09 November 2017
EMA/774645/2017

Assessment report

Jorveza

International non-proprietary name: budesonide

Procedure No. EMEA/H/C/004655/0000

Note

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

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Administrative information

Name of the medicinal product:	Jorveza
Applicant:	Dr. Falk Pharma GmbH Leinenweberstr. 5 79108 Freiburg Germany
Active substance:	budesonide
International Non-proprietary Name/Common Name:	budesonide
Pharmaco-therapeutic group (ATC Code):	intestinal antiinflammatory agents, corticosteroids acting locally (A07EA06)
Therapeutic indication(s):	Jorveza is indicated for the treatment of eosinophilic esophagitis (EoE) in adults (older than 18 years of age).
Pharmaceutical form(s):	Orodispersible tablet
Strength(s):	1 mg
Route(s) of administration:	Oral use
Packaging:	blister (Alu/Alu)
Package size(s):	20 tablets, 30 tablets, 60 tablets, 90 tablets and 100 tablets

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List of abbreviations

Term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AIH	Autoimmune hepatitis
AMS	Avoidance, modification, and slow eating
ATC	Anatomical Therapeutic Chemical
AUCss,0-12h	AUC calculated based on plasma concentrations following drug administration from the first time point (t = 0) up to 12 h after dosing (ss – at steady state, Day 7)
AUCss,0-24h	AUC calculated based on plasma concentrations following drug administration from the first time point (t = 0) up to 24 h after dosing (ss – at steady state, Day 7)
AUCss,0-tlast	AUC calculated based on plasma concentrations following drug administration from the first time point (t = 0) up to the time point of the last quantifiable concentration above the limit of quantitation (tlast) (ss – at steady state, Day 7)
BID	Twice daily
BMI	Body mass index
CEP	Certificate of Suitability of the Ph. Eur.
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CYP	Cytochrome P450
d	Day
DB	Double blind (phase)
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EEsAI	Eosinophilic Oesophagitis Activity Index
EEsAI-PRO	Eosinophilic Oesophagitis Activity Index – Patient-Reported Outcome
EMA	European Medicines Agency
EoE	Eosinophilic oesophagitis
EoE-QoL-A	Adult Eosinophilic Oesophagitis Quality of Life questionnaire
eos	Eosinophils
EOT	End of treatment
EU	European Union
FAS	Full analysis set
FAS-DB	Full analysis set-double blind (phase)
FAS-FU	Full analysis set-follow-up (phase)
FAS-OLI	Full analysis set-open-label induction (phase)
FU	Follow-up
GC	Gas Chromatography
GERD	Gastroesophageal reflux disease
hpf	High-power field
HPLC	High performance liquid chromatography
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IL	Interleukin
IMP	Investigational medicinal product
IR	Infrared
ITT	Intention-to-treat
LOCF	Last observation carried forward
LC-MS/MS	Tandem mass spectrometry detection
LF	Linearity factor
LOCF	Last observation carried forward
MAH	Marketing Authorisation Holder
MD	Multiple dose
modSHS	Modified Short Health Scale

MS	Mass spectrometry
NRS	Numerical rating scale
OD	Once daily
OLI	Open-label induction (phase)
PatGA	Patient's Global Assessment
PBC	Primary biliary cirrhosis
PD	Pharmacodynamic(s)
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PP	Per-protocol
PP-DB	Per-protocol-double blind
PPI	Proton pump inhibitor
PPI-REE	Proton pump inhibitor-responsive oesophageal eosinophilia
PRA	Patient's Response Assessment
PRO	Patient reported outcome
PT	Preferred term
QoL	Quality of life
R	Reference dose
RCI	Repeated confidence interval
RH	Relative Humidity
SAE	Serious adverse event
SAF	Safety set
Scr 2	Screening visit 2
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TAMC	Total Aerobic Microbial Count
TEAE	Treatment-emergent adverse event
TLC	Thin layer chromatography
TYMC	Total Combined Yeasts/Moulds Count
VAS	Visual analogue scale
VDQ	Visual Dysphagia Question
WD	Withdrawal
XRPD	X-ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Dr. Falk Pharma GmbH submitted on 11 May 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Jorveza, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 September 2016.

Jorveza was designated as an orphan medicinal product EU/3/13/1181 on 5 August 2013 in the following condition: treatment of eosinophilic oesophagitis.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Jorveza as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

The applicant applied for the following indication: Jorveza is indicated for the treatment of eosinophilic esophagitis (EoE) in adults (older than 18 years of age).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Not applicable

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.

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 26 June 2014. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Harald Enzmann Co-Rapporteur: Tomas Boran

- The application was received by the EMA on 11 May 2017.
- Accelerated Assessment procedure was agreed-upon by CHMP on 21 April 2017
- The procedure started on 15 June 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 August 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 22 August 2017. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 1 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 12 September 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 5 October 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 October 2017.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 3 November 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 3 November 2017.
- During the meeting on 9 November 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Jorveza on 9 November 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Eosinophilic oesophagitis is a relatively new disease entity that has been described in the early 90s only. Although no single feature defines EoE, a constellation of compatible demographic, clinical, endoscopic, and histologic findings establish the diagnosis.

2.1.2. Epidemiology

Different studies with different methodologies have shown that there is a steady and relatively rapid increase in the incidence and prevalence of the condition during the last decade, or since the first description. According to the newest publications from Europe, the US and Canada, the incidence of the disease ranges between 6 and 13 new cases per year per 100,000 inhabitants. The latest prevalence data from Europe and the US have shown a prevalence of up to 40-56 cases per 100,000 inhabitants. (Lucendo et al; UEG Journal 2017). The disease is similarly observed in children, also with increasing incidence, however, with higher variability between the studies.

The disease may occur at any age, but has a clear peak in adults at the age of 30-50 years. A clear male predominance has been observed in all studies, with a recent meta-analysis showing a ratio of 2.01 (95% CI 1.64-2.48) (Arias Aliment Pharmacol Ther 2016).

The disease is burdened with a considerable influence on Quality of Life, and with the danger of long-term complications such as oesophageal fibrosis, food impaction, need for oesophageal dilation manoeuvers etc. However, an influence on overall life expectancy has not been observed. There is no associated mortality.

EoE is quite frequently associated with allergic disease, including asthma, allergic rhinitis, atopic dermatitis, and manifestations of food allergies. Previously, EoE has been considered a manifestation of gastroesophageal reflux disease (GERD), to which the observation of a response to PPI ("PPI responsive EoE" (=PPI-REE)) treatment in patients with EoE has contributed. According to the newest European consensus guideline, PPI-REE and EoE, are indistinguishable from one another and should be regarded to be within the same disease spectrum because they are clearly different from GERD, and the term "PPI-REE" is intended to be abandoned in the future (See Lucendo et al UEG Journal 2017). Because of this increase in patient population the prevalence could be higher than mentioned above.

2.1.3. Biologic features, Aetiology and pathogenesis

The pathogenesis of EoE is not completely understood. However, it is generally accepted that it results from a complex interplay between genetic, environmental, and host immune system factors.

The male predominance of eosinophilic esophagitis, as well as studies of family history and twin concordance and genome-wide association studies, suggest that there is a genetic component to eosinophilic esophagitis. Genome-wide association studies have reported three genes with proposed functional sequelae (the genes encoding thymic stromal lymphopoietin (TSLP), eotaxin-3, and calpain-14) as being altered in EoE.

Environmental factors blamed to play a role are similar to those assumed to be responsible for the increases in other allergic disease entities: Birth by caesarean section, premature delivery, antibiotic exposure during infancy, lack of breast-feeding, living in an area of lower population density, and lack of early exposure to microbes.

Similar to other allergic disease entities, there is support for the concept that eosinophilic esophagitis is an entity mediated by (an exaggerated) type 2 helper T (Th2) cell activity mainly regulated by TSLP. Th2-associated cytokines / chemokines such as interleukin (IL-) 4, Il-5, Il-13, chemokine (C C motif) ligand (CCL)-17 and CCL 18 play an important role in the pathogenesis of EoE. Th2 signals, among them most important IL-13, activate a specific, complex transcriptional profile in oesophageal epithelial cells, encompassing more than 500 genes, among them a strong induction of the gene CCL-26, coding for the cytokine eotaxin-3 and a reduction of genes

involved in the oesophageal barrier function (Desmoglein-1, Filaggrin). The damage caused by the chronic inflammation of the oesophageal epithelium promotes oesophageal remodelling processes which result in sub-epithelial fibrosis and the formation of strictures.

2.1.4. Clinical presentation, diagnosis and prognosis

In adults and adolescents the disease is mainly diagnosed after presentation of the patients with dysphagia, pain on swallowing (odynophagia) and complications, such as food impaction. This is different from children, where a variety of nonspecific symptoms, such as feeding difficulty, nausea and vomiting, heartburn, and failure to thrive are observed.

The final diagnosis of EoE is, however, only made after upper GI endoscopy, including biopsy of the oesophageal mucosa, the diagnosis of eosinophil infiltration of the oesophagus, and the exclusion of other disease entities, such as GERD, Achalasia, Coeliac disease, Crohn's Disease, and several connective tissue diseases (e.g. scleroderma). The endoscopic presentation of EoE is quite variable. The most common endoscopic findings in EoE patients are white specks, representative of oesophageal exudates, mucosal oedema, linear furrows, oesophageal rings and – as a result of chronic remodelling – strictures.

Eosinophil infiltration of the mucosa as such – although pathognomonic for EoE – is regarded to be a histological finding that needs interpretation in the clinical context, because it can also be found in a variety of other conditions.

During the course of the disease, patients often develop strategies to avoid symptoms, such as eating slowly, chewing carefully, cutting food into small pieces, lubricating foods with sauces, swallowing with frequent liquid intake, and avoiding foods likely to cause symptoms. Such 'coping' strategies develop gradually over years and may ultimately lead to a reduced symptom awareness which can delay the diagnosis of EoE by years in many patients.

As reported above, the disease leads to a considerably reduced Quality of Life, and – along with remodelling of the oesophagus – to the development of oesophageal strictures, and the subsequent need for dilation manoeuvers. Rarely, complications such as oesophageal perforation and rupture of the oesophagus from forceful retching (Boerhave's syndrome) have been observed. EoE has not been observed to be associated with the development of cancer and does not reduce life expectancy.

2.1.5. Management

The current management of EoE is based on the need to improve both the clinical symptoms, as well as the oesophageal inflammation.

Whereas the earlier American Practice Guidelines published in 2013 for the part of the treatment with medicinal products refer to the use of topical corticosteroids only, and PPI-REE as a different disease entity, the newer European Consensus Guideline (Lucendo) clearly recommend for the use of PPIs, and even long-term treatment with PPIs in those patients responding to the treatment. A clear recommendation for the use of topical steroids, however, is also included in the European guideline, without clearly denominating a "first line" or "second line" therapy.

a) Off label use of Proton-pump inhibitors:

A recent systematic review with meta-analysis, including 33 studies with 619 patients with suspected EoE, has shown that PPIs led to histological remission (defined by <15 eos/hpf) in 50.5% (95% CI 42.2– 58.7%) and

symptomatic improvement in 60.8% (95%CI 48.38–72.2%) of cases. However, this analysis also included several “low-quality” studies, and the authors cautioned about the heterogeneity in results, and potential for publication bias. Several randomised, controlled trials, published since 2011 have shown (histological) remission rates of 33% to 36% with PPIs. Therefore, PPI therapy may only be effective in a minority of patients. Whereas PPIs are all licensed for the treatment of reflux oesophagitis and Non-erosive reflux disease, a specific indication for EoE or PPI-REE is not part of the prescribing information.

b) Experimental and off-label use approaches in EoE, including topical steroids:

There have been reports referring to treatments with immunomodulators, such as azathioprine, biologicals (infliximab [anti TNF-alpha], omalizumab [anti-IgE], reslizumab, mepolizumab [anti-Il-5), CRTH-2 antagonists, anti-IL-13 antibodies), anti-leukotriene approaches (montelukast) and mast-cell stabilizers (cromolyn sodium), most of which have not been successful. Currently, IL-4 ABs, and anti-TGF-beta 1 medications are under development.

Systemic corticosteroids have also been documented to be efficacious, but were usually associated with high rates of systemic adverse effects. Recent reviews/guidelines do clearly not recommend the use of systemic corticosteroids, apart from refractory cases, including the most recent European consensus guidelines.

The majority of data referenced refer to the off-label of experimental use of topically acting corticosteroids, out of which the best studied medications are budesonide, and fluticasone. Both substances are usually used from inhaler preparations, which are either (after application without spacer) swallowed, or which are opened and used for the preparation of individually prepared suspensions.

For the demonstration of efficacy of these treatment modalities, two meta-analytic reviews are available (Chuang 2015 and Sawas 2015). The analysis by Chuang included 7 studies, and the one by Sawas included 11 studies. The European consensus guideline clearly recommends the use of topical steroids in the disease.

c) Dietary therapy:

Dietary treatment documented in the literature are elemental diet (amino-acid based liquid formula), elimination diet based on allergy testing, and the so-called “six-food elimination diet” (SFED). The majority of data available refers to the treatment of children, whereas the treatment under consideration is intended to be used in adults. Dietary treatment is usually associated with a relevant burden to patients, and long-term compliance remains an issue.

The European Consensus Guideline recommends that there is only a limited place for elemental diet in EoE, which is recommended only after failure of medical treatment. The consensus has voted against a recommendation for food allergy testing and diets based on these tests, due to unreliability of the results, and relatively low rates of treatment success. A more positive vote was given for the SFED, or for an empiric four-food elimination diet (FFED).

d) Oesophageal dilation:

This form of therapy is only used to treat acute episodes of severe dysphagia and/or oesophageal stenosis, and/or concomitant food impaction. The method, however, is effective in providing long-lasting symptom relief in patients with EoE and small diameter stenosis. However, in most patients dilation is associated with post-procedural pain and dilation has no impact on the underlying inflammatory process in the oesophagus. It is additionally referred to the fact that reviews of this treatment modality recommend to restrict oesophageal dilation for episodes of symptomatic small diameter stenosis and to combine it with medicinal or dietary therapy.

Unmet medical need:

The symptoms, as well as the nature of the disease are thought to be generally progressive with persistent symptoms and inflammation, leading to impairment of quality of life, and in the long-term to oesophageal remodelling resulting in stricture formation, and other functional abnormalities.

There is currently no medicinal product licensed for the treatment of the disease, and other treatment modalities are either burdened with compliance problems, and/or limited efficacy, or reserved for the treatment of complications.

About the product

Budesonide is a well-known, highly potent, non-halogenated glucocorticosteroid. The applicant is the MAH of several budesonide preparations which have been licensed since 1998 and an abundance of clinical data is available for budesonide in multiple pharmaceutical formulations (e.g. orodispersible tablet, gastro-resistant capsule, gastro-resistant granules, rectal foam) for various indications.

Budesonide 1 mg orodispersible tablets are white or almost white, round, biplane tablets with a smooth surface and facet. The tablets are placed on the tip of the tongue for disintegration. The dissolved material is subsequently swallowed with saliva little by little. The un-dissolved tablet must not be chewed or swallowed.

Type of Application and aspects on development

The applicant received Scientific Advice in the year 2014 for the toxico-pharmacological as well as the clinical development programme. Main discussion points at that time were the planned study duration as well as the choice of the primary endpoint for the planned pivotal trial (for induction treatment). The following points deserve further consideration:

- The applicant proposed to use a newly developed patient-reported outcome measure (PRO) to be used as primary endpoint. This was not endorsed by the CHMP because – among other deficiencies – full validation of the instrument was unlikely to be available before the conduct of the phase 3 study. Instead, the applicant was advised to use a simple Likert-scales or NRS based evaluation of the main symptoms. The use of a combined endpoint documenting symptom-based response/remission as well as histological remission was endorsed.

- The use of placebo was considered appropriate.

- CHMP agreed that a 40% superiority against placebo would be regarded to be clinically relevant.

- There was reluctance on the side of the CHMP to accept a 25% superiority for the maintenance phase of the planned clinical trials to be clinically relevant, based on the fact that the natural history of the disease is currently not fully known. This reluctance also related to the unknown safety profile at the time of advice, and the unresolved question whether patients would need maintenance treatment as permanent administration of the drug, or whether an intermittent treatment could be similarly effective. There were also concerns with the proposed definition of relapse for the planned maintenance study.

- The initially proposed duration of 4 weeks for the pivotal efficacy study was questioned.

- The proposed duration of the proposed maintenance trial (48 weeks) was endorsed.

- With regard to the proposed inclusion criteria, the CHMP recommended a minimum duration to be defined at inclusion of the patients, as well as exclusion of patients with PPI responsive EoE, and the consideration of the impact of dietary therapy at inclusion.

- With regard to the proposed interim analysis, both for the induction, as well as for the maintenance phase 3 trials, the CHMP gave several caveats with regard to the statistical planning and data integrity, and stated a clear preference for a blinded analysis of the data only. Issues were discussed along the requirements of the "Reflection paper", and the applicant was clearly instructed to argue their case for interim analyses in the context of the Reflection Paper, and to provide much more detail on how the interim analyses would be implemented in practice, with a discussion of the issues involved – particularly the exclusion of any operational bias and the non-homogeneity of effects.

- There were no specific concerns with regard to the monitoring of safety related to HPA axis suppression.

- A general caveat was given with regard to the plan to conduct one-pivotal study only.

- Although the overall size of the programme was considered sufficient based on the "well-known" status of the substance, and the orphan status of the compound, the overall size was not considered impressive.

The applicant has partly taken up the concerns of the CHMP. The overall size of the database is not relevantly different from what has been discussed during the Scientific Advice, and the proposed interim analysis has been conducted as proposed initially. However, the applicant has taken up the cautionary notes on the symptom-based component of the primary endpoint, as well as on the study duration.

The assumptions of the advice were based on the presentation of the total development programme. At the time of this assessment, the long-term efficacy and safety study (the "maintenance study") was still ongoing and is not be part of this application. However, the convincing nature of the data, and the unclear need for maintenance treatment, along with the unmet medical need, allow to conclude the risk-benefit ratio of the product.

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the non-availability of licensed medicinal products, as well as the character of alternative treatments (off-label use of products intended for different purposes with unsuitable presentation, emergency character of dilation therapy in late stage disease only, and the complicated nature and questionable compliance with dietary therapy) in conjunction with the demonstration of a relevant symptom burden, reduction of quality of life, as well as potential serious and severe consequences with regard to the development of complications and its therapy. The applicant has substantiated the claim that the unmet medical need can be addressed by presenting study results of high statistical significance as well as clinical relevance.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as orodispersible tablets containing 1 mg of budesonide as active substance.

Other ingredients are: disodium hydrogen citrate, anhydrous monosodium citrate, sodium hydrogen carbonate, sucralose, povidone K25, docusate sodium, mannitol, macrogol 6000 and magnesium stearate.

The product is available in blister pack consists of a cold-formable aluminium bottom foil and an aluminium lidding foil [20 µm] as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

Budesonide is a mixture of the C-22*S* (epimer A) and the C-22*R* (epimer B) epimers of 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione corresponding to the molecular formula $C_{25}H_{34}O_6$. It has a relative molecular mass of 430.5 and the following structure:

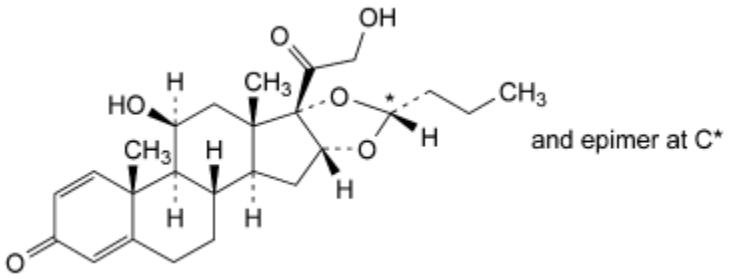

Figure 1: active substance structure

Budesonide is a white or almost white, crystalline powder, practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96 per cent).

As there is a monograph of budesonide in the European Pharmacopoeia (Ph. Eur.), the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for budesonide which has been provided within the current Marketing Authorisation Application. Sites for micronisation of budesonide are reported on the CEP. Additional test for residual solvents by GC (methanol) and test for particle size for non-micronized and micronized active substance are described. The holder of the certificate has declared the absence of material of human or animal origin used in the manufacture of the substance.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the CEP.

Specification

The active substance specification includes all the tests described in the current Ph. Eur. monograph for budesonide: appearance (visual), identity (IR, TLC, colour reaction), related substances (HPLC), epimer A (HPLC), loss on drying (Ph. Eur.) and assay (HPLC); with additional tests for particle size (microscopic) and residual solvents (GC) which are described on the CEP. The analytical methods used have been adequately described in the monograph and CEP and are valid. Ph. Eur. reference standards are used where appropriate. Batch analysis data on 3 production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

The active substance is packed in a double low density polyethylene bag. The bag is closed with a plastic noose, placed alternatively into a fibre carton drum or containers, depending on size, and then in carton boxes.

Stability data from 20 batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed container with no special storage conditions.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The proposed dosage form is an orodispersible tablet. The tablets are white or almost white, round, biplane (ø 7 mm x 2.2 mm) with a smooth surface and facet.

One unit contains 1 mg of budesonide with a total tablet mass of 141.40 mg, so that less than 1% of the composition account for the active substance (i.e. a low dose tablet).

The active substance is a potent glucocorticosteroid with a high topical anti-inflammatory activity and low systemic effects. The applicant has experience in the development of effervescent dosage forms. For example, budesonide 3 mg effervescent tablets, another development project of the applicant, are used to prepare an oral suspension for mouthwash prior to administration (indication: Graft-versus-host disease). When dropped in water the effervescent reaction is initiated and the tablet disintegrates.

The development of Jorveza was based on the theory that instead of preparing and administering an aqueous suspension, the mild effervescent reaction that is initiated in the presence of water could allow the direct oral application of a tablet by placing it on the tip of the tongue. This type of administration activates the *in situ* disintegration of the tablet, so that the dosage form disperses in the mouth. Two different strengths (budesonide 1 mg and 2 mg orodispersible tablets) were used as investigational medicinal products in the proof-of-concept, dose-finding and formulation selection studies.

Budesonide 1 mg orodispersible tablets were chosen for commercialisation. The formulation used during clinical studies is the same as that intended for marketing. The orodispersible tablets are intended to be placed on the tip of the tongue for disintegration. After swallowing, the budesonide-loaded saliva lines the mucosa of the oesophagus and delivers the active substance to the site of action. The ability to hold the active substance in the oesophagus and to increase the contact time is supported by using a surfactant in the formulation that might facilitate the fusion of the layers and thereby enabling bioadhesion. The finished product is therefore not considered to be an immediate release form in the sense that there is not a rapid systemic absorption from the lower gastrointestinal tract after being swallowed.

The budesonide has a consistent crystalline structure confirmed by XRPD and melting point analysis of commercial batches. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or national pharmacopoeial standards. There are no novel excipients used in the finished product formulation. The excipients chosen, their concentration, and the characteristics with potential impact to the finished product performance have been adequate discussed. The compatibility of the components of the finished product was confirmed in long-term and accelerated stability studies. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The primary packaging is Alu / Alu blister strips. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: wet granulation, drying, blending, compression and primary packaging. The manufacturing process is considered a standard manufacturing process. Despite the low content of the drug substance in the formulation (less than 1%) the data already presented in the process validation report demonstrate that content uniformity is not a critical quality attribute of drug product. Critical steps of manufacturing process have been identified, proposed equipment used for manufacture have been described and ranges of acceptance criteria have been substantiated.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. The manufacturing process has been validated by studies on three full scale production batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form; appearance of tablet (visual), appearance of blister (visual), resistance to crushing (Ph. Eur.), disintegration time in water (Ph. Eur.), loss on drying, average mass, uniformity of dosage units (Ph. Eur.), identity (HPLC, UV), assay (HPLC), related substances (HPLC), tightness of primary packaging and microbiological quality (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three full scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from seven batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH), up to 18 months under intermediate term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of budesonide 1 mg orodispersible tablets placed on stability are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, resistance to crushing, disintegration time in water, loss on drying, average mass, uniformity of dosage units, identity, assay, related substances, tightness of primary packaging and microbiological quality. The analytical procedures used are stability indicating.

It is known that temperature and humidity can affect the stability of effervescent / orodispersible tablets. In general long-term storage under intermediate and accelerated conditions is not tolerated as the effervescent reaction can be initiated.

In addition, one batch of tablets was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Control samples and the samples of the primary packed tablets comply

with the finished product specification whereas the samples without primary packaging (“deblistered tablets”) result in a decrease of the content and an increase of the impurities.

