EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 March 2020
EMA/199925/2020

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jorveza

International non-proprietary name: budesonide

Procedure No. EMEA/H/C/004655/X/0007/G

Note

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

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List of abbreviations

Term	Explanation
ACR	Accumulation ratio
ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
AUC_{0-12h}	Area under the curve from 0 to 12 hours
BID	Twice daily
BUL	Budesonide orodispersible tablets
CCL	Chemokine (C-C motif) ligand
CI	Confidence interval
CYP	Cytochrome P450
DB	Double blind
EEsAI	Eosinophilic Oesophagitis Activity Index
EEsAI-PRO	Eosinophilic Oesophagitis Activity Index – Patient-Reported Outcome
EMA	European Medicines Agency
EoE	Eosinophilic oesophagitis
EoE-QoL-A	Eosinophilic Esophagitis Quality of Life Questionnaire
eos	Eosinophils
EOT	End of treatment
EU	European Union
FAS	Full analysis set
FU	Follow-up
GERD	Gastroesophageal reflux disease
hpf	High-power field
IgE	Immunoglobulin E
IL	Interleukin
IMP	Investigational medicinal product
LOCF	Last observation carried forward
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NRS	Numerical Rating Scale
OLI	Open-label induction
PatGA	Patient's Global Assessment
PBC	Primary biliary cirrhosis
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol
PPI	Proton-pump-inhibitor
PPI-REE	Proton-pump-inhibitor-responsive oesophageal eosinophilia
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient reported outcome
PSUR	Periodic safety update report
PT	Preferred term
R	Reference dose
SAE	Serious adverse event
SAF	Safety analysis set
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TGF-β	Transforming growth factor-beta
Th2	T-helper cell type 2
TSLP	Thymic stromal lymphopoietin

1. Background information on the procedure

1.1. Submission of the dossier

Dr. Falk Pharma GmbH submitted on 12 July 2019 a group of variations consisting of an extension of the marketing authorisation and the following variations:

Variation(s) requested		Type
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	IB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to add a new strength of 0.5 mg for budesonide orodispersible tablets, grouped with:
- A type II variation (C.I.6) - Extension of indication to include the maintenance of remission for Jorveza (0.5 mg and 1 mg orodispersible tablets); as a consequence, sections 4.2, 4.8 and 5.1 of the SmPC are updated to reflect the recommended daily dose and duration of treatment of Jorveza for the maintenance of remission, to update the list of adverse reactions and the clinical efficacy and safety information based on the results of the phase III clinical study BUL-2/EER. The relevant sections of the PL are updated accordingly. In addition, a revised RMP (version 2.0) has been submitted to reflect the results of this study and to align with the GVP Module V (rev 2) template. The MAH also took the opportunity to bring the product information in line with the latest QRD template (version 10.1).
- A type IB variation (B.II.e.5.a.2) – To add a new pack-size of 200 x 1 orodispersible tablets (unit dose) in a blister for Jorveza 1 mg orodispersible tablet (EU/1/17/1254/006)

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

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

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

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 MAH 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.

Protocol assistance

The applicant received protocol assistance from the CHMP on 26 June 2014. The protocol assistance pertained to non-clinical and clinical aspects of the dossier. The protocol assistance was received in the context of the initial MAA.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: Tomas Radimersky

The application was received by the EMA on	12 July 2019
The procedure started on	15 August 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	4 November 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	5 November 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	12 November 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2019
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	12 December 2019
The MAH submitted the responses to the CHMP consolidated List of Questions on	23 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	25 February 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	19 March 2020

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	26 March 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Eosinophilic oesophagitis (EoE) is an inflammatory condition of the oesophagus which causes symptoms including dysphagia and obstruction of the oesophagus. It is a relatively new disease entity that has been defined as a distinct clinicopathologic syndrome in the early 1990s only.

Although no single feature defines EoE, a constellation of compatible demographic, clinical, endoscopic, and histologic findings establish the diagnosis.

On 8 January 2018, Jorveza (budesonide) was approved for the treatment of EoE in adults (older than 18 years of age) as a daily dose of 2 mg orodispersible tablets (1 mg in the morning and 1 mg in the evening) for a treatment duration up to 6 to 12 weeks.

