CBG MEB

Public Assessment Report

Scientific discussion

Zephirus 120 µg/20 µg and 240 µg/20 µg, inhalation powder, hard capsule

(budesonide/salmeterol xinafoate)

NL/H/3241/001-002/DC

Date: 2 December 2015

This module reflects the scientific discussion for the approval of Zephirus 120 µg/20 µg and 240 µg/20 µg, inhalation powder, hard capsule. The procedure was finalised on 23 July 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

A list of literature references is given on page 31.

List of abbreviations

AE	Adverse Event
ALT	Alanine transaminase
AST	Aspartate Transaminase
ATS	American Thoracic Society
AUC	Area Under the Curve
BCF	Bioconcentration Factor
BID	Twice daily
BTS	British Thoracic Society
BUSAL	Budesonide-Salmeterol (Zephirus)
CI	Confidence Interval
C_{max}	Maximal concentration
CEP	Certificate of Suitability to the European Pharmacopoeia
CHMP	Committee for medicinal products for human use
CMR	Carcinogenic, Mutagenic and Reproductive
CMS	Concerned Member State
COPD	Chronic Obstructive Pulmonary Disease
CPMP	Committee for proprietary medicinal products
CRF	Case Report Form
DPI	Dry Powder Inhaler
EDQM	European Directorate for the Quality of Medicines
ECG	Electrocardiogram
EMA	European Medicine Agency
Epimer A	Budesonide 22S
Epimer B	Budesonide 22R
ERA	Environmental Risk Assessment
ERS	European Respiratory Society
EU	European Union
EWP	Efficacy Working Party
FDC	Fixed Dose Combination
FEV_1	Forced Expiratory Volume in 1 second
FPD	Fine Particle Dose
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GS	Stimulating Guanine-nucleotide–binding protein
H	Hour
HDPE	High density polyethylene
HPA	Hypothalamic Pituitary Adrenal
HPLC	High pressure liquid chromatography
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid Steroid
ITT	Intent-To-Treat
Kg	Kilogram
L	Litre
LABA	Long acting β2-agonist
LC	Liquid chromatography
LD50	Dose which is lethal for 50% of the population
LLOQ	Lower Limit of Quantification
M	Mean
MAH	Marketing Authorisation Holder
MDI	Metered Dose Inhaler
Min	Minute
mL	Millilitre
NOEC	No Observed Effect Concentration
OIP	Orally Inhaled Product
PBT	Persistent, Bioaccumulative and Toxic
PD	Pharmacodynamic

PEC	Predicted Environmental Concentration
PEF	Peak Expiratory Flow
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
Vd	Volume of distribution
vPvB	very Persistent and very Bioaccumulative

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Zephirus 120 µg/20 µg and 240 µg/20 µg, inhalation powder, hard capsule from Laboratoires SMB S.A.

The product is indicated in the regular treatment of asthma in adults where use of a 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.

A comprehensive description of the indications and posology is given in the SmPC.

Zephirus contains salmeterol and budesonide, which have different modes of action and show additive effects in terms of reduction of asthma symptoms. The specific properties of each of the two substances are discussed below.

Budesonide
Budesonide given by inhalation has a glucocorticosteroid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma with less adverse events than when corticosteroids are administered systemically. The exact mechanism responsible for this anti-inflammatory effect is unknown.

Salmeterol
Salmeterol is a selective long-acting (12 hours) β_2-adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor. Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting β_2-agonists.

This decentralised procedure concerns an application for a new fixed dose combination (FDC) in accordance with Article 10b of Directive 2001/83/EEC of an inhalation powder with two known active substances: salmeterol xinafoate and budesonide. The active substances budesonide and salmeterol xinafoate contained in the medicinal product are not qualified as a new active substance in itself, as it concerns a fixed combination of compounds already approved as free combination therapy.

The concerned member states (CMS) involved in this procedure were Belgium and Luxembourg.

Justification of Zephirus dosage strengths
The posology follows the posology of the individual components budesonide and salmeterol. The higher *in vitro* lung deposition (quantified by the fine particle dose on a multistage impactor) of budesonide and salmeterol from Zephirus administered with the AXAHALER device versus the lung deposition of the two dry powder inhaler (DPI) reference mono-products justifies this decreased nominal dose.
A specific formulation patented technology combined with an optimal DPI device, results in an optimal lung deposition for both drugs. Therefore, Zephirus 150/25 and 300/25 provide an equivalent lung dose as:

Zephirus 150/25	↔	PULMICORT TURBUHALER (budesonide 200 µg)
Zephirus 150/25	↔	SYMBICORT TURBUHALER (budesonide 200 µg)
Zephirus 300/25	↔	PULMICORT TURBUHALER (budesonide 400 µg)
Zephirus 150/25 or 300/25	↔	SEREVENT DISKUS (salmeterol 50 µg)

The proposed posology for Zephirus is one inhalation (120 micrograms/20 micrograms or 240 micrograms/20 micrograms) twice daily. In accordance with current guidance, the delivered dose is used in the label. However, in all study reports the nominal dose 150 micrograms/25 micrograms and 300 micrograms/25 micrograms for both strengths had been used and, therefore, in this report reference to the two doses is made based on the nominal dose i.e. 150 micrograms/25 micrograms and 300 micrograms/25 micrograms.

CHMP decision on Labazenit

Initially, Laboratoires SMB S.A. submitted on 28 September 2011 an application for marketing authorisation to the European Medicines Agency (EMA) for this budesonide/salmeterol FDC under the name "Labazenit", through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The Netherlands and Ireland were the rapporteur and co-rapporteur, respectively (EMEA/H/C/002201).

On 21 March 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation, as the benefits of the medicine had not been shown to outweigh its risks.

The applicant requested a re-examination of the opinion. After considering the grounds for this request, the CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorisation on 27 June 2013.

The CHMP's main concerns were:

- Study BUSAL III-02-1 was 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 did 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).

For further information on this decision, refer to the Public Assessment Report (ref. EMA/465765/2013) and 'Questions and answers - Refusal of the marketing authorisation for Labazenit (budesonide/salmeterol)' (ref. EMA/391542/2013), available on the EMA website.

With this decentralised procedure for Zephirus (NL/H/3241/001-002/DC) a new submission is started; this submission includes two new pharmacokinetic studies: BUSAL-SD131 and BUSAL-SD132, performed according the guideline for orally inhaled products (OIP).

Scientific advice

Scientific Advice was given by the CHMP on 21 January 2010 (EMA/CHMP/SAWP/14715/2010) with respect to the submission of the product called Labazenit (EMEA/H/C/002201). However, the results of the studies in the clinical package at that time did not allow for a positive opinion. No further scientific advice, central or national, was asked for the additional program.

Paediatric development

A waiver for paediatric trials was granted on 31 March 2010, for all subsets of the paediatric population in accordance with Article 11(1)(c) of Regulation (EC) No 1901/2006, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for the condition asthma for paediatric patients (EMEA-000623-PIP01-09).

CHMP guidelines

The Committee of Human Medicinal Products (CHMP) guidance of the European Medicines Agency (EMA) to be considered in the present submission encompassed:

- Note for Guidance on fixed medicinal products (CPMP/EWP/240/95)

- Note for Guidance on Investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1corr**)
- Note for Guidance on Clinical Investigation of Medicinal Products in the treatment of Asthma (CPMP/EWP/2922/01)
- Note for Guidance on 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).

In line with the Note for Guidance on fixed dose combination medicinal products (CPMP/EWP/240/95), the proposed clinical development was performed according to the requested indication. The proposed FDC was indicated as second line therapy, when monotherapy with inhaled corticosteroids and 'as needed' inhaled short acting β2-agonists had not demonstrated beneficial effects (patients not adequately controlled).

International Guidances
The following International therapeutic guidances were also followed to support the FDC development program:

- The Global Initiative for Asthma: GINA Report, Global Strategy for Asthma Management and Prevention, updated 2010.
- ERS guideline
- Management of Asthma BTS Guidelines British Thoracic Society (BTS) 2008. - updated June 2009.
- Canadian Thoracic Society: 2010 CTS Guideline - Asthma Management Continuum – Consensus Summary for children six years of age and over, and adults.
- American Thoracic Society (ATS) guidelines.
- US recommendations for asthma: National Asthma Education and Prevention Program-Expert Panel Report 3 – Guidelines for the Diagnosis and Management of Asthma – 2007).