Based on available stability data, the proposed shelf-life of 2 years with the storage condition “Do not store above 25 °C. Store in the original package in order to protect from light and moisture.” as stated in the SmPC (section 6.3) was considered acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical and pharmaceutical 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 clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Budesonide 1 mg orodispersible tablet is a new medicinal product developed by the applicant as a treatment for active eosinophilic oesophagitis (EoE).

The active ingredient of Budesonide 1 mg orodispersible tablet is budesonide, a non-halogenated glucocorticoid derived from 16α-hydroxyprednisolone.

From the non-clinical point of view the active compound budesonide is well known. The effects observed in animal models comply with the effects seen with other glucocorticoids.

Regarding the current application it should be kept in mind that a systemic exposure with budesonide is not required to achieve pharmacodynamic activity in the current indication eosinophilic esophagitis. However, the general toxicity/ safety depends with the exception of local effects on the systemic exposure. From the non-clinical point of view the main aspects of the current application are whether or not the systemic exposure achieved by the use of budesonide orodispersible tablet is lower or at least equal to the exposure which can be achieved by the use of the already approved budesonide containing products. In this case the safety data obtained in the clinical use of the last 20 years can be easily transferred to the product under review. The second main aspect is the local tolerance of the medicinal product under review.

The Applicant summarizes in its dossier studies and bibliographic data of several galenic formulation of budesonide in different indications covering inflammatory gastrointestinal diseases.

Orodispersible tablets in early stages of its development were called 'effervescent tablets'. Effervescence process starts and stimulates the production of saliva over 90 to 120 seconds, containing 1 mg budesonide as active substance. Orodispersible tablets are an uncoated formulation to be placed in the mouth where they disperse rapidly. Immediate release orodispersible tablets facilitate that relatively high local budesonide concentrations can be achieved in the oesophageal mucosa.

The main difference between budesonide 3 mg effervescent tablets and orodispersible tablets 1 and 2 mg is interchange of sweetener to avoid the degradation of active substance. No safety concerns can be expected in the amount of sweetener used. Formulations are thus considered as comparable in terms of toxicity testing.

2.3.2. Pharmacology

The anti-inflammatory effects of budesonide are considered well known. With the exception of one safety pharmacology study no new studies on pharmacodynamics have been provided. Bibliographic data covering the period of October 2013 until March 2017 were newly added.

Primary pharmacodynamic studies

The effects of glucocorticoids are a result of several molecular mechanisms due to the pleiotropic effects of glucocorticoid receptors on multiple signalling pathways (Rhen and Cidlowski: NEngJMed 2005: Antiinflammatory Action of Glucocorticoids —New Mechanisms for Old Drugs). The activity of glucocorticoids is mediated by specific cytoplasmic glucocorticoid receptors, expressed in virtually all cells (Andus and Targan: Inflammatory Bowel Disease: From Bench to Bedside 1994, Stoeck et al: J Pharmacol ExpTher1994: In Vitro and in Vivo Anti-Inflammatory Activity of the New Glucocorticoid Ciclesonide, Pelaia et al: J Cel lPhysiol 2007: Effects of TGF-ß and Glucocorticoids on Map Kinase Phosphorylation, IL-6/IL-11 Secretion and Cell Proliferation in Primary Cultures of Human lung Fibroblasts , Paolieri et al: Allergy1997: Inhibition of adhesion molecules by budesonide on a human epithelial cell line (lung carcinoma), Dorscheid et al: AmJRespirCritCareMed 2001: Apoptosis of Airway Epithelial Cells Induced by Corticosteroids). The multiple mechanisms of action include direct and indirect genomic regulation and non-genomic activation of anti-inflammatory pathways (Rhen and Citlowski: NEngJMed 2005: Antiinflammatory Action of Glucocorticoids —New Mechanisms for Old Drugs, Möllman et al.: Kluwer 1996: Principles of topical versus systemic corticoid treatment in inflammatory bowel disease, Esmailpour et al: EurJPharmSci 1998: Binding kinetics of budesonide to the human glucocorticoid receptor, Thalen et al: ActaDermatolVenerol 1989: Development of Glucocoticosteroids with Enhanced Ratio between Topical and Systemic Effects, Stoeck et al: JPharmacolExpTher 2004: In Vitro and in Vivo Anti-Inflammatory Activity of the New Glucocorticoid Ciclesonide).

The anti-inflammatory activity of budesonide in the mucosa of the gastrointestinal tract (Sokulsky et al: AmJPhysiolGastrointest 2016: TRAIL deficiency and PP2A activation with salmeterol ameliorates egg allergen-driven eosinophilic esophagitis , Fabia et al: UlcExpColitis 1993: The effect of locally or systemically administered budesonide on acetic acid-induced acute colitis in the rat, Fabia et al: AlimentPharmacolTher 1994: Topical anticolitic efficacy and selectivity of the glucocorticoid budesonide in a new model of acetic acid-induced acute colitis in the rat, van Rees et al: Gastroenterology 1993: Effect of Local Budesonide Treatment in experimental inflammatory bowel disease, Martinsson et al: JPharmacolExpTher 1999: Beneficial Effects of Ropivacaine in Rat Experimental Colitis, Jacobson et al Gastroenterology 1993: Budesonide Enemas prevent Extensive Changes in the enteric nervous system in rats with experimental colitis, Sanovic et al:

AmJPathol 1999: Damage to the Enteric Nervous System in Experimental Colitis , Palmen et al.: DigDisSci1998: Effects of Local Budesonide Treatment on the Cell-Mediated Immune Response in Acute and Relapsing Colitis in Rats , Boyed et al: ScandJGastroenterol 1995: Effects of Plain and Controlled-Ileal-Release Budesonide Formulations in Experimental Ileitis, Hardtke-Wolenski et al.: Hepatology 2013: Genetic Predisposition and Environmental Danger Signals Initiate Chronic Autoimmune Hepatitis Driven by CD41 T Cells, Gustafsson et al: ScandJGastroenterol 2001: Topical and Oral Anti-inflammatory Activity of Budesonide Compared with Oral Prednisolone in an Animal Model Using Allergen-induced Gut Mucosal Exudation of Plasma as a Marker), in particular the oesophageal mucosa is considered as primary dynamic activity. A systemic uptake is not required to exert this effect. Budesonide is taken up into the cells of the mucosa and submucosa of the gastrointestinal tract, where it exerts its activity. Budesonide was not directly tested in models of eosinophilic esophagitis (EoE). The general effect of glucocorticoids was demonstrated by treatment of ovalbumin-induced EoE in mice with dexamethasone (Sokulsky et al: AmJPhysiolGastrointest 2016: TRAIL deficiency and PP2A activation with salmeterol ameliorates egg allergen-driven eosinophilic esophagitis). The glucocorticoid treatment significantly reduced oesophageal inflammation and the infiltration of eosinophils and mast cells in the oesophageal mucosa. Furthermore, the features of tissue remodelling as oesophageal circumference and fibrosis were significantly reduced compared to untreated mice and the expression of cytokines associated with the induction of EoE was reduced. The mechanism of action in EoE treatment is thought to be common to all glucocorticoids. Beside of that budesonide was shown to be effective in several models of gastrointestinal inflammation in the past (Fabia et al: UlcExpColitis 1993: The effect of locally or systemically administered budesonide on acetic acid-induced acute colitis in the rat, Fabia et al: AlimentPharmacolTher 1994: Topical anticolitic efficacy and selectivity of the glucocorticoid budesonide in a new model of acetic acid-induced acute colitis in the rat, van Rees et al: Gastroenterology 1993: Effect of Local Budesonide Treatment in experimental inflammatory bowel disease, Martinsson et al: JPharmacolExpTher 1999: Beneficial Effects of Ropivacaine in Rat Experimental Colitis, Jacobson et al Gastroenterology 1993: Budesonide Enemas prevent Extensive Changes in the enteric nervous system in rats with experimental colitis, Sanovic et al: AmJPathol 1999: Damage to the Enteric Nervous System in Experimental Colitis, Palmen et al.: DigDisSci1998: Effects of Local Budesonide Treatment on the Cell-Mediated Immune Response in Acute and Relapsing Colitis in Rats , Boyed et al: ScandJGastroenterol 1995: Effects of Plain and Controlled-Ileal-Release Budesonide Formulations in Experimental Ileitis, Hardtke-Wolenski et al.Hepatology 2013: Genetic Predisposition and Environmental Danger Signals Initiate Chronic Autoimmune Hepatitis Driven by $CD4^+$ T Cells, Gustafsson et al: ScandJGastroenterol 2001: Topical and Oral Anti-inflammatory Activity of Budesonide Compared with Oral Prednisolone in an Animal Model Using Allergen-induced Gut Mucosal Exudation of Plasma as a Marker).

Secondary pharmacodynamic studies

The references provided include studies showing effects on electrolyte transport (Sandle: Gut 1991: Segmental variability of glucocorticoid induced electrolyte transport in rat colon, Alvaro et al.: JHepatol 2000: Corticosteroids modulate the secretory process of intrahepatic biliary epithelium), studies on anti-inflammatory activities of budesonide in various animal models of topical inflammation (Brattsand Glucocorticoids 1989: Development of Glucocorticoids with Lung selectivity, Brattsand et al.: EurJRespirDis 1982: Development of New Glucocorticosteroids with a Very High Ratio Between Topical and Systemic Activities, Brattsand et al: JSteroidBiochem 1982: Influence of 16α, 17α–Acetal Substitution and Steroid Nucleus Fluorination on the Topical to Systemic Activity Ratio of Glucocorticoids, Hiroi et al.: FoliaPharmacolJapon 1985: Anti-inflammatory Effects of Budesonide) and in vitro and in vivo studies in models of pulmonary inflammation (Persson et al: IntArchAllergyApplImmunol 1989: Budesonide Reduces Sensitivity to Antigen but does Not Alter Baseline Tone

or Responsiveness to Carbachol, Terbutaline, and Enprofylline in IgE-Sensitized Guinea-Pig Tracheae, Andersson et al: Biochemical and Biophysical Research communications 1992: Regulation of Lung Endothelin Content by the Glucocorticosteroid Budesonide, Jansson et al.: VasculPharmacol 2005: Effects of budesonide and N-acetylcysteine on acute lung hyperinflation, inflammation and injury in rats, Werner-Klein et al.: PulmPharmacolTher 2008: Development and characterisation of a novel and rapid lung eosinophil influx model in the rat , Stoeck et al.: JPharmacolExpTher 2004: In Vitro and in Vivo Anti-Inflammatory Activity of the New Glucocorticoid Ciclesonide). Some studies investigate the anti-cancer activity of budesonide in the lung (Wattenberg and Estensen: Carcinogen 1997: Studies of chemopreventive effects of budenoside on benzo[a]pyrene-induced neoplasia of the lung of female A/J mice, Wattenberg et al: Carcinogen 2000: , Chemoprevention of pulmonary carcinogenesis by brief exposures to aerosolized budesonide or beclomethasone dipropionate and by the combination of aerosolized budesonide and dietary myo-inositol, Wang et al : CancerRes 2003: Mice with Alterations in Both p53 and Ink4a/Arf Display a Striking Increase in Lung Tumor Multiplicity and Progression: Differential Chemopreventive Effect of Budesonide in Wild-type and Mutant A/J Mice, Balansky et al.: ProcNatIAcadSciUSA 2006: Influence of FHIT on benzo[a]pyrene-induced tumors and alopecia in mice: Chemoprevention by budesonide and N-acetylcysteine). No information was provided on other types of cancer.

Safety pharmacology programme

The applicant performed one in vitro pharmacology safety study (BUB-6) evaluating the effect of budesonide on hERG channels. The effect of budesonide was tested up to 150 µM concentration (corresponding to a 58.37 % inhibition of hERG-mediated currents). Due to poor solubility, the previously intended higher range of concentrations (500µM and 1000µM) was not feasible to test. Nonetheless, the range of tested concentrations distinctly exceeded the expected maximal plasma concentration (790 to 26 000 – times higher) observed in clinical settings.

The obtained data revealed that estimated IC_{50} (106 µM) is well above the expected clinical plasma concentration (approximately 18 000 - times). Therefore, based on the study results, there is no expected potential risk for QT interval prolongation in the proposed posology.

The literature review on the safety pharmacology of budesonide is considered adequate (Nishimura et al. Kisotorinsho 1985: General Pharmacological Study of budesonide, Angelo-Katthar and Thulesius: GenPharmac 1985: Vascular effects of glucocorticosteroids with special reference to budesonide). No potential risks were raised at clinically relevant concentrations (the maximal plasma concentration observed in the PK study (BUU-1/BIO) was 2.56 ng/mL).

Pharmacodynamic drug interactions

No data on pharmacodynamic drug interactions are available.

2.3.3. Pharmacokinetics

The pharmacokinetic data submitted by the Applicant consists of published references, studies performed to obtain MA for other budesonide containing products as publications or applicants own data and new studies which have been performed to obtain MA for budesonide orodispersible tablets. These new studies are local tolerance studies in the hamster cheek model at which toxicokinetic parameters were obtained in parallel; in vitro studies investigating enzyme inhibition and induction and pharmacokinetic drug-drug interaction studies.

Bibliographic data on the absorption of budesonide have been provided for mouse, rat and dog (Andersson et al.: ActaPharmacolToxicol 1986: Tissue Distribution and Fate of Budesonide in the Mouse, Ryrfeldt et al.: JSteroidBiochem 1979: Pharmacokinetic Studies of a potent Glucocorticoid (Budesonide) in Dogs by High-Performance Liquid Chromatography, Miller-Larsson et al.: APT 2001: Gut Mucosal Uptake and Retention Characteristics Contribute to the High Intestinal Selectivity of Budesonide Compared with Prednisolone in the Rat). Another set of studies have been performed by the Applicant in support of the MA of budesonide containing rectal foam in dogs. Since MA has already been obtained for these products the relevance of these studies appears to be low.

The studies with budesonide orodispersible tablets and similar products (oral rinsing solution and oral suspension) in the hamster cheek model are GLP compliant. The plasma concentration of budesonide and its metabolites was quantified by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS). The results show that budesonide is rapidly absorbed. The plasmatic concentration of budesonide and its metabolites 6-ß-hydroxy-budesonide and 16-α-hydroxyprednisolon increased dose dependently and c_{max} was reached approximately 1.5 hours after administration. The metabolism was rapid and the baseline plasmatic budesonide/metabolite concentration was reached within 8 hours. The results are in a good agreement with published data and results obtained in the past - although it should be noticed that the absorption of the different products depend on the respective formulation targeting different intestinal tissues. The results obtained in the hamster cheek model are in a good agreement with results obtained in humans. In man the t_{max} was reached within 1 hour showing a low bioavailability of only 9%.

Regarding the tissue distribution the Applicant refers to published data (Andersson et al.: ActaPharmacolToxicol 1986: Tissue Distribution and Fate of Budesonide in the Mouse, Ryrfeldt et al.: EurJRespirDis 1982: Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid) showing a rapid uptake and extensive distribution of budesonide and a high protein binding of approximately 90%. Further studies showed that budesonide forms fatty acid conjugates generating intracellular depots which may slowly release active budesonide. These depots may be responsible for budesonide´s prolonged activity. Such effects have been shown in lung tissues. In vitro studies suggest, that budesonide might be a weak substrate of P-pg; however it remains unclear in how far this contributes to budesonide´s low bioavailability.

Regarding the metabolism and metabolic pathways the Applicant refers to published data (Tunek et al.: DrugMetDisp 1997: Reversible Formation of Fatty Acid Esthers of Budesonide, an Antiasthma Glucocorticoid, in Human Lung and Liver Microsomes, Wieslander et al.: AmJRespirCellMolBiol 1998: Pharmacologic Importance of the Reversible Fatty Acid Conjugation of Budesonide Studied in a Rat Cell Line In Vitro, Jendbro et al.: DrugMetabDipos 1982: Pharmacokinetics of Budesonide and its Major Ester Metabolite After Inhalation and intravenous administration of budesonide in the rat, Andesson et al.: JSteroidBiochem 1982: In vitro Biotransformation of Glucocorticoids in Liver and Skin Homogenate Fraction From Man, Rat and Hairless Mouse, Ryrfeldt et al.: EurJRespirDis 1982: Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid, Edsbäcker et al.: -DrugMetabolDispos 1987: Liver Metabolism of Budesonide in Rat, Mouse, and Man, Andersson et al.: ActaPharmacolToxicol 1986: Tissue Distribution and Fate of Budesonide in the Mouse, Ryrfeldt et al.: JSteroidBiochem 1979: Pharmacokinetic studies of a potent glucocorticoid (Budesonide) in Dogs by High Performance Liquid Chromatography, Jönsson et al: DrugMetaDispos 1995: Budesonide is metabolized by Cytochrome P450 3A (CYP3A4) Enymes in Human Liver, Lu et al.: DrugMetDisp 2008: Prediction of Pharmacokinetic Drug-Drug Interactions Using Human Hepatocyte Suspension in Plasma and Cytochrome P450 Phenotypic Data. II. In Vitro-in Vivo Correlation with Ketoconazole, Zimmermann et al.: EurJPharmSci 2009: PXR-mediated induction of human CYP3A4 and mouse Cyp3a11 by the glucocorticoid budesonide) showing that budesonide is rapidly metabolized during the first pass through the liver forming the metabolites

6-ß-hydroxy-budesonide and 16-α-hydroxyprednisolon. Studies with human liver microsomes indicate that budesonide is mainly metabolized by CYP3A4 subfamily of the P450 isoenzymes. The isoenzmyes CYP1A2 and 2C9 may contribute to a much lesser extent. CYP3A4 is not only located in the liver but also in the gut wall and some effects have to be anticipated; however no animal data was shown to differentiate between gut and liver metabolism. However, one reference show that enterobacteria may contribute to the budesonide degradation (Yadva et al. IntJPharmaceut 2013: Colonic bacterial metabolism of corticosteroids).

The Applicant provided two studies *(BUB-3/XT135043; BUB-4/XT133057)* investigating enzyme induction and inhibition by budesonide. The inhibition study showed that budesonide may be a very weak CYP3A4 inhibitor (IC_{50}>1130 ng/mL). The study on enzyme induction revealed no relevant inductive potential on CYP1A2, CYP2B6, CYP2C9 and CYP3A4/5. Furthermore the Applicant referred to published data leading to the conclusion that the risk for budesonide mediated drug interactions is rather low (Dilger et al: InflammBowelDis 2004: Identification of Budesonide and Prednisone as Substrates of the Intestinal Drug Efflux Pump P-glycoprotein, Arya et al.: JPharmPharmacol 2005: Brain permeability of inhaled corticosteroids , Maier et al.: BrJPharmacol 2007: Effects of budesonide on P-glycoprotein expression in intestinal cell lines, Crowe and Tan: ToxicolApplPharmacol 2012: Oral and inhaled corticosteroids: Differences in P-glycoprotein (ABCB1) mediated efflux). The proposed SmPC for Jorveza reflects these findings.

No new studies are provided investigating the excretion of budesonide. Published data show that the main route of elimination is fecal due to biliary excretion (Andersson et al.: ActaPharmacolToxicol 1986: Tissue Distribution and Fate of Budesonide in the Mouse, Ryrfeldt et al.: JSteroidBiochem 1979: Pharmacokinetic studies of a potent glucocorticoid (Budesonide) in Dogs by High Performance Liquid Chromatography). Renal elimination was also demonstrated but to a much lesser extent. From studies in nursing mothers receiving maintenance treatment for asthma with inhaled budesonide it is known that the substance is excreted into the milk (Fält et al: JAllergyClinImmunol 2007: Exposure of infants to budesonide through breast milk of asthmatic mothers). No animal or human data are available after oral administration.
The Applicant provided furthermore one study investigating potential pharmacokinetic drug-drug interactions via the P-gp (MDR-1), BCRP (ABCG2), OATP1B1, OATP1B3 transporters (BUB-5/DM0104). Budesonide´s influence on P-gp and BCRP was tested with adequate marker substances to a budesonide concentration up to 100 µM. The influence on OATP1B1 and OATP1B3 was tested up to 300 nM budesonide. At the highest concentration tested, budesonide inhibited P-gp and BCRP to 92.7 and 62.5%. The calculated IC_{50} values were 9.78 and 43.1 µM, respectively. OATP1B1 and OATP1B3 activity was not inhibited by budesonide at any concentration. The Applicant points out further that the IC_{50} value for P-gp is more than 10-fold higher than the maximum expected concentration in the intestinal lumen on the apical side of the enterocytes after administration of budesonide orodispersible tablet as calculated according to the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**; 2012).

The Applicant argued furthermore that the IC_{50} is also more than 6500-fold higher than the total C_{max} reached after administration of budesonide orodispersible tablet in EoE patients provided a C_{max} of 0.64 ng/ml is assumed. Thus, a clinically relevant inhibition of intestinal and systemic P-gp can be sufficiently excluded. Likewise the inhibition of BCRP is considered clinically not relevant as the IC_{50} of BCRP inhibition is even higher than the IC_{50} for P-gp inhibition. Based on net efflux ratios across cell layers in absence and presence of an inhibitor, it was suggested that budesonide may be a weak substrate for P-gp, but no substrate for BCRP. The accumulation of budesonide in OATP1B1-expressing cells was more than 2-fold higher than in controls. However, this accumulation was not reproducible and not affected by known inhibitors. Therefore, budesonide is not or possibly only a weak substrate of OATP1B1. No accumulation was observed in OATP1B3-expressing cells, indicating that budesonide is not a substrate for OATP1B3.

Conversely in vitro interaction studies (Lu et al.: Drug Metab Dispos 2008 and Jönsson et al.: Drug Metab Dispos. 1995) have demonstrated strong inhibition of the metabolic degradation of budesonide by specific inhibitors of CYP3A4; i.e. ketoconazole. Contrary to CYP3A4 inhibitors, compounds or drugs such as carbamazepine and rifampicin, which are able to induce CYP3A4, might reduce the systemic exposure but probably also the local exposure at the gut mucosa by an accelerated metabolism of budesonide. This drug interaction does not influence the safety of budesonide but might reduce the therapeutic efficiency. Accordingly a recommendation to the SmPC and PIL was added to use other medicinal products applied to throat at least 30 min before or after Jorveza.

2.3.4. Toxicology

Single dose toxicity

The Applicant referred mainly to published data to show the single dose toxicity in mice, rats and dogs (Ito et al.: Kisotorinsho 1985: Toxicity Study of Budesonide). The results show that the acute toxicity depends on the route of administration. The LD_{50} values ranged between 53.6 and 173 mg/kg for s.c. administration, between 98.9 and 320 mg/kg for i.v. administration and between 138 and 300 mg/kg for the i.p. route. In contrast, after oral administration, LD_{50} values between >3200 mg/kg and >10,000 mg/kg were obtained. Moreover, the study BUF-11/Preclin was conducted by the Applicant to establish the toxicity of the test substance following single intravenous administration to NMRI mice. Whereas this study did not reveal any at this time point unknown toxic effect of budesonide it might has minor relevance for this application as it was aimed to provide comparative data for the main degradation product of the foam. The toxicity of budesonide depends highly on the route of administration with the oral route being the lowest. This apparently reflects the rather low bioavailability due to low systemic uptake.

Repeat dose toxicity

Regarding the repeated dose toxicity studies the Applicant referred to published data obtained in rats in dogs (Sato et al.: Kisotorinsho 1985: Toxicity Study of Budesonide, Ekman et al.: DrugRes 1987: toxicity study of the New glucocorticosteroid Budesonide in Rats, Tanimoto et al.: Kisotorinsho 1985: Toxicity Study of Budesonide) and the Applicant's own data obtained for the MA of the budesonide containing rectal foam already approved in the past. In these studies budesonide induced the expected systemic effects typical for glucocorticoids. The extent of effects is related to the systemic exposure and was therefore dependent on the dose and the route of administration. Administration of high doses of budesonide by all routes resulted in weight loss and death caused by emaciation. There was also enlargement of the liver associated with increased glycogen storage.