In the present application, the MAH proposes to extend the current indication to a maintenance therapy with a treatment duration to be determined by the treating physician and to include a new strength 0.5 mg orodispersible tablet. In addition, the MAH is adding a new pack-size for Jorveza 1 mg (200 orodispersible tablets).

2.1.2. Epidemiology and risk factors

EoE is one of the most prevalent esophageal diseases and the leading cause of dysphagia and food impaction in children and young adults.

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 have shown a prevalence of up to 40-56 cases per 100,000 inhabitants[1]. The disease is similarly observed in children, also with increasing incidence, however, with higher variability between the studies. Due to the unmet medical need in the paediatric population the applicant was strongly encouraged at the time of initial marketing authorisation to further develop Budesonide in this area.

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 an odd ratio (OR) of 2.01 (95% CI 1.64-2.48)[1,2].

[1] Lucendo AJ, Molina-Infante J, Arias Á et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J. 2017 Apr;5(3):335-58

[2] Arias A, Perez-Martinez I, Tenias JM et al. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. Aliment Pharmacol Ther. 2016 Jan;43(1):3-15

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 obviously no associated mortality.

EoE is quite frequently associated with allergic disease, including asthma, allergic rhinitis, atopic dermatitis, and manifestations of food allergies. Previously, EoE was considered a manifestation of gastroesophageal reflux disease (GERD), to which the observation of a response to proton-pump inhibitors (PPI) ("PPI responsive EoE" (=Proton-pump-inhibitor-responsive oesophageal eosinophilia (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[1].

2.1.3. Biologic features, aetiology and pathogenesis

EoE is defined as a chronic, immune-mediated, antigen-triggered oesophageal disease characterised by symptoms related to oesophageal dysfunction and eosinophil-predominant inflammation.

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 EoE, as well as studies of family history, twin concordance and genome-wide association studies that identified three genes as being altered (the genes encoding thymic stromal lymphopoietin (TSLP), eotaxin-3, and calpain-14), suggest a genetic disposition of EoE.

While the true environmental "cause" of EoE has not yet been determined, and there may be multiple factors at play, there are several possibilities. According to Runge et al 2015[3], these could, among other, due to exposition to aeroallergens (e.g. pollen), living in cold and dry climates, living in rural areas, food-based allergens, antibiotic use during the first year of life, breastfeeding and penicillin allergies[4].

Similar to other allergic disease entities, there is support for the concept that EoE 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 stage/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.

[3] Runge TM, Dellon ES. Do we know what causes eosinophilic esophagitis? A mechanistic update. Curr Gastroenterol Rep. 2015 Sep;17(9):33

The final diagnosis of EoE is, however, only made after upper gastro intestinal (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[5] 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[1] clearly recommend 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 is not part of the prescribing information.

[5] Dellon et al. ACG Clinical Guideline: Evidenced Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE). Am J Gastroenterol. 2013 May;108(5):679-92

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 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[6,7]. 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 product under consideration has been licensed for the treatment of EoE in 2018 with dosing recommendations referring to short-term treatment up to 12 weeks maximum only. At the time of evaluation of the compound (with the only strength being 1 mg orodispersible tablet), there was no full

[6] Chuang MY, Chinnaratha MA, Hancock DG et al.Topical Steroid Therapy for the Treatment of Eosinophilic Esophagitis (EoE): A Systematic Review and Meta-Analysis. Clin Transl Gastroenterol. 2015 Mar 26;6
[7] Sawas T, Dhalla S, Sayyar M et al. Systematic review with meta-analysis: pharmacological interventions for eosinophilic oesophagitis. Aliment Pharmacol Ther. 2015 May;41(9):797-806

clear picture of the need for continuous treatment, and the applicant presented data that were directing towards the possibility that intermittent treatment could indeed suffice in this population. However, newer data have made it more likely (and led to respective recommendations in the newer treatment guidelines on both sides of the Atlantic) that a continuous maintenance treatment is necessary. Therefore, at the time of submission of the data underlying this grouped variation procedure, there was still an unmet medical need with regard to long-term continuous treatment in order to prevent relapse.

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 0.5 mg/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

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

The applicant has submitted an application for an extension of marketing authorisation for Jorveza, under Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I (point 2c) grouped with an extension of indication, under Article 16 of Commission Regulation (EC) No 1234/2008 and a type IB variation to add a new pack size.