The MAH followed CHMP guidance documents that were in force at the time of conductance of the clinical studies.

II. QUALITY ASPECTS

II.1 Introduction

Zephirus 120 µg/20 µg is a clear, colourless capsule of 15.9 mm containing a white powder, printed with "B120 S20" in black.
Each capsule contains 150 micrograms of budesonide and 25 micrograms of salmeterol (as xinafoate). Each delivered dose (i.e. the dose leaving the mouthpiece) contains 120 micrograms of budesonide and 20 micrograms of salmeterol (as xinafoate).

Zephirus 240 µg/20 µg is a clear, colourless capsule of 15.9 mm containing a white powder, printed (black) with one ring and "B240 S20" in black.
Each capsule contains 300 micrograms of budesonide and 25 micrograms of salmeterol (as xinafoate). Each delivered dose (i.e. the dose leaving the mouthpiece) contains 240 micrograms of budesonide and 20 micrograms of salmeterol (as xinafoate).

The package is a HDPE bottle closed with a polypropylene screwcap which contains desiccant containing 60 hard capsules, with an inhaler made from plastic materials provided in each pack.

The inhaler body and cap are made from acrylonitrile butadiene styrene, push buttons are made from methyl methacrylate acrylonitrile butadiene styrene. Needles and springs are made from stainless steel.

The excipients inside the capsule are lactose monohydrate and lactose anhydrous. The capsules are made of hypromellose.

II.2 Drug Substances

The drug products contain two well-known active substances which are described in the European Pharmacopoeia (Ph.Eur.), salmeterol xinafoate and budesonide.
Budesonide is a corticosteroid, a mixture of two epimers (22R and 22S), a white to off-white, tasteless, odourless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Polymorphism is not described for budesonide.

Salmeterol xinafoate is the racemic form of 1-hydroxy-2-naphtoic acid salt of salmeterol. 36.3 µg of salmeterol xinafoate is equivalent to 25 µg of salmeterol base. It is slightly soluble in ethanol, chloroform and isopropanol; and sparingly soluble in water. Two polymorphs of salmeterol xinafoate are described in the literature. Both suppliers synthesise the stable form I.

For both substances, two suppliers are used, and for all four suppliers Certificates of Suitability (CEP) have been provided. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore, no details on the manufacturing process have been included.

Quality control of drug substances
For both budesonide and salmeterol xinafoate the MAH applies the specifications and methods of the Ph.Eur. monograph with the additional tests and requirements indicated on the Certificates of Suitability, and additional requirements for particle size distribution tested with a validated, in-house laser diffraction method. Batch analytical data demonstrating compliance with the drug substance specification have been provided of three batches from both suppliers.
Batch analytical data demonstrating compliance with the drug substance specification have been provided of three batches from both suppliers of each active substance.

Stability of drug substances
Both active substances are stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The inhalation device is CE marked and well-known. The device has less airflow resistance than the comparator product devices, which makes it more suitable for patients with a low peak inspiratory flow. The MAH has adequately described all aspects applicable to inhalation powders that are mentioned in the Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products. Characterisation has been done on clinical batches with the Multistage Liquid Impinger and control specifications have been set based on these characterisations. The MAH 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 deposition patterns.
In-vitro comparison of the proposed products with reference products and with each other (both strengths) have been adequately performed in line with section 5.2 of the OIP Guideline and the method described in the Ph.Eur. Monograph 2.9.18. The applied statistics are acceptable. Likely due to the use of a mixture of anhydrate and monohydrate lactose instead of only lactose monohydrate as carrier excipient, the products 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 Zephirus 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.

Manufacturing process
The manufacturing process concerns straightforward mixing of the blend and subsequent filling of the capsules. As salmeterol xinafoate content is low, blending and homogeneity are critical and are controlled routinely during manufacture. The process has been adequately validated on several pilot-scale- and two full-scale commercial scale batches. In view of these data and also because it has been demonstrated that the drug product manufacturer has extensive experience with the production of a comparable product, additional pre-approval validation is not required.

Control of excipients
The excipients used are described in a pharmacopoeia and analysed in accordance. Lactose anhydrate and lactose monohydrate are controlled according to the monographs and methods of the Ph.Eur. Additional tests for particle size are included as release tests. Information on the quantitative composition of the hypromellose shell and the qualitative composition of the applied black ink has been provided together with adequate quality references of their components.

Quality control of drug product
The specification includes relevant tests with validated methods and limits for appearance, identification, assay (HPLC), average and uniformity of delivered dose, and fine particle dose of both active substances, water and microbiological purity. Degradation products are specified and controlled for budesonide and salmeterol. The limits are acceptable. Shelf-life specifications are similar to the release specifications. Batch analyses data of seven pilot- and two full-scale batches of the drug product have been provided and confirm compliance with the set drug product specifications. Batch analysis results have been provided of the batches used in the clinical studies.

Stability of drug product
Stability data on the product has been provided for six pilot-scale batches stored at 25°C/60%RH (36 months), 30°C/75% RH (30 months), and 40°C/75%RH (up to 6 months) and for two industrial batches stored at 25°C/60%RH (24 months), 30°C/75% RH (30 months) and 40°C/75%RH (6 months), both in the commercial packaging. The only trend observed is a decrease in assay of salmeterol in the accelerated stability studies (20-30%), and, only slightly, also in the intermediate- and long-term stability studies. Out-of-specification results are only encountered at accelerated conditions and, only after 30 months, also at 30°C/75% RH. Uniformity of delivered of budesonide did once not comply (after 6 months storage at 40°C/75%RH). In view of these results, the proposed shelf-life and storage condition (36 months if stored below 30°C) are acceptable. As the HDPE bottle protects from light and the product is sensitive for moisture, an additional storage condition ‘Store in the original package to protect from light and moisture’ is applied.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Zephirus 120 µg/20 µg and 240 µg/20 µg, inhalation powder, hard capsule have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

In the initial Labazenit submission, three new repeated dose studies were provided with the combination of salmeterol and budesonide: a 28-day study in rats and 14-day and 3-month studies in dogs. A literature overview was provided regarding the pharmacology, pharmacokinetics and

toxicology of salmeterol and budesonide separately. No new non-clinical studies were provided for Zephirus. This is endorsed, as salmeterol and budesonide are well-known active substances.

III.2 Pharmacology

Salmeterol

Salmeterol is an inhaled long-acting β_2-adrenergic agonist. β_2-Adrenergic agonists produce their effects through interaction with specific β_2-adrenergic receptors present in high concentration in lung tissue. 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 the formation of cyclic adenosine monophosphate and the activation of protein kinase A. 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 β_1 and β_3-adrenergic receptors.

Salmeterol possesses additional 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. 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.

Pharmacological side effects of β_2-agonist treatment are tremor, subjective palpitations and headache. These effects tend to be transient and to reduce with regular therapy. β_2-agonists have a potential to cause adverse cardiovascular effects, due to the coexistence of β_1- and β_2-adrenoreceptors in the heart. β-agonists are also known to decrease plasma potassium levels by stimulation of β_2-adrenoreceptors in the liver and skeletal muscle. Furthermore, β_2-adrenoceptor agonists have potent muscle anabolic effects.

Budesonide

Budesonide is an inhaled glucocorticosteroid. The anti-inflammatory properties of glucocorticoids are manifested by repression of inflammatory genes expression, including among others cytokines, chemokines, adhesion molecules, inflammatory molecules. 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. The glucocorticoid forms a complex with the glucocorticoid receptor which translocates from the cytosol to the nucleus where it exerts an effect on gene transcription. 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.

Corticosteroids stimulate the transcription of $ß_2$-receptors. Both systemic corticosteroids and inhaled corticosteroids reverse $ß_2$-receptor downregulation after exposure to high doses of short-acting $ß_2$-agonists. Corticosteroids also reportedly modulate the efficiency of coupling between the $ß_2$-receptor and its associated stimulatory guanine-nucleotide–binding protein.

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 major local side effects of inhaled corticosteroids include oral candidiasis, hoarseness and disphonia.

Combination of salmeterol and budesonide

It has been observed that $ß_2$-agonists and corticosteroids interact in a beneficial way. While chronic use of salmeterol as monotherapy reduces β_1- and β_2-adrenoreceptor density, inhaled corticosteroids have been shown to up-regulate β_2–adrenoreceptor expression. Long-acting $ß_2$-agonists have been shown to enhance the effects of corticosteroids, a process that may occur through priming of the glucocorticoid receptor for activation. In addition it has been shown that translocation of the glucocorticoid receptor from the cell cytosol to the nucleus is increased by the addition of a long-acting $ß_2$-agonist.