These effects are consistent with the known lipodystrophy caused by glucocorticoids (Drugs Ther Perspect 2008). The effects on the immune system included decreased WBC, lymphocyte and platelet counts associated with atrophy of the thymus and spleen. Lymphoid depletion was observed throughout the lymphoid system including various lymph nodes, spleen and thymus gland; these observations are consistent with the anti-inflammatory actions of glucocorticoids. The increased incidence of skin abscesses and necrotic foci accompanied by bacterial colonies in heart, liver and kidneys seen in several studies was likely associated with the anti-inflammatory actions of glucocorticoids and is therefore considered as secondary effect. There was an increased incidence of gastric mucosal ulcers, sometimes accompanied by peritonitis or haemorrhage; gastric ulcers are a known systemic side effect of glucocorticoids in the clinic (Drugs Ther Perspect 2008). There was

also atrophy of the adrenal glands, which may be related to the known adrenal suppression (reduction of endogenous cortisol) by glucocorticoids in the clinic (Rhen and Cidlowski 2005; Drugs Ther Perspect 2008). Topical application of budesonide also resulted in thinning or atrophy of the treated skin. From a formal point of view the safety ratio between human to animal doses tested is very small and would have been a point for discussion for a new clinical entity. However, overall, there were no new and unexpected findings which are reported by the Applicant and none have to be expected.

Genotoxicity

Evaluation of the genotoxic and carcinogenic potential of budesonide was mainly based on published data (Fujii et al: Kisotorinhso 1985: Toxicity Study of Budesonide, Ryrfeldt et al: ToxicolPathol 1982: Liver Tumors in Male Rats Following Treatment with Glucocorticosteroids). There was no evidence for a relevant genotoxic potential of budesonide. Budesonide showed the same rat specific carcinogenic effects as other glucocorticoids. In conclusion, results resemble those known for other glucocorticoids.

Carcinogenicity

See “Genotoxicity” above.

Reproduction Toxicity

Information on reproductive toxicity of budesonide was based on published data (Toteno et al: Kisotorinsho 1985: Toxicity Study of Budesonide, Kilhström and Lundberg: Arzneimittelf 1987: Teratogenicity Study of the New Glucocorticosteroid Budesonide in Rabbits) which is agreed. All aspects of male and female fertility as well as of prenatal and postnatal development had been investigated in rats, and prenatal development in a second species, the rabbit, too.

The results of these studies resemble those which are already known from other glucocorticoids (e.g. foetal deaths, intrauterine growth retardation, and skeletal abnormalities).

Budesonide for oral use has already been licensed in Europe for other gastrointestinal indications with daily doses above the maximum recommended dose for Jorveza (9 mg versus 2 mg). Therefore no unknown risk will be associated with a lower daily dose in pregnant women.

The information provided in section 4.6 of the SmPC is in line with the information for already licensed oral budesonide products to be used at higher daily doses for the treatment of other gastrointestinal disorders.

At present juvenile toxicity is not an issue as treatment of the paediatric population is not indicated yet.

Toxicokinetic data

See below “local Tolerance”

Local Tolerance

The Applicant has performed new local tolerance studies using the hamster cheek pouch model to investigate the properties of budesonide orodispersible tablets and similar budesonide containing products (oral suspension/ rinsing solution). These studies were accompanied by toxicokinetic evaluations which allow the calculation of animal to human safety factors based on pharmacokinetic data obtained in hamsters and human

patients. The local tolerance studies revealed no significant local effects (please see below). For the orodispersible tablet the safety factor for local effects was at least 13 times based on cmax or 10 times based on allometric scaling of the applied dose. However, the applied doses were high enough to induce significant systemic toxicity. Based on this finding steroid-like adverse effects have also to be expected in humans. Considering this aspect a comparison of human exposure data should be applied. The use of 3 mg Budenofalk hard capsule results in a c_{max} of 1-2 ng/ml (SmPC Budenofalk 3 mg magensaftresistente Hartkapseln) whereas the use of the current orodispersible tablet was calculated to result in a c_{max} of 0.64 ng/ml. Based on these considerations further adverse effects as already known for the use of budesonide containing product are not expected from the non-clinical point of view. Despite the severe systemic effects observed in hamsters only minimal irritation of the epithelium of the cheek pouches, tongue and oesophagus was observed. Epithelial atrophy was the main histopathological finding in cheek pouch, tongue and oesophagus. The thinning of the epithelium was considered as a typical glucocorticoid effect and assumed to be at least partly caused by systemically available budesonide. Thus, from the viewpoint of potential local effects, budesonide orodispersible tablets at the proposed clinical use are not expected to induce irritating effects at the oesophageal mucosa. Similar results were obtained with the oral suspension/ rinsing solution. The Applicant provided furthermore several studies concerning the local tolerance of budesonide containing products intended for rectal application which are mostly already approved within Europe. The results do not lead to the conclusion that the orodispersible tablet will cause further unwanted effects.

Other toxicity studies

The body of data was further enlarged by published references investigating effects of budesonide on stomach, skin and eye as well as potential phototoxic and allergic effects and sensitization. None of these references showed relevant findings.

2.3.5. Ecotoxicity / environmental risk assessment

For the active ingredient budesonide a preliminary tailored environmental risk assessment was provided.

Table 6 Summary of main study results

Substance (INN/Invented Name):					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.23			Potential PBT: N, but B
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	3.23			
	BCF				pending
Persistence	DT50 or ready biodegradability				pending
Toxicity	NOEC or CMR				pending
PBT-statement :	pending				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined with prevalence and treatment regime	0.00008	µg/L			> 0.01 threshold: N
Other concerns (e.g. chemical class)	Budesonid is a glucocorticoid and, as such, is considered a potential endocrine disruptor and therefore the potential endocrine activity of this compound was investigated in an appropriate chronic test system with relevant endpoints.				Other concern: Y
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Ready Biodegradability Test	OECD 301	not readily biodegradable			
Aerobic Transformation in Aquatic Sediment systems	OECD 308	Pending, expected end 2018			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
		NOEC		µg/L	species

Metabolism bridging study in vitro; human S9, rainbow trout S9		S9 incubated in vitro metabolite profile was found to be remarkably faster in humans (24.81 - 48.71 minutes) than in rainbow trouts (199.83 and 268.27 minutes)	Metabolic stability in fish > humans
Fish FLC	OPPTS 850.1500	Expected end 2018	
Phase IIb Studies			
Bioaccumulation	OECD 305	Pending, expected end 2018	

Budesonide is a glucocorticoid and, as such, is considered a potential endocrine disruptor and therefore the potential endocrine activity of this compound was investigated in an appropriate chronic test system with relevant endpoints.

The environmental risk assessment for budesonide can however not be finished until the ongoing test on transformation in aquatic sediment systems (OECD 308), bioaccumulation study (OECD 305) and fish full life-cycle Test (OPPTS 850.1500) are completed by end of 2018.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the submission of the outstanding reports on the test on transformation in aquatic sediment systems (OECD 308), the bioaccumulation study (OECD 305) and the fish full life-cycle Test (OPPTS 850.1500) by end of 2018, to which the applicant committed.

2.3.6. Discussion on non-clinical aspects

The literature review on the safety pharmacology of budesonide is considered adequate.

In vitro studies have demonstrated strong inhibition of the metabolic degradation of budesonide by specific inhibitors of CYP3A4; i.e. ketoconazole. In humans a clear influence of ketoconazole on the pharmacokinetics of budesonide was observed. The Applicant pointed out that a potential inhibition of the metabolic degradation of budesonide should be considered, when strong CYP3A4 inhibitors are administered concomitantly. This interaction can lead to enhanced systemic exposure with budesonide and therefore probably to enhanced systemic side-effects. Potent inhibitors of CYP3A4 are ketoconazole, ritonavir, itraconazole, clarithromycin, cobicistat, and grapefruit juice. As there are not enough data to give recommendations for an adjustment of doses, the combination of budesonide with strong CYP3A4 inhibitors should be avoided as outlined in 4.5 of the SmPC.

The Applicant performed one in vitro pharmacology safety study evaluating the effect of budesonide on hERG channels. Based on the study results, there is no expected potential risk for QT interval prolongation in the proposed posology.

From pharmacokinetic and toxicology perspective, there are no concerns to the approval. Toxicokinetic exposures reached in local tolerance studies in hamsters were comparable and appropriate to exceed the systemic exposure in patients. The non-clinical data package is sufficient to allow safety concerns extrapolation

to humans. No new adverse effects are expected in clinical use with maximal daily dose of 2 mg budesonide orodispersible tablets.

Minor concerns to the Environmental Risk Assessment Report in line with the EMA Guidelines on ERA can be addressed post authorisation. The environmental risk assessment for budesonide cannot be finished until the ongoing test on transformation in aquatic sediment systems (OECD 308), bioaccumulation study (OECD 305) and fish full life-cycle Test (OPPTS 850.1500) are completed by end of 2018 and will be submitted upon finalisation.

2.3.7. Conclusion on the non-clinical aspects

The application is considered approvable from the non-clinical data view point.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The applicant has – based on the well-known status of the substance, and the documented efficacy of other compounds with the similar or comparable substances – only conducted a limited development programme, consisting of 1 phase I PK/PD study, one phase II dose-finding study, and the pivotal phase III study.

- Tabular overview of clinical studies

Type of Study	**Study Identifier;**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s);** **Dosage Regimen;** **Route of Administration**	**Number and Type of Subjects Treated;** **Demographics**	**Duration of Treatment**	**Study Status;** **Type of Report**
PK	BUU-1/BIO;	Describe the PK of budesonide administered as orodispersible (formerly called effervescent) tablets in healthy subjects and in patients with active EoE	Open, fixed treatment order, single- and multiple-dose, 2-centre, phase I	1 mg and 2 mg budesonide orodispersible tablets 3 mg budesonide capsules Healthy subjects and Patients S.D. and M.D. 3 mg capsule 1x 1 mg tablet 1x 2 mg tablet 2x2 mg tablet	13 healthy subjects treated M: 6, F: 7 Age: Range: 31–53 y Mean ± SD: 43.8 ± 6.7 y 12 healthy subjects completed M: 6, F: 6 Age: Range: 34–53 y Mean ± SD: 44.9 ± 5.7 y 12 patients with EoE treated and completed M: 10, F: 2 Age: Range: 20–62 y Mean ± SD: 39.3 ± 13.2 y	Healthy subjects S.D. Patients S.D. MD: 1 week	Completed

Type of Study	Study Identifier;	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number and Type of Subjects Treated; Demographics	Duration of Treatment	Study Status; Type of Report
Efficacy/ Safety	Supportive study BUU-2/EEA;	Primary: -Assess efficacy of 2×1 mg/d or 2×2 mg/d budesonide orodispersible tablets and 2×2 mg/d oral budesonide viscous suspension vs. placebo for the induction treatment of active EoE Secondary: -Identify optimum dose -Study safety and tolerability	Double-blind, double-dummy, randomised (1:1:1:1 ratio), 4 parallel groups, multi-centre, placebo-controlled, dose-finding, confirmatory phase II	1 mg and 2 mg budesonide orodispersible tablets 5 mL budesonide viscous suspension Placebo orodispersible tablet Placebo viscous suspension Double-dummy technique to achieve full blinding All study medication taken p.o., BID (morning and evening) over a 14-day continuous period.	76 adult patients with EoE (FAS and safety populations) 75 patients completed. 1 patient was prematurely withdrawn due to an intolerable AE (swollen lips and skin exanthema) BUL 1 mg BID: 19 BUL 2 mg BID: 19 BUU 2 mg BID: 19 Placebo: 19 M: 63, F: 13 Age: Range: 18–70 y Mean ± SD: 39.7 ± 13.1	2 weeks	Completed

Type of Study	Study Identifier;	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number and Type of Subjects Treated; Demographics	Duration of Treatment	Study Status; Type of Report
Efficacy/ Safety	Pivotal study BUL-1/EEA; Tab-Id.: 5.3.5.1 BUL-1/EEA	Primary: efficacy of 2×1 mg/d budesonide orodispersible tablets vs. placebo Secondary: -Study safety and tolerability	Double-blind, randomised (2:1 ratio), 2 parallel group, multi-centre, placebo-controlled, comparative, confirmatory, phase III	1 mg budesonide orodispersible tablets (BUL) Placebo orodispersible tablet All study medication taken p.o., BID (morning and evening) over a 6-week continuous period. Patients who entered the optional open-label induction (OLI) treatment period thereafter were treated with BUL 1 mg BID for an additional 6 weeks.	88 patients with confirmed EoE BUL 1 mg BID: 59 M: 48, F: 11 Age: Range: 18–69 y Mean ± SD: 37.0 ± 11.47 Placebo BID: 29 M: 25, F: 4 Age: Range: 26–64 y Mean ± SD: 36.9 ± 9.20 51 patients entered the OLI phase Placebo→BUL: 28 BUL→BUL: 23	6-week DB treatment period followed by optional 6-week OLI treatment with BUL 1 mg BID for eligible patients	Completed

2.4.2. Pharmacokinetics

Absorption

The applicant has conducted study BUU-1/BIO, a single- and multiple dose PK and PD study, in order to primarily characterise the pharmacokinetics of the new pharmaceutical formulation, and compare it to the well-established (reference) capsule-formulation used in IBD/AIH.

In this study, the single-dose as well as the multiple dose administration of different doses of the orodispersible tablets have been compared to the reference formulation both in healthy volunteers as well as in patients with EoE. The overall study plan and conduct is considered satisfactory.

The single-dose PK of the new formulation is characterised by a short lag-time and early peak concentration of 1 hour only, and rapid elimination with an elimination half-life of about 2 hours. The pharmacokinetics of the compound is linear over the tested dose range from 1 mg to 4 mg in single-dose.

The overall results of the study, in comparison to the used reference formulation of budesonide (Budenofalk) capsules are shown in the following table:

Table 7 Budesonide **plasma** pharmacokinetic parameters after single dose administration as orodispersible tablets (1 mg (SD1), 2 mg (SD2), 4 mg (SD3)) or as oral capsule (3 mg (R)) in healthy subjects

	R (n = 12)*	**SD1 (n = 12)**
C_{max} [ng/mL]	0.72±0.55 [0.36 - 1.07]	0.44±0.31 [0.24- 0.63]
t_{lag} [hr]	3.00 (2.98 - 6.00)	0.17 (0.00 - 0.33)
t_{max} [hr]	5.00 (3.98 - 12.00)	1.00 (0.50 - 2.00)
$t_{1/2}$ [hr]	3.56 (2.00 - 38.46)	2.13 (0.68 - 3.59)
AUC_{0-12h} [hr*ng/ml]	3.25±1.30 [2.25 - 4.25]	1.44±0.99 [0.81 - 2.07]
$AUC_{0-tlast}$ [hr*ng/ml]	3.12±1.41 [2.04 - 4.20]	1.10±0.98 [0.48 - 1.72]
AUC_{0-inf} [hr*ng/ml]	5.41±3.46 [2.52 - 8.31]	1.50±1.08 [0-81 - 2.19]
CL/f [L/hr]	706.52±331.06 [429.75 - 983.29]	992.94±664.59 [570.68 - 1415.20]
Vz/f [L]	5979.62±4555.59 [2171.06 - 9788.19]	2391.93±892.60 [1824.79 - 2959.06]
CL/f/kg [L/hr/kg]	9.70±4.90 [5.61 - 13.80]	14.61±9.86 [8.34 - 20.87]
Vz/f/kg [L/kg]	80.46±59.24 [30.93 - 129.98]	35.52±14.94 [26.03 - 45.02]
%AUC [%]	29.03 (9.80 - 84.09)	26.94 (12.85 - 57.77)
F_{rel} (SD1/R)**	0.75±0.31 [0.49 -1.02]	
	R (n = 12)*	**SD2 (n = 12)**
C_{max} [ng/mL]	0.72±0.55 [0.36 - 1.07]	0.90±0.68 [0.46 - 1.33]
t_{lag} [hr]	3.00 (2.98 - 6.00)	0.17 (0.00 - 0.33)
t_{max} [hr]	5.00 (3.98 - 12.00)	0.84 (0.67 - 3.00)
$t_{1/2}$ [hr]	3.56 (2.00 - 38.46)	2.00 (1.34 - 6.62)
AUC_{0-12h} [hr*ng/ml]	3.25±1.30 [2.25 - 4.25]	2.92±2.38 [1.41 - 4.43]
$AUC_{0-tlast}$ [hr*ng/ml]	3.12±1.41 [2.04 - 4.20]	2.71±2.49 [1.13 - 4.29]
AUC_{0-inf} [hr*ng/ml]	5.41±3.46 [2.52 - 8.31]	3.15±2.66 [1.45 - 4.84]
CL/f [L/hr]	706.52±331.06 [429.75 - 983.29]	997.93±532.69 [659.48 - 1336.39]
Vz/f [L]	5979.62±4555.59 [2171.06 - 9788.19]	2969.98±1407.41 [2075.76 - 3864.21]
CL/f/kg [L/hr/kg]	9.70±4.90 [5.61 - 13.80]	14.59±8.10 [9.44 - 19.74]
Vz/f/kg [L/kg]	80.46±59.24 [30.93 - 129.98]	44.68±25.21 [28.67 - 60.70]
%AUC [%]	29.03 (9.80 - 84.09)	17.09 (5.78 - 26.05)
F_{rel} (SD2/R)**	0.72±0.31 [0.46 - 0.98]	
	R (n = 12)*	**SD3 (n = 12)**
C_{max} [ng/mL]	0.72±0.55 [0.36 - 1.07]	1.89±1.25 [1.09 - 2.68]
t_{lag} [hr]	3.00 (2.98 - 6.00)	0.17 (0.00 - 0.33)
t_{max} [hr]	5.00 (3.98 - 12.00)	0.67 (0.47 - 2.00)
$t_{1/2}$ [hr]	3.56 (2.00 - 38.46)	2.59 (1.45 - 10.37)
AUC_{0-12h} [hr*ng/ml]	3.25±1.30 [2.25 - 4.25]	5.64±4.24 [2.95 - 8.34]
$AUC_{0-tlast}$ [hr*ng/ml]	3.12±1.41 [2.04 - 4.20]	5.43±4.36 [2.66 - 8.20]
AUC_{0-inf} [hr*ng/ml]	5.41±3.46 [2.52 - 8.31]	6.31±5.11 [3.07 - 9.56]
CL/f [L/hr]	706.52±331.06 [429.75 - 983.29]	923.13±487.11 [613.63 - 1232.63]
Vz/f [L]	5979.62±4555.59 [2171.06 - 9788.19]	3828.88±2963.66 [1945.86 - 5711.90]
CL/f/kg [L/hr/kg]	9.70±4.90 [5.61 - 13.80]	13.63±8.07 [8.50 - 18.76]
Vz/f/kg [L/kg]	80.46±59.24 [30.93 - 129.98]	57.10±45.44 [28.23 - 85.98]
%AUC [%]	29.03 (9.80 - 84.09)	9.94 (6.32 - 44.35)
F_{rel} (SD3/R)**	0.85±0.42 [0.50 - 1.20]	

The main result of the study has shown that the relative bioavailability of the new formulation appears to be lower than the one of the reference formulation, although the comparison of the dose-normalised overall

exposure did not exclude equality for all doses tested. This slight discrepancy can be explained by the short observation time and resulting incomplete coverage of the concentration time profile.

When comparing similar doses of the two compounds, the peak exposure has been demonstrated to be higher than for the reference. However, when the proposed therapeutic dose of 1 mg (single dose) is administered in comparison to a single dose of the reference formulation, both the overall and peak exposure are clearly below those of the reference.

In multiple-dose administration, the PK profile is not relevantly altered, and there is little, if any, accumulation.

The PK of the new compound appears to be altered in patients as compared to healthy volunteers, with a reduced clearance, and prolonged elimination half-life (4.5 hours), which is shown in the following table (for multiple dose administration):

Table 8: Budesonide plasma pharmacokinetic parameters following multiple dose oral administration of budesonide orodispersible tablets (4 mg once daily in the morning) for 7 days (MD) in healthy subjects and in patients with eosinophilic esophagitis

	Healthy subjects (n = 12)	Patients (n = 12)
$C_{ss,max}$ [ng/mL]	1.68±1.26 [0.88 - 2.48]	2.19±1.13 [1.47 - 2.91]
t_{lag} [hr]	0.00 (0.00 - 0.33)	0.00 (0.00 - 0.17)
$t_{ss,max}$ [hr]	0.83 (0.50 - 3.00)	1.33 (0.50 - 2.00)
$t_{1/2}$ [hr]	3.01 (1.19 - 6.38)	4.43 (2.99 - 7.80)
$AUC_{ss,0-12h}$ [hr*ng/ml]	5.84±4.12 [3.22 - 8.46]	8.56±4.47 [5.72 - 11.40]
$AUC_{ss,0-24h}$ [hr*ng/ml]	6.45±4.61 [3.52 - 9.38]	9.98±5.41 [6.54- 13.42]
$AUC_{ss,0-tlast}$ [hr*ng/ml]	5.68±4.23 [2.99 - 8.37]	8.48±4.58 (5.57 - 11.39)
ACR	1.07±0.22 [0.93 - 1.21]	0.93±0.17 [0.82 - 1.03]
LF	1.00±0.26 [0.83 - 1.17]	0.79±0.16 [0.69 - 0.90]

This was attributed by the applicant to an altered biotransformation via CYP3A4 (lower activity in patients as compared to healthy volunteers), however this has to be considered to be partly speculative. From a theoretical point of view reduced influence of intestinal CYP3A4, as well as reduced hepatic “first-pass” metabolism, due to partial absorption in the oesophagus, which circumvents the portal circulation could also play a role. Appropriate information on increased peak plasma concentrations in Patients and an increase in AUC_{0-12} compared to healthy subjects is outlined in the SmPC.

No studies on the influence of food have been performed with the new formulation. The literature shows a negligible influence of food on the PK of budesonide. Although the data have been collected with a delayed release capsule formulation, the results as such can be extrapolated (Brunner M et al: Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation. Br J Clin Pharm 2006; 61: 31-38 and Lundin P et al: Effect of food on the pharmacokinetics of budesonide controlled ileal release capsules in patients with active Crohn’s disease. Aliment Pharmacol Ther 2001; 15: 45-51). However, the proposed mode of intake is of course after a meal, because it is (reasonably) assumed that intake with or before a meal would relevantly reduce the local exposure of the oesophageal mucosa for which it is thought that it plays a major role for the therapeutic effects to take place. Based on this assumption, even a relevant reduction of the systemic exposure could be fully acceptable, as this might only be expected to further reduce the danger for the typical systemic glucocorticoid (adverse) effects. The deduction of the mode of intake with regard to food on clinical and practical considerations is deemed acceptable. Due to the assumed preferential local action of the compound, a

½ hour interval without any food intake after the intake of the medication is included into the recommendations for intake, in order to avoid a relevant reduction of local exposure. Similarly, the intake of any other locally acting products in the mouth, throat, or oesophagus should be avoided within 30 minutes before and after the intake of the product, in order to avoid potential pharmacodynamics interactions.

Distribution

During study BUU-1/BIO, the apparent volumes of distribution (Vz/f) ranges from 2391.93 to 3828.88 l for the single-dose administration in healthy volunteers, and 3291.81 l for single dose administration in patients. The weight-based volume of distribution was 35.52 to 57.10 l/kg in healthy volunteers and 42.46 l/kg in patients.

The volume of distribution for the reference (capsule) preparation, ranged from 2518.04 l in patients to 5079.62 l for healthy volunteers. The weight-based volume of distribution of the reference was 80.46 l/kg in HVs and 33.57 l/kg in patients.

Elimination

The PK study confirmed the fact known from the literature that budesonide is quantitatively metabolised and excreted mainly by renal secretion as metabolites, as no mother compound has been found to be excreted into urine (See also: Edsbäcker S and T Andersson: Pharmacokinetics of Budesonide (Entcort TM EC) capsules for Crohn's Diesease. Clin Pharmacol 2003, 43: 803-821.) The median elimination half-life is 2 - 3 hours in healthy subjects and 4 - 5 hours in EoE patients. Clearance of budesonide is about 13 – 15 L/hour/kg in healthy subjects and 6.54 ± 4.4 L/hour/kg in EoE patients. Budesonide is eliminated only in marginal if any amounts by the kidney. No budesonide, but only budesonide metabolites were detected in urine.