In the context of the initial MAA, the applicant received a protocol assistance from CHMP on 26 June 2014. The protocol assistance pertained to non-clinical and clinical aspects of the dossier.

Within this grouped variation the MAH follows the recommendation of the CHMP at the time of initial marketing authorisation to present long-term treatment data and to evaluate whether a continuous long-term treatment is necessary in the population.

2.2. Quality aspects

2.2.1. Introduction

This application is a line extension to the already approved Jorveza 1 mg orodispersible tablets. This line extension involves the addition of a 0.5 mg strength orodispersible tablet, an extension of indication and change in pack size of the finished product. The finished product part of the dossier and sections 4.2, 4.8, 5.1 and 6.5 of the SmPC are updated.

The finished product is presented as orodispersible tablets containing 0.5 mg of budesonide as active substance.

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

The product is available in blister packs consisting of a cold-formable aluminium bottom foil and an aluminium lidding foil [20 µm].

2.2.2. Active Substance

The active substance part of the dossier submitted for this line extension is identical to that submitted and approved in the previous application for Jorveza 1 mg orodispersible tablets by the centralised procedure.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development
Jorveza 0.5 mg orodispersible tablets are white or almost white, round, biplane (ø 7 mm) with a smooth surface and facet.

The qualitative and quantitative composition of the 0.5 mg orodispersible tablets and existing Jorveza 1 mg orodispersible tablets is identical (except for the amount of the active substance). Both dose strengths can be differentiated by the labelling design and the layout of the secondary packaging of the finished product. Additionally, the 0.5 mg orodispersible tablets are debossed with "0.5" on one side.

The budesonide has a consistent crystalline structure (crystallinity >90%), confirmed by XRPD and melting point analysis of commercial batches. The active substance is micronised prior to finished product manufacture. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, or with other accepted pharmacopoeia standards (i.e. B.P., German Drug Codex). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The compatibility of the components of the finished product was confirmed during the initial MA application of Jorveza 1 mg orodispersible tablets.

The active substance is a potent glucocorticosteroid with a high topical anti-inflammatory activity and low systemic effects. Jorveza 0.5 mg orodispersible tablets have been developed as an extension to the centrally authorised marketing authorisation for Jorveza 1 mg orodispersible tablets. Due to the similarity of the formulations additional development studies were not conducted.

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.

As for the existing 1 mg orodispersible tablets, the 0.5 mg orodispersible tablets are 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 manufacturing process that had been developed for Jorveza 1 mg orodispersible tablets at the pilot scale was also used for Jorveza 0.5 mg orodispersible tablets. Based on the results of the pilot scale process development studies performed with Jorveza 1 mg orodispersible tablets the same process was established for Jorveza 0.5 mg orodispersible tablets for commercial supply. This approach is justified taking into consideration the orphan nature of the product and the fact that pilot scale

equipment is to the same extent qualified as production scale equipment. In addition, the finished product manufacturing site and the manufacturer of the active substance were unchanged.

Due to the extremely low amount of active substance in the formulation (i.e. < 0.5%) and potential losses during processing the batch formula allows a manufacturing overage for budesonide.

A short-term storage of the granules and the final blend is allowed for a maximum period of 7 days. The final 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 (final mixture with all excipients), compression and primary packaging.

The process is considered to be a non-standard manufacturing process as the active substance accounts for less than 2% of the composition (i.e. a low dose tablet). Detailed description of the manufacturing process has been provided. Critical steps of manufacturing process have been identified, proposed equipment used for manufacture has 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, namely: 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 by content uniformity (Ph. Eur.), identity (HPLC, UV), assay (HPLC), related substances (HPLC), tightness of primary packaging and microbiological quality (Ph. Eur.).

The finished product is released on the market based on the release specifications, through traditional final product release testing.

The specifications of Jorveza 0.5 mg orodispersible tablets are identical to those of 1 mg orodispersible tablets except for purity. In this line extension, a previously unspecified impurity has been identified and specified in the specification. The impurity limits are in line with the identification and qualification thresholds set out in ICH Q3B(R2) guideline. In addition, the specification for sum of all impurities has been adapted accordingly.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data of three production scale batches of finished product resulting in values below 30% of PDE for each elemental impurity, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

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 production 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 six production scale batches of finished product stored for up to 18 months under long term conditions (25 ºC / 60% RH), 12 months under intermediate conditions (30°C / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product (one clinical and three validation batches) are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested in line with the shelf-life specification. The analytical procedures used are stability indicating.