Based on this, the combination of salmeterol and budesonide is a suitable combination for the treatment of asthma.

III.3 Pharmacokinetics

Budesonide consists of a one-to-one mixture of epimers with 22R and 22S configuration. Both epimers seem to have the same qualitative pharmacological effects, however epimer 22R is 2 to 3 times as potent as epimer 22S.

The MAH provided two new studies for the validation of the determination of salmeterol and budesonide in dog plasma. This method was well validated and accuracy, precision and recovery were all within acceptable limits and dilution integrity was confirmed. Furthermore, storage stability of the plasma samples was confirmed for both compounds.

Overall, the time to reach maximum plasma levels was not altered when comparing the situation in which budesonide and salmeterol were given as single compound and when they were given in combination. In a 14-day combination study in dogs (study 9015) the 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 probably due to the difference in exposure time (factor 5). The C_{max} and AUC values were though not a factor 5 lower in the low concentration combination group, indicating no linear relationship between dose and exposure but more details on linearity cannot be given based on this pre-clinical study. The high concentration combination group displayed comparable C_{max} and AUC values; although overall they seemed a bit lower than in the compound only groups. Due to large standard deviations this cannot be confirmed. No information was provided on the volume of distribution of the combination of budesonide and salmeterol. Based on information provided for budesonide and salmeterol as single compounds, it is suggested that the combination has a large Vd since both salmeterol and budesonide are widely distributed when given alone.

No new studies were submitted on the distribution, metabolism or excretion of the combination of budesonide and salmeterol. As no information is available about the bioavailability of both compounds when given in combination, it is not clear whether administering the drugs in combination would alter the distribution of the compounds. 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. Based on the present information on the distribution of salmeterol as summarized by the MAH, some accumulation cannot be ruled out when the combination of budesonide and salmeterol is used daily.

Both compounds are metabolized by CYP3A(4/5), which is also present in lung tissue and as both will reach the lungs first before entering the systemic circulation, metabolism of both compounds may occur in the lungs. As no information is provided about metabolism in the lung, it cannot be assessed to what extent this occurs and whether interactions on metabolism are expected locally in the lung.

Because in humans salmeterol is mainly excreted via faeces and budesonide via urine, no direct interactions are likely on the level of excretion.

No new non-clinical studies were provided on the pharmacokinetic interaction potential when salmeterol and budesonide are given in combination. The human pharmacokinetic interaction study revealed no differences in pharmacokinetic profile of each of the compounds when the drugs were administered in combination compared to the situation in which they were administered separately, indicating no pharmacokinetic interactions between budesonide and salmeterol. Still, interactions via CYP3A4 (or 3A5) in the lung cannot be ruled out. Furthermore, part of the human population has more 3A4 than 3A5 in the lungs whereas for the other part it is the other way round. This may lead to differences in effective local concentrations. However, in the light of the available clinical data, this is not expected to have a significant impact on safety and efficacy.

III.4 Toxicology

Acute toxicity studies conducted in mice, juvenile and adult rats and dogs showed salmeterol to be a relatively non-toxic molecule. The LD50 values for budesonide 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.

The toxicity profile of salmeterol after repeated dose administration includes mainly tachycardia, vasodilatation, increased muscle development and hypokalemia. In rats, increased food consumption and ovarian follicular cysts were observed. In dogs, myocardial papillary fibrosis was observed.

The toxicity of budesonide is characterised by a reduction in blood leukocytes, lymphocytes 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. The toxicity of budesonide administered by inhalation is low, due to its low bioavailability coupled to an extensive first pass metabolism. In rats, increased erythrocyte counts and hemoglobin concentrations as well as a reduction in food intake and a decrease in body weight gain were observed. In dogs, increases in serum total cholesterol and triglycerides were observed as well as atrophy of the fascicular and reticular zones in the adrenals, and hypertrophy of the liver due to increased glycogen content. 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 in the combination studies was 11-12 times and 16-19 times the human exposure based on AUC and C_{max} respectively. The maximum exposure to salmeterol was 57 times and 19 times the human exposure based on AUC and C_{max} respectively.

The bridging study in the rat was not validated as per ICH standards and, therefore, the use of this study to quantitatively determine exposure margins would not be appropriate. This stated, the rat study did not identify significant toxicity findings even at high dose and nothing untoward with respect to known adverse effects of high doses of the 2 compounds based on observations and necropsy. Therefore, qualitatively the study is adequate. The dog studies provide adequate assurance of safety margins of exposure as these are validated studies. Those studies did not reveal any findings raising any specific concerns.

Salmeterol and budesonide did not show genotoxic potential in standard batteries of tests.

In carcinogenicity studies with salmeterol, increased incidences of tumours were observed in the mesovarium in the rat and in the uterus in the mouse (leiomyomas) and in the pars anterior of the pituitary in the rat. Leiomyomas are believed to be an adaptive physiological response to continuous relaxation of the smooth muscle and are considered not clinically relevant because mouse uterus and rat mesovarium are described as uniquely sensitive to the pharmacological effects of β2-agonists. Regarding pituitary adenomas it is suggested that treatment with salmeterol merely accelerated the progression from hyperplasia to adenoma rather than initiating tumour formation. Clear safety margins have been reported at no effect doses. In carcinogenicity studies with budesonide, an increase in the incidence of gliomas was observed in one rat study, but not in two additional rat studies. No increases in tumours were observed in mice.

In reproductive toxicology studies, salmeterol did not affect fertility and was not teratogenic in rats. Salmeterol caused several malformations and delayed ossification in rabbits. In the peri- and post-natal development stage in rats salmeterol was fetotoxic and decreased the fertility of the survivors. Salmeterol xinafoate crossed the placenta in mice and was excreted in the milk. In a fertility study with budesonide in rats, decreases in maternal body weight gain, prenatal viability and viability of the young at birth and during lactation were observed. As with other glucocorticoids, budesonide produced fetal loss, decreased pup weight and skeletal abnormalities in rats and rabbits (subcutaneous

administration). 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.

No specific local tolerance studies were performed. 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.

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.

Drug substance impurities of budesonide and salmeterol meet the requirements of the monographs of the European Pharmacopoeia. Drug product impurities are specified below the qualification threshold.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Salmeterol $PEC_{SURFACEWATER}$ value is below the action limit of 0.01 µg/L and thus a phase II assessment is not necessary. With respect to PBT-assessment, no definitive conclusions are possible because study reports regarding the determination of log Kow are lacking. However this is acceptable, considering the fact that no increased use of the active substances is expected due to registration of this product.

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 is a potential endocrine disruptor. According to EMA guidance (EMEA/CHMP/SWP/ 4447/00 corr1, Chapter 3) it may, therefore, be addressed with regard to environmental risks, irrespective of the quantity released into the environment. However the active substance is already on the market and the proposed product is unlikely to increase the amount released into the environment.

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		

Conclusions on studies
Determination of log Kow was not sufficiently addressed for both salmeterol and budesonide. However, the active substances are already on the market and the proposed product is unlikely to increase the amount released into the environment. Therefore, an ERA is not considered necessary. Furthermore the reported values for the Log Kow were taken from sources that have already been reviewed. With respect to budesonide; the data indicate that it does not need to be investigated for persistence, bioaccumulation and toxicity.

IV. CLINICAL ASPECTS

IV.1 Introduction

Compared to the clinical dossier submitted for the centralised procedure, EMEA/H/C/002201/0000, two new lung deposition studies, SMB-BUSAL-SD131 and SMB-BUSAL-SD132, are submitted in order to support the comparable lung deposition of Zephirus compared to Pulmicort and Symbicort.

As this application concerns a new fixed dose combination of a LABA and an ICS, following objectives need to be taken into account:

Step-up indication
- demonstration that both strengths of Zephirus result in a higher efficacy than an ICS monotherapy (also at a higher dose).

Substitution indication
- demonstration of similar bronchodilation with a comparator product containing salmeterol

Both indications
- Establishment of the same inflammation control and bronchodilation by budesonide
- Establishment of the dose response between Zephirus 150/25 µg and Zephirus 300/25 µg
- Establishing the safety profile up to one year of administration, at the maximum dose.

