure as the budesonide reference products (Pulmicort and Symbicort).

Also, considering that in the Labazenit dossier, the goal of the PK studies was not to demonstrate the bioequivalence with the reference products containing budesonide, but to support the clinical data and to demonstrate that the delivery of the active ingredients versus the reference mono-products results in a similar and at least non-inferior bioavailability, the Applicant maintains that the PK data actually support the view that the Labazenit product will deliver sufficient budesonide to the airways and safely to control inflammation and symptoms in a comparable way as budesonide delivered by the reference FDC.

4. Particular benefit of Labazenit's formulation over similar existing products

The applicant's position is that the pharmaceutical development program of Labazenit has demonstrated that the administration of an improved formulation (a patented mixture of budesonide and salmeterol blended with anhydrous lactose (main carrier) and lactose monohydrate (carrier of small particles)) through an optimal delivery system (a low resistance to airflow capsule based device – the Axahaler) results in:

- Improved compliance (ease of use and the possibility to check for the full delivery of the dose).
- Lower nominal and delivered doses of budesonide than those achieved from the marketed mono and combo therapies (Pulmicort and Symbicort Turbohaler) leading to a similar lung deposition profile at the optimal flow of each device.
- Lower airflow dependency of budesonide from Labazenit than from the Turbohaler device, resulting in a higher FPD from Labazenit versus the marketed products at lower inhalation airflows (and therefore possibly a better control of asthma in those patients).
- Lower variability in the delivery of dose of budesonide from Labazenit than from the Turbohaler device.
- Lower nominal and delivered doses of salmeterol than those achieved from the marketed monotherapy leading to a similar lung deposition profile at all tested airflows.

In addition the Applicant brought forward observations regarding the assessment process and the evolution of major objections throughout the procedure.

Additional expert consultation – Report from the ad-hoc expert group meeting held on 11 June 2013

Following a request from the Applicant at the time of the re-examination, the CHMP convened an ad-hoc expert group meeting inviting the experts, including patient representatives, to provide their views on the questions posed by the CHMP, taking into account the Applicant's response to the grounds for refusal.

1. Does the SAG consider the comparability of anti-inflammatory control by budesonide adequately demonstrated between Labazenit and the reference product solely on basis of the PK studies, considering also the scientific arguments in favor and against dose normalisation for Fine particle Dose (FPD)?

There was consensus amongst the experts that the Applicant did not demonstrate comparability of anti-inflammatory control by budesonide between Labazenit and the reference product on the basis of the PK studies results. In the PK study BUSAL-SD-111 a lower lung deposition and therefore a lower exposure of budesonide with Labazenit compared with the active comparator, Symbicort, was observed. Bioequivalence of the budesonide compound between Labazenit and the active comparator could only be demonstrated by the Applicant after correction by FPD. There was consensus amongst the experts that the FPD correction performed by the Applicant is not acceptable. Apart that it was not pre-specified in the study protocol, the FPD correction is not scientifically proven as being the only factor to take into account. Other factors than the particles' size should be taken into account such as the anatomy of the airway and the airflow. Airflow parameters (time and profile) should have been prospectively controlled in the PK studies as well as the particles distribution. The bioequivalence of budesonide in Labazenit therefore remains to be proven.

2. Does the SAG considers the comparability of anti-inflammatory control by budesonide adequately demonstrated between Labazenit and the comparator in clinical studies taking into consideration the PK data supportively?

The experts were in agreement that superiority of Labazenit over the budesonide comparator has been demonstrated by the Applicant in the clinical studies in terms of mean change from baseline to week 12 in morning PEF. However, the absence of a dose response between the two strengths of Labazenit in study BUSAL- III-02-01 is of concern. One of the reasons for such results could be that the study was not powered sufficiently to observe a dose-response between the two Labazenit strengths or that the endpoints selected were not sensitive enough to show a difference. For instance, the results of study BUSAL-III-02-01 on the morning PEF values were conflicting since the results with the 150/25 dose were better than with the 300/25 dose throughout the study.

Therefore the experts all agreed that comparability of anti-inflammatory control by budesonide has not been adequately demonstrated between Labazenit and the comparator. The clinical studies' results cannot compensate for the lack of bioequivalence showed in the PK studies' results.

An expert highlighted that both budesonide and salmeterol are well known compounds with recognized efficacy and well characterized safety profile. In principle a comparable anti-inflammatory control as the budesonide comparator would have been expected with Labazenit if both the dose and the lung deposition could be shown to be comparable with the active comparator treatment.