At long term storage conditions, all results (including impurities) complied with the proposed finished product specification. In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Both control samples and the samples of the primary packed tablets complied with the finished product specification whereas the samples without primary packaging ("deblistered tablets") resulted in a decrease of approximately 30 % of the budesonide content and an increase of the impurities as out-of-specification.

Orodispersible tablets are required to be protected from moisture. It was demonstrated that there is no transmission or absorption of moisture or leakage and the foil packages including the seals remain tightly closed over the period tested.

Based on available stability data, the proposed shelf-life of 24 months 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) is acceptable. The following sentence was also added to SmPC section 4.2: "The orodispersible tablet should be taken immediately once removed from the blister package".

Adventitious agents

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

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

This is a line extension to the already approved Jorveza 1 mg orodispersible tablets. No new active substance information has been submitted in this procedure. The development of Jorveza 0.5 mg orodispersible tablets was based on the existing 1.0 mg orodispersible tablets. Information on development, manufacture and control of the 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. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant confirms that no new studies have been conducted between the initial submission and the actual procedure. A literature search on preclinical data for budesonide for the relevant time period (March 2017 to July 2019) has been performed. The available new bibliographic data did not identify any change to the current risk/ benefit profile from the preclinical perspective. The applicant did not submit an updated non-clinical documentation.

2.3.2. Ecotoxicity/environmental risk assessment

The initial environmental risk assessment (ERA) had been assessed within a type IB application (EMEA/H/C/004655/IB/0002) at the beginning of 2019. For the present extension of application, an updated ERA was provided, including new $PEC_{surfacewater}$ calculations, taking into account the new additional indication and consequently an updated risk characterisation for the surface water and groundwater compartment. The respective risk quotients remain below 1 and a risk is not indicated.

CHMP concluded that the present extension to Jorveza will not pose a risk to the environment when used in accordance with the SmPC.

Table 1 **Summary of main study results**

Substance (INN/Invented Name): Budesonide			
CAS-number (if available): 51333-22-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.23	Not Potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.23	Potentially B
	BCF	9	not B
Persistence	$DT_{50,\ 12\ °C,\ Sediment}$	62.6 d	not P
Toxicity	NOEC, Fish-FLC (*Danio rerio*)	0.032 µg/L	T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined (prevalence)	0.00017	µg/L	> 0.01 mg/L threshold (N)
Other concerns (e.g. chemical class)	*Potential Endocrine Disruptor*		(Y)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Soil type / $K_{F,\ Ads.}$: Clay 41; Silt Loam 22; Loam 19; Silt 17; Loamy Sand 31	No correlation with OC
Ready Biodegradability Test	OECD 301	Not Readily Biodegradable	

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308 (all SFO)	$DT_{50,\ 12\ °C\ water}$ = 14.7 d $DT_{50,\ 12\ °C\ sediment}$ = 62.6 d $DT_{50,\ 12\ °C\ whole\ system}$ = 38.6 d % shifting to sediment = 68.6 % (30 d) Mineralisation: 86.2 %			No sediment dwelling organism test required due to specific work mechanism of Budesonide
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test *(Pseudokirchneriella subcapitata)*	OECD 201	NOEC	≥ 7900	µg/L	Limit test
Daphnia sp. Reproduction Test (*Daphnia magna*)	OECD 211	NOEC LOEC EC_{10} EC_{50}	3360 6950 3990 5300	µg/L	Most sensitive endpoint: mortality of offspring
Fish, Full Life Cycle Test/*Danio rerio*		NOEC LOEC	0.032 0.1	µg/L	Most sensitive endpoint: 28 d survival of F1 generation
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	10^6	µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF_{ss} BCF_L	5-6 8-9	L/kg	Measured BCF at steady state. No depurination stage included in test due to low BCF value. 5% lipid normalization of BCF.

2.3.3. Discussion on non-clinical aspects

No new non-clinical studies have been submitted in support of the present application. The benefit risk assessment will be based on clinical data. This is considered acceptable.