Good Clinical Practice (GCP)
During the centralised procedure for Labazenit, a triggered 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 FEV1 and FVC. It was highlighted 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 have 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 measurements, which should not differ by > 5% or by 0.1 L, whichever is the greatest.

The inspection's outcome recommended that a statistical reanalysis of the FVC and FEV1 parameters should be performed with the highest values recorded in the CRF for study BUSAL-III-02-1. As requested, a statistical reanalysis of the highest FEV1, and FVC for week 12 was submitted by the MAH during the evaluation as were the spirometric values measured in the safety phase of the study from week 12 to week 24.The differences with the originally presented values were small.

IV.2 Pharmacokinetics

This application for Zephirus concerns a new fixed dose combination (FDC) of two well-known products used in the treatment of asthma: budesonide and salmeterol xinafoate.
Because the fine particle fraction is higher for Zephirus than for the comparator monotherapies (Pulmicort Turbuhaler and Serevent Diskus), a lower nominal dose in both active ingredients budesonide and salmeterol is used for Zephirus than in the comparator monotherapies (Pulmicort and Serevent Diskus) to obtain a similar fine particle dose (FPD) and a similar lung deposition of each drug.
The objectives of the PK studies are to support the safety and efficacy of Zephirus observed in the clinical phase II and phase III studies, by demonstrating that the lower nominal dose results in comparable lung deposition of budesonide and salmeterol for Zephirus as for the comparator monotherapy products, to support dose proportionality of Zephirus 150/25 µg and Zephirus 300/25 µg, and finally to establish absence of pharmacokinetic interaction between budesonide and salmeterol when administered together.
These objectives are in agreement with the guidelines on fixed dose combination CHMP/EWP/240/95 and on the investigation of bioequivalence, CPMP/QWP/EWP/1401/98 rev.1, and on orally inhaled products (CPMP/EWP/4151/00 Rev. 1).

Five single dose and two steady-state studies pharmacokinetic studies were initially submitted and assessed in the centralised procedure (refer to the EPAR for Labazenit). Studies were conducted in healthy subjects and in subjects with persistent mild asthma. For this decentralised procedure (Zephirus), two additional studies were submitted: SMB-BUSAL-SD131 and SMB-BUSAL-SD132.

Design of the studies is presented in **Table 1**.

Table 1 Overview of pharmacokinetic studies

Study N° (year)	N° of subjects	Design	Product	Strengths (µg)	Aim
SMB-BUSAL-SD033 (2003)	24 healthy subjects	Single dose 3-way cross-over	Zephirus Zephirus Pulmicort	300/25 150/25 2x200	- comparative budesonide exposure - dose proportionality
SMB-BUSAL-SS032 (2003)	24 healthy subjects	Multiple dose 3-way cross-over	Zephirus Pulmicort Serevent	1x300/25 2x200 1x50	comparative exposure budesonide and salmeterol
SMB-BUSAL-SS071 (2007)	36 healthy subjects	Multiple dose 2-way cross-over	Zephirus Pulmicort+Serevent	150/25 200+50	comparative exposure budesonide and salmeterol
SMB-BUSAL-SD101 (2010)	40 healthy subjects	Single dose 4-way cross-over	Zephirus SMB Budesonide* SMB Salmeterol* SMB Bud+Salm*	2x300/25 2x300 2x25 2x(300+25)	interaction
SMB-BUSAL-DP102 (2010)	40 asthma patients	Single dose 2-way cross-over + charcoal	Zephirus Zephirus	300/25 150/25	dose proportionality
SMB-BUSAL-SD111 (2012)	40 asthma patients	Single dose 2-way cross-over + charcoal	Zephirus Symbicort	150/25 160/4.5	comparative lung deposition budesonide

SMB-BUSAL-SD121 (2012)	32 healthy subjects	Single dose 2-way cross-over	Zephirus 2x150/25 Serevent 2x50	comparative exposure salmeterol
SMB-BUSAL-SD131 (2013)	42 asthma patients	Single dose 2-way cross-over + charcoal	Zephirus 2x150/25 Symbicort 2x160/4.5	comparative lung deposition budesonide
SMB-BUSAL-SD132 (2013)	42 asthma patients	Single dose 2-way cross-over + charcoal	Zephirus 2x150/25 Pulmicort 2x200	comparative lung deposition budesonide

Budesonide is a 1 **:** 1 racemic mixture of 2 epimers, (22*R* – epimer B in this document)- and (22*S* – epimer A in this document). According to the Ph. Eur. monograph, the epimer A should be 40.0 percent to 51.0 percent of total budesonide.
In glucocorticoid receptor affinity studies, the 22R form of budesonide was two times as active as the 22S epimer. *In vitro* studies indicate that the two forms of budesonide do not interconvert. Further, *in vitro* studies demonstrated that epimer 22R is metabolized in the liver more rapidly than epimer 22S.
Little information of the pharmacokinetics of the enantiomers is available. Following iv administration of budesonide, Ryrfeldt (1984) and Pedersen et al (1987) have demonstrated that clearance of the 22R epimer is faster than clearance of the 22S epimer. In the study by Pedersen, also a faster clearance of the 22R epimer was observed following nebulization of budesonide in 6 asthmatic children. On the other hand, there was no apparent difference in pharmacokinetics between 22R and 22S epimer of budesonide following inhalation of budesonide aerosol in 9 healthy subjects (Minto et al. 2000) although the intersubject variability in budesonide pharmacokinetics was very high.
Budesonide pharmacokinetics were demonstrated to be similar in healthy volunteers and subjects with asthma (Thorsson et al. 2001, Harrison et al. 2003).

Methods
Concentrations of budesonide (epimers A and B) and salmeterol in human plasma were measured using LC/MS/MS methods. The lower limit of quantification (LLOQ) levels for the budesonide enantiomers 22.5-50 pg/ml and 15 pg/ml for salmeterol were relatively high compared to the plasma concentrations of budesonide and salmeterol. For the Zephirus 150/25 µg strength, C_{max} for budesonide and salmeterol were less than 10x the LLOQ in studies SS032, SD033, SS071 and SD101. Therefore, AUC levels could not be determined accurately for budesonide when Zephirus or the respective mono-products were administered at the lowest therapeutic dose in these studies. In study DP102 (dose proportionality) and studies SD111, SD131 and SD132 (lung deposition PK) the analytical assay was improved and evaluation of the low budesonide strength of Zephirus was possible. Sufficient robustness of the analytical assay, by means of incurred sample reanalysis, was demonstrated in the newer studies SD111, SD121, SD131 and SD132.
As many of the salmeterol measurements fell below the LLOQ, the MAH omitted the data from salmeterol from the study reports (studies SD033, SS071). In study SD-121, with a more robust analytical method, the bioavailability of salmeterol between Zephirus and Serevent Diskus was compared following a higher than recommended dose to increase the salmeterol plasma concentrations. Comparison of pharmacokinetics of salmeterol between Zephirus and salmeterol mono-product was based on results from study SD121 only.

In the older studies, 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-time (ct) curve could not be fully characterised when the low budesonide dose was administered. Therefore, AUC values from studies SS071 and SD033 with the low Zephirus strength should be considered very cautiously. However, sufficient data with respect to low strength budesonide PK is obtained from the PK studies conducted at ≥ 2012 i.e., studies SD111, SD131 and SD132. Data of the high Zephirus strength could be assessed using data from all studies.
Subjects with budesonide predose concentrations >5% of C_{max} were not always excluded from the pharmacokinetic and statistical analysis. Additional analysis excluding of all subjects with >5% C_{max} predose values was conducted, and did not change the point estimate and 90% CI to a relevant extent.

Pharmacokinetic results

Study SD101 showed that there is no difference in pharmacokinetics of budesonide and salmeterol when administered separately compared to Zephirus 300/25 µg FDC; 90% CI for C_{max} and AUC of budesonide and salmeterol were within the 80-125% range demonstrating the absence of a pharmacokinetic interaction between budesonide and salmeterol.

Zephirus 300/25 and Zephirus 150/25 µg are considered dose proportional with respect to budesonide PK based on results from studies SD033 and DP102, supported by *in vitro* data. The deposition profile of salmeterol was the same for Zephirus 150/25 µg and 300/25 µg in study DP102.