The patients' representatives stressed that the uncertainty around the dose of Labazenit to be used, taking into account the data presented by the Applicant, was of concern. From a patient's perspective the treatment goal of asthma should be to take the lowest possible dose of medication to obtain the maximal effect. The other patients' representative added that combined medicines is a good development principle as taking two different medications using the same inhaler is more convenient for patients. However the biggest concern remains the safety issue, especially the uncertainty of the doses used to control the disease process.

Additional information provided by the Applicant

During the Oral Explanation on 24 June 2013, the Applicant proposed to perform a post-authorisation study to confirm that no loss of inflammation control occurs with Labazenit. This study would compare the rate of asthma exacerbations or time to first asthma exacerbation with both dosage strengths of Labazenit versus budesonide alone

Overall conclusion of the CHMP on the grounds for re-examination presented by the Applicant during the Oral Explanation on 24 June 2013

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the Applicant and considered the views of the advisory expert group meeting held on 11 June 2013.

CHMP position on ground 1

Labazenit is a new fixed-dose combination (FDC) of the ICS budenoside and the LABA salmeterol for the treatment of asthma in adult patients in a step-up and a substitution indication. The proposed posology for Labazenit is one inhalation (120 micrograms/20 micrograms or 240 micrograms /20 micrograms) twice daily.

The present application was submitted according to Article 10b) of Directive 2001/83/EC as amended (fixed combination application). According to the CHMP Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev. 1) for any individual fixed combination it is necessary to assess the potential advantages in the clinical situation against possible disadvantages, in order to determine whether the product meets the requirements of the standards and protocols with respect to efficacy and safety. Potential advantages of fixed combinations include:

- an improvement of the benefit/risk due to addition or potentiation of therapeutic activities of their substances, which results in e.g. a level of efficacy above the one achievable by a single substance with an acceptable safety profile. This advantage can be referred to the applied "step-up indication".
- a simplification of therapy by decreasing the number of individual dose units to be taken by the patient, which simplifies therapy and may improve patient compliance. This advantage can be referred to the "substitution indication".

To fulfil the requirements according to the Guideline on Clinical Development of Fixed Combination Medicinal Products, the Applicant submitted four phase III studies:

- Study BUSAL III-02-1, the pivotal study, aimed to demonstrate that both dosage strengths of Labazenit result in a higher efficacy than an ICS mono therapy (even at a higher dose) (step-up indication).
- Studies BUSAL-III-08-1 and BUSAL-III-05-1 compared Labazenit with marketed ICS/LABA combinations.
- 1 year safety follow up study, study BUSAL III-06-1 which was performed to assess the safety of one year treatment with Labazenit 300/25 µg.

In addition, the Applicant submitted 7 PK studies:

- to evaluate if an interaction occurs between budesonide and salmeterol in the budesonide/salmeterol fixed dose combination.
- to evaluate the dose proportionality of budesonide between the dosage strengths of Budesonide/salmeterol (containing respectively 150 and 300 µg of budesonide).
- to support the lower nominal dose by comparative bioavailability between Pulmicort Turbuhaler and Serevent Diskus and Labazenit.

The intention of the study program was to evaluate clinical efficacy and safety of the new FDC within the clinical programme carried out in the intended population.

In August 2009 the CHMP Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for Use in the Treatment of Asthma in Children and Adolescents (CPMP/EWP/4151/00 Rev. 1) came into force describing a cascade through *in vitro* development to PK to PD and ultimately to longer-term clinical studies. The guideline further describes in chapter 6.2.3.3 the requirements for developing combination products. Taken into account the specific situation within the fixed dose ICS/LABA combination, the guideline requires showing therapeutic equivalence specifically for both LABA and the ICS. Taken into account the step-wise approach and in case that for either the LABA or for the ICS components (or for both) equivalence in terms of PK cannot be proven, the efficacy of the LABA component can be assessed following inhalation of a single dose through either measurement of bronchodilatation over at least 80% of the duration of action or bronchial challenge studies; the efficacy of the ICS component will be assessed through the study of multiple dose inhalations over time.

As part of the SA (EMA/CHMP/SAWP/14715/2010) concerning pre-clinical and clinical development, the Applicant was advised by the CHMP that only study BUSAL III-02-1 "comes near to fulfilling the required criteria for a pivotal efficacy study". The CHMP further acknowledged that there were no differences in efficacy between the two strengths of the new FDC. Regarding the two efficacy studies BUSAL-III-08-1 and BUSAL-III-05-1 the CHMP noted that "both lack assay sensitivity and therefore it is not certain whether the same conclusion might have been drawn had different strengths/dose regimens been compared". The CHMP concluded that "considerable additional clinical work is required".