Dose proportionality and time dependencies

- **Dose proportionality**

Dose proportionality was assessed within study BUU-1/BIO with an analysis of dose-normalised plasma PK parameters, which is shown in the following two tables:

Table 9: Budesonide dose-normalized plasma pharmacokinetic parameters after single dose administration as orodispersible tablets (1 mg (SD1), 2 mg (SD2), 4 mg (SD3)) or as oral capsule (3 mg (R)) in healthy subjects

	R (n = 12)*	SD1 (n = 12)
C_{max} [ng/mL]	0.24±0.18 [0.12 - 0.36]	0.44±0.31 [0.24 - 0.63]
$AUC_{0\text{-tlast}}$ [hr*ng/ml]	1.04±0.47 [0.68 - 1.40]	1.10±0.98 [0.48 - 1.72]
$AUC_{0\text{-inf}}$ [hr*ng/ml]	1.80±1.15 [0.84 - 2.77]	1.50±1.08 [0.81 - 2.19]
	R (n = 12)*	**SD2 (n = 12)**
C_{max} [ng/mL]	0.24±0.18 [0.12 - 0.36]	0.45±0.34 [0.23 - 0.67]
$AUC_{0\text{-tlast}}$ [hr*ng/ml]	1.04±0.47 [0.68 - 1.40]	1.36±1.24 [0.56 - 2.15]
$AUC_{0\text{-inf}}$ [hr*ng/ml]	1.80±1.15 [0.84 - 2.77]	1.57±1.33 [0.73 - 2.42]
	R (n = 12)*	**SD3 (n = 12)**
C_{max} [ng/mL]	0.24±0.18 [0.12 - 0.36]	0.47±0.31 [0.27 - 0.67]
$AUC_{0\text{-tlast}}$ [hr*ng/ml]	1.04±0.47 [0.68 - 1.40]	1.36±1.09 [0.67 - 2.05]
$AUC_{0\text{-inf}}$ [hr*ng/ml]	1.80±1.15 [0.84 - 2.77]	1.58±1.28 [0.77 - 2.39]

Source: Section 14.2, Table I.7.3
$AUC_{0\text{-inf}}$, $AUC_{0\text{-tlast}}$, C_{max}, are summarized as arithmetic mean±SD [95% CI]
* n = 8 for $AUC_{0\text{-inf}}$, n = 9 for $AUC_{0\text{-tlast}}$.

Table 10: Dose-normalized ratios and differences between the test single dose oral administration as orodispersible tablets (1 mg (SD1), 2 mg (SD2), 4 mg (SD3)) and the reference 3 mg oral dose (R) administered as capsules in healthy subjects

	SD1 / R (n = 12)*
Ratio C_{max}	2.61±1.86 [1.43 - 3.80]
Ratio $AUC_{0\text{-12h}}$	1.28±0.50 [0.89 - 1.67]
Ratio $AUC_{0\text{-tlast}}$	0.94±0.41 [0.63 - 1.25]
Ratio $AUC_{0\text{-inf}}$	0.75±0.31 [0.49 - 1.02]
Difference t_{max} [hr]	-4.17 (-10.67 - -1.98)
	SD2 / R (n = 12)*
Ratio C_{max}	2.48±1.52 [1.51 - 3.44]
Ratio $AUC_{0\text{-12h}}$	1.19±0.44 [0.85 - 1.53]
Ratio $AUC_{0\text{-tlast}}$	1.11±0.42 [0.78 - 1.43]
Ratio $AUC_{0\text{-inf}}$	0.72±0.31 [0.46 - 0.98]
Difference t_{max} [hr]	-4.33 (-11.00 - -2.65)
	SD3 / R (n = 12)*
Ratio C_{max}	2.57±1.56 [1.58 - 3.56]
Ratio $AUC_{0\text{-12h}}$	1.19±0.27 [0.97 - 1.40]
Ratio $AUC_{0\text{-tlast}}$	1.19±0.30 [0.96 - 1.42]
Ratio $AUC_{0\text{-inf}}$	0.85±0.42 [0.50 - 1.20]
Difference t_{max} [hr]	-4.33 (-10.33 - -3.00)

The linearity factor (LF) value in patients is less than the expected value 1.00 (meaning expected increase in AUC with repeated dosing) which is ruled out by the confidence limits. In healthy subjects, however, the mean LF value is the expected value of 1.00. Dose proportionality has roughly been shown.

- **Time dependency**

Based on the results of study BUU-1/BIO, there was no, or if any, minor budesonide accumulation as shown by its accumulation ratio (ACR) in both healthy subjects and patients with CIs not excluding the value 1 and a mean value in patients below 1.

Pharmacokinetics in target population

The relevant comparisons for the demonstration of the PK in the target population (as compared to healthy volunteers) can be taken from study BUU-1/BIO. For the comparisons are based on the single- and multiple-dose evaluations of the 4 mg dose please refer to above chapter on absorption where the study results are described.

Special populations

No studies on the influence of age, gender, intake of food or the influence of hepatic and renal impairment on the PK of budesonide from the new formulation have been conducted. The applicant entirely relies on the data available from the literature (See: Edsbäcker 2003 (as given above); Lundin PDP et al: Pharmacokinetics of budesonide controlled ileal release capsules in children and adults with active Crohn's disease. Aliment Pharmacol Ther 2003; 17: 85-92; Rautiainen H et al: Pharmacokinetics and bone effects of budesonide in primary biliary cirrhosis. Aliment Pharmacol Ther 2006; 24: 1545-1552; Hempfling W, Grunhage F, Dilger K, Reichel C, Beuers U, Sauerbruch T. Pharmacokinetics and pharmacodynamic action of budesonide in early- and late-state primary biliary cirrhosis. Hepatology. 2003;38(1):196-202).

With regard to renal impairment, the literature does not provide relevant studies, and the applicant proposes to use the compound with caution in renally impaired patients. Whereas in general, based on the known excretion of metabolites in urine only, it can be assumed that no relevant alterations of PK takes place in mildly to moderately impaired patients, and these may reasonably be treated with additional caution as outlined in the SmPC. However, due to the lack of PK data, the effects of budesonide PK have to be considered unpredictable for severely impaired patients and these patients should not be treated as outlined in the SmPC.

For patients with liver impairment some literature data is available (see above references showing data in PBC-patients), which indicate a relevant increase of plasma levels, depending on the severity of the impairment. Additional data from the applicant themselves for their capsule formulation, however, show that the presence of liver disease and/or cirrhosis (without signs of impaired liver function) does not relevantly influence the PK. However, because no systematic data are available, the compound should not be administered in patients with liver impairment as outlined in the SmPC.

The influence of age has been found to be negligible in the available literature. Additional explorative evaluations of the pharmacokinetic data have revealed that the PK is overall not relevantly dependent on the factors age and gender.

Pharmacokinetic interaction studies

As known from the literature, budesonide is metabolised by the Cytochrome P 450 3A4, and has no or low affinity to the related CYP3A5, and to the frequently associated transporter P-glycoprotein (See: Jönsson G et al: Budesonide is metabolized by cytochrome P450 3A (CYP3A) enzymes in human liver; Drug Metab Dispos 1995; 23: 137-142; Ufer M et al: Influence of CYP3A4, CYP3A5, and ABCB1 genotype and expression on budesonide pharmacokinetics: A possible role of intestinal CYP3A4 expression. Clin Pharmacol Ther. 2008;84:43-46).

The applicant has, in addition, tested a variety of cytochromes and transporters in vitro, and no potential for interaction has been detected (see preclinical assessment). The potential for interaction with inhibitors or inducers of CYP3A4 is known from the literature (See: Seidegard J: Reduction of the inhibitory effect of ketoconazole on budesonide pharmacokinetics by separation of their time of administration. Clin Pharmacol Ther 200; 67:13-17) The two main metabolites of budesonide, 16α-hydroxyprdednisolone, as well as 6β-hydroxybudesonide are known to have no relevant glucocorticoid activity.

The analysis of the potential influence of genetic variations with regard to the metabolism of the compound has shown that only a minor clinical impact of genetic variations of CYP3A4 on drug metabolism has been documented. Moreover, CYP3A4 is minimally expressed in oesophagus, so it is not likely that the genetic polymorphism will have significant influence on budesonide metabolism.

In the PK study conducted, the exposure to these metabolites has been shown to be higher after the administration of the orodispersible tablet formulation as compared to the capsule formulation on a dose-normalised basis, which was confirmed with the higher excretion in urine.

Both a high inter-subject as well as a high intra-subject variability was observed in the study BUU-1/BIO for the novel formulation as well as reference marketed formulation. This is in agreement with literature data for other budesonide formulations, and no further information is requested.

2.4.3. Pharmacodynamics

Mechanism of action

Budesonide is a non-halogenated glucocorticosteroid, which acts primarily anti-inflammatory via binding to the glucocorticoid receptor. In the treatment of EoE with Jorveza, budesonide inhibits antigen-stimulated secretion of many pro-inflammatory signal molecules such as thymic stromal lymphopoeitin, interleukin-13 and eotaxin-3 in the esophageal epithelium, which results in a significant reduction of the esophageal eosinophilic inflammatory infiltrate.

Primary and Secondary pharmacology

The applicant has conducted only very limited investigations into the pharmacodynamics of the compound as part of the Phase I PK study. This is – similar to the PK development programme – based on the fact that the substance budesonide is well known, and effects of glucocorticosteroids do clearly not need to be characterised any further.

The effects of topically acting glucocortocosteroids on the inflamed oesophageal mucosa of EoE patients have also extensively been described in the literature (See e.g.: Gross KL and JA Cidlowski: Tissue-specific glucocorticoid action: a family affair. Trends Endocrinol Metab. 2008; 19: 331-339; Straub RH and M Cutolo:

Glucocorticoids and chronic inflammation. Rheumatology, 2016; 55: Suppl 2: ii6-ii14), and the main molecular mechanism appears to be the anti-inflammatory activity on the expression of IL-13 and eotaxin. Glucocorticosteroids have also been shown to restore cell integrity by elevating the production of tight junction and cell adhesion proteins. In addition, glucocorticosteroids have been shown to reverse fibrotic remodelling of the oesophagus by reducing profibrotic cytokines.

During the multiple-dose administration (7 days) of the PK study BUU-1/BIO, the included 12 patients also reported their symptomatic response (with a non-validated symptom score), which showed a slight, but relatively inconsistent, and not statistically significant reduction of the symptoms. The effects on the blood eosinophil counts were, however, showing a marked reduction, thus clearly indicating pharmacodynamic activity.

During study BUU-1/BIO, the applicant also investigated the development of the endogenous (morning) cortisol levels in comparison to the reference formulation, thus investigating the potential influence of the compound on the HPA-axis. All single-dose observations did not show relevant effects on endogenous cortisol levels in comparison to the reference formulation.

However, after multiple-dose administration, the endogenous cortisol levels were clearly lowered (compared to the single-dose reference intake), both in healthy subjects, as well as in EoE patients. This was also reflected in the urinary excretion of cortisol, which also showed a relevant decrease after multiple-dose administration. The clinical relevance of these alterations of endogenous cortisol plasma levels and urinary excretion can, however, not be assessed from the data presented, because the dose administered was higher than the therapeutic dose, and no placebo comparison was included. A theoretical potential for the influence of the compound on the HPA-axis can be assumed and is outlined in 4.4 of the SmPC. Systemic glucocorticosteroid effects are an important potential risk in the RMP.

2.4.4. Discussion on clinical pharmacology

This is a new pharmaceutical formulation (orodispersible tablet) of a well-known substance, which is used both as orally and rectally administered pharmaceutical forms, as well as inhaled products in different indications. Systemic exposure with budesonide is not required to achieve pharmacodynamic activity in the current indication eosinophilic esophagitis. However, the general toxicity/ safety depend with the exception of local effects on the systemic exposure.

The applicant presents publications together with a limited development programme with regard to the documentation of pharmacokinetics. The development programme therefore partly relies on the extrapolation of data and known properties of the substance from other medicinal product, which is considered an overall reasonable strategy.

In addition to literature provided to describe the clinical pharmacology of the product the applicant presents one study, conducted in healthy volunteers and in patients (Study BUU-1/BIO) of which the main purpose was to compare the PK and bioavailability of the proposed orodispersible tablet formulation to the well-known (delayed release) capsule formulation, which was used as reference.

Based on similar amounts administered, it has been shown that the new compound is unlikely to develop a relevantly higher exposure, although the peak concentrations in plasma, due to the nature of the pharmaceutical form, are increased. However, comparing the recommended single doses for clinical treatment,

the exposure to the patients is clearly expected to be lower than for the capsule formulation. This lower exposure is partly counteracted by a higher exposure detected in patients as compared to healthy volunteers.

The data generated have also been used to prove the linear pharmacokinetics of the new compound, as well as exclude any relevant accumulation over time. Weight and sex do not have a relevant influence on the PK of the compound.

The applicant also relies on data publicly available for the active substance budesonide on metabolism and excretion. Budesonide undergoes extensive biotransformation by CYP3A4 in the mucosa of the small intestine and in the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1% of that of budesonide. CYP3A5 does not contribute significantly to the metabolism of budesonide.

The median elimination half-life is 2 - 3 hours in healthy subjects and 4 - 5 hours in EoE patients. Clearance of budesonide is about 13 – 15 L/hour/kg in healthy subjects and 6.54 ± 4.4 L/hour/kg in EoE patients. Budesonide is eliminated only in marginal if any amounts by the kidney. No budesonide, but only budesonide metabolites were detected in urine.

Investigations in special populations, such as dedicated studies in patients with hepatic and renal impairment were not carried out with Jorveza. Therefore instruction how to deal with these patients has to be deduced from the known data and has to follow a principle of caution. A relevant proportion of budesonide is metabolised in the liver by CYP3A4 and, as the systemic exposure of budesonide is considerably increased in patients with impaired hepatic function, the product is not recommended for use in these patients.

With regard to renal impairment, the literature does not provide relevant studies. Because budesonide is not excreted via the kidneys but only its metabolites it can be assumed that no relevant alterations of PK takes place in mildly to moderately impaired patients. Patients with mild to moderate impairment may therefore be treated with caution with the same doses as patients without renal impairment. Renal function should be closely monitored. However, due to the lack of PK data, the effects of budesonide PK have to be considered unpredictable for severely impaired patients and these patients should not be treated.

Information on hepatic and renal impairment is appropriately outlined in the SmPC.

Co-treatment with potent CYP3A inhibitors such as ketoconazole, ritonavir, itraconazole, clarithromycin, cobicistat, and grapefruit juice, may cause a marked increase of the plasma concentration of budesonide and are expected to increase the risk of systemic side effects. Therefore, concomitant use should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects.

Ketoconazole 200 mg once daily orally increased the plasma concentration of budesonide (3 mg single dose) approximately 6-fold during concomitant administration. When ketoconazole was administered approximately 12 hours after budesonide, the plasma concentration of budesonide increased approximately 3-fold.

This information is appropriately described in the SmPC.

The pharmacodynamic investigations performed during the early development did not relevantly contribute to the further characterisation of the compound. However, the PD of glucocorticosteroids in general, and of budesonide in particular, are well known and are not considered to need additional elucidation.

No specific studies are available demonstrating the delivery of budesonide to the oesophageal mucosa. The applicant mainly puts forward the argument that the strong and rapid histological resolution of the inflammation

in the oesophageal mucosa indicates sufficiently that after application of the orodispersible tablets, budesonide is appropriately and sufficiently available at the oesophageal epithelium and/or mucosa which is considered acceptable.

The proposed recommendation for the intake of the orodispersible tablet is “after a meal”. This method of application is considered appropriate with regard to the local exposure of the oesophagus, which is the target of the treatment.

2.4.5. Conclusions on clinical pharmacology

The study presented on the PK of the new formulation with the well-known substance budesonide is considered adequate to characterise the PK profile of the compound. Other necessary data to enable the safe and efficacious use of the compound can be derived from the data available in the public domain. The products can be considered approvable from the pharmacology view point.

2.5. Clinical efficacy

2.5.1. Dose response study

The supportive and dose-response study, Study BUU-2/EEA, was a double-blind, double-dummy, randomized, placebo-controlled phase II study on the efficacy and tolerability of a 14-day treatment with budesonide effervescent tablets vs. viscous budesonide suspension vs. placebo in patients with eosinophilic esophagitis.

The primary objectives of the trial was the assessment of efficacy of different doses of budesonide effervescent tablets (2x1 mg/d and 2x2 mg/d) compared to oral viscous budesonide suspension (2x2 mg/d) and placebo. The secondary objectives were to identify the optimum dose for the induction of remission in EoE, and to assess safety and tolerability, patients QoL, and patient’s preferences with regard to treatment

The study was conducted according to a 2-stage group sequential test design. The planned interim analysis was justified with a reference to the ‘Reflection paper on methodological issues in confirmatory clinical trials with an adaptive design’ (CHMP/EWP/2459/02) because no reliable estimate of the magnitude of the expected treatment effect with the new pharmaceutical formulations was possible.

The two co-primary endpoints in this study were the rate of histological remission, defined as a mean of <16 eos/mm^2 hpf at week 2 and the change in the mean numbers of eos/mm^2 hpf (eosinophil load) from baseline to week 2 (LOCF). Secondary endpoints included the rate of histological remission, histological response, the change in peak eos, and endoscopic scores, as well as the evaluation of different dysphagia and pain questionnaires, global assessment tools (by the physician) and Quality of Life.

The study was stopped early at the interim analysis due to overwhelming efficacy. 77 patients were randomised and included in the final analysis. There were only 2 withdrawals during the study. The baseline demographics and other baseline parameters were not relevantly different between the treatment groups.

The evaluation of the co-primary endpoints showed the following results:

Table 11: Histological remission (final analysis; FAS and PP evaluation):

		Number (%) of patients in histological remission defined as mean of <16 eos/mm² hpf at week 2 (LOCF)			
		BUL 1mg BID	**BUL 2mg BID**	**BUU 2mg BID**	**Placebo**
FAS	n (%)	19/19 (100.0%)	18/19 (94.7%)	18/19 (94.7%)	0/19 (0%)
	$Diff_{verum-placebo}$	100%	94.7%	94.7%	
	[95% CI]	[64.7%; 100%]	[57.6%; 99.5%]	[57.6%; 99.5%]	
	p-value (1-sided)	**<0.0001**	**<0.0001**	**<0.0001**	
PP	n (%)	19/19 (100.0%)	17/17 (100.0%)	17/17 (100.0%)	0/17 (0%)
	$Diff_{verum-placebo}$	100%	100%	100%	
	[95% CI]	[63.1%; 100%]	[61.3%; 100%]	[61.3%; 100%]	
	p-value (1-sided)	**<0.0001**	**<0.0001**	**<0.0001**	

Source: Appendix 8.2, Tables 2-1.2 (FAS) and 2-1.2 (PP)

Table 12: Change in mean numbers of eos/mm2 hpf (final analysis) (FAS, PP)

	BUL 1mg BID	BUL 2mg BID	BUU 2mg BID	Placebo	Total
FAS	**(n = 19)**	**(n = 19)**	**(n = 19)**	**(n = 19)**	**(n = 76)**
Mean (SD)	-120 (79.3)	-128 (78.5)	-97 (124.3)	-8 (157.9)	-87 (122.8)
n	n = 19	n = 18	n = 18	n = 19	n = 74
Median	-90	-105	-43	23	-74
Range	(-302.8, -22.6)	(-282.7, -37.3)	(-526.3, -10.3)	(-409.1, 293.2)	(-526.3, 293.2)
PP	**(n = 19)**	**(n = 17)**	**(n = 17)**	**(n = 17)**	**(n = 70)**
Mean (SD)	-120 (79.3)	-119 (70.4)	-98 (127.9)	-11 (167.0)	-88 (122.6)
n	n = 19	n = 17	n = 17	n = 17	n = 70
Median	-90	-104	-41	23	-77
Range	(-302.8, -22.6)	(-275.0, -37.3)	(-526.3, -10.3)	(-409.1, 293.2)	(-526.3, 293.2)

Source: Appendix 8.2, Tables 2-1.6.1 (FAS) and 2-1.6.1 (PP)

All comparisons yielded p-values <0.003 in the FAS, and <0.007 in the PP populations

Similar results were also shown for the secondary endpoints relating to endoscopic or histological evaluation. All symptomatic endpoints showed more inconsistent results overall, potentially pointing to a generally too short treatment duration.

2.5.2. Main study(ies)

Double-blind, randomized, placebo-controlled, phase III trial on the efficacy and tolerability of a 6-week treatment with budesonide effervescent tablets vs. placebo for induction of clinicopathological remission in adult patients with active eosinophilic esophagitis

Methods

Study Participants

Patients to be included into the study had to be of 18 to 75 years of age and had to have active EoE defined as a previously objective verified diagnosis of EoE (based on symptoms history and histological criteria), as well as – at the time of inclusion – the occurrence of at least one of the following clinical symptoms:

- Dysphagia at least one day in the last 7 days with a severity of ≥4 points on a 10-point NRS or
- Pain on swallowing on at least one day during the last 7 days with a severity of ≥4 on an 10- point NRS

Patients were also required to have a peak eosinophil count of ≥65/mm^2 per at least 1 hpf out of a total of 6 hpfs derived from the six biopsy specimens at the screening endoscopy.

In addition, the patients global assessment of severity was required to score also at least 4 on a 10-point NRS at baseline.

Patients were excluded if the following was applicable:

- Presence of acid regurgitation and/or heartburn and endoscopic signs of GERD (LA classification of at least A) or abnormal pH-monitoring results during the last 6 months.

- Patients with a PPI-responsive eosinophilic oesophagitis defined as “having (1) a typical EoE symptom presentation, (2) have had GERD diagnostically excluded, and (3) demonstrated a clinico-pathologic response to PPIs.

The presence of other relevant diseases (e.g. scleroderma, achalasia, other relevant causes for oesophageal eosinophilia, GI diseases such as coeliac disease, IBD, and infections of the upper GI tract) had to be excluded.

Treatments

The patients received the budesonide 1 mg orodispersible tablet formulation, given twice a day, or the respective placebo-orodispersible tablet matching the active medication. Batch numbers and expiry dates of the batches used in the trial are documented in the report. The treatment was to be continued for 6 weeks, and could be extended with another 6-week open-label period in eligible patients.

All patients eligible for open-label-treatment had the option to enter a 6-week treatment with 2 x 1 mg/d budesonide orodispersible tablets. Eligible were patients who were not in clinico-pathological remission at completion of the DB-treatment phase, or who were prematurely withdrawn due to lack of efficacy after at least 4 weeks of treatment and who showed no change or a deterioration in the Patient’s Global Assessment (PatGA) concerning the severity of EoE symptoms compared to baseline at their last visit in the DB-treatment phase, or patients experiencing a food impaction at any time which needed endoscopic intervention.

Objectives

Primary objective of this study was:

• To assess the efficacy of 2 x 1 mg/d budesonide orodispersible tablets vs. placebo for the induction of clinico-pathological remission in adult patients with active eosinophilic esophagitis (EoE).

Secondary objectives of this study were:

• To study safety and tolerability in the form of adverse events and laboratory parameters,

• To assess patients’ quality of life (QoL).

Exploratory objectives of this study were:

• To study biomarkers in EoE.

Outcomes/endpoints

The primary efficacy variable was defined as the rate of patients with clinico-pathological remission at week 6 (LOCF) defined as fulfilling both of the following criteria:

- Histological remission, i.e., peak of <16 eos/mm^2 hpf at week 6 (LOCF), AND

- Resolution of symptoms (i.e., no or only minimal problems). In addition, any patient in need of endoscopic intervention (e.g. for food impaction or dilation) was counted as treatment failure).

The secondary outcomes were defined as follows:

a) the a-priori ordered (hierarchical) secondary endpoints:

- Rate of patients in histological remission (less than 16 eos/mm^2 hpf at week 6 (LOCF)

- change in peak eos/mm^2 from baseline to week 6

- The rate of patients with a resolution of symptoms (defined similar to the clinical part of the primary endpoint)

- The rate of patients with total weekly "Eosinophilic Esophagitis Activity Index-PRO (EEsAI-PRO) score of less than or equal to 20 at week 6

- The rate of patients with an improvement from baseline to week 6 (LOCF) in the weekly Visual Dysphagia Question (VDQ) score

- The rate of patients with an improvement from baseline to week 6 in the weekly "Avoidance Modification, and Slow-eating" (AMS) score.

b) the other "exploratory" secondary endpoints only (not subject to any confirmatory testing strategy:

- Change from baseline in the Patient's Global Assessment (PatGA) concerning the severity of EoE symptoms (0-10 NRS)

- Rate of patients with overall symptoms resolution defined as PatGA ≤2 at week 6 (LOCF)

- Change from baseline in the Physician's Global Assessment of EoE activity (0-10 NRS)

- Course and change from baseline in number of days with a dysphagia rating of '0-2' on a 0-10 NRS for dysphagia in the week prior to the visit,

- Rate of patients with no or only minimal problems in dysphagia (resolution of dysphagia) defined as a severity of ≤2 points on 0-10 NRS for dysphagia on each day in the week prior to a visit

- Time to first resolution of clinical symptoms (i.e., no or only minimal problems) defined as the first of 7 consecutive days each with a severity of ≤2 points on 0-10 NRS for dysphagia and each with a severity of ≤2 points on 0-10 NRS for pain during swallowing, respectively

- Rate of patients with total weekly EEsAI-PRO score of ≤20 in the course of the trial,

- Course and change from baseline in total modified EEsAI endoscopic instrument score (0-9) and its 'inflammatory signs' (0-4) and 'fibrotic signs' (0-4) subscores,

- Rate of patients with 'no endoscopic findings' (endoscopist's overall assessment of EoE activity) at week 6 (LOCF),

- Change from baseline in blood eosinophil counts,

- Course and change from baseline in modified Short Health Scale (modSHS),

- Course and change from baseline in the Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A) Questionnaire.