Results of the 5 comparative bioavailability PK studies in which the budesonide plasma profile could be determined adequately are summarised in Table 2.
Data of Zephirus 300/25 µg could be assessed using data from all studies because plasma concentrations were high enough to determine pharmacokinetics sufficiently adequate. Comparable exposure of budesonide for the highest strength Zephirus 300/25 µg and the comparator product Pulmicort Turbuhaler 2x200 µg was indicated by results from studies SS033 and SD032 following single and multiple dose inhalation. At single dose ratio and 90% CI for total budesonide AUC_t and C_{max} were 1.08 (0.87-1.33) and 1.16 (0.94-1.42), respectively, and at steady-state ratio and 90% CI for $AUC\tau$ was 0.94 (0.79-1.12) and for C_{max} 1.02 (0.90-1.15).

Table 2 Comparative bioavailability for budesonide – across study comparison between Zephirus and Pulmicort and Symbicort. Studies SS032 and SD033 were conducted in healthy volunteers (without charcoal), studies SD111, SD131 and SD132 in patients with mild asthma (with charcoal block)

Budesonide Epimer A					
study		Reference product	Zephirus	90 % CI Range	Point estimate (%)
SS032 Zephirus 300/25 vs Pulmicort 2x200	AUC_τ (pg.h/ml)	1994 ± 884	1746 ± 922	71-103	85.1
	C_{max} (pg/ml)	897 ± 376	880 ± 436	85-107	95.5
SD033 Zephirus 300/25 vs Pulmicort 2x200	AUC_t (pg.h/ml)	1606 ± 943	1632 ± 804	84-130	104.2
	C_{max} (pg/ml)	575 ± 311	624 ± 262	92-134	111.1
SD111 Zephirus 150/25 vs Symbicort 160/4.5	AUC_t (pg.h/ml)	687 ± 697	535 ± 722	68.5 - 88.8	78
	C_{max} (pg/ml)	238 ± 120	177 ± 68	70.3 – 91.0	80
SD131 Zephirus 150/25 vs Symbicort 160/4.5	AUC_t (pg.h/ml)	717 ± 286	762 ± 291	94.4 – 124.2	108
	C_{max} (pg/ml)	302 ± 129	330 ± 169	94.7-124.0	108
SD132 Zephirus 150/25 vs Pulmicort 200	AUC_t (pg.h/ml)	831 ± 476	762 ± 299	85.8-108.0	96
	C_{max} (pg/ml)	292 ± 139	316 ± 149	96.8-120.7	108

Budesonide Epimer B					
study		Reference product	Zephirus	90 % CI Range	Point estimate (%)
SS032 Zephirus 300/25 vs Pulmicort	AUC_τ (pg.h/ml)	1138 ± 749	1430 ± 2151	83-136	106.6
	C_{max} (pg/ml)	644 ± 253	776 ± 428	95-132	112.2

2x200					
SD033 Zephirus 300/25 vs Pulmicort 2x200	AUC_t (pg.h/ml)	834 ± 375	928 ± 563	85-134	106.7
	C_{max} (pg/ml)	409 ± 215	501 ± 231	100-157	125.0
SD111 Zephirus 150/25 vs Symbicort 160/4.5	AUC_t (pg.h/ml)	378 ± 258	298 ± 122	72.3 – 95.4	83
	C_{max} (pg/ml)	192 ± 97	158 ± 64	77.4 – 94.3	86
SD131 Zephirus 2x150/25 vs Symbicort 2x160/4.5	AUC_t (pg.h/ml)	450 ± 129	618 ± 169	123.4 - 165.2	143
	C_{max} (pg/ml)	236 ±112	335 ± 190	121.9 – 161.4	140
SD132 Zephirus 2x150/25vs Pulmicort 2x200	AUC_t (pg.h/ml)	518 ± 362	577 ± 222	106.7 - 137.6	121
	C_{max} (pg/ml)	232 ± 114	323 ± 160	124.2 - 155.7	139

Three comparative PK studies with charcoal administered (SD111, SD131, SD132) provided support that the lower nominal dose of Zephirus results in comparable lung deposition exposure of budesonide with Zephirus 150/25 as for Pulmicort 200 µg and Symbicort 160/4.5 µg. The PK parameters and statistical analysis are shown in Table 2. The results from the 3 studies were somewhat divergent. In study SD111, budesonide exposure was 17 and 23% lower (epimer A and B, respectively) for Zephirus. In studies SD131 and SD132, exposure to epimer A was bioequivalent, 90% CI was within 80-125%, for Zephirus and Symbicort and Pulmicort but exposure of epimer B was 43 and 21% higher for Zephirus. Zephirus C_{max} for epimer A and epimer B were comparable, which is expected for a racemic mixture, while for Symbicort and Pulmicort C_{max} of epimer B was 20% lower compared to epimer A. The MAH showed the batches of Busal had a higher epimer B to epimer A ratio 1.1 and 1.33 than the batches of Symbicort and Pulmicort 1.04, 1.05 and 0.95, respectively. All batches were within the acceptance range 0.95-1.5 of the Ph.Eur. monograph. The different epimer B to epimer A ratio was reflected in the pharmacokinetic results similarly for Busal as for Symbicort and Pulmicort. The AUC of epimer B compared to epimer A is lower in Zephirus and reference products. This can be explained by the faster metabolic clearance of epimer B compared to epimer A (Ryrfeldt, 1984).

The plasma concentration curves of budesonide for all studies are shown in **Figure 1** for epimer A and in **Figure 2** for epimer B. The inhaled dose of budesonide administered in the PK studies was not the same across the studies e.g. one/two puffs, high/low dose. Therefore, the graphical illustration of this across study comparison was presented with a normalisation to the dose corresponding to one inhalation (i.e 150 µg for Zephirus, 200 µg for Pulmicort and 160 µg for Symbicort). **Figure 3** shows there is a full overlap in budesonide pharmacokinetics following inhalation between Zephirus and the Reference products for epimer A.
Figure **5** shows a great overlap between Zephirus and Pulmicort and Symbicort suggesting comparable or slightly higher exposure for epimer B. The considerable interstudy variability can be caused by different analytical methods and different study designs i.e. healthy volunteers (without charcoal) had higher budesonide exposures compared to subjects with mild asthma (using a charcoal block to prevent the gastrointestinal absorption). Results of both budesonide epimers support a comparable lung deposition and total systemic exposure to budesonide of Zephirus compared to Symbicort and Pulmicort.

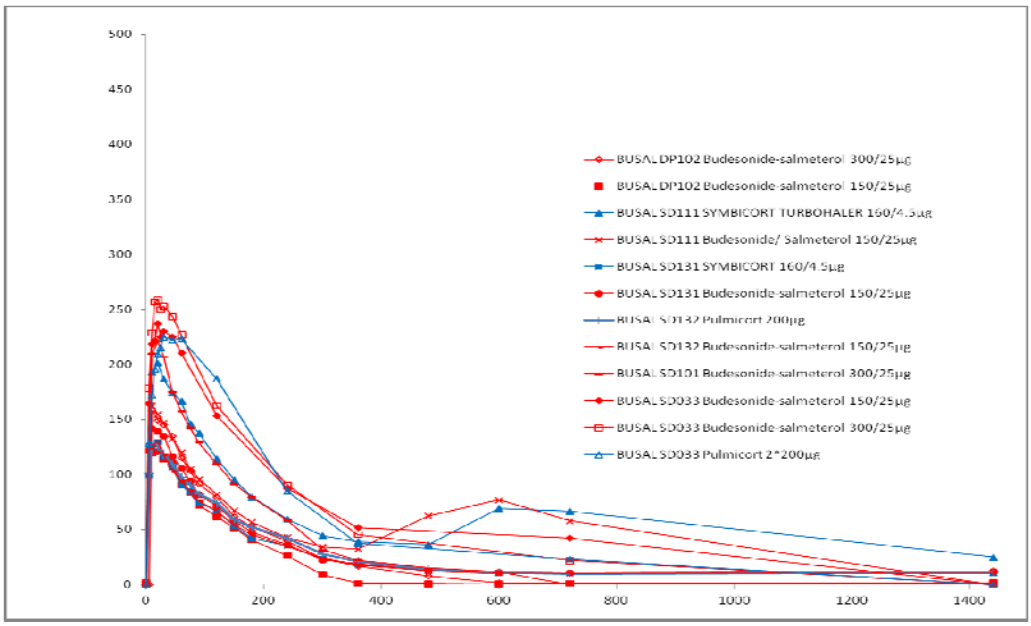

Figure 4 Across study comparison of budesonide epimer A plasma concentrations. Plasma concentrations were dose normalised to the dose corresponding to one inhalation. Zephirus is depicted in red and reference products Pulmicort and Symbicort are depicted in blue.