As supported by the CHMP, the Applicant conducted two further studies:

- Study SMB-BUSAL-DP102 which was a single dose, double-blind, 2-treatment, 2-period, 2-sequence, randomised, crossover study in 40 mild persistent asthmatic patients, with at least 3 days of wash-out to evaluate dose proportionality of Labazenit 300/25 and 150/50. Active charcoal was administered orally in order to prevent any gastro-intestinal absorption of the active ingredients. However, PK parameters were not dose proportional for budesonide since exposure was slightly higher for Labazenit 300/25 µg than for 150/25 µg.

- Study BUSAL II-10-2 which was conducted to evaluate the systemic effect on the HPA-axis by the course of plasma cortisol and urine cortisol in Labazenit 300/25 µg BID and 150/25 µg BID compared to Pulmicort Turbuhaler 400 µg BID and Serevent Diskus 50 µg BID and compared to placebo in mild persistent asthmatic patients. The highest recommended dose was used. The primary endpoint considering, 24-hour AUC for plasma cortisol remained stable in the placebo group while it decreased in all active treatment groups. Labazenit 300/25 µg appeared to decrease serum cortisol (AUC0-12 h) more than Labazenit 150/25 µg and Pulmicort Turbohaler 400 µg+ Serevent Diskus 50 µg. However, when assessing equivalence between the different treatment groups cortisol suppression could be considered being equivalent because the 99.15% CI was included in the predefined [-20%;+20%] equivalence margin, which was supported by bibliographical data.

Two additional PK studies were submitted by the Applicant during the evaluation to further establish the comparability of budesonide and salmeterol versus reference products Symbicort Turbuhaler 160/4.5 µg (study SMB-BUSAL-SD111) and Serevent Diskus 50 µg (study BUSAL-SD121), respectively, for both claimed indications, by means of showing bioequivalence.

Study SMB-BUSAL-SD111 compared the lung deposition of budesonide after a single-dose of Labazenit 150/25 µg versus a single dose of Symbicort Turbuhaler 160/4,5 µg. The study was performed in 40 asthma patients and active charcoal was administered. The bioavailability of budesonide was higher following inhalation of Symbicort Turbuhaler compared to the bioavailability of budesonide following inhalation of Labazenit 150/25 µg [Budenoside Epimer A Ratio test/reference AUC 78 (90%CI 69-89), Cmax 80 (90%CI 70-91); Budenoside Epimer B Ratio test/reference AUC 84 (90%CI 73-96), Cmax 85 (90%CI 77-94)]. Equivalence for the ICS component of the Labazenit FDC to the comparator Symbicort in terms of PK has not been demonstrated in this study. The concern remains that the available PK data does not support comparable anti-inflammatory control by budesonide between Labazenit and the reference product as it showed a lower bioavailability of budesonide from Labazenit, indicating lower deposition of budesonide in the lungs. It is agreed, that clinical data can overrule differences obtained in PK studies. However, neither study BUSAL III-02-1 for the "step-up"-indication nor studies BUSAL-III-08-1 and BUSAL-III-05-1 for the "substitution"-indication are considered to be sufficient as discussed below.

The Applicant argues that the PK studies were not conducted to show bioequivalence and that the differences for the ICS component in terms of PK versus the comparator Symbicort were not relevant. The CHMP does not share the Applicant's view and would like to point out that PK data may be more discriminating than PD or clinical data. However, without having the PK data on hand and even when not following the OIP guidance, the clinical programme would be also insufficient since:

- Studies of at least 6 months duration would be needed according to the Note for Guidance on the Clinical Investigation of Medicinal Products in the treatment of Asthma (step-up-indication and substitution indication).
- Studies having assay sensitivity would be needed according to the Note for Guidance on Choice of Control Group in Clinical Trials (substitution indication).