An updated ERA was submitted including new $PEC_{surfacewater}$ calculations, taking into account the new additional indication and consequently an updated risk characterisation for the surface water and groundwater compartment. The respective risk quotients remain below 1 and a risk is not indicated. The present application does not pose a risk to the environment when used in accordance with the SmPC.

2.3.4. Conclusion on the non-clinical aspects

The benefit-risk balance of Jorveza remains unchanged from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

This submission concerns the introduction of a new strength (0.5 mg orodispersible tablet), the increase of the treatment duration (to be determined by the treating physician) with submission of the respective long-term clinical data (study BUL-2/EER), as well as the addition of a pack size designed for the long-term treatment.

In addition, the MAH submitted the results of a pharmacokinetics (PK) study (study BUL-6/BIO) which has been extended to additionally compare the PK of the two dose strengths (0.5 mg and 1 mg).

No other new PK, or pharmacodynamics (PD) data are submitted, but the revised clinical overview submitted refers to the data presented at initial MAA in 2017. This report includes reference to the previous assessment as made public in the EU Public Assessment Report (EPAR) comprising the previously submitted data, as well as the summary of evaluation of the new data submitted for this grouped variation.

The overview of the submitted study BUL-2/EER is presented in Table 2. The overview of the clinical studies (PK study BUU-1/BIO, supportive efficacy/safety study BUU-2/EEA, pivotal efficacy/safety study BUL-1/EEA) submitted in the context of the initial MAA can be found in the EPAR for Jorveza.

GCP

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

The MAH 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

Table 2 **Tabular overview of the main clinical study submitted in this application**

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-2/EER	Primary: - Assess efficacy of a 48-week treatment with 2×0.5 mg/d or 2×1 mg/d budesonide orodispersible tablets vs. placebo for the maintenance of clinicopathological remission in adult patients with EoE. Secondary: - Study safety and tolerability in the form of AEs and laboratory parameters -Assess patients' QoL. Open-label re-induction (OLRI) and open-label extension (OLE) phase: - Study re-induction of clinical response in patients with a clinical or histological relapse or having experienced a food impaction which needed endoscopic intervention, - Study maintenance of clinical remission in patients who completed the DB phase without a clinical or histological relapse. Exploratory objectives: -Study biomarkers in EoE.	Double blind (DB), randomised (1:1:1 ratio), parallel-group, multicentre, placebo-controlled, comparative, confirmatory, phase III **Study phases**: Open-label induction (OLI): 6 weeks with BUL 1 mg BID for patients not participating in BUL-1/EEA DB: 48 weeks OLRI: 6 weeks (optional for patients with clinical or histological relapse or food impaction requiring endoscopy in DB phase) OLE: 96 weeks (optional) FU: 4 weeks (mandatory).	0.5 mg budesonide (BUL) orodispersible tablets 1 mg budesonide (BUL) orodispersible tablets Placebo orodispersible tablets BUL 0.5 mg BID: 0.5 mg budesonide orodispersible tablet BID BUL 1 mg BID: 1 mg budesonide orodispersible tablet BID Placebo: Placebo orodispersible tablet BID All study medication taken p.o., BID morning and evening after the meal (with no eating or drinking within 30 min after IMP intake) Patients who entered the optional OLRI phase were to continue with BUL 1 mg BID treatment for 6 weeks. Patients who entered the optional OLE phase were to continue treatment with BUL 0.5 mg BID (with optional dose escalation to 2×0.5 mg BID) up to 96 weeks.	204 patients with confirmed EoE treated in the DB phase (FAS-DB and SAF-DB populations) 63 patients (9 BUL 0.5 mg, 9 BUL 1 mg, 45 Placebo) were prematurely withdrawn from DB phase, mostly due to lack of efficacy. BUL 0.5 mg BID: 68 M: 57, F: 11 Age: Range: 19-69 y Mean ± SD: 36 ± 10.9 BUL 1 mg BID: 68 M: 57, F: 11 Age: Range: 18-64 y Mean ± SD: 37 ± 11.1 Placebo BID: 68 M: 55, F: 13 Age: Range: 18-64 y Mean ± SD: 36 ± 9.9 After the DB phase, 82 patients continued with the OLRI phase, 105 patients continued with the OLE phase, 8 patients continued with the FU phase, and 9 patients did not participate in any further study phase	6-week OLI (patients not participating in BUL 1/EEA study) 48-week DB 96-week OLE 6-week OLRI	OLI, DB phases Completed OLRI, OLE phases ongoing Final Study Report (DB/OLI)