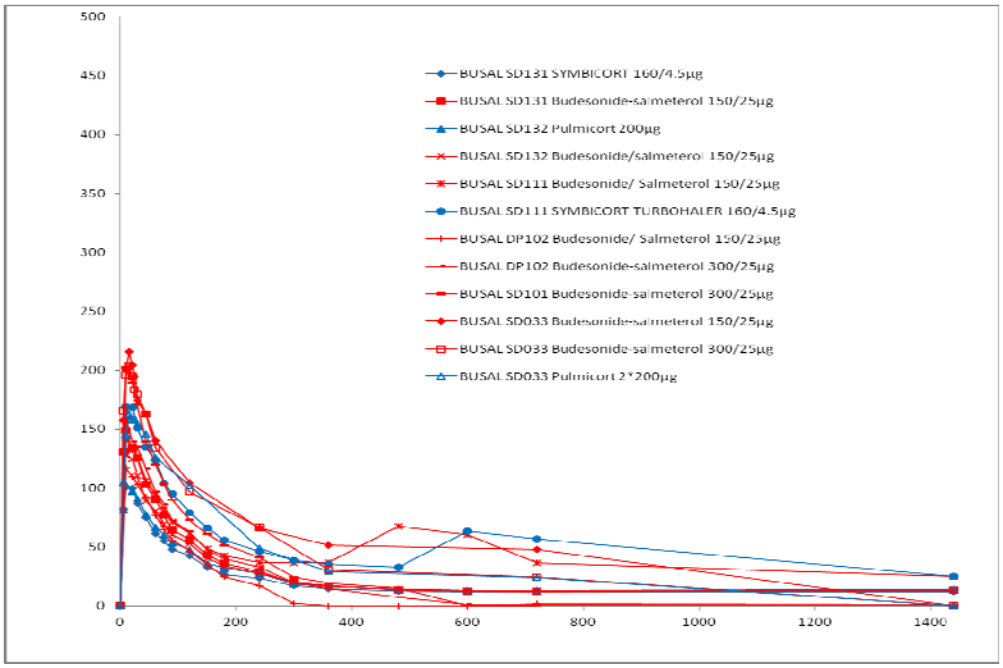

Figure 5 Across study comparison of budesonide epimer B plasma concentrations. Plasma concentrations were dose normalised to the dose corresponding to one inhalation. Zephirus is depicted in red and reference products Pulmicort and Symbicort are depicted in blue.

Overall, across study comparison for both strengths does not indicate a relevant difference in lung deposition and systemic exposure to budesonide following Zephirus compared to Pulmicort or Symbicort inhalation.

Salmeterol

As many of the salmeterol data fell below the LLOQ, the MAH omitted the data from salmeterol from

the study reports (SS032, SD033, SS071). 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. Salmeterol was not analysed in studies SD111, SD131, and SD132. Comparison of bioavailability of salmeterol between Zephirus and Serevent Diskus, following a higher than recommended dose to increase the salmeterol plasma concentrations, is based on results from study SD121 only. Results are summarised in **Table 3**.

Table 3 Pharmacokinetic parameters of salmeterol following inhalation of 2 puffs of Zephirus 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

Based on the results in study SD-121 in healthy volunteers, mean systemic bioavailability of salmeterol was 17% (AUC) and 31% (C_{max}) higher following inhalation of Zephirus 150/25 µg compared to Serevent Diskus 50 µg indicating that the lung deposition of salmeterol following Zephirus inhalation is comparable or higher than for Serevent Diskus. Comparable bronchodilation and safety between Zephirus and Serevent Diskus is evaluated in the pharmacodynamic and clinical studies.

IV.3 Pharmacodynamics

The MAH has performed one pharmacodynamic study to investigate the effect on the hypothalamic–pituitary–adrenal axis: Study SMB-BUSAL II-10-2.

Study SMB-BUSAL II-10-2
In this randomized, cross-over, partially-blinded study two doses of the Zephirus 300/25 µg BID and 150/25 µg BID are compared to Pulmicort Turbuhaler 400 µg BID, Serevent Diskus 50 µg BID and placebo.

Study participants were male and female corticosteroid naïve patients 18 to 70 years old, with a diagnosis of mild persistent asthma. Patients received each treatment for 10 days separated by wash-out periods of at least 21 days.

The primary endpoint is change from baseline in AUC of 24-hour plasma cortisol (mean change from baseline to day 11 of each period) with an equivalence margin for the difference [-20%; + 20%].
The equivalence margin of 20% used in the BUSAL-II-10-2 trial is supported by literature data (Donnelly et al (1997), Martin et al (2002) and Szefler et al (2005)).

The null hypothesis was that Zephirus 300/25 µg BID and Pulmicort Turbuhaler 400 µg BID + with Serevent Diskus 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 Zephirus 300/25 µg BID and Pulmicort Turbuhaler 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.

Contrasts were calculated between all treatment pairs. 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.

Results

In the intent-to-treat (ITT) population set, all randomized patients (40) 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 all active treatments, a decrease in the mean AUC of 24-hour plasma cortisol from baseline to day 11 was observed (Table 4).

Primary endpoint

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

- Zephirus 300/25 µg: -13.67±3.05 % (Lsmeans ± SE)
- Zephirus 150/25 µg: -6.49±3.09 % (Lsmeans ± SE)
- Pulmicort Turbuhaler 400 µg and Serevent Diskus 50 µg: -7.45±3.09 % (Lsmeans ± SE).

Table 4: AUC0-24h for plasma cortisol - ITT population

ITT population (N=40)					
		Zephirus 300/25 µg N=39	Zephirus 150/25 µg N=39	Placebo N=38	Pulmicort Turbuhaler 400 µg + Serevent Diskus 50 µg N=39
AUC 0-24 h 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 Lsmeans ± SE	591.33 ± 804.51 -658.02 ± 127.89	-443.64 ± 1135.51 -385.63 ± 129.4	-2.28 ± 786.25 38.55 ± 129.48	-402.94 ± 1059.65 -409.91 ± 129.34
Relative change AUC D11 -baseline (%)	m ± SD Lsmeans ± SE	-12.59 ± 19.20 -13.67 ± 3.05	-7.37 ± 19.20 -6.49 ± 3.09	2.45 ± 20.84 2.99 ± 3.09	-7.30 ± 24.41 -7.45 ± 3.09

** 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 Zephirus 150/25 µg.*

A higher decrease was observed with Zephirus 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, Zephirus 300/25 µg and Zephirus 150/25 µg showed to be both equivalent to the association of Pulmicort Turbuhaler 400 µg and Serevent Diskus 50 µg. The 99.15% confidence interval (CI) of [-17.31%; 4.87%] included in the [-20%; +20%] equivalence margin defined in the protocol for Zephirus 300/25 µg and 0.95±4.16% (p=0.82) with a CI of [-10.21%; 12.11%] for Zephirus 150/25 µg.

Moreover, Zephirus 300/25 µg and Zephirus 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%]) (Table 5).

Table 5: 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
Zephirus 300/25 µg vs. Pulmicort 400 µg + Serevent 50 µg	0.1355	-6.22 ± 4.14	[-17.31 - 4.87]
Zephirus 300/25 µg vs. Zephirus 150/25 µg	0.0864	-7.17 ± 4.14	[-18.29 - 3.94]
Zephirus 300/25 µg vs. placebo	0.0001	-16.66 ± 4.14	[-27.77 - -5.55]
Zephirus 150/25 µg vs. placebo	0.0247	-9.49 ± 4.16	[-20.65 - 1.68]
Zephirus 150/25 µg vs. Pulmicort 400 µg + Serevent 50 µg	0.8197	0.95 ± 4.16	[-10.21 - 12.11]
Pulmicort 400 µg + Serevent 50 µg 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.

Only the Pulmicort Turbuhaler 400 µg + Serevent Diskus 50 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:

- Zephirus 300/25 µg (and 150/25 µg) and Pulmicort Turbuhaler 400 µg + Serevent Diskus 50 µg.
- Zephirus 300/25 µg and 150/25 µg and the placebo treatment.
- Zephirus 300/25 µg and Zephirus 150/25 µg.