In study BUSAL III-02-1 both Labazenit 150/25 µg and Labazenit 300/25 µg treatments were superior to Pulmicort after 12 weeks of treatment for the primary parameter PEF. The switch from Pulmicort after 12 weeks to Labazenit 150/25 µg or Labazenit 300/25 µg resulted in statistically significant increases in morning PEF values from week 12 to week 18 and 24 within both treatment groups. However, for PEF neither at week 12 nor at week 24 the difference between Labazenit 150/25 µg and Labazenit 300/25 µg was statistically significant. The mean morning PEF values with the lower dose were even better than with the higher dose at both time points. A clinically dose response difference between the two doses of Labazenit has therefore not been demonstrated. Failure to show a significant difference in clinical effect between both strengths demonstrates a failure to discriminate between the two dosages known to be different and renders the study inconclusive. More knowledge of the relationships among dose and clinical response would be needed for the safe and effective use of the combination in individual patients.

The Note for Guidance on the Clinical Investigation of Medicinal Products in the treatment of Asthma requires clinical trials of at least six month duration. But studies with duration of 8-12 weeks are considered only reliable by the OIP guideline for showing equivalence as a means to compare ICS/LABA combination products. The study duration of study BUSAL-III-02-1 was not questioned by the CHMP during the evaluation. However, since the Applicant claims that the intention of the study programme was not to show equivalence but rather to show superiority against the mono-substances the study duration would have to be a concern and studies of at least 6 months duration would be needed because of the chronic and variable characteristics of asthma (as discussed above).

The ICS in Labazenit FDC was proposed at two different dosage strengths (Budesonide 150 µg and 300 µg) by the Applicant in order to allow prescribers flexibility in achieving and maintaining adequate control of asthma. However, even doubling the dose of budesonide has no clear impact on the efficacy parameters which questions the suitability of the proposed ICS dose strengths. Further, once asthma control has been achieved guidelines recommend reduction of the dose of treatment necessary. For the comparator Symbicort (budesonide/formoterol) the following doses are approved: 80/4,5 µg, 160/4,5 µg, 320/9 µg. They allow titration of the medication much further down than Labazenit 300/25 µg and 150/25 µg, where the lowest dose corresponds with regard to the budesonide component to Pulmicort 200 µg. It remains unclear as to whether lower strengths of the fixed-dose combination budenoside/salmoterol might also be clinically effective.

The Applicant further argued that for no ICS-LABA combinations significant dose-response effect for all marketed and investigated combinations has been demonstrated. The dose-response curve has traditionally been considered "flat" for ICS. One of the reason explaining the lack of dose response ins study BUSAL-III-02-01 is that it was performed on the plateau of the dose response curve and not on the uprising part of the curve. However, dose-response depends also on the parameter being measured and the severity of the asthma. One published dose-response study for the budesonide-formoterol combination was located by the Applicant [Aubier M et al (2010)]. This was an open, randomised, parallel-group, 6-month multicentre study in patients with moderate-to-severe asthma who were symptomatic despite daily use of an ICS with or without LABA. A total of 8,424 patients were randomized to budesonide/formoterol 160/4.5 µg, one (1 x 2) or two (2 x 2) inhalations b.i.d. The primary outcome variable was time to first severe asthma exacerbation. In the total study population, the time to first severe asthma exacerbation was prolonged by 18% with 2 x 2 versus 1 x 2 (hazard ratio 0.82; p=0.03). Lung function (peak expiratory flow) was the only statistically significant predictor of a better response to 2 x 2. The mean daily ICS doses were 737 and 463 µg in the 2 x 2 and 1 x 2 groups, respectively. No clinically important differences between the 1 x 2 and 2 x 2 groups were seen in changes in ACQ-5 scores, day- and night-time symptoms or in lung function values.

In terms of *in vitro* dose response of budesonide between Labazenit 150/25 µg and 300/25 µg the conclusions of the CHMP cannot be reversed based upon no new data been presented. The CHMP review of the points presented by the Applicant does not change its initial conclusions.

PK parameters were nearly dose proportional for budesonide since in the lung deposition study SMB-BUSAL-DP102 budesonide exposure was slightly higher for Labazenit 300/25 µg than for 150/25 µg.

On the basis of the PK data, a dose-response can be expected according to the Applicant. However, dose-proportionality and dose-response are two different things. The question remains why study BUSAL III-02-1 failed to discriminate between two treatments known to be different in terms of PK data. The Applicant conducted as recommended during the SA a study, study BUSAL-II-10-2, to evaluate the systemic effects of the two strengths of the fixed-dose combination compared with placebo through measurement of 24-hour plasma cortisol. But even in this study Labazenit 300/25 µg and Labazenit 150/25 µg were equivalent (and not superior) in decreasing the AUC of 24-hour plasma cortisol.