Sample size

For the sake of sample size estimation, the applicant assumed a "conservative" rate of clinical-pathological remission of 10% in the placebo group, and of 50% for the active treatment group. Simulation with a 2X1 randomisation ratio yielded a sample size of 54 patients in the active and 27 patients in the placebo group to achieve and overall power of >90%. This sample size was increased assuming a 10% drop-out rate. A total of

90 patients were therefore to be randomised for the first part of the trial. The average sample size of the adaptive design was 81 patients under the null and 57.6 patients under the alternative hypothesis.

Randomisation

Patients who gave their written consent and met the respective enrolment criteria at the screening visit were uniquely identified by a 5-digit enrolment (i.e., screening) number, consisting of a unique 3-digit centre number followed by a consecutive ascending 2-digit screening number, allocated in the order of their screening within each centre.

Once the subject was considered qualified for entry into the treatment phase of the study, i.e., the patient met all inclusion criteria and did not fulfil any of the exclusion criteria after screening, a randomization number was allocated to the patient via the interactive web-response system (IWRS), integrated in the eCRF. This consecutive ascending 4-digit random number served to randomly allocate a treatment group to each patient, according to their sequential entrance into the double-blind phase of the trial, by means of a computer-generated central randomization list. Randomization was performed using randomly permuted blocks. No stratification of randomized treatment assignment based on centre, age, sex, or other characteristics was performed.

Blinding (masking)

Budesonide and placebo orodispersible tablets were identical in appearance. Blinding was therefore assured for patients and investigators. With regard to the interim analysis conducted, the interim analysis already concluded a termination of the study, and a sample-size increase was not necessary. It can therefore be assumed that the blinding of the study was not endangered by the interim analysis conducted.

Statistical methods

The evaluation of primary and secondary efficacy endpoints was performed for the full analysis set of the double-blind phase (FAS-DB; intention-to-treat [ITT] analysis, including all randomized patients (as randomized) who received at least one dose of IMP during the DB phase), and for the per-protocol analysis set (per-protocol [PP] analysis). The primary analysis set for efficacy analyses was the FAS-DB.

The primary efficacy variable in this clinical trial was clinico-pathological remission at week 6 (LOCF). The primary efficacy variable was subjected to a confirmatory statistical analysis ($\alpha = 0.025$, one-sided) in the context of a two-stage adaptive study design (see below).

The primary hypothesis to be tested was

H0: $\pi_{Pla} \geq \pi_{Eff}$ against H1: $\pi_{Pla} < \pi_{Eff}$,

where π_{Pla} and π_{Eff} denote the rate of clinico-pathological remission in the placebo and active treatment group, respectively. This hypothesis was tested at a one-sided type I error rate level of 0.025 using Fisher's exact test.

For confirmatory hypothesis testing at the interim analysis as well as at the final analysis, the inverse normal method of combining the p-values of Fisher's exact test for comparing two rates was used. For estimating the treatment effect, the difference between the remission rates of active treatment against placebo and the corresponding two-sided 95% repeated confidence interval (RCI) is provided.

The study was planned to be conducted according to a 2-stage adaptive test design with O'Brien and Fleming shaped boundaries. The interim analysis aimed to verify the assumptions of the sample size calculation or to recalculate sample size based on the effect size estimations of the interim analysis. Additionally, stopping for early efficacy was possible if the inverse normal test statistic exceeded the critical value. To prevent release of unblinded interim data, and thus to protect the integrity of the continuing trial, the interim analysis was performed by a sponsor-independent statistician who provided the analysis results to a sponsor-independent Data Monitoring Committee (IDMC). The IDMC could also have considered a recommendation towards continuing the trial in spite of the test statistic exceeding the critical value if they believed that further substantiation of the positive result was needed. Similarly, the IDMC could have recommended stopping for futility if the observed p-value was higher than 0.5 at the interim analysis; the probability of this happening has been 65% under the null hypothesis and 0.001 under the assumed effect of 0.4 difference in remission rates. The interim analysis was planned after observation of 54 FAS (-DB) patients, i.e. at an information rate of 0.667, and the final analysis was planned after observation of additional 27 FAS (-DB) patients.

The test statistic for the first stage was thereby given as Φ-1(1-p1) and the test statistic for the second stage was planned to be $\sqrt{0.667} \times \Phi$-1(1-p1) + $\sqrt{(1-0.667)} \times \Phi$-1(1-p2). For confirmatory hypothesis testing at the interim analysis as well as at the final analysis, the inverse normal method of combining the p-values was planned to be used. The following critical values and significance levels were planned to be applied at the 2 stages using the inverse normal method:

Table 13

Stage	Information rate	Critical Value	Sign.level (one-sided)	Alpha spent
1	0.667	2.452	0.0071	0.0071
2 (final)	1.0	2.003	0.0226	0.0250

Calculations were performed using the software ADDPLAN® version 6.1.1 (licensed by ADDPLAN, Inc., an ICON Clinical Research, LLC company), which is designed for the purpose of planning and conducting clinical trials based on adaptive group-sequential test designs using the inverse normal combination test principle.

The trial was stopped after the interim analysis with an overrun of 34 FAS-DB patients. The confirmatory analysis as defined for the interim analysis was repeated with any overrun patients who had been randomized between randomization of the last patient included in the interim analysis and randomization stop. The primary confirmatory analysis is based on the results obtained in the total patient population. A Cochran-Mantel-Haenszel test was computed using treatment group and stage 1/overrun as a stratification factor to gather information on potential heterogeneity of treatment effects before and after the interim analysis. Similarly, full information on the results for all components of the primary endpoint are provided for stage 1 and for overrun patients separately.

A sensitivity analysis was performed using the FAS-DB and a logistic regression model for the remission rate with treatment group as a factor and screening overall peak eos values and baseline weekly sum of dysphagia NRS and baseline weekly sum of pain during swallowing NRS score as covariates. Should the observed numbers of remitters and non-remitters not have allowed a joint model containing these variables, separate sensitivity analyses were to be performed by entering each of the baseline variables separately.

The evaluation of the secondary efficacy variables was performed for the FAS-DB and for the PP set. Efficacy significance testing continued in hierarchical fashion in support of labelling claims for six key secondary

endpoints as defined above until the first of these comparisons of BUL 1mg BID versus Placebo showed a one-sided p-value >0.025 (FAS-DB). All other secondary evaluations had exploratory character only.

The following methods were used to perform inferential statistics for key secondary endpoints:

- Dichotomous key secondary endpoints (key secondary endpoints no. 1, 3, 4, 5, and 6) were analysed using Fisher's exact test (test for superiority, one-sided alpha level of0.025). The denominator was all patients included in the respective analysis set. Dichotomous target variables with a corresponding baseline measurement (key secondary endpoints no. 1, 4, 5, and 6) were analysed in addition using logistic regression and including the baseline value(s) in addition to treatment group.

- Change in the peak eos/mm2 hpf was analysed by fitting a linear least squares model with treatment effect and baseline value as covariate.

Missing values of the efficacy and safety laboratory parameters at the EOT/withdrawal visit DB were replaced by the last measurement (last measured week, if appropriate) obtained during DB treatment (last observation carried forward; LOCF). Baseline values were carried forward for patients who provided no post-baseline data. This approach was justified by the facts that the patients have been off anti-inflammatory or EoE-specific treatment, or dietary restrictions for ≥4 weeks prior to the baseline assessments, meaning that no worsening after baseline was to be expected on one hand, and that spontaneous remissions were highly unlikely to occur.

The analysis of influence of countries, centres, and other covariates were handled as follows: Primary and key secondary efficacy endpoints are presented stratified by country and stratified by centre. As centre 401 recruited more than 25% of all FASDB patients, the primary endpoint is presented stratified by centre 401 versus all other centres pooled.

The primary analysis was not adjusted for covariates. However, the primary and key secondary efficacy parameters were analysed descriptively with respect to the following subgroups:

- Stage 1 and overrun patients, respectively

- Localization of the inflammation at baseline (unique categories):

  - Proximal, median, and distal oesophagus, respectively,

  - 1, 2, or 3 oesophageal segments affected. An oesophageal segment was defined as affected by inflammation if the peak number of eos/mm^2 hpf was ≥ 16.

- Concomitant use of PPIs (yes/no) during the DB phase (Entries on the concomitant medication page of the eCRF medications were classified as PPI (yes/no), unless they were stopped before or at the day of the baseline visit or initiated only at or after the date of the DB EOT visit.),

- History of allergic diseases (yes/no),

- Baseline PatGA, (As frequency for PatGA group 3 was very low, PatGA groups 3 and 4 were pooled. In addition, PatGA groups 8 and 9 were also pooled because of low frequencies in both groups),

- Duration of disease (i.e., time from first symptoms to baseline [years]): < median (years) and ≥ median (years),

- History of any dietary approach to treat EoE (yes/no) [post-hoc analysis only performed for the primary endpoint for the FAS-DB].

Results

Participant flow

126 patients were screened for the study, and 38 patients were finally not eligible for randomisation (screen failure rate: 30%). The reasons for non-inclusion into the study were violation of in- or exclusion criteria in all of these patients, except 3 with "other" reasons, of which 2 were not randomised due to the early stop of the study. The disposition of the patients is shown in the following table:

Table 14: Disposition of patients study BUL-1/EEA; (FAS)

	Number (%) of patients		
	Placebo	BUL 1mg BID	Total
Randomized & treated	29 (100.0%)	59 (100.0%)	88 (100.0%)
Full DB treatment phase completed	25 (86.2%)	56 (94.9%)	81 (92.0%)
DB treatment phase prematurely terminated	4 (13.8%)	3 (5.1%)	7 (8.0%)
No OLI IMP used	1 (3.4%)	36 (61.0%)	37 (42.0%)
OLI phase entered & treated	28 (96.6%)	23 (39.0%)	51 (58.0%)
Full OLI phase completed	27 (93.1%)	23 (39.0%)	50 (56.8%)
OLI phase prematurely terminated	1 (3.4%)	0 (0.0%)	1 (1.1%)
Follow-up visit not performed*	21 (72.4%)	45 (76.3%)	66 (75.0%)
Follow-up visit performed	8 (27.6%)	14 (23.7%)	22 (25.0%)

Source: Appendix 8.2.1, Tables 1.1.1.1 (SCR), 1.1.3 (FAS-DB), and 1.1.4.3 (FAS-DB), and 2.1 (FAS-OLI).
Note: Percentages were calculated out of numbers of DB-treated patients.
* A follow-up visit not performed means that the patient was considered for immediate transition into the subsequent BUL-2/EER trial.

All 4 and 3 premature terminations during the double-blind phase of the study were related to a "lack of efficacy".

No patient (0%) of the Placebo group versus 30 patients (50.8%) of the BUL 1mg BID group were considered to continue with the BUL-2/EER maintenance of remission trial directly following the DB treatment phase.

After the OLI treatment phase, 7/28 patients (25.0%) in the Placebo→BUL group performed a follow-up visit, i.e., 21/28 patients (75.0%) of this group were considered for immediate transition to the subsequent BUL-2/EER maintenance of remission trial. In the BUL→BUL group, 8/23 patients (34.8%) performed a follow-up visit after the OLI phase, and 15/23 patients (65.2%) were considered for immediate transition to the subsequent BUL-2/EER maintenance of remission trial.

Recruitment

First patient enrolled: Screened: 11 Nov 2015 / Randomized: 04 Dec 2015

Last patient completed: Double-blind treatment phase: 04 Aug 2016

Open-label induction phase: 26 Sep 2016

Follow-up phase: 04 Oct 2016

The study was conducted as a multi-centre study in BE, DE, ES, CH, NL, and UK.

Conduct of the study

There were no general protocol amendments during the course of the study. There were 2 local protocol amendments for the UK, which were related to the inclusion of female patients with child-bearing potential.

The study was stopped early after the interim analysis. At this time-point, 18 patients in the placebo and 36 patients (54 patients in total) in the active treatment group were included. Thus, the “overrun”-cohort included 34 additional patients recruited while the interim analysis was conducted (11 in the placbo, and 23 in the active treatment group).

In the Placebo group a total of six major protocol violations were observed in three patients (10.3%), in the BUL 1mg BID group a total of nine major and five minor protocol violations were recorded in eleven patients (18.6%). The corresponding tables for the PP set show no major violations as all such patients were excluded from the PP set. They show that the five minor violations in patients of the BUL 1mg BID group all occurred in PP patients, i.e., in patients without any major protocol violation.

Table 15: Reasons resulting in the exclusion from the PP analysis set (FAS-DB)

	Number of violations leading to exclusion from the PP analysis set		
Reason for exclusion (violation classified as major)	Placebo (n = 29)	BUL 1mg BID (n = 59)	Total (n = 88)
Inclusion criterion violated	1	2	3
Exclusion criterion violated	0	2	2
Prohibited concomitant medication	1	1	2
Insufficient compliance (DB IMP)	2	1	3
DB EOT visit > 3 days after last IMP intake or not assessable	1	0	1
No value on treatment for at least one of the three components of the primary endpoint	1	0	1
Other protocol violation*	0	3	3

* Patient 116-02: GERD according to endoscopic signs (hernia). Patients 116-07 and 116-10: Probably developed a secondary reflux disease (no hernia).

Baseline data

The main baseline characteristics of the patients included in the FAS population are shown in the following table:

Table 16: Baseline demographics (FAS-DB)

		Placebo (n = 29)	BUL 1mg BID (n = 59)	Total (n = 88)
Sex				
Male	n (%)	25 (86.2%)	48 (81.4%)	73 (83.0%)
Female	n (%)	4 (13.8%)	11 (18.6%)	15 (17.0%)
Race				
White	n (%)	29 (100%)	59 (100%)	88 (100%)
Smoking habits				
Current	n (%)	0 (0%)	3 (5.1%)	3 (3.4%)
Former	n (%)	3 (10.3%)	5 (8.5%)	8 (9.1%)
Never	n (%)	26 (89.7%)	51 (86.4%)	77 (87.5%)
Age [years]	Mean (SD)	36.9 (9.20)	37.0 (11.47)	37.0 (10.72)
	Range	26 - 64	18 - 69	18 - 69
Height [cm]	Mean (SD)	178.3 (8.03)	176.7 (8.26)	177.2 (8.17)
	Range	163 - 196	155 - 193	155 - 196
Weight [kg]	Mean (SD)	81.4 (14.24)	76.2 (10.80)	77.9 (12.21)
	Range	59.0 – 130.0	57.7 – 105.0	57.7 – 130.0
BMI [kg/m²]	Mean (SD)	25.6 (4.08)	24.4 (2.86)	24.8 (3.34)
	Range	20.3 – 35.3	18.0 – 34.7	18.0 – 35.3

Source: Appendix 8.2.1, Table 1.3.1.1 (FAS-DB).

There were no statistically significant differences between the treatment groups for any of those baseline parameters.

The mean duration since the diagnosis was about 50 months, and 136 months since the first symptoms. Only a tiny minority of patients (2 and 1 in the placebo and active groups) were newly diagnosed patients. Only about 10% of the patients used a PPI (although in all of them PPI treatment was deemed unsuccessful). Almost all patients experienced some grade of dysphagia, whereas only about half of the patients experienced odynophagia. The majority (about 90%) of patients had experienced food impaction, and about 80% had a history of allergic disease. More than half of the patients were assessed as having moderate, and one third was assessed to have severe inflammation by endoscopic assessment with no differences between the treatment groups. The majority of patients (51% to 57%) experienced dysphagia at least 4 times weekly, with about 40% to 44% patients suffering daily from this symptom. There were no relevant or significant differences with regard to the baseline EEsAI scores, the dysphagia NRS scores (which was at almost 6 at baseline), or the pain on swallowing scores, as well as for the patient's and physician's global assessment.

There was some discrepancy with regard to the duration of the last episode of EoE, which was 3 months for the placebo, and 1.8 months for the active treatment group (median). The duration of the last "remission phase" as reported by the patients was 7.8 months, and 9.1 months in the placebo and active treatment groups.

Just under 50% of the patients had been taking an elimination diet at inclusion, of which none of the patients took an elemental diet (with amino-acid-based complete liquid formulation), and the majority took a non-directed elimination diet not based on allergy test results. Almost all patients indicated a poor efficacy of these therapies (9/10 in the placebo, and 20 of 24 in the active treatment group). Also, the symptoms were assessed as unchanged or worsened after such therapies by the majority of patients (9/10 in the placebo, and 19/24 in the actively treated group). 3/10 and 11/24 patients assessed the tolerability of these therapies as "poor".

Numbers analysed

The total (FAS) randomised (and treated) population comprised 88 patients, of which 29 were in the placebo and 59 in the budesonide group.

In the interim analysis, a total of 54 patients (18 in the placebo, and 36 in the active treatment group) were included.

There were 4 premature discontinuations (13.8%) in the placebo group, and 3 (5.1%) in the active treatment group, all of which occurred due to a "lack of efficacy"

The PP analysis set comprises 77 patients (Placebo: 26 patients; BUL 1mg BID: 51 patients). A total of 11 FAS-DB patients (12.5%) were excluded from the PP analysis set, thereof, 3 of 29 patients (10.3%) in the Placebo group and 8 of 59 patients (13.6%) in the BUL 1mg BID group.

The reasons for the exclusion from the PP analysis are given in the following table:

Table 17: Reasons resulting in the exclusion from the PP analysis set (FAS population)

	Number of violations leading to exclusion from the PP analysis set		
Reason for exclusion (violation classified as major)	Placebo (n = 29)	BUL 1mg BID (n = 59)	Total (n = 88)
Inclusion criterion violated	1	2	3
Exclusion criterion violated	0	2	2
Prohibited concomitant medication	1	1	2
Insufficient compliance (DB IMP)	2	1	3
DB EOT visit > 3 days after last IMP intake or not assessable	1	0	1
No value on treatment for at least one of the three components of the primary endpoint	1	0	1
Other protocol violation*	0	3	3

* Patient 116-02: GERD according to endoscopic signs (hernia). Patients 116-07 and 116-10: Probably developed a secondary reflux disease (no hernia).

Source: Appendix 8.2.1, Table 1.1.1.2 (FAS-DB).

Note: Multiple reasons for exclusion were applicable for some patients.

The open-label extension population ("FAS-OLI") comprises 51 patients, of which 28 received placebo and 23 received active medication during the double-blind phase.

The population undergoing a follow-up visit (=not recruited for the long-term study) ("FAS-FU") comprises all patients for whom a follow-up visit was performed, i.e., 22 patients overall, 8 patients in the Placebo group and 14 patients in the BUL 1mg BID group.

Outcomes and estimation

The study was planned to be conducted according to a 2-stage adaptive test design. The study recruited 88 patients with a 2:1 randomisation ratio. The study was stopped early after the interim analysis for overwhelming efficacy. At this time-point, 18 patients in the placebo and 36 patients (54 patients in total) in the active treatment group were included.

At baseline, there were not relevant or statistically significant differences between the treatment groups. There was only a limited number of 7 premature discontinuations (4 in the placebo, and 3 in the active treatment group), which all occurred due to lack of efficacy.

The primary endpoint evaluation is shown in the following table, showing the data for the interim analysis the "overrun patients" and the final analysis:

Table 18 Clinical-pathological remission rate at DB week 6 (FAS and PP population, LOCF):

	FAS-DB			PP		
	Placebo	BUL 1mg BID	One-sided p-value from Fisher's exact test	Placebo	BUL 1mg BID	One-sided p-value from Fisher's exact test
Stage 1	0/18 (0.0%)	20/36 (55.6%)	0.00002274	0/15 (0.0%)	17/30 (56.7%)	0.00010857
Overrun	0/11 (0.0%)	14/23 (60.9%)	0.0005871	0/11 (0.0%)	14/21 (66.67%)	0.0002467
Overall	0/29 (0.0%)	34/59 (57.6%)	0.00000001	0/26 (0.0%)	31/51 (60.8%)	0.00000002

Source: Appendix 8.2.2, Tables 1.1.1 and 1.1.4.1 (FAS-DB), and Tables 1.1.1 (PP) and 1.1.4.1 (PP).

The following table shows the analysis according to the protocol for the a priori ordered key secondary endpoints (FAS analysis only), which includes the two components of the primary endpoint also, but is shown here again for completeness:

Table 19: A priori ordered key secondary endpoints (FAS population):

A priori ordered key secondary endpoints:		Placebo (n=29)	BUL 1mg BID (n=59)	p-value (one-sided)
1. Rate of patients with histological remission at week 6 (LOCF)*	n (%)	0/29 (0.0%)	55/59 (93.2%)	<0.0001#
2. Change in the peak eos/mm² hpf from baseline to week 6 (LOCF)**	Mean (SD)	-4.3 (135.64)	-225.5 (150.37)	<0.0001°
3. Rate of patients with resolution of symptoms on each day in the week prior to week 6 (LOCF)	n (%)	4/29 (13.8%)	35/59 (59.3%)	<0.0001#
4. Rate of patients with a total weekly EEsAI-PRO score of ≤ 20 at week 6 (LOCF)	n (%)	2/29 (6.9%)	30/59 (50.8%)	<0.0001#
5. Rate of patients with an improvement from baseline to week 6 (LOCF) in the weekly VDQ score	n (%)	11/29 (37.9%)	30/59 (50.8%)	0.1804#
6. Rate of patients with an improvement from baseline to week 6 (LOCF) in the weekly AMS score	n (%)	3/29 (10.3%)	7/59 (11.9%)	0.5703#§

* For this analysis not evaluable results were set to 'No'.

The first four of the six a priori ordered key secondary endpoints showed also a highly significant superiority of BUL 1mg BID over placebo in a confirmatory sense (all four one-sided p-values were <0.0001).

Time to a regular meal endpoint: In the Placebo group, for 19/29 patients (65.5%) the time to eat a regular meal (last 7 days) remained unchanged from baseline to DB week 6 (LOCF), for 5/29 patients (17.2%), the time shortened, and for 4/29 patients (13.8%), the time increased in the FAS-DB. In the BUL 1mg BID group, for 30/59 patients (50.8%) the time to eat a regular meal (last 7 days) remained unchanged from baseline to DB week 6 (LOCF), for 22/59 patients (37.3%), the time shortened, and for 3/59 patients (5.1%), the time increased in the FAS-DB. 1 and 4 patients in the two groups were not assessable.

Modified Short Health Scale endpoint: For all four questions of the modSHS – 'symptom burden', 'social function', 'disease-related worry', and 'general well-being' – the improvement (absolute change) in mean as well as median scores from baseline to DB week 6 (LOCF) was much bigger and clinically relevant in the BUL 1mg BID group than in the Placebo group as shown in the following table:

Table 20: Modified Short Health Scales (FAS-DB)

Modified Short Health Scale		Placebo n = 29		BUL 1mg BID n = 59	
		Baseline	Wk 6 (LOCF)	Baseline	Wk 6 (LOCF)
Symptom burden	**Mean (SD)**	55 (18.1)	38 (25.1)	58 (23.5) [n=58]	27 (27.1)
Social function	**Mean (SD)**	46 (24.3)	32 (23.1)	55 (29.0)	26 (27.1)
Disease-related worry	**Mean (SD)**	52 (26.8)	44 (28.6)	57 (26.4)	37 (29.6)
General well-being	**Mean (SD)**	35 (29.0)	26 (24.3)	40 (23.3)	24 (22.9)

Range of each score: 0-100. Lower numbers indicate higher Quality of Life
Source: Appendix 8.2.2, Tables 1.3.27.1, 1.3.27.3, 1.3.27.5, 1.3.27.7 (FAS-DB).

EoE-QoL-A endpoint:

The mean overall score (which includes 30 items) in this endpoint was 2.32 and 2.26 at baseline for the placebo and budesonide groups, respectively. This change to the end of week 6 to a mean of 2.56 in the placebo and 2.85 in the active treatment group (FAS population) which was not significant. In summary, the improvements in the BUL 1mg BID group were higher than in the Placebo group for both EoE-QoL-A overall scores as well as for each of the five sub-scores. Highest and statistically significant differences between placebo and BUL 1mg BID were seen for mean absolute changes of the impact on eating patterns and diet, for both, the 10-item sub-score and the 4-item subs-core.