Secondary outcome: Mean change from baseline in C_{max} for plasma cortisol
C_{max} 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.

IV.4 Clinical efficacy

The applied indication should be considered as two different steps in the asthma treatment: both a step-up and a substitution indication. Hence, both need a different approach in establishing efficacy and safety of the new product.

The phase II studies were conducted in order to establish the similarity between salmeterol as component of the new Zephirus and Serevent for the substitution indication. BUSAL II-03-1 and BUSAL II-10-1 are bronchodilation studies after single dose.

Table 6 : Overview of the Phase II Clinical efficacy studies with Zephirus

Study Ref.	BUSAL-II-03-1	BUSAL-II-10-1
Performance of study	1 centre in Poland, 19 May 2004 to 26 July 2004	4 centers in Macedonia. 25 September 2010 to the 22 November 2010.
Population	Moderate persistent asthma	Moderate to severe persistent asthma
Methods	Controlled single-blinded	Controlled partially blinded
Duration	Single dose	Single dose
Treatment groups	Zephirus 150/25 µg vs. SEREVENT DISKUS 50 µg	Zephirus 150/25 µg vs. Zephirus 150/12.5 µg vs. Zephirus 150/6.25 µg vs. SEREVENT DISKUS 50 µg vs. SEREVENT EVOHALER 25 µg vs. SEREVENT EVOHALER 2x25 µg
Total randomized patients	35	48

(N=123)		

An overview of the phase III studies is given in Table 7.

Table 8 : Overview of the Phase III Clinical efficacy studies with Zephirus

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

BUSAL III-02-1, the pivotal study, aimed to demonstrate that both dosage strengths of Zephirus result in a higher efficacy than an ICS monotherapy (also at a higher dose), i.e. the step-up indication.
Moreover, the persistence of the efficacy was measured to establish control for up to 6 months for Zephirus 150/25 µg and for up to 12 months for Zephirus 300/25 µg in order to support both the step-up indication and the substitution indication.

BUSAL-III-08-1 and BUSAL-III-05-1 are two supportive studies to compare Zephirus with established FDCs, in order to put the improvements obtained with the fixed combination into perspective. It was aimed to demonstrate non-inferiority of each strength of Zephirus to a reference marketed ICS/LABA combination.

The main findings of the clinical efficacy program are briefly discussed below. A more detailed description of the studies is given in the Public Assessment Report on Labazenit (ref. EMA/465765/2013), available on the EMA website.

Step-up indication
Demonstration that both dosage strengths of Zephirus result in a higher efficacy of budesonide than an ICS monotherapy i.e. Pulmicort, is needed especially to support the step-up indication.

In study BUSAL III-02-1, three study arms were included: Zephirus 150 µg/25 µg bid, Zephirus 300 µg/25 µg bid and Pulmicort 400 µg bid. The study design makes a comparison of a FDC with a lower ICS dose (Zephirus 150 µg/25 µg) with a doubled dose of ICS (Pulmicort 400 µg). For the primary endpoint, Peak Expiratory Flow (PEF), both Zephirus 150/25 µg and Zephirus 300/25 µg treatments were superior to Pulmicort 400 µg after 12 weeks of treatment (Zephirus 150/25 µg vs. Pulmicort: $p<0.001$; Zephirus 300/25 µg vs. Pulmicort: $p=0.004$).
Even when adjusting for performing 3 comparisons, the (non)-significance of the comparisons remain the same, i.e. the Zephirus formulations are still superior to Pulmicort by at least 15 L/min. Also after 12 weeks the switch from Pulmicort to either Zephirus 150/25 µg or Zephirus 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 the two Zephirus strengths (150/25 µg and 300/25 µg) 150/25) was statistically significant.

During the GCP inspection, it was noticed that the secondary parameter spirometric values (FEV_1, FEV_1 % 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 known whether the highest of the lowest of the three reproducible measurements were used. The MAH 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.

Dose response inhaled corticosteroids
A dose response between the two doses could not be established clinically as no difference between the two strengths of Zephirus were observed for PEF, neither at week 12 nor at week 24 in study BUSAL III-02-1.

Comparable anti-inflammatory treatment
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 for the therapeutic equivalence regarding the ICS doses.

As further proof for similar inflammation control, exacerbation numbers or rates, especially of severe exacerbations could have been used as the parameter to demonstrate equivalent anti-inflammatory control between Zephirus and Pulmicort, provided that the numbers are large enough and the study is of sufficient duration (> 1 year). However, in the Phase III studies, the numbers of exacerbations were too small and the study duration too short 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.

Substitution indication
Demonstration of similar bronchodilation, asthma control and asthma inflammation with the reference formulations need to be established.

Salmeterol
Study BUSAL II-10-1 was the main study to demonstrate similar bronchodilation of salmeterol between Zephirus and the reference product Serevent. This study was designed to prove bronchodilation equivalence between Zephirus and Serevent: patients were symptomatic according to GINA criteria, and different dosages of Zephirus with respect to salmeterol were used (25, 12.5 and 6.25 µg) and compared to different dosages of Serevent administered as DPI (25 µg) or MDI (25 or 50 µg).

The primary efficacy variable was the mean change in FEV_1,max (L); the mean change for Zephirus 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).
In the centralised procedure 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 FEV_1 over 12 h was comparable between the two groups: Zephirus 150/25 µg 7.03 ± 18.28 L, Serevent Diskus 8.30 ± 16.31, difference -0.92 ± 2.81; 95% CI -6.46 – 4.62; p=0.74. Also various other secondary efficacy endpoints, FEV_1 $AUC_{8\text{-}12\ h}$, PEF and FVC, were not statistically different.

The MAH has submitted 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 higher and lower doses became apparent after 6 h of dosing, especially after the 12 h observation period.

The dose related duration of bronchodilation is also described for salmeterol's main comparator, formoterol. The observed dose related duration of bronchodilation seems, therefore, a class characteristic, which supports the observed difference in AUC FEV_1 8-12 h between the different doses of salmeterol in study BUSAL-II-10-1.

Altogether, the data provide evidence that the bronchodilatory effect of Zephirus 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 Zephirus and Serevent Diskus resulted in similar broncholilatory effects of salmeterol and the difference was within the predefine equivalence range. However, the study design is not sensitive to assess comparability of the bronchodilation effect of salmeterol conclusively 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. Nevertheless, the study might be considered supportive for showing no differences between Zephirus and Serevent.

Budesonide
The same results and conclusions are applicable as for the step-up indication (see above). Equivalence regarding the number of exacerbations has not been demonstrated.

Comparison of Zephirus with other approved LABA/ICS fixed combinations
For this purpose, two supportive studies, studies BUSAL III-05-1 and BUSAL III-081, were performed. In these studies one dose of Zephirus was compared with one dose of a fixed dose combination.
In both studies, for both morning PEF and FEV_1, and the symptomatic secondary efficacy variables, treatment with Zephirus 300/25 µg did not show statistically significant differences compared with the comparators. The improvements in PEF and FEV_1 from baseline were clinically relevant.
However, in both studies only one dose of Zephirus (150/25 or 300/25 µg) and comparator was tested, employing a design not sensitive to conclusively assess comparability of the anti-inflammatory effect of budesonide.

Both indications
Persistence of efficacy
For demonstration of the long term safety and efficacy of Zephirus, study BUSAL III-05-01 was continued open label for up to 24 weeks as study BUSAL III-06-01. BUSAL III-06-1 evaluated the long term effect on the improvement of lung function and asthma control symptoms for both Zephirus 300/25 µg. Improvements in lung function and asthma symptom control obtained during the blind part of the study were sustained during the extension phase.
However, for this study patients were recruited from the open label 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 other patients.
Post hoc analyses demonstrated no differences in demographics, FEV_1, PEF, asthma control between the patients of study BUSALIII/05/II who did or did not enter the extension study BUSALIII-06-01 and adverse events, although the number of treatment related adverse 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 also shown that an experienced exacerbation did not introduce a bias.
However, because study BUSAL III-06-01 lacks a comparison with a currently approved comparable asthma treatment, it is difficult to determine the comparative benefit.