The applicant has further conducted two studies comparing Labazenit with the marketed ICS/LABA combinations Seretide and Symbicort. Both studies investigated one strength only, study BUSAL III-05-1 the highest strength and BUSAL III-08-1 the lowest strength of Labezenit. ICS shows often a flat dose-response curve and demonstration of equivalence in anti-inflammatory efficacy requires the demonstration of a dose-response relationsship. Therefore, the OIP-guideline states that the study design should include two doses in order to show a significant statistical dose response relationsship. Since only one dose was evaluated in studies BUSAL III-05-1 and BUSAL III-08-1 assay sensitivity of these studies is lacking. Thus, it remains unclear, whether the studies are sensitive to show differences between Labazenit and the comparator products. Summarized, non-inferiority in both studies is not proven.

The Applicant requested that the Labazenit dossier should be assessed based on the same scientific reasonings as Flutiform Affilia 50/5, 125/5 and 250/10 micrograms pressurised inhalation, suspension, fixed-dose combination products containing the active drug substances fluticasone propionate and formoterol fumarate in three strengths. These applications have been submitted according to Directive 2001/83/EC, Article 10b through the Decentralised Procedure and were referred to the CHMP (EMEA/H/A-29/1326) since no agreement could be reached within the DC-procedure and within the CMD(h)-Referral. The clinical development programme was designed to compare the efficacy and safety of Flutiform with its individual components administered separately, and with its individual components administered together but inhaled from separate inhalers. Additional supportive studies compared the efficacy and safety of Flutiform with other combination therapies including Seretide. Although the applications may be in some way comparable, the different study designs and the different package of studies, preclude a direct comparison. Thus, the objections raised in the case of Flutiform cannot simply be extrapolated to this procedure.

The CHMP concludes that the comparability of anti-inflammatory control by budesonide has not been adequately demonstrated between Labazenit and the comparators in clinical studies. Therefore, Ground 1 of refusal remains unresolved.

CHMP position on ground 2

The Applicant disputed the validity of using PK data for demonstrating therapeutic equivalence with respect to efficacy. In this respect PK studies, provided that they have been designed and conducted adequately, have been accepted by the CHMP in the OIP guideline as surrogate for comparison of efficacy even though exposure is a “post-event” (step 2). Further, lack of PK equivalence can be overruled by PD and /or clinical studies with sufficient assay sensitivity (step 3).

SMB-BUSAL SD111 has been conducted to demonstrate the bioavailability of the fixed dose combination Labazenit 150/25 µg versus the reference product Symbicort Turbuhaler 160/4.5µg administered with active charcoal. Importantly, Symbicort Turbuhaler 160/4.5 µg has been chosen instead of Pulmicort Turbuhaler 200 µg because the in vitro testing has demonstrated a lower intra and inter-batch variability of the delivered dose and the Fine Particle Dose (FPD). The 90 % confidence interval for budesonide (epimer A and epimer B) was not in the predetermined norms of 80-125 % for the for the rate and extent of absorption since the bioavailability of Labazenit 150/25 µg was lower than the bioavailability of Symbicort Turbuhaler 160/4.5 µg. Only when corrected for the FPD value the bioavailability of budesonide from both products was similar.

FPD correction may only be considered acceptable if a clear IV/IVC for FDP has been established previously between the in vitro parameters and the pharmacokinetic parameters (systemic safety and lung deposition) and if the FPD correction has been pre-defined in the study protocol. However, with regard to study SMB-BUSAL SD111 the FPD correction is not acceptable since the adjustment was not pre-specified in the protocol and no in-vitro/in-vivo correlation has been provided for any of the products.

The difference in exposure are not relevant according to the Applicant because the difference was in the same order of magnitude as other sources of variance for a given orally inhaled compound.

Several inhaled drugs are available with a marked variety of devices from the same MAH. These products require different inhalation techniques and in practice a patient is advised to have all inhalation medication by the same inhalation device (either pMDI of DPI) depending on his/her ability to handle the device. So, it is well recognised that the use of different devices may result in different lung depositions and systemic exposure and are not necessarily interchangeable without dose adjustments.

The Applicant considers the intra-subject variability in inhalation of OIP is very high leading to different exposure on each occasion. Highly variable drug products (HVDP) are those whose intra-subject variability for a parameter is larger than 30%. If an Applicant suspects that a drug product can be considered as highly variable in its rate and/or extent of absorption, a replicate cross-over design study can be carried out. Further, those HVDP can be, if justified, assessed with a widened acceptance range for Cmax. The variability in pharmacokinetics of budesonide and salmeterol following oral inhalation is not considered to be an obstacle for demonstration of equivalence.