The further secondary endpoints were almost all in full concordance with the primary and first four secondary endpoints, including symptomatic, endoscopic, histological, as well as physiological (eosinophil blood counts) evaluations. There were relevant effects with regard to the Quality of Life evaluations based on the "Modified Short Helath Scale" (MSH), but only inconsistent effects (as shown for single domains) in the EoE-QoL endpoint evaluations.

Open-label extension phase:

The following table shows the analysis of the open-label extension phase (OLI) for a couple of endpoints that were also part of the evaluations in the double-blind phase:

Table 20: Further exploratory secondary endpoints OLI phase

Further exploratory secondary endpoints OLI phase		Placebo→BUL (n = 28)	BUL→BUL (n = 23)
1. Rate of patients with clinico-pathological remission at OLI week 6 (LOCF)	n (%)	22 (78.6%)	16 (69.6%)
2. Rate of patients with histological remission at OLI week 6 (LOCF)	n (%)	25 (89.3%)	19 (82.6%)
3. Change in the peak eos/mm² hpf from week 6 DB (EOT/withdrawal) to week 6 OLI (LOCF)	Mean (SD)	-205.81 (105.700)	-12.26 (62.560)
4. Rate of patients with resolution of symptoms on each day in the week prior to week 6 OLI (LOCF)	n (%)	23 (82.1%)	17 (73.9%)
5a. Rate of patients with PRA of at least 'a little improved' compared to week 6 DB in the course of the OLI phase (LOCF)			
OLI week 2	n (%)	23 (82.1%)	17 (73.9%)
OLI week 4	n (%)	26 (92.9%)	19 (82.6%)
OLI week 6	n (%)	24 (85.7%)	19 (82.6%)
OLI week 6 (LOCF)	n (%)	24 (85.7%)	20 (87.0%)
5b. Rate of patients with PRA of at least 'moderately improved' compared to week 6 DB in the course of the OLI phase (LOCF)			
OLI week 2	n (%)	15 (53.6%)	12 (52.2%)
OLI week 4	n (%)	16 (57.1%)	16 (69.6%)
OLI week 6	n (%)	20 (71.4%)	13 (56.5%)
OLI week 6 (LOCF)	n (%)	20 (71.4%)	14 (60.9%)
5c. Rate of patients with PRA of at least 'much improved' compared to week 6 DB in the course of the OLI phase (LOCF)			
OLI week 2	n (%)	7 (25.0%)	3 (13.0%)
OLI week 4	n (%)	8 (28.6%)	6 (26.1%)
OLI week 6	n (%)	16 (57.1%)	9 (39.1%)
OLI week 6 (LOCF)	n (%)	16 (57.1%)	9 (39.1%)

Ancillary analyses

The applicant has analysed the results of the trial with regard to different factors, such as the stage of enrolment (already given above), country of recruitment, localisation of inflammation, use of PPIs during the DB phase etc. and generally found highly concordant results across the analyses, which is shown in the following table:

Table 21: Clinical-pathological remission at DB week 6 (LOCF) by subgroups – BUL-1/EEA (FAS and PP populations)

	Number (%) of patients			
	FAS-DB		PP	
	Placebo N = 29	BUL 1 mg BID N = 59	Placebo N = 26	BUL 1 mg BID N = 51
Stage				
Stage 1	0/18 (0.0%)	20/36 (55.6%)	0/15 (0.0%)	17/30 (56.7%)
Overrun	0/11 (0.0%)	14/23 (60.9%)	0/11 (0.0%)	14/21 (66.7%)
Country				
Germany	0/12 (0.0%)	19/31 (61.3%)	0/9 (0.0%)	17/27 (63.0%)
Netherlands	0/1 (0.0%)	1/2 (50.0%)	0/1 (0.0%)	1/2 (50.0%)
Spain	0/10 (0.0%)	12/24 (50.0%)	0/10 (0.0%)	11/20 (55.0%)
Switzerland	0/6 (0.0%)	2/2 (100.0%)	0/6 (0.0%)	2/2 (100.0%)
Centre 401 vs. all other centres pooled				
Centre 401	0/6 (0.0%)	10/18 (55.6%)	0/6 (0.0%)	9/14 (64.3%)
All other centres pooled	0/23 (0.0%)	24/41 (58.5%)	0/20 (0.0%)	22/37 (59.5%)
Localisation of inflammation at baseline				
Proximal oesophagus				
No	0/4 (0.0%)	5/12 (41.7%)	0/4 (0.0%)	4/10 (40.0%)
Yes	0/25 (0.0%)	29/47 (61.7%)	0/22 (0.0%)	27/41 (65.9%)
Median oesophagus				
No	0/3 (0.0%)	4/7 (57.1%)	0/3 (0.0%)	3/6 (50.0%)
Yes	0/26 (0.0%)	30/52 (57.7%)	0/23 (0.0%)	28/45 (62.2%)
Distal oesophagus				
No	0/1 (0.0%)	1/3 (33.3%)	0/1 (0.0%)	1/3 (33.3%)
Yes	0/28 (0.0%)	33/56 (58.9%)	0/25 (0.0%)	30/48 (62.5%)
Extent of inflammation at baseline: Number of oesophageal segments affected				
1	0/2 (0.0%)	3/6 (50.0%)	0/2 (0.0%)	3/6 (50.0%)
2	0/4 (0.0%)	4/10 (40.0%)	0/4 (0.0%)	2/7 (28.6%)
3	0/23 (0.0%)	27/43 (62.8%)	0/20 (0.0%)	26/38 (68.4%)

	Number (%) of patients			
	FAS-DB		PP	
	Placebo N = 29	BUL 1 mg BID N = 59	Placebo N = 26	BUL 1 mg BID N = 51
Concomitant use of PPIs during the DB phase				
No	0/26 (0.0%)	29/52 (55.8%)	0/23 (0.0%)	26/44 (59.1%)
Yes	0/3 (0.0%)	5/7 (71.4%)	0/3 (0.0%)	5/7 (71.4%)
History of allergic diseases				
No	0/6 (0.0%)	8/12 (66.7%)	0/5 (0.0%)	7/10 (70.0%)
Yes	0/23 (0.0%)	26/47 (55.3%)	0/21 (0.0%)	24/41 (58.5%)
PatGA at baseline				
3 or 4	0/5 (0.0%)	9/12 (75.0%)	0/4 (0.0%)	9/11 (81.8%)
5	0/7 (0.0%)	11/16 (68.8%)	0/5 (0.0%)	11/15 (73.3%)
6	0/5 (0.0%)	5/8 (62.5%)	0/5 (0.0%)	4/6 (66.7%)
7	0/8 (0.0%)	4/13 (30.8%)	0/8 (0.0%)	2/9 (22.2%)
8 or 9	0/4 (0.0%)	5/10 (50.0%)	0/4 (0.0%)	5/10 (50.0%)
Time since first symptoms[a]				
not evaluable	0/0 (0.0%)	0/1 (0.0%)	0/0 (0.0%)	0/0 (0.0%)
< median	0/15 (0.0%)	18/28 (64.3%)	0/14 (0.0%)	16/25 (64.0%)
≥ median	0/14 (0.0%)	16/30 (53.3%)	0/12 (0.0%)	15/26 (57.7%)
History of any dietary approach to treat EoE				
No	0/17 (0.0%)	22/31 (71.0%)	---	---
Yes	0/12 (0.0%)	12/28 (42.9%)	---	---

BID: twice daily; BUL: budesonide orodispersible tablet; DB: double blind: EoE: eosinophilic oesophagitis; FAS: full analysis set: N: total number of patients in treatment group; PatGA: Patient's Global Assessment; PP: per-protocol; PPI: proton pump inhibitor.

a Median time since first symptoms: 9.5 years (calculated based on FAS-DB patients, BUL-1/EEA)

The applicant points out that there was no relevant difference in the rate of clinic-pathological remission according to the localisation of the inflammation in the oesophagus, and in fact – with regard to the histological remission endpoints, statistical significance was achieved in all parts of the oesophagus, and thus the chosen pharmaceutical form of orodispersible tablet is suitable for EoE treatment irrespective of the localisation of the (most severe) disease within the oesophagus.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22 Summary of Efficacy for trial BUL-1/EEA

Title: Double-blind, randomized, placebo-controlled, phase III trial on the efficacy and tolerability of a 6-week treatment with budesonide effervescent tablets vs. placebo for induction of clinicopathological remission in adult patients with active eosinophilic esophagitis			
Study identifier	BUL-1/EEA		
Design	Double-blind, randomized, placebo controlled study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 weeks not applicable 6 weeks
Hypothesis	Superiority of budesonide 1 mg orodispersible tablet taken twice daily versus placebo		
Treatments groups	Budesonide orodispersible tablet 1 mg		Twice daily intake; 6 weeks, n=59
	Placebo (identical to active)		Twice daily intake; 6 weeks, n=29
Endpoints and definitions	Primary endpoint	Rate of Clinico-pathological remission	Composite (at individual level) of histological remission, i.e., peak of <16 eos/mm^2 hpf at week 6 (LOCF), AND Resolution of symptoms (i.e., no or only minimal problems) defined as a severity of ≤2 points on 0 to 10-point (0-10) NRS for dysphagia AND a severity of ≤2 points on 0-10 NRS for pain during swallowing on each day in the week prior to week 6 (LOCF)
	Key Secondary endpoint	Rate of patients with histological remission	See above for histological remission
	Key Secondary endpoint	Change in peak eos/mm2 hpf from baseline	N/A
	Key Secondary endpoint	Rate of patient with a resolution of symptoms during last week	See second part of the primary endpoint
	Key Secondary endpoint	Rate of patients with a EEsAI-PRO score of ≤20	EEsAI-PRO is a patient reported outcome based on evaluation of three key symptoms and the assessment of food avoiding strategies of the patients assessed with the AMS and VDQ scores. It ranges from 0 to 100. The score has been partially validated.
Database lock	04 Aug 2016		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (“FAS” population) 6 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Budesonide 1 mg BID	
	Number of subject	29	59	
	Rate of clinico-pathological remission	0/29 (0.0%)	34/59 (57.63%)	
	Difference between proportions [95% RCI]		57.63% [38.22%; 71.97%]	
	endpoint statistic			P=0.000002

Analysis description	**Secondary analyses**		
		Placebo	Budesonide 1 mg BID
Effect estimate per comparison	Histological remission rate	0/29 (0.0%)	55/59 (93.2%)
		P-value	<0.0001 (one sided)
	Change in peak eos/mm2 hpf from baseline	-4.3	-225.5
		SD: 135.64	SD: 150.37
		P-value	<0.0001 (one sided)
	Rate of patient with a resolution of symptoms during last week	4/29 (13.8%)	35/59 (59.3%)
		P-value	<0.0001 (one sided)
	Rate of patients with a EEsAI-PRO score of ≤20	2/29 (6.9%)	30/59 (50.8%)
		p-value	<0.0001 (one sided)

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

No pooled analysis or analysis across trials is presented.

Clinical studies in special populations

No studies in special populations were conducted. With regard to the age of the patients, the protocol had specified that patients up to an age of 75 could be included. At inclusion, the mean age of the patients was 37 years, and the oldest patient was 69 years of age. Therefore, a subgroup analysis according to the age categories of 65-74, 75-84, and older than 85 is not sensible.

Also, there was a clear male preponderance within the study, and only 15 female patients (4 in the placebo and 11 in the active treatment group) were recruited. An analysis according to gender is therefore also not presented. This is also applicable to race, because 100% white patients have been recruited.

Supportive study(ies)

The supportive phase 2 study BUU-2/EEA has been described under dose-finding.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

For the demonstration of clinical efficacy, the applicant has conducted a limited programme, consisting of one placebo-controlled phase II dose-finding trial, and one pivotal phase III trial, comparing the final dose determined in the phase II trial with placebo treatment for a duration of 6 weeks.

The justification for conducting only a limited programme and presenting only one pivotal trial is for the major part based on the availability of a wealth of literature documenting the benefits of the administration of corticosteroids in patients with EoE, including budesonide. Whereas most of the publications referred to in the systematic reviews and meta-analyses published include the administration of “extemporaneous” applications of inhalational medicinal products, several publications are also available with the administration of budesonide oral suspensions. Relevant differences in the results (related to the histological response) between these studies have not been detected.

The pivotal study BUL-1/EEA as well as the phase II study BUU-2/EEA have included an appropriate population of patients diagnosed with EoE according to the current state of the art. The inclusion was based on the presence of endoscopic and histological signs of inflammation and eosinophilia using the consensus definitions published in both European as well as US practice guidelines. The population included also had to suffer from a certain degree of clinical symptoms, which were assumed to denote a symptomatic population enabling the demonstration of a clinical response also. Because no consensus on the definition of severity of symptoms and of the disease itself exists, the threshold chosen were to some extent arbitrary, but are overall considered acceptable to ensure the inclusion of a patient population suffering from relevant symptoms.

For the phase 3 trial, it was in addition reassured that patients had not been responsive to a PPI therapy, which had previously been regarded to be the first line of therapy in these patients, in order to differentiate these patients, suffering from “PPI-responsive oesophageal eosinophilia” from those with “true” EoE. Meanwhile, however, the PPI-responsive patients would rather be regarded to be a subgroup within the normal disease spectrum of EoE (according to the 2017 European clinical practice guideline). Special requirements for the treatment history with regard to “dietary therapies” (and their success or failure) were not required in both trials.

In addition, relevant other diseases potentially mimicking the clinical picture of EoE were excluded, and all patients underwent endoscopic examination at the inclusion into the study. All histological evaluations were conducted by centralised evaluations, representing the state of the art.

The phase II study conducted compared two different doses of the orodispersible tablet (1 mg and 2 mg BID) with the administration of an oral suspension (2 mg BID) and placebo for a duration of 14 days. This treatment duration has to be regarded to be relatively short, and has in fact been shown to be too short in order to fully assess potential differences between the doses administered, especially for the clinical outcomes (symptoms), which are thought to show a slower response than the histology.

The co-primary endpoints in the phase II trial were the rate of histological remission, with the “standard” definition of mean of <16 eos/mm^2 hpf and the rate of histological response (defined as a peak eos count of less than 65 per mm^2 hpf. Secondary endpoints included the evaluation of endoscopic scores and subscores, the course of the dysphagia score, the overall improvement score, and the evaluation of the rate of responders (defined as a decrease of at least 3 points in the dysphagia score from baseline), the change in the Visual Dysphagia Questionnaire (VDQ) from baseline, which was an assessment of the “virtual” avoidance of certain

food items by the patients, the changes in chest and upper abdominal pain symptoms, the blood eosinophil counts, the Physician's Global Assessment, and the assessment of the Quality of Life.

These endpoints are considered acceptable for the purpose of a phase 2 and dose-finding exercise, in order to have to focus on the evaluation of histological and "objective" parameters, such as histological evaluation, endoscopic observation, and laboratory measurements (such as blood eosinophil counts). At the time of conduct of the trial, obviously no "standardised" method to assess the course of the symptoms was available, and therefore the chosen parameters appear to be adequate.

The phase 3 trial was a placebo-controlled trial with the final dose of 1 mg BID selected for evaluation, and a duration of 6 weeks double-blind treatment. An open-label extension phase was offered to those patients not satisfactorily treated during the first 6 weeks. All patients successfully treated with the compound could be recruited for the following long-term ("maintenance") efficacy trial, which was ongoing at the time of submission of the data and will only be finalised in the year 2019. The longer treatment duration in this trial was the result of the discussions in the Scientific Advice, which referred to the data available in the literature which showed regularly treatment durations of up to 12 weeks.

Different to the phase II trial, the study used a "composite" primary endpoint (at the individual patient level) using a responder analysis with the criteria "histological remission" (defined similar to the phase II trial), and resolution of symptoms defined as a severity of ≤2 points on 0 to 10-point (0-10) NRS for dysphagia and a severity of ≤2 points on 0-10 NRS for pain during swallowing on each day in the week prior to week 6 (LOCF). The latter component of the primary evaluation also reflects the recommendations of the CHMP during the Scientific Advice, where the applicant proposed to use a newly developed PRO instrument, the "EEsAI-PRO" as the second component of the primary evaluation. However, this PRO was not considered acceptable by CHMP because a full validation would not have been available before the conduct of the study, and there were obvious problems with the rating of the food intake identified. Following the recommendation of the CHMP, the applicant's choice to base the main symptom evaluation on a simple (0-10 NRS-scale) evaluation of the main symptoms of EoE, dysphagia and pain on swallowing (odynophagia) is therefore welcomed and considered fully acceptable. The use of a composite of histology and symptoms also reflects the recommendations of learned societies in the field.

The applicant has chosen to include 6 secondary "key" endpoints which were subject to a hierarchical testing procedure. These included the single components of the primary endpoint (2), the change in peak eos/mm^2, the rate of patients with an EEsAI-PRO of less than 20 (a threshold defined to denote clinical remission during the validation work carried out for the PRO), and the rate of patients with an improvement in the two food-avoidance components of the EEsAI-PRO, the VDQ and AMS scores.

There were several other secondary endpoints encompassing both symptomatic, as well as global ratings by the patients and the physicians, different aspects of the endoscopic analyses, as well as "objective" endpoints such as blood eosinophil counts, and also two instruments to measure quality of life.

A selection of these endpoints was also used to measure the therapeutic effects during the open-label extension part of the study.

Both, the phase II and the phase III study were conducted with a 2-stage adaptive design with one interim analysis, which encompassed an unblinded look at the data by an IMDC, and stopping rules for success of the trial, as well as rules for the increase of the sample size. For both studies, an adequate clinical justification was presented to use the adaptive design. However, several concerns for the use of such a design in the setting of one pivotal trial were brought to the attention of the applicant during the Scientific Advice, which were not all

taken on board. The methodology used for the sample size estimation, the conduct of the interim analysis, and the statistical methods for evaluation appeared to be adequate already at the time of the Scientific Advice. However, there was the unresolved concern of the (even unintentional) spread of study results, and the influence on the further recruitment and conduct of the study. However, in both trials, the interim analysis results led to the conclusion to stop the study for overall success. Consequently, the patients recruited during the conduct of the interim analysis were the only ones recruited in addition to the “interim population” and there was finally no indication that the interim analysis had influenced the further recruitment, or the “overrun” patients were different from their baseline properties from the population recruited in stage 1. It is also clear that a considerable part of the endpoints were “objective” endpoints, based on the central histological reading of biopsies, which would have been unlikely influenced by any knowledge on the stop or increase of the size of the study. The statistical methodology both with regard to planning and evaluation of the study are therefore considered acceptable.

The main population for the evaluation of the data is the so-called “FAS”-population, which clearly is a population complying with the ITT principle. In addition, a per-protocol (PP) population was defined which excluded the patients with major protocol deviations. Adequate justifications for exclusion of all those patients have been found. The main imputation method for dealing with missing data was “last-observation carried forward” (LOCF) which was completed with an analysis resembling an “as treated” approach. However, the number of missing data was small, and generally no differences were observed between the LOCF and other analyses.

The randomisation in the two studies was done by randomly permuted blocks. No stratification factors were used for randomisation. Blinding was assured by the identical appearance of placebo and active medication in the phase III trial, and by double-dummy methods in the phase II trial. Randomisation as well as blinding methods appear to be adequate.

Efficacy data and additional analyses

At baseline, in both trials, the baseline demographic characteristics, as well as disease history and severity of endoscopic histological, as well as symptomatic findings were comparable. The studies recruited a relatively young population with a mean age of about 40 years in the phase II and 37 years in the phase III study, and with a clear preponderance of the male sex (83% in both studies). Almost exclusively white patients were recruited into the trials. Phase III study recruited a population unresponsive to PPI therapy, which is regarded to be the primary target population of a glucocorticoid treatment in the disease, according to the European as well as US guideline recommendations. The phase III trial included a population that had been treated previously with dietary therapy unsuccessfully (albeit “undirected” in the majority of patients) in about 50%.

For study BUU-2/EEA, the interim analysis showed that for both components of the primary endpoint a highly statistically significant difference for all active treatment groups compared to placebo could be shown, with the histological remission rates ranging from 93% to 100%, with the 100% achieved in the group with the lowest dose of 1 mg BID, whereas in the placebo group, none of the patients had achieved histological remission. The mean number of eos were reduced by a range of 59 to 97 in the active treatment groups, whereas for the placebo group, an increase of 14 was seen. The results of the final analysis (including the overrun patients) were quite similar to the interim analysis.

Highly (clinically) relevant and statistically significant differences were also seen in the endpoints histological response rate, mean change in endoscopic score, endoscopic intensity score, endoscopy VAS score and peripheral eosinophil count. The evaluation of the symptomatic endpoints as well as the ratings of the questions

on the eating behaviour, as well as the quality of life evaluation in this trial, however, showed rather inconsistent results not demonstrating statistical significance, and sometimes not even indicating any numerical difference to placebo.

Similar to the missing of the demonstration of differences to placebo, there was also no indication of a dose-response relationship, favouring any of the doses (or formulation) included.

Therefore, although the phase II study was formally a successful study, it must be concluded that the objective to determine the most adequate dose could not be met, at least from the efficacy point of view. Nevertheless, the choice of the lowest dose – which was used in the phase III study – can be considered to be rational with the underlying assumptions on the possibility of systemic (adverse) effects of steroids. However, the "optimal" dose in the sense of the "minimal dose still sufficiently effective with the least number of safety problems" may have missed, and the argumentation of the applicant based on a literature study, which was conducted with a different formulation in a different population is not fully acceptable. However, the final dose can be accepted based on the results of the phase III study which showed overall convincing results.

The phase III study BUL-1/EEA recruited 88 (2:1 randomisation) patients overall, of which 54 were included into the interim analysis, at which the study was stopped for overwhelming efficacy. The overrun population comprised 34 patients. Exclusions from the PP population were 6 patients in the placebo, and 9 patients in the active treatment group. 51 patients were included in the open-label extension phase, with 28 coming from the former placebo group, and 22 from the active treatment group. There were 4 and 3 discontinuations in the placebo and active treatment groups, all due to lack of efficacy, indicating already the potential for higher efficacy in the active treatment group.

At the interim analysis, the primary endpoint was met by none of the patients in the placebo group, and by 55.6% patients in the active treatment group. The overrun population results did not relevantly differ from this result, and the overall results had a 0% and 57.6% responder rate. Similar observations were made for the histological remission rates, for which again no placebo patient achieved remission, but about 90% of the actively treated patients. The rates of remission on symptoms were also relevantly different, albeit with a remission rate in the placebo group of almost 14%, and 59% in the active treatment group. For this analysis a slight discrepancy was observed for the placebo remission rates between the stage 1 and overrun patients. However, the overrun population in the placebo group only included 11 patients. Similar results were achieved in the PP analyses.

Two more of the additional key secondary endpoints, the change in peak eosinophil count (histology) and the responder rate according to the EEsAI-PRO score also showed clinically relevant and highly statistically significant differences between the treatment groups in favour of budesonide.

However, the hierarchical testing had to be stopped after the analysis of the VDQ score which – similar to the AMS score – did not show a relevant or statistically significant difference. For the AMS score response rates, not even a numerical difference was seen. These two scores – which are also part of the total EEsAI-PRO score – had already been criticized during the Scientific Advice, and the applicant attributes the failure to show an effect for these scales on the reluctance of the patients to change eating habits at short notice/within a short time. Whereas this is not completely implausible, the choice of the foods evaluated, and method of evaluation could also be responsible for the missing responsiveness of these scores. Overall, the missing changes in these scores, and the obvious reluctance of the patients to change their eating habits is not taken as an argument against efficacy of the compound.

The further secondary endpoints, such as numerical pain on swallowing and dysphagia scales, as well as Patient's and Physician's Global Assessments, Patient's Response Assessment, the "time to first resolution of symptoms", the overall patient satisfaction, the endoscopic evaluations (total EEsAI endoscopy score and inflammatory signs subscore, endoscopist's overall assessment), and the peripheral eosinophil counts, although formally exploratory evaluations only, were all significantly in favour of the active treatment group, thus demonstrating a high consistency of the results across a wide variety of symptomatic, global, endoscopic, and laboratory-based endpoints.

The results with regard to the Quality of Life endpoints are rather heterogeneous and do not unanimously allow a conclusion of a clear influence on Quality of Life in these patients. However, according to the CHMP's understanding of Health-Related Quality of Life, the proposed treatment duration (even if the 12 weeks are considered) falls short of the necessary observation time for any claim on Health Related Quality of Life. However, some beneficial effects have been detected, especially for the SHS scale indicating an improvement of the well-being of the patients.