2.4.2. Pharmacokinetics

The PK parameters of budesonide 1 mg orodispersible tablets were evaluated in a phase I open label PK study (BUU-1/BIO) in the context of the initial MAA. The assessment of the study results can be found in the EPAR for Jorveza and a summary of the results for the absorption, distribution and elimination can be found in the next relevant sections of this report.

In support of the present application, the MAH implemented the PK characterisation of the 0.5 mg tablet as an additional treatment arm into a recent clinical trial (Study BUL-6/BIO). This study was an open-label, randomised, 3-period, 3-sequence, single dose change-over trial in 18 male and female healthy volunteers (sex ratio 1:1). The dose proportionality is presented in this report.

Absorption

Following administration of Jorveza, budesonide is rapidly absorbed. Pharmacokinetic data following administration of single doses of 1 mg budesonide to fasted healthy subjects in two different studies show a median lag time of 0.17 hours (range 0.00 – 0.52 hours) and a median time to peak plasma concentration of 1.00-1.22 hours (range 0.50 – 2.00 hours). The mean peak plasma concentration was 0.44 – 0.49 ng/mL (range: 0.18-1.05 ng/mL), and the area under the plasma-concentration–time curve ($AUC_{0-\infty}$) was 1.50 – 2.23 hr*ng/mL (range: 0.81-5.14 hr*ng/mL).

Single dose pharmacokinetic data in fasted patients with EoE are available with 4 mg budesonide: Median lag-time was 0.00 hours (range 0.00 – 0.17), median time to peak plasma concentration was 1.00 hour (range 0.67 – 2.00 hours); peak plasma concentration was 2.56 ± 1.36 ng/mL, and AUC_{0-12} was 8.96 ± 4.21 hr*ng/mL.

Patients showed a 35% increase in peak plasma concentrations and a 60% increase in AUC_{0-12} compared to healthy subjects.

Dose proportionality of the systemic exposure (C_{max} and AUC) from 0.5 mg orodispersible tablets to 1 mg orodispersible tablets has been demonstrated.

Distribution

The apparent volume of distribution following oral administration of 1 mg budesonide to healthy subjects was 35.52 ± 14.94 L/kg and 42.46 ± 23.90 L/kg following administration of 4 mg budesonide to patients with EoE. Plasma protein binding is on average 85-90%.

Metabolism

Metabolism of budesonide is decreased in EoE patients compared to healthy subjects resulting in increased plasma concentrations of budesonide.

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.

Elimination

The median elimination half-life is 2 - 3 hours in healthy subjects (receiving 1 mg budesonide) and 4 - 5 hours in EoE patients (receiving 4 mg budesonide). 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

The study BUL-6/BIO has evaluated dose-proportionality of the new dose-strength to the previously licensed strength of 1 mg.

Study BUL-6/BIO was an open-label, randomised, 3-period, 3-sequence, single dose change-over trial in 18 male and female healthy volunteers (sex ratio 1:1; mean age 43.7 years, mean BMI 24.75 kg/m^2). The subjects received treatments with an oral suspension containing 1 mg budesonide, Jorveza 1 mg tablet and Jorveza 0.5 mg tablet, each separated by a wash-out phase of at least 3 days. All subjects completed the trial.

The study also determined the disintegration kinetics of the orodispersible tablets by documenting the time span as well as the number of swallowing actions until complete disintegration.

Mean plasma concentration vs. time curves of budesonide after administration of Jorveza 0.5 mg and Jorveza 1 mg are shown in Figure 1.