Variability in fine particle dose between batches is a recognized problem to demonstrate equivalence based on PK, but the Applicant can select the batches used for the comparison and may select test and reference products as similar as possible in all their in vitro parameters.

The Applicant presented newly pooled data from the PK studies SMB-BUSAL SD033, SMB-BUSAL SS032, SMB-BUSAL SS071 and SMB-BUSAL SD111. However, only study SMB-BUSAL SD111 used charcoal blockage methodology and measured pulmonary deposition. In contrast to that the other three PK studies measured systemic exposure and thus, pooling of data is not considered acceptable.

The Axahaler is a mono-dose inhaler having less airflow resistance than comparator devices such as Turbohaler and Diskus. It is agreed that less airflow resistance than the comparator devices may allow special categories of patients with relatively low pulmonary function (e.g. elderly people, patients with severe asthma) to inhale and get an optimal therapeutic dose into the lungs. Further the Applicant claims that the new device improve compliance due to the fact that the device is easy to use and has the possibility to check for the full delivery of the dose. However, this assumption has not been substantiated by clinical data. On the other hand, since after each usage a new capsule needs to be inserted treatment with the Axahaler may be not very convenient for the patient, especially when used from elderly people or severely ill patients.

The performance of the device (Axahaler) intended for drug administration to the lungs in comparison to the reference device has been taken into account sufficiently by the CHMP and considered adequate with regards to the therapeutic outcome of the finished drug product intended for marketing authorisation. The quality attributes of Labazenit cannot outweigh the fact that the clinical performance has not been sufficiently demonstrated. The current negative benefit/risk ratio cannot be modified by the device properties. Nonetheless the device properties are an integral part of the clinical performance of the finished drug product, which means the good performance properties of the device is appropriately covered in the CHMP AR.

To conclude PK data did not demonstrate comparable anti-inflammatory control by budesonide between Labazenit and the reference product as it showed a lower bioavailability of budesonide from Labazenit, indicating lower deposition of budesonide in the lungs. Therefore, Ground 2 of refusal remains unresolved.

Regarding the point raised by the Applicant about the assessment process it should be noted that the scientific view evolves during the procedure. Also to note that Rapporteurs' assessment reports are provided to the Applicant for information only; they reflect the position of the Rapporteurs at that time and are not binding on the CHMP.

Overall, based on the assessment of the detailed grounds for re-examination submitted by the Applicant, the CHMP concluded that the benefit/risk profile of Labazenit remains unfavourable.

Recommendations following re-examination

Based on the arguments of the Applicant and all the supporting data on quality, safety and efficacy for Labazenit proposed for:

Labazenit is indicated in the regular treatment of asthma in adults where use of a combination medicinal product (inhaled corticosteroid and long-acting β_2-agonist) is appropriate:

- *Patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting β_2-agonists.*

  or

- *Patients already adequately controlled on both inhaled corticosteroids and long-acting β_2-agonists.*

the CHMP re-examined its initial opinion and in its final opinion recommends the refusal of the granting of the marketing authorisation for Labazenit. The CHMP considers that:

Whereas

- The comparability of anti-inflammatory control by budesonide has not been adequately demonstrated between Labazenit and the comparator in clinical studies. Study BUSAL III-02-1 is considered not sensitive to demonstrate comparable anti-inflammatory control of budesonide between Labazenit and the comparator as there is no difference in effect between the two Labazenit doses investigated in the study. The supportive studies BUSAL III-05-1 and BUSAL III-08-1 had the limitation that only one dose of both, Labazenit and the comparator, was tested hence employing a design not sensitive to conclusively assess comparability.
- The available pharmacokinetic data does not support comparable anti-inflammatory control by budesonide between Labazenit and the reference product as it showed a lower bioavailability of budesonide from Labazenit, indicating lower deposition of budesonide in the lungs. Only by correcting for Fine Particle Dose (FPD) was it possible to demonstrate comparable bioavailability, but this is not considered appropriate since the FPD correction was not pre-specified and such correction is not acceptable unless specific requirements are met (e.g. clear in vitro/in vivo correlation has to be established).

The CHMP remains of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the efficacy of the above mentioned medicinal product is not properly or sufficiently demonstrated.

Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation for Labazenit.