In the analysis of the time-course related improvements in clinical symptoms, it was detected that the response rates/clinical efficacy was still improving at the time of analysis, allowing a suspicion that the treatment duration chosen for the trial (6 weeks) had even been potentially too short for a considerable part of the patients.

This is clearly corroborated by the results of the open-label extension phase, where the primary endpoint was met by about 70% of the patients on active medication during the first 6 weeks, and by almost 80% of the patients previously treated with placebo. The analysis of the time-course for the placebo population (in the double-blind phase) indicated that all efficacy parameters had already reached a "plateau-phase" after 4 weeks, and therefore, the assumption that higher response rates would be achieved by longer placebo treatment appears not to be reasonable. The results of the open-label extension phase are therefore regarded to overall support the proposed treatment duration of 6 weeks, plus 6 weeks extension, if a sufficient response to treatment has not been achieved.

The applicant has also investigated the overall consistency of the results of the trial and looked into the subgroups of patients divided according to country of origin, the size of the centre, the baseline grade of inflammation, the localisation of the oesophageal inflammation, the patient history according to presence of allergies, and use of dietary therapy, as well as duration of the disease, and did not find any relevant differences, except for the fact that it appeared that patients with a long-standing history of the disease and those with a previous dietary therapy appear to be more difficult to treat, which is not considered surprising.

The applicant has additionally analysed whether the response to treatment or the need for a prolongation of therapy beyond the primary period of 6 weeks can be detected from demographic parameters at baseline. However, neither the literature, nor the analyses of the pivotal trial could show reliable predictive features for treatment success. The best correlations were found for the severity of symptoms at trial entry, but with still a high level of uncertainty so that no recommendation was included into the prescribing information at this time.

2.5.4. Conclusions on the clinical efficacy

The applicant has presented a limited amount of clinical data in support of the efficacy of the new formulation. This was based on the overall database available, which has led to the recommendation of learned societies to treat these patients with topical corticosteroids for the induction of remission, both in adult as well as paediatric EoE patients. Therefore, it is considered reasonable that the applicant presents only a "confirmation of known data" with one single pivotal trial to demonstrate efficacy of the compound.

The phase II study conducted has provided a convincing proof of principle again for this treatment, and has shown a high and consistent (across doses) effects on the histological features of the disease, even if treated for only the short period of 2 weeks. However, the trial is overall considered a relatively weak dose-finding exercise because it failed to determine any difference between the doses tested. Whereas it is fully accepted that the lowest dose investigated in this phase II trial was taken forward into phase III, the trial did also not provide adequate data to prepare the phase III trial adequately with regard to the necessary proof of efficacy for symptoms, because it was too short in duration to show relevant effects.

The applicant has therefore chosen to use a 2-stage adaptive design again in phase III, despite the fact that the exact pre-conditions for using such a design according to the respective CHMP guideline were not fulfilled. However, based on the well-established nature of the compound, and the data available for the substance class overall, and due to the actual conduct as well as results of the interim analysis (planned and conducted without relevant deficiencies and with an early stop of the trial), the presentation of such a trial design is considered acceptable.

The phase III trial has shown overall highly significant and clinically convincing results with regard to the superiority of the active medication compared to placebo. This superiority was detected consistently for the vast majority of endpoints, including histological, endoscopic, and symptomatic evaluations. A surprisingly high consistency was also seen for relevant subgroups of the patient population, despite the limited sample size.

This study did not investigate whether – after an initial treatment course of 6-12 weeks – a longer treatment period would be needed. As indicated above, the applicant has planned for the conduct of a long-term efficacy ("maintenance") study, for which the patients successfully treated in study BUL-1/EEA could be recruited. This trial is ongoing at the time of assessment and is planned to be finalized in 2019. Time to relapse is expected to be relatively long for patients (in fact this was based on the observations in the study population included into the phase III trial), however, divergent results with regard to the risk of relapse are available from the literature. Presentation of long-term treatment data, and the evaluation of whether a continuous long-term treatment is necessary in the population is not considered needed for this marketing authorisation application on short term use However, the completion of study BUL-2/EER and the presentation of the data for evaluation is recommended to the applicant to evaluate the usefulness of this formulation on long term treatment.

A further study in children is planned with a suspension formulation. The applicant did not apply for a marketing authorization in children and adolescents. However the unmet medical need in the paediatric population is considered to be as high as in adults. The applicant is therefore strongly encouraged for further development of Budesonide in this area.

2.6. Clinical safety

Patient exposure

As displayed in the Chapter 3 on clinical efficacy and Chapter 2 on pharmacology, the development programme for this medicinal product was rather limited in size and numbers. The overall exposure in terms of numbers included in the presented clinical development programme is displayed in the following table:

Table 23: Overall extent of exposure in clinical trials

Clinical study	Number of subjects / patients treated	
	Budesonide	**Placebo**
Clinical pharmacology study BUU-1/BIO		
Healthy subjects	13	NA
Patients	12	NA
Pivotal clinical study BUL-1/EEA		
DB phase	59	29
OLI phase	28[a]	–
Supportive clinical study BUU-2/EEA	57[b]	19
TOTAL	**169**	**48**

BUL: budesonide orodispersible tablet; BUU: budesonide viscous suspension; DB: double blind; OLI: open-label induction; NA: not applicable.
Source: BUU-1/BIO (5.3.3.1), Section 10.1; BUL-1/EEA (5.3.5.1) Appendix 8.2.1, Table 1.1.1..1; BUU-2/EEA (5.3.5.1), Appendix 8.2, Table 1-3.
[a] patients who received Placebo in the DB phase and received BUL 1 mg twice daily (BID) in the OLI phase
[b] all patients who received BUL (budesonide orodispersible tablets) or BUU (budesonide viscous suspension)

Adverse events

During the PK/PD study BUU-1/BIO a total of 18 AEs occurred in 8/13 (61.5%) healthy subjects, and 17 AEs occurred in 11/12 (91.7%) patients. The incidence of AEs was generally similar across treatments and similar between populations. There was no increase in AEs during the multiple-dose period compared to the single-dose periods. In both patients and healthy volunteers, the frequency of adverse events was highest in the reference treated group with no meaningful differences between the orodispersible tablet/suspension formulation groups. No meaningful comparisons appear possible, because no placebo group was included in the study. The only events which occurred in more than 1 subject were fatigue (documented in three healthy volunteers in the 1 mg OD Budesonide orodispersible tablet group) and diarrhoea (documented in 2 patients in the multiple-dose orodispersible tablet group).

In study BUU-2/EEA, 32 patients experienced at least 1 AE within the scope of this study. Proportions of patients with at least 1 AE were larger in the budesonide groups (36.8%, 57.9%, and 63.2% in the BUL 1mg BID, BUL 2mg BID, and BUU 2mg BID groups) than in the placebo group (10.5%). The following table shows the events by PT classification:

Table 24: Patients with at least 1 TEAE by PT

Table 50: Patients with at least 1 TEAE by PT (SAF)

PTs	Number (%) of patients with at least 1 TEAE			
	BUL 1mg BID (n = 19)	BUL 2mg BID (n = 19)	BUU 2mg BID (n = 19)	Placebo (n = 19)
Esophageal candidiasis*	2 (10.5%)	1 (5.3%)	3 (15.8%)	---
Fungal esophagitis*	1 (5.3%)	2 (10.5%)	---	---
Nausea	---	2 (10.5%)	---	1 (5.3%)
Headache	1 (5.3%)	1 (5.3%)	1 (5.3%)	---
Nasopharyngitis	2 (10.5%)	---	---	---
Dyspepsia	---	---	2 (10.5%)	---
Hypertension	1 (5.3%)	---	---	---
Pruritus	1 (5.3%)	---	---	---
White blood cell count increased	1 (5.3%)	---	---	---
Local swelling	---	1 (5.3%)	---	---
Gastric cyst	---	1 (5.3%)	---	---
CRP increased	---	1 (5.3%)	---	---
Blood cortisol decreased	---	1 (5.3%)	---	---
Erosive esophagitis	---	1 (5.3%)	---	---
Odynophagia	---	1 (5.3%)	---	---
Oral mucosal blistering	---	1 (5.3%)	---	---
Vomiting	---	1 (5.3%)	---	---
Abdominal pain upper	---	---	1 (5.3%)	---
ALT increased	---	---	1 (5.3%)	---
Bowel movement irregularity	---	---	1 (5.3%)	---
Deafness	---	---	1 (5.3%)	---
Gastroesophageal reflux disease	---	---	1 (5.3%)	---
Lip oedema	---	---	1 (5.3%)	---
Mucous stools	---	---	1 (5.3%)	---
Oropharyngeal pain	---	---	1 (5.3%)	---
Urticaria	---	---	1 (5.3%)	---
Deterioration of eosinophilic esophagitis	---	---	---	1 (5.3%)

***suspected cases based on macroscopic findings, for histological analysis and confirmation of suspected cases see comment below**

Source: Appendix 8.2, Table 3-1.1.3.2 (SAF)

In the pivotal study BUL-1/EEA, the incidence of AEs was generally higher in the active treatment group as compared to placebo (66.1% vs. 41.4% of the patients experiencing adverse events). An event rate of around 60% was also reached during the open-label extension phase of the study, both in patients previously treated with placebo, as well as those previously treated with the active medication.

The following two tables show the adverse events frequency during the double-blind treatment period by SOC and PT:

Table 25: Patients with at least on TEAE during double-blind treatment phase of study BUL-1/EEA, according to SOC

System Organ Class	Number (%) of patients with at least one DB TEAE	
	Placebo (n = 29)	BUL 1mg BID (n = 59)
Blood and lymphatic system disorders	1 (3.4%)	---
Eye disorders	---	1 (1.7%)
Gastrointestinal disorders	3 (10.3%)	10 (16.9%)
General disorders and administration site conditions	1 (3.4%)	---
Immune system disorders	1 (3.4%)	---
Infections and infestations	6 (20.7%)	21 (35.6%)
Injury, poisoning and procedural complications	1 (3.4%)	1 (1.7%)
Investigations	---	5 (8.5%)
Musculoskeletal and connective tissue disorders	---	1 (1.7%)
Nervous system disorders	1 (3.4%)	5 (8.5%)
Psychiatric disorders	1 (3.4%)	---
Renal and urinary disorders	---	1 (1.7%)
Respiratory, thoracic and mediastinal disorders	2 (6.9%)	2 (3.4%)
Skin and subcutaneous tissue disorders	---	1 (1.7%)
Surgical and medical procedures	---	1 (1.7%)
Vascular disorders	---	3 (5.1%)

DB TEAE: double-blind treatment-emergent adverse event
Source: Appendix 8.2.3, Table 1.1.7 (SAF-DB).

Table 14: Patients with at least one DB treatment-emergent AE by PT occurring in at least 2 patients; study BUL-1/EEA

Preferred term	Number (%) of patients with at least one DB TEAE	
	Placebo (n = 29)	BUL 1mg BID (n = 59)
Gastroesophageal reflux disease	---	3 (5.1%)
Nausea	---	2 (3.4%)
Suspected local fungal infection*	---	14 (23.7%)
Candida infection	---	2 (3.4%)
Esophageal candidiasis	---	10 (16.9%)
Oral candidiasis	---	2 (3.4%)
Oropharyngeal candidiasis	---	3 (5.1%)
Nasopharyngitis	1 (3.4%)	2 (3.4%)
Pharyngitis	2 (6.9%)	1 (1.7%)
Blood cortisol decreased	---	3 (5.1%)
Headache	1 (3.4%)	4 (6.8%)
Asthma	2 (6.9%)	---
Hypertension	---	2 (3.4%)

DB TEAE: double-blind treatment-emergent adverse event
* Patients with more than one fungal infection event may appear several times in different subcategories, but are counted only once in the "Suspected local fungal infection" category.
Source: Appendix 8.2.3, Table 1.1.7 (SAF-DB) and Table 1.1.19.6 (SAF-DB).

The assessment of causality as performed by the investigators, showed only 1 event of insomnia in the placebo group assessed as related to study medication, whereas for the active treatment group, 1 event each were considered related of "dyspepsia" "faeces soft", "nausea", "polyuria", and "hypertension". Events assessed as related, and occurring more than once were "gastroesophageal reflux disease", "candida infection", "oral candidiasis", "oropharyngeal candidiasis", as well as "blood cortisol decreased".

During the open-label extension phase of study BUL-1/EEA, a total, 24 AEs occurred in 16 patients (57.1%) in the Placebo→BUL group and 35 AEs occurred in 14 patients (60.9%) in the BUL→BUL group. There was no AE occurring between the double-blind and the open-label extension phase, and all 24 AEs in the open-label

extension study were TEAEs. A total of 16 AEs in 13 patients (46.4%) in the Placebo→BUL group and 11 AEs in 6 patients (26.1%) in the BUL→BUL were rated as ADRs, as a causal relationship with budesonide was considered at least possible. The tables are shown in the following, according to SOC and PT:

Table 26: Patients with at least one treatment-emergent AE by SOC; open-label extension of study BUL-1/EEA

System Organ Class	Number (%) of patients with at least one OLI TEAE		
	Placebo→BUL (n = 28)	BUL→BUL (n = 23)	Total (n = 51)
Blood and lymphatic system disorders	---	1 (4.3%)	1 (2.0%)
Ear and labyrinth disorders	---	1 (4.3%)	1 (2.0%)
Gastrointestinal disorders	2 (7.1%)	3 (13.0%)	5 (9.8%)
General disorders and administration site conditions	---	2 (8.7%)	2 (3.9%)
Infections and infestations	12 (42.9%)	4 (17.4%)	16 (31.4%)
Investigations	1 (3.6%)	1 (4.3%)	2 (3.9%)
Musculoskeletal and connective tissue disorders	1 (3.6%)	1 (4.3%)	2 (3.9%)
Nervous system disorders	1 (3.6%)	4 (17.4%)	5 (9.8%)
Psychiatric disorders	1 (3.6%)	1 (4.3%)	2 (3.9%)
Respiratory, thoracic and mediastinal disorders	---	1 (4.3%)	1 (2.0%)
Surgical and medical procedures	1 (3.6%)	---	1 (2.0%)

OLI TEAE: open-label induction treatment-emergent adverse event
Source: Appendix 8.2.3, Table 2.1.7 (SAF-OLI).

Table 16: Patients with at least one treatment-emergent AE by preferred term (only preferred terms occurring in at least 2 patients overall); open-label extension phase; study Bul-1/EEA:

Preferred term	Number (%) of patients with at least one OLI TEAE		
	Placebo→BUL (n = 28)	BUL→BUL (n = 23)	Total (n = 51)
Gastroesophageal reflux disease	1 (3.6%)	2 (8.7%)	3 (5.9%)
Local fungal infection*	10 (35.7%)	4 (17.4%)	14 (27.5%)
Candida infection	1 (3.6%)	2 (8.7%)	3 (5.9%)
Esophageal candidiasis	8 (28.6%)	1 (4.3%)	9 (17.6%)
Oral candidiasis	1 (3.6%)	---	1 (2.0%)
Oropharyngeal candidiasis	1 (3.6%)	2 (8.7%)	3 (5.9%)
Headache	1 (3.6%)	4 (17.4%)	5 (9.8%)

OLI TEAE: open-label induction treatment-emergent adverse event
* Patients with more than one fungal infection event may appear several times in different subcategories, but are counted only once in the "Local fungal infection" category.
Source: Appendix 8.2.3, Table 2.1.7 (SAF-OLI) and Table 2.1.19.6 (SAF-OLI).

The events occurring more than once, and assessed as at least potentially related to study medication were the following: GERD (2), Candida infection (3), oesophageal candidiasis (9), oropharyngeal candidiasis (3).

The applicant has re-evaluated the AEs reporting oesophageal fungal infections on the phase II as well as the phase III study by histology, and found some reduction of rate of these events. This could be attributable to the fact that both, the symptoms as well as the endoscopic appearance of EoE and oesophageal candidiasis cannot readily be differentiated, but may also be attributed to "sampling error".

The applicant has further clarified that the vast majority of cases of fungal infection were asymptomatic (only one of the cases was symptomatic), and that most of the cases were of mild severity and were successfully treated with local and systemic antimycotic medication during the trial. The occurrence of fungal infection and their treatment appears not to have an influence on the efficacy of the compound.

At the request of the CHMP, the applicant has additionally evaluated the safety database of the ongoing long-term trial BUL-2/EER in a blinded manner. This analysis, based on 177 patients with unknown treatment duration, could overall not reveal new safety concerns, and the preliminary data did not show an increase of adverse events rates of the known events detected in the short-term studies.

Serious adverse event/deaths/other significant events

There were no serious AEs and no deaths during the course of the three studies reported.

Laboratory findings

Apart from the changes seen in the eosinophil count (which showed a reduction), there were no fully consistent and clinically relevant changes in any of the laboratory parameters, or vital signs and physical examinations.

Safety in special populations

No analyses in relevant subpopulations or special populations are presented. An analysis of adverse events in patients with older age (those above 65, 75, or even 85) appeared not sensible because the overall number of such patients was too low (in fact the oldest patient was 69 years of age). The applicant has therefore analysed an age cut-off at 35 years. However, any relevant differences between young and older patients could not be detected. A similar analysis with similar results was conducted for gender.

Immunological events

No special reports on immunological events have been presented by the applicant.
There were 3 events during the clinical development programme (see also discontinuations below) potentially related to immunological events, which were labelled as cases of “lip oedema” and of which two cases have been identified as being related to the intake of the study medication. Obviously, in one case, the lip oedema was associated with oral paraesthesia, but in none of the cases was there any indication of systemic involvement, such as skin efflorescences, influence on blood pressure (in the sense of a syncopal event), or any difficulty in breathing. Therefore, while the causation of systemic allergic reaction cannot be excluded in the future, there is currently no clear indication that the three cases were involving any systemic allergic reaction

Safety related to drug-drug interactions and other interactions

With regard to potential changes in the safety profile by drug-drug interactions, the applicant referred to theoretical considerations only and the data from pharmacovigilance with their capsule formulations used in IBD. An additional analysis of the clinical data was performed, but did not reveal meaningful results, because most of the concomitant medication was given during the endoscopic procedures as part of the trial conduct, and the adverse events reported for these cases were also mostly related to the endoscopic procedures performed. A conclusion with regard to the causation of adverse events by concomitant medication cannot be drawn.

Discontinuation due to adverse events

There was one withdrawal from the PK study BUU-1/BIO (1 patient taking reference treatment (budesonide capsules) experiencing nausea and vomiting, as well as headache), and one withdrawal from the phase 3 study BUL-1/EEA in a placebo patient experiencing food impaction during the placebo-controlled phase, as well as 1 further withdrawal due to 2 AEs in one patient in the open-label extension phase (the patient had a lip edema and oral paraesthesia (mild intensity, assessed as probably/likely related to the study drug, and with a positive de-challenge). There was one event in study BUU-2/EEA which led to discontinuation, which related to another case of lip edema (oral suspension group, 5 days after start of treatment

Post marketing experience

At submission of the dossier Jorveza was not marketed. No post authorization data were submitted.

2.6.1. Discussion on clinical safety

The applicant has presented the analysis of safety based on the analysis of the three new trials conducted separately, and not analysed the safety data in a pooled way. Considering the relevant differences of the trials, especially with regard to the treatment duration, doses and different pharmaceutical formulations used, this is overall considered acceptable.

The safety database for this application is considered to be limited, consisting of the analysis of three studies. These comprise 25 subjects (13 healthy volunteers and 12 patients) exposed in the phase I study, 57 patients exposed in the phase II study, and 59 patients exposed in the phase III study to any dose and formulation of budesonide.

The time of exposure was for single-dose as well as for 7 day treatments (in cross-over manner) in the phase I trial, and for 2 weeks in the phase II trial. In the phase III trial, the mean exposure was 41 days in the double-blind phase, and 43 days for the 28 patients entering the open-label extension phase from the placebo group. 23 patients were treated for a duration of approximately 12 weeks.

During the phase 1 trial, the rate of adverse events was higher in the patients (91.7%) as compared to the healthy volunteers (61.5%). In healthy volunteers the vast majority of events was rated as mild, and only slightly more than half of the events were assessed as potentially related to the intake of the study medication.

Due to the missing of an untreated (or placebo) control group, no clear conclusions are possible, but there was the impression that the number of adverse events was reduced for the orodispersible tablet, as well as the oral suspension formulation as compared to the capsule formulation.

During the phase II study, the proportion of patients experiencing AEs were higher in the active treatment groups compared to placebo, with higher rates of about 60% in the higher dose groups (of the ODT and suspension formulations). The number of AEs was 9, 14 and 14 in the active treatment groups (1 mg BID, 2 mg BID and suspension group), as compared to 2 in the placebo group. Of these 40 events, 17 were rated as related to the study medication.

The only events occurring more than once in any of the treatment groups were oesophageal candidiasis, fungal oesophagitis, nausea, nasopharyngitis, and dyspepsia, which were more frequent in one of the active treatment groups, but not consistently so throughout all active treatment groups. This was only applicable to the event “oesophageal candidiasis”, which can therefore be attributed already to be linked to the treatment with budesonide, independent of dose and formulation. The applicant has further investigated these events post-hoc,

because the macroscopic signs of fungal infections and of eosinophilic oesophagitis are very similar, and this evaluation confirmed the fungal infection in 6 out of 9 patients (in 1 patient, no material was available), 2 in each of the three active treatment groups. Risk of fungal infections was added to the RMP as important identified risk and the product information raises appropriate warnings to this risk.

During the double-blind phase of the phase III trial, a total of 12 events (concerning 41.1% of the patients) occurred in the placebo group, and 39 events (concerning 66.1% of the active treatment groups) occurred. Of these, only 1/12 in the placebo, but 23/39 events in the active treatment group were assessed as at least possibly related to the study drug. The rate of events during the open-label extension phase was almost similar in both treatment groups included (concerning around 60% of the patients).

The events for which a difference disfavouring the active treatment is obvious and were occurring more than once are from the following SOC level: Gastrointestinal disorders (10.3% vs. 16.9%), Infections and infestations (20.7% vs. 35.6%), Investigations (0% vs. 8.5%), nervous system disorders (3.4% vs. 8.5%), and vascular disorders (0% vs. 5.1%).

At the PT level this applies to the following events: Gastroesophageal reflux disease (0% vs. 5.1%), Nausea (0% vs. 3.4%), candida infection (localisation not stated; 0% vs. 3.4%), oesophageal candidiasis (0% vs. 16.9%, oral candidiasis (0% vs 3.4%), oropharyngeal candidiasis (0% vs. 5.1%), blood cortisol decreased (0% vs 5.1%), headache (3.4% vs. 6.8%), and hypertension (0% vs. 3.4%). Almost all of these events would be considered as adverse drug reactions due to their known relationship to corticosteroid intake, as well as biological plausibility. Biological plausibility is, however, not so obvious for GERD, and for nausea, and for the event of dyspepsia assessed as related to study drug intake (without occurrence in the placebo group). Due to the high numbers observed – and discrepancy to the event rate in placebo treated patients – GERD has been labelled as adverse reaction in the PI.

Similar rates and character of events have been observed during the open-label phase of the phase III study, with higher rates of fungal infections in those patients previously treated with placebo.

The majority of fungal infections in the phase III trial could be confirmed histologically (although not all), but most of these events did not show endoscopic or clinical signs of fungal infection. In fact, only one of these events has been diagnosed based on the occurrence of symptoms only. Fungal infections have been treated during the study, and most of the events have been classified as resolved at the end of the observation period. A recommendation to treat fungal infection is therefore included in the PI.

The majority of patients experienced AEs of “mild” (Placebo: 9 of 29 patients [31.0%]; BUL 1mg BID: 37 of 59 patients [62.7%]), or “moderate” (Placebo: 2 of 29 patients [6.9%]; BUL 1mg BID: 7 of 59 patients [11.9%]) intensity. “Severe” AEs occurred in one patient (3.4%) in the Placebo group (food impaction) and in no patient in the BUL 1mg BID group. This was quite similar for the open-label extension phase.

There were no serious AEs or deaths during the conduct of any of the studies.

Although during the double-blind trial, the monitoring of morning cortisol showed some decrease over time, this was also seen in the placebo group, and no clear difference between the treatments emerged. Parameters such as bone alkaline phosphatase (AP), osteocalcin, urine pyridinoline-creatinine ratio and urine desoxypyridinoline-creatinine ratio, which were measured to detect a possible osteoporosis-promoting effect of budesonide, showed mostly no relevant changes to baseline after a six-week treatment with 1 mg BID. The slight decreases of osteocalcin, and urine pyridinoline-creatinine ratio were not seen to be clinically relevant compared to the placebo group. Similar findings were reported during the open-label extension phase. However, the influence of systemic corticosteroids on bone formation/resorption is a well-known fact, and remains at least

a potential danger for the treatment, although this can be rated to be low for the currently proposed short-term treatment period.