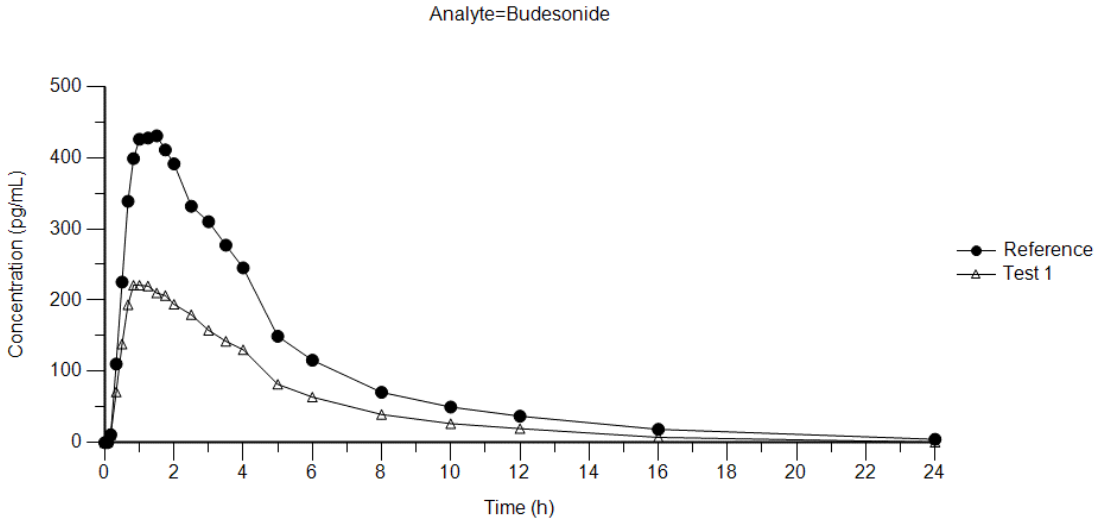

Figure 1 Mean plasma concentration vs. time curves of budesonide after oral single dose administration of Jorveza 0.5 mg (Test 1) and Jorveza 1 mg orodispersible tablet (Reference) under fasting conditions to 18 subjects

The results in tabular form for the two strengths of the orodispersible tablet are shown in Table 3 and Table 4.

Table 3 PK parameters of budesonide after single dose administration of Jorveza 0.5 mg

Parameter	$AUC_{0\text{-}tlast}$ (h*pg/mL)	$AUC_{0\text{-}inf}$ (h*pg/mL)	C_{max} (pg/mL)	t_{max} (h)	t_{last} (h)	$t_{1/2}$ (h)	t_{lag} (h)
N	18	18	18	18	18	18	18
Mean	1090	1170	256	1.07	14.1	3.92	0.152
SD	499	506	102	0.450	3.52	1.16	0.0816
Min	508	565	118	0.500	8.02	2.07	0.00
Median	916	1000	242	1.00	14.0	3.96	0.170
Max	2240	2320	478	2.00	24.0	7.03	0.330
Geometric Mean	1000	1080	237	0.983	13.7	3.76	NC
CV% Geometric Mean	43.80	41.34	42.72	45.17	24.77	29.87	NC

Table 4 PK parameters of budesonide after single dose administration of Jorveza 1 mg

Parameter	$AUC_{0\text{-}tlast}$ (h*pg/mL)	$AUC_{0\text{-}inf}$ (h*pg/mL)	C_{max} (pg/mL)	t_{max} (h)	t_{last} (h)	$t_{1/2}$ (h)	t_{lag} (h)
N	18	18	18	18	18	18	18
Mean	2130	2230	490	1.22	17.8	4.64	0.149
SD	1070	1080	222	0.492	4.80	1.37	0.103
Min	904	1020	182	0.670	12.0	2.52	0.0800
Median	1680	1800	443	1.02	16.0	4.90	0.170
Max	4960	5140	1050	2.00	24.0	6.98	0.520
Geometric Mean	1900	2010	444	1.13	17.2	4.43	0.129
CV% Geometric Mean	50.66	48.45	49.11	41.47	27.36	32.21	54.74

The evaluation of bioequivalence yielded the results as shown in Table 5.

Table 5 Parametric point estimates and 90 % confidence intervals determined for the PK parameters of budesonide; comparison of Jorveza 0.5 mg vs. Jorveza 1 mg (dose-adjusted)

Parameter	Observations	Point Estimate	90 % confidence interval		CV_{ANOVA} (%)
			Lower Limit (%)	Upper Limit (%)	
$AUC_{0\text{-}inf}$	36	107.26	99.7	115.38	12.55
$AUC_{0\text{-}tlast}$	36	105.16	97.79	113.09	12.49
C_{max}	36	106.56	97.16	116.88	15.91

Similar results were achieved for the evaluation of the two metabolites 6ß-hydroxybudesonide, and 16α-hydroxyprednisolone.

Based on these results, the MAH concludes on dose-adjusted bioequivalence, and consequently on dose-proportional PK of the new 0.5 mg strength.

The evaluation of the time span until complete disintegration showed a mean time span of 6.14 minutes for the lower strength, and 6.36 min for the higher strength (median 4.68 and 4.48 minutes, range 2.0-14.6 and 2.0-23.3 min). The number of swallowing actions until complete disintegration was 9.8 and 9.4 with the lower and higher strength respectively (range 2-18 for the lower and 3-21 for the higher strength.

Time dependencies

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.

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 for the new formulation have been conducted. At time of initial MAA, the applicant entirely relied on the data available from the literature[8,9,10,11].

With regard to renal impairment, there are currently no data available for patients with renal impairment. Because budesonide is not excreted via the kidneys, patients with mild to moderate impairment may be treated with caution with the same doses as patients without renal impairment. Budesonide is not recommended for use in patients with severe renal impairment.

For patients with liver impairment some literature data is available (see above references showing data in primary biliary cholangitis (PBC)-patients), which indicate a relevant increase of plasma levels of budesonide, depending on the severity of the impairment. However, no systematic study investigating different levels of hepatic impairment is available. Patients with hepatic impairment should not be treated.

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

The safety and efficacy of Jorveza in children and adolescents under the age of 18 years have not been established. No data are yet available.

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[12,13].

In the context of the initial MAA, the MAH had, in addition, tested a variety of cytochromes and transporters in vitro, and no potential for interaction had been detected. The potential for interaction with inhibitors or inducers of CYP3A4 is known from the literature[14] . The two main metabolites of budesonide, 16α-hydroxyprednisolone, 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 in the context of the initial MAA, the exposure to these metabolites has been shown to be higher after the administration of the orodispersible tablet formulation as compared

[8] Edsbäcker S and T Andersson: Pharmacokinetics of Budesonide (Entcort TM EC) capsules for Crohn's Diesease. Clin Pharmacol 2003, 43: 803-821.
[9] 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.
[10] Rautiainen H et al: Pharmacokinetics and bone effects of budesonide in primary biliary cirrhosis. Aliment Pharmacol Ther 2006; 24: 1545-1552.
[11] 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.
[12] Jönsson G et al: Budesonide is metabolized by cytochrome P450 3A (CYP3A) enzymes in human liver; Drug Metab Dispos 1995; 23: 137-142.
[13] 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.
[14] 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.

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

The pharmacodynamics of budesonide are well known and no new relevant studies on the mechanism of action of the compound have been conducted by the MAH and no new data have been submitted for the PD and PK/PD part of the documentation.

In the context of the initial MAA, study BUU-1 has also investigated the influence of EoE symptoms in the patient population, as well as – for all participants – the influence of the budesonide administration on endogenous cortisol plasma levels and urine excretion. Therefore, these two elements contribute to the demonstration of pharmacodynamics and are briefly discussed in this chapter.

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 lymphopoietin, interleukin-13 and eotaxin-3 in the oesophageal epithelium, which results in a significant reduction of the oesophageal eosinophilic inflammatory infiltrate.

Primary and Secondary pharmacology

The MAH has conducted only very limited investigations into the pharmacodynamics of the compound as part of the Phase I PK study submitted at time of initial MAA. 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 glucocorticosteroids on the inflamed oesophageal mucosa of EoE patients have also extensively been described in the literature[15,16] , 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 MAH also investigated the development of the endogenous (morning) cortisol levels in comparison to the reference formulation, thus investigating the potential influence of

[15] Gross KL and JA Cidlowski: Tissue-specific glucocorticoid action: a family affair. Trends Endocrinol Metab. 2008; 19: 331-339
[16] Straub RH and M Cutolo: Glucocorticoids and chronic inflammation. Rheumatology, 2016; 55: Suppl 2: ii6-ii14

the compound on the hypothalamic-pituitary-adrenal axis (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.

2.4.4. Discussion on clinical pharmacology

The MAH has conducted only very limited investigations into the characterisation