IV.5 Clinical safety

Budesonide and salmeterol have been in therapeutic use, alone and in combination, for may 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, 301 patients, of whom 109 (36%) exposed for at least 24 weeks, received Zephirus 150/25 µg and 553 patients, of whom 406 (73%) were exposed for 24 weeks and 101 (18%) exposed for 1 year to Zephirus 300/25 µg. However, no long term safety data (52 weeks) of the lower dose of Zephirus 150/25 were provided. According to the ICH E1A guideline “Population exposure: the extent of population exposure to assess clinical safety”, the MAH provided 12 months safety data for the highest strength of Zephirus (300 µg/25 µg) which is considered sufficient. Long term use is included as missing information in the Risk Management Plan (RMP).

One of the specific adverse events (AEs) of interest is asthma 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.

Other specific AEs of interest related to 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 serious adverse event (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 SmPC and as important identified risks in the RMP.

It is known that cortisol can be suppressed by a synthetic glucocorticosteroid like budesonide, even when inhaled. Zephirus 300/25 µg appears to decrease serum cortisol (AUC0-12 h) stronger than Zephirus 150/25 µg and Pulmicort Turbuhaler 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 SmPC and as important identified risk in the 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 elderly patients due to the limited data available has been included in section 4.2 of the SmPC and use in patients over 65 years old is included as missing information in the RMP.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Zephirus.

- Summary table of safety concerns as approved in RMP

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Asthma exacerbation	Section 4.4 and 4.8 of the SmPC.	N/A
Paradoxical bronchospasm	Section 4.4 and 4.8 of the SmPC.	N/A
Adrenergic cardiac effects	Section 4.4, 4.5 and 4.8 of the SmPC.	N/A
Respiratory disorders	Section 4.4 and 4.8 of the SmPC	N/A
Hyperglycaemia	Section 4.4 and 4.8 of the SmPC	N/A
Hypokalemia	Section 4.4, 4.5 and 4.8 of the SmPC	N/A
QTc prolongation	Section 4.4, 4.5 and 4.8 of the SmPC	N/A
Adrenal suppression	Section 4.4 and 4.8 of the SmPC.	N/A
Growth retardation	Section 4.4 and 4.8 of the SmPC.	N/A
Cataracts	Section 4.4 and 4.8 of the SmPC.	N/A
Glaucoma	Section 4.4 and 4.8 of the SmPC.	N/A
Bone density decreased	Section 4.4 and 4.8 of the SmPC.	N/A
Hypersensitivity	Section 4.3 and 4.8 of the SmPC.	N/A
Important Potential Risks		
Off-label use	N/A	N/A
Missing Information		
Use by Children (Age <18 years)	Section 4.2 and 5.1 of the SmPC.	N/A
Use by elderly (age > 65 years)	Section 4.2 of the SmPC.	N/A
COPD	N/A	N/A
Other ethnical subgroup population than Caucasian	Section 4.4 of the SmPC.	N/A
Long-term use	Section 4.4 and 4.8 of the SmPC.	N/A
Use in patients with hepatic pathology	Section 4.2 of the SmPC.	N/A

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

Clinical pharmacology
Pharmacokinetics of Zephirus have been investigated sufficiently for the development of a new fixed-dose combination with known active substances.

- PK data and *in vitro* data support the dose proportionality with respect to budesonide between Zephirus 300/25 µg and Zephirus 150/25 µg.
- There is no pharmacokinetic interaction between budesonide and salmeterol.
- Based on the results in study SD121 in healthy volunteers, systemic bioavailability of salmeterol was somewhat higher following inhalation of Zephirus 150/25 µg compared to Serevent Diskus 50 µg.
- In five studies budesonide exposure following inhalation of Zephirus was compared with the references products Pulmicort/Symbicort. The results together showed no indication of a relevant difference in lung deposition or systemic exposure to budesonide following inhalation of Zephirus as compared to Pulmicort or Symbicort, thus supporting the lower nominal dose of budesonide for Zephirus.

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. Zephirus 300/25 µg appeared to decrease serum cortisol (AUC0-12 h) more than Zephirus 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.

Clinical efficacy
Step-up indication
Zephirus demonstrated that the addition of a LABA to an ICS increased lung function and decreased asthma symptoms, supporting the step up indication. In addition, comparability of inflammation control as efficacy measure of budesonide needs to be established. As there was no dose response between the two different doses of Zephirus, the study design was not sensitive to assess comparability conclusively.

Additional evidence for comparability could also not be derived from exacerbations as exacerbations were not defined and collected in the different studies in the same way. In study BUSAL III-05-1 slightly more exacerbations were observed with Zephirus than with Seretide. However, the numbers are small and the study duration was too short to be conclusive.

Nevertheless, the lung deposition PK studies SD131 and SD132 provided proof for comparable inflammation control. These studies were conducted with 2 puffs of Zephirus in order to improve the analysis of budesonide in plasma. Furthermore patients were trained in order to improve the technique of inhalation. However, during the previous centralised procedure (EMEA/H/C/002201), the available pharmacokinetic data did not support comparable anti-inflammatory control by budesonide: the lung deposition of both epimers of budesonide was demonstrated to be ~20% lower for Zephirus 150/25 µg than for Symbicort Turbuhaler 160/4.5 µg.
The apparent differences in comparative bioavailability between the studies can be in part due to the nature of the products: for orally inhaled products the specifications for the uniformity of delivered dose release are wider, typically ± 25%, instead of the more common specification seen with oral dosage forms of ± 5%. All these specifications are in accordance with the European Pharmacopoeia.
In addition the inhalation technique of the subject affects the amount of product inhaled. For these reasons, more variability in outcome of comparative bioavailability studies can be expected. The variability in the results of the three lung deposition PK studies is in the same range as the product specifications. Therefore, based on the data of all 3 lung deposition studies, a comparable inflammation control by budesonide in Zephirus as with the reference product can be expected.

Substitution indication
In the centralised procedure the CHMP was already able to conclude on the non-inferiority of the salmeterol component. Pharmacokinetic data comparing salmeterol of Zephirus with Serevent Diskus

indicated a higher exposure of salmeterol for Zephirus. However, non-inferiority of the salmeterol component was concluded based on the totality of evidence available in the clinical studies despite the CI found. No new or additional data were needed.

As for the step-up indication, comparability of budesonide anti-inflammatory control in Zephirus and Pulmicort can be expected based on the budesonide exposure in the three PK lung deposition studies.

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 Zephirus 300/25 µg and Zephirus 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 long term 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 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 Zephirus 300/25 µg appears to induce a stronger decrease than Zephirus 150/25 µg and the active comparator (budesonide + salmeterol), but the difference is within the predefined equivalence margins.
Overall, the safety profile of Zephirus is considered sufficiently characterized and can be satisfactorily managed in clinical practice.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The developed questionnaire contained 18 questions specific to Zephirus and 3 specific to the format of the package leaflet. The questions addressed all the key safety issues and concerns of Zephirus. The questions were open. Both the first and the second test round met the success criteria of 90% of the subjects being able to locate the requested information, and of those, 90% being able to give the correct answer, to indicate that they understood the information presented.
The general impression of the PL (content, language and layout) was mostly positive. No changes were made to the leaflet during or after testing.
Overall, the test results 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Zephirus 120 µg/20 µg and 240 µg/20 µg inhalation powder, hard capsule has a proven chemical-pharmaceutical quality. Adequate information has been provided on the development, manufacture and control of the drug product. The non-clinical documentation in support of this fixed dose combination containing well known active substances is satisfactory.

During the initial centralised procedure for Labazenit (= Zephirus) the clinical studies were insufficient to conclude comparable inflammation control for budesonide. The one available lung deposition PK study showed a lower bioavailability of budesonide from the fixed dose combination, suggesting lower deposition of budesonide in the lungs. However, the two newly submitted studies BUSAL-SD131 and BUSAL-SD132 indicate a comparable or higher lung deposition for Zephirus 150/25 µg compared to

Symbicort and Pulmicort, respectively. Taking all results together a comparable inflammation control by budesonide in Zephirus compared to the reference products can be expected.

The adverse events of budesonide and salmeterol have been previously characterised. From the clinical programme, there is no evidence that there is an additive effect when administered together via the same inhaler.

The SmPC, package leaflet and labelling are in the agreed templates and cover appropriate information to enable safe and effective use of Zephirus.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that Zephirus demonstrated adequate evidence of efficacy for the approved indication, and an acceptable level of safety. The overall benefit/risk balance of Zephirus is positive for the proposed indications i.e. both a step-up and substitution indication. The decentralised procedure was finished with a positive outcome on 23 July 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached

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