No special safety data with regard to potential for drug-drug interactions, or according to special patient groups (e.g. on pregnancy and lactation and renally or hepatically impaired) are available and this is outlined as missing information in the RMP. Based on the limited evaluations possible, an influence of gender and age on the rates of adverse events appears unlikely.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

2.6.2. Conclusions on the clinical safety

The evaluation of the small safety database has shown that the new orodispersible tablets containing 1 mg budesonide, and administered twice daily to an EoE population is unlikely to exert the typical “systemic” effects of corticosteroids. There were some reports on the influence on the blood cortisol level, as well as reports on arterial hypertension aggravated, which belong to the spectrum of these systemic effects. However, typical effects such as Cushing’s Syndrome, psychiatric disorders, eye disorders such as glaucoma or cataract, duodenal or gastric ulceration (although one ulcer was seen in the open-label extension phase), were currently not observed for the compound. The known systemic effects, however, remain a theoretical possibility and “systemic glucocorticosteroid effects” are an important potential risk in the RMP.

The known potential of the immunosuppressive action of glucocorticosteroids, however, was shown in the clinical programme through the development of high rates of oral, pharyngeal, and, mainly, oesophageal fungal infections. The clinical relevance of these infections, however, has to be assessed as low, and the overwhelming majority was only diagnosed by endoscopy/histology, and did not have “symptomatic” consequences for the patients. Some of these events were diagnosed endoscopically only, and could not be confirmed histologically. However, it is unclear whether these latter cases are really mistaken ongoing sequelae of EoE, or were indeed fungal infections which only missed a histological proof in the biopsies taken. Nevertheless, the high rate of especially oesophageal infections (>20%) is of concern. The concern may be less strong in a setting where treatment is stopped after a course of 6 or 12 weeks treatment, however, it may be more relevant once the need for ongoing treatment (“maintenance”) is identified. The preliminary data shown from the long-term trial do at this time-point not indicate a relevant increase of the rates of fungal infections.

The further effects identified as risks are either well known effects of budesonide (headache) or are presumably related to the influence of high concentrations of budesonide on the lower oesophagus sphincter or the stomach, relating to the observed cases of nausea, dyspepsia, as well as gastroesophageal reflux disease, the two latter of which, have been decided to be labelled as adverse drug reactions and are outlined in 4.8 of the SmPC.

Overall, as for other formulations of budesonide, the safety profile appears to be acceptable, because only a low risk of systemic effects has been identified. Local effects, however, appear to play a higher role (as compared to what is known for the capsule formulation), with the occurrence of a high rate of fungal infections and some “functional” complaints of the upper digestive tract, such as reflux complaints and nausea. This is appropriately addressed in RMP and product information.

The following risks have to be considered identified based on the evaluation of the available safety data: local fungal infections (mouth, pharynx, and oesophagus), nausea, dyspepsia, interaction with CYP3A4 inhibitors, gastroesophageal reflux disease, increased cortisol levels and lip oedema. However, not all of them are considered important.

The currently unaddressed patient populations comprise the safety in pregnancy and lactation, and the use in patients with severely impaired renal function

2.7. Risk Management Plan

Safety concerns

Table 24: Summary of the safety concerns

Important identified risks	• Risk of local fungal infections • Gastroesophageal reflux disease • Hypersensitivity reactions including lip edema • Interactions with CYP3A4 inhibitors
Important potential risks	• Cushing's syndrome • Muscle effects (including muscle and joint pain, muscle weakness, muscle twitching) • Osteoporosis • Psychiatric effects (including depression, euphoria, hyperactivity, anxiety) • Infections • Eye affections (including glaucoma, cataract, blurred vision) • Hypokalaemia • Gastric or duodenal ulcer • Hyperglycaemia, particularly in diabetic patients • Adrenal suppression • Growth retardation (in off-label paediatric use)
Missing information	• Safety in pregnancy and lactation • Use in patients with severely impaired renal function

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Table 25 – Summary table of the risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Risk of local fungal infections	Yes Proposed text in the SmPC: • Special warnings and precautions for use in section 4.4 • Undesirable effects in section 4.8 Prescription only medicine	No
Gastroesophageal reflux disease	Yes Proposed text in the SmPC:	No

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Undesirable effects in section 4.8 Prescription only medicine	
Hypersensitivity reactions including lip edema	Yes Proposed text in the SmPC: • Undesirable effects in section 4.8 Prescription only medicine	No
Interactions with CYP3A4 inhibitors	Proposed text in the SmPC: • Special warnings and precautions for use in section 4.4 • Interaction with other medicinal product and other forms of interaction in section 4.5 Prescription only medicine	No
Cushing's syndrome	Yes Proposed text in the SmPC: • Undesirable effects 4.8 Prescription only medicine	No
Muscle effects	Yes Proposed text in the SmPC: • Undesirable effects 4.8 Prescription only medicine	No
Osteoporosis	Yes Proposed text in the SmPC: • Undesirable effects 4.8 Prescription only medicine	No
Psychiatric effects	Yes Proposed text in the SmPC: • Undesirable effects 4.8 Prescription only medicine	No
Infections	Yes Proposed text in the SmPC: • Special warnings and precautions for use in section 4.4 • Undesirable effect in section 4.8 Prescription only medicine	No
Eye affections	Yes Proposed text in the SmPC: • Special warnings and precautions for use in section 4.4 • Undesirable effect in section 4.8 Prescription only medicine	No
Hypokalaemia	Yes Proposed text in the SmPC: • Undesirable effects 4.8 Prescription only medicine	No
Gastric or duodenal ulcers	Yes Proposed text in the SmPC: • Special warnings and precautions for use in section 4.4 • Undesirable effect in section 4.8 Prescription only medicine	No
Hyperglycaemia	Yes Proposed text in the SmPC: • Special warnings and precautions for use in section 4.4 • Undesirable effect in section 4.8 Prescription only medicine	No
Adrenal suppression	Yes Proposed text in the SmPC: • Special warnings and precautions for use in section 4.4	No

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Undesirable effect in section 4.8 Prescription only medicine	
Growth retardation (in off-label paediatric use)	Yes Proposed text in the SmPC: • Posology and method of administration in section 4.2 • Undesirable effect in section 4.8 Prescription only medicine	No
Safety in pregnancy and lactation	Yes Proposed text in the SmPC: • Fertility, pregnancy and lactation in section 4.6 • Preclinical safety data in section 5.3 Prescription only medicine	No
Safety in patients with severely impaired renal function	Yes Proposed text in the SmPC: • Posology and method of administration in section 4.2 • Pharmacokinetic properties in section 5.2 Prescription only medicine	No

Conclusion

The CHMP considered that the risk management plan version 1.3 (dated 8 November 2017) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Taking into account the specific indication and specific route of administration that leads to different safety concern consequences, e. g. potential for off label use in children and missing data on long term use as well as uncertainties regarding systemic effects (potential risks), the CHMP is of the opinion that a separate entry in the EURD list for Jorveza is needed, as it cannot follow the already existing entry for budesonide. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. 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

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant is applying for the indication “Treatment of eosinophilic oesophagitis”. This condition has not been subject of a MAA for a medicinal product before. The condition itself was described in the early 1990s, and during the last 10 years scientific consensus in the field, defined the disease, its epidemiology, aetiology and pathophysiology, clinical manifestations, as well as treatment and prognosis.

The disease is defined by an eosinophil invasion to and inflammation of the oesophageal lining, presenting clinically in adults with relevant complaints such as dysphagia, odynophagia, food avoidance behaviour, and – in more advanced stages – the development of oesophageal fibrosis and stenosis, including the clinical manifestation of food impaction.

The anti-inflammatory treatment proposed with the substance under evaluation addresses – by its mode of action – clearly the identified molecular pathways of inflammation, and has shown – even before the conduct of any trial with the product under consideration – to induce a rapid reduction of the inflammatory changes in the mucosa.

Whereas the postulate of both, clinicians as well as pathologists/pathophysiologists, has been that eosinophil blood cells are not regular part of the oesophageal mucosa, and should therefore completely be abolished from the oesophageal mucosa, the last years have brought about the development of consensus criteria what an “eosinophilic inflammation of the oesophagus” constitutes, and how its restitution should be defined.

In addition, there was growing consensus in the scientific community, that the treatment aims should not only be based on a success in the treatment of the inflammatory, histologically diagnosed sequelae, but also benefit the patients from the point of symptoms, improvement of quality of life, as well as normalisation of eating behaviour and prevention of complications such as oesophageal fibrosis and food impaction.

3.1.2. Available therapies and unmet medical need

The current treatment modalities rely on one part on the off-label use of available medicinal products. These comprise proton-pump inhibitors, which can be used to treat EoE patients, in a clinical situation that has previously been described as PPI-responsive EoE, but which is now considered to present a part of the continuous spectrum of the disease. However, the success of the treatment is most likely limited to a minority of the patients, and none of the PPIs is currently licensed for the indication EoE.

The other main part of the treatment with medicinal products is based on the extemporaneous use of inhalational topical corticosteroid medications (to be opened and swallowed, or used to prepare suspensions), with the inherent dangers of missing standardisation, and inconsistent treatment results.

The condition can also be treated with dietary treatment, of which for at least 3 modalities (elemental diet, exclusion diet based on allergy testing, and “elimination diets” (e.g. SFED, FFED)) clinical data are available, and of which the latter has shown the most promising results and may indeed be considered to be used before, in addition to, or after failing of, treatment with medicinal products.

Further treatments available only refer to the treatment of complications of the disease such as food impaction and oesophageal strictures, which need endoscopic intervention (extraction procedure, and/or dilation).

Due to the fact that no licensed medicinal products are available for the condition, there is a clear unmet medical need.

3.1.3. Main clinical studies

The applicant has presented study BUL-1/EEA as the one and only pivotal study for the current development. The study was a randomised, placebo-controlled parallel-group, multi-centre double-blind study in patients with EoE being unresponsive to PPIs.

The diagnosis of EoE was based on the current histological standard definitions of an increased number of eosinophil in the histological specimens (defined as No. of eosinophils per square mm high-power field), and with a relevant symptom burden based on the evaluation of dysphagia and odynophagia complaints being present at inclusion into the trial. Patients included were endoscoped and biopsied and thus an adequate diagnosis was (including the exclusion of relevant potential other diseases) assured. About half of the included patient population has previously already been treated with dietary treatment.

The study was a relatively small study comprising 88 patients which were randomised unequally (2:1) to active (orodispersible budesonide tablet dosed 2x1 mg daily) and placebo treatment, and treated in double-blind manner for 6 weeks. Patients could enter an open-label extension phase of further 6 weeks if not satisfactorily treated at the end of the double-blind period.

The main objectives of the trial were the evaluation of efficacy as well as of safety of the compound. The chosen primary endpoint, which was a combined (at the individual level of the patient) evaluation of the histological normalisation (with the reduction of eosinophil infiltration to the consensus defined success criteria), and a relevant reduction of the main symptoms, based on simple 0-10-point NRS scales as previously recommended by CHMP advice (termed “clinico-pathological remission”). The chosen endpoint therefore adequately addresses the recommendations of the scientific consensus in the field and the recommendations of the CHMP.

3.2. Favourable effects

The primary endpoint in the clinical trial was met by 57.5% of the patients, whereas no patient in the placebo group met this endpoint at the end of the trial. The result is highly statistically significant (p=0.00000002 one sided). The success of the treatment was even higher for the influence on the histology part of the primary endpoint, because for this, also none of the placebo-treated patients, but almost 90% of the actively treated patients reached the treatment goal of remission. However, also the resolution of the symptoms (defined as no or minimal symptoms only) was achieved by only 13.8% in the placebo group, and by almost 60% in the actively treated group.

Concordant with the primary evaluation, two of the other “key secondary endpoints” (the change in peak eos per hpf, and the rate of patients with a total weekly EEsAI-PRO score below or similar to 20) also showed clinically relevant, and statistically significant differences between the treatment groups. However, the other two “key secondary endpoints”, the VDQ and the AMS scores, which both evaluate the avoidance behaviour with regard to food, only showed a moderate difference for one (the VDQ with 37.9% and 50.8% showing improvement) and

no difference for the other (the AMS with success rates of 10.3% and 11.9% in the placebo, and active treatment groups, respectively), and both not being statistically significant.

Contrary to the latter results, the further evaluation of single symptoms, the global assessment by patients and physicians, the endoscopic evaluation based on overall and single-item scores, and further histological and lab-based evaluations showed a high consistency of the results with the primary evaluation, and the four first key secondary endpoints.

Despite the small size of the database, the applicant was also able to show a high consistency of the results according to subgroups, such as country, size of the centre, localisation of the inflammation in the oesophagus, the presence of absence of allergic disease in patients, the level of complaints at baseline, the duration of disease, and the previous use of dietary treatment.

The further evaluation of the course of the symptomatic improvements during the first 6 weeks has shown that patients were still improving during the last 2 weeks of treatment, whereas for placebo, the effects had already shown to “plateau”. It is therefore not unreasonable to assume that a longer treatment could even bring about a higher rate of symptomatic success, whereas for placebo patients this might not be expected.

The prolonged treatment data available do confirm the assumptions for the added benefits of longer-term treatment because the primary endpoint was met in almost 70% of the patients previously treated in the double-blind phase with active medication after the additional 6-week treatment course. The success rate in the patients previously treated with placebo was 78.6% after the additional 6-week treatment period.

The study on one hand confirms the high rate of success reported in other studies in the field with the use of topical steroids. However, the study is difficult to compare with other studies with regard to the symptomatic part of the endpoint, which has been quite diverse in the literature, and which had not previously been regularly included in the primary evaluation.

3.3. Uncertainties and limitations about favourable effects

As has been shown in the display of the main results, there was no obvious effect on the avoidance strategies of the patients with regard to food intake. It is reasonable to assume that these behavioural changes only take place over longer periods of time, and can therefore not be determined by such a small study with short duration only.

Similarly, the prevention of complications of the disease has only been insufficiently studied, because only one patient (in the placebo group) during the course of the study developed a food impaction.

There are important subgroups of patients for which the available information is too limited to draw conclusions which relates to the female gender (only 15 patients included in the pivotal trial were female), and to elderly patients (the oldest patient included into the phase III study was 69). The influence of age has been found to be negligible in the available literature. Additional explorative evaluations of the pharmacokinetic data have revealed that the PK is overall not relevantly dependent on the factors age and gender furthermore based on the limited evaluations possible, an influence of gender and age on the rates of adverse events appears unlikely.

The small study conducted was also not able to answer the question whether the resolution of symptoms, and more so, the resolution of the inflammation does indeed bring about the prevention of the fibrosis and stenosis development, and food impaction events. For these endpoints, the trial was too short and too small to answer these questions.

Whether there is a need for continued treatment is currently unclear and therefore the treatment duration is limited to 6 - 12 weeks as described in 4.2 of the SmPC.

3.4. Unfavourable effects

The known immunosuppressive effects of budesonide have shown to cause a relatively high rate of fungal infections in all tissues exposed to (local) high concentrations of the active substance, such as the mouth, pharynx and oesophagus. The rate of such infections is obviously up to 5% of the patients for the mouth and pharynx, and about up to 20% for the oesophagus. This is regarded to be a high occurrence rate considering the short treatment period of only 6 weeks.

In addition, almost similar rates for these infections occur in those being treated in the open-label extension phase with pervious placebo treatment, and the rate seems to be little lower in those previously treated with active medication. The intake of the orodispersible tablets also induces additional upper GI symptoms such as dyspepsia, nausea and gastroesophageal reflux symptoms in up to 5% of the patients. The orodispersible tablets also induce the known effects of budesonide in some patients (e.g. such as headache with about 7%), and the adverse effects “blood cortisol decreased” and hypertension (up to 5%), which relate to the known systemic effects of all glucocorticosteroids. None of any other observed adverse event occurred at a frequency higher than in the placebo group, or was attributed to be causally related to the study drug intake, or occurred more than once only during the trial programme.

However, the analysis of single cases of lip oedema revealed a potential for the causation of immunological/allergic reactions. All these adverse reactions are appropriately listed in the product information.

The vast majority of adverse events were described as mild, and only a minority as moderate and none (in the active treatment group) to be severe in intensity. There were no serious adverse events, nor any deaths, during the course of the pivotal study.

3.5. Uncertainties and limitations about unfavourable effects

For the main identified unfavourable effects, the fungal infections, the applicant has partly investigated the histology specimens to prove or disprove the presence of fungal infection, which showed that in the smaller part of the events, such an infection could not be verified. However, it is unclear whether this relates to a real effect, because no culture (or other microbiological method, e.g. PCR-based methods) has been performed to exclude fungal infection, and because the biopsy specimens only cover a minority of the oesophageal lining. However, it is acknowledged that fungal infection and EoE may not readily be distinguishable from endoscopic inspection only and that a part of the fungal infections in the oesophagus might have been misdiagnosed.

The causation of upper GI symptoms such as nausea, dyspepsia and reflux complaints remains (patho)-physiologically unexplained, but may indeed be related to the high exposure to corticosteroids, with an influence on gastric and lower oesophageal sphincter motility. However, or the time being, the events have to be labelled as adverse reactions. Gastroesophageal reflux disease is important potential risks within the RMP.

Also, whether the cases of hypertension are indications of systemic effects will remain uncertain, similar to the clinical meaningfulness of the “investigation-based” adverse events of “cortisol decreased”. Therefore, a clear conclusion whether the compound is able to relevantly influence the HPA-axis and cause the known systemic adverse effects of glucocorticosteroids, and at which frequency, also remains unclear and systemic glucocorticosteroid effects are defined as important potential risk in the RMP.

The low number of female patients included into the trial, and the overall young age of the patient population prevents firm conclusion on differences or similarities with regard to gender and age however based on the limited evaluations possible, an influence of gender and age on the rates of adverse events appears unlikely. Similarly, an analysis looking into the potential for drug-drug interactions and their influence on unfavourable effects, turned out to be not meaningful due to the small size of the database.

3.6. Effects Table

Table 26. Effects Table for Jorveza.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
"Clinico-pathological remission"	Rate of patients showing <1 eos/mm^2 hpf and a pain and dysphagia score of ≤2	%	34/59 (57.6%)	0/29	Evidence strong, high statistically significant, and clinically relevant. No uncertainties.	BUL-1 EEA
Histological remission	Same as first component of the above	%	55/59 (93.2%)	0/29	Similar to the above. However, does not include patient well-being	BUL-1 EEA
Clinical remission	Same as second component of the above	%	35/59 (59.3%)	4/29 (13.8%)	Similar to the above.	
Change in peak eos/mm^2	Change from baseline to week 6	N/mm^2 hpf	-225.5	-4.3	Similar to the above but does also not include patient well-being	BUL-1 EEA
EEsAI-PRO remission	Rate of pats. With EEsAI-PRO ≤20	%	30/59 (50.8%)	2/29 (6.9%)	Similar to the above. Validation of the instrument, however, not complete	BUL-1 EEA
VDQ score responder	Rate of patients with improvements	%	30/59 (50.8%)	11/29 (37.9%)	Numerical superiority only, no statistical significance. Clinical relevance unclear	BUL-1 EEA
AMS score responder	Rate of patients with improvements	%	7/59 (11.9%)	3/29 (10.3%)	Factually no difference. Clinical relevance unclear.	BUL-1 EEA
Global Assessment of remission	Rate of patients with Patient's Global Assessment ≤2	%	38/59 (64.4%)	7/29 (24.1%)	Evidence strong, statistically significant, clinically relevant	BUL-1 EEA
Endoscopic remission	Rate of patients with 'no endoscopic findings'	%	36/59 (61.0%)	0/29	Evidence strong, highly statistically significant, clinically relevant.	BUL-1 EEA
Unfavourable Effects						
Fungal infection of the oesophagus	Endoscopic diagnosis	%	17-20%	0	Evidence strong, final frequency questionable (misdiagnosis), clinical meaningfulness unclear (symptoms?)	BUL-1 EEA

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Fungal infection of the mouth and pharynx	Diagnosis via oral inspection	%	8.5%	0	Similar to the above	BUL-1 EEA
Upper GI tract complaints: Nausea, dyspepsia, GERD	Subjective complaints of the patients	%	Nausea: 3.4%, GERD: 5.1%, dyspepsia 1.5%	0	Evidence moderate, pathophysiological mechanism unclear, Clinically relevant	BUL-1 EEA
Systemic adverse effects (hypertension, cortisol decreased)	Laboratory values/physical signs	%	Hypertension 3.4%, cortisol decreased 5.1%	0	Hypertension: Evidence weak (2 events only), compatible with known glucocorticoid effects, clinically relevant. Cortisol decrease: Evidence moderate, known for glucocorticoids, clinical meaning unclear	BUL-1 EEA
Headache	Subjective complaints of patients	%	6.8%	3.4%	Evidence strong, known effect of budesonide, clinical meaningfulness moderate	BUL-1 EEA

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The single pivotal trial BUL-1/EEA was able to show not only the well-known effects on the resolution of the eosinophil infiltrations into the oesophageal mucosa as described in the literature, but also a highly significant, and overall clinically most relevant reduction of the symptoms to a level which patients perceived as either “no or minimal” only. The previous results of the trials published in the field have therefore been confirmed, despite the relatively short treatment duration, for the endoscopic and histological evaluations. But as one of few studies only, a clinically highly relevant and convincing benefit in symptom improvement has been shown. It appears somehow self-evident that this could be attributed to the new pharmaceutical form, designed for and directed at the treatment of oesophageal inflammation. In addition, a multitude of evaluations of symptoms other than the (component of the) primary endpoint, of endoscopic signs, and of additional histological evaluations have also shown a high magnitude of superiority of the active treatment over placebo, indicating a high clinical relevance. Despite the small trial size, a high concordance of the results according to relevant subgroups could be shown, which indicates an unexpected high robustness of the results.

Concentrating on the histological picture, it has been shown that more than 90% of the patients can expect the full resolution of the eosinophil inflammation, thereby providing the pre-condition for the prevention of the long-term sequelae of the disease, the development of fibrosis and stenosis of the oesophagus, and its complications. In addition, the observed (almost full) symptom resolution in about 60% of the patients, which is 4-5 times more likely to occur than for placebo after 6 weeks, may even be increased to 85% (34 patients in the initial treatment phase and 16 in the open-label extension phase), if the treatment is prolonged to 12 weeks.

Contrary to this, the course of the symptom severity in the placebo group during the first 6 weeks of treatment have indicated that for placebo treatment, no further improvement can be expected after 4 weeks. The trial results have also indicated that the deterioration of the quality of life of the patients suffering from EoE could be reversed according to the evaluation of the two Quality of Life scales used in the trial. However, the observation time appeared to be too short to allow conclusions on clear improvements in QoL.

As a consequence of the limited programme conducted, the safety database is limited. The evaluation of the safety database did not reveal completely unexpected findings, but confirmed the known adverse event/reaction profile of the substance budesonide. However, the phase 2 as well as the phase 3 study showed a high rate of fungal infections, both of the oesophagus as well as the oral cavity (including the pharynx), which may total to about 30% of the population treated obviously related to the high (local) exposure of the oral and oesophageal mucosa. These infections, however, did not lead to treatment discontinuation, were mostly asymptomatic, and were in their majority treated successfully with standard antifungal treatments. Other adverse reactions obviously only concern “functional” effects such as nausea, dyspepsia, and reflux complaints, as well as headache. The influence on the HPA axis, and endogenous cortisol levels appear to be minor, however, some cases of “decreased cortisol” and of “hypertension” have been reported, which have to be assumed to be related to this.

3.7.2. Balance of benefits and risks

The demonstrated benefits with the high superiority against the comparator, the clinical relevance of the effects both with regard to the treatment effects on the underlying pathophysiology and the immediate symptomatic benefits to the patients are regarded to clearly outweigh the identified risks, which are – apart from the localised fungal infections and the functional upper GI complaints – not qualitatively different from what is known for other formulations of the active substance.

The use of this medication is expected to meet a clear unmet medical need, even if used in the short-term context only as proposed.

3.8. Conclusions

The overall B/R of Jorveza is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Jorveza is favourable in the following indication:

Jorveza is indicated for the treatment of eosinophilic esophagitis (EoE) in adults (older than 18 years of age)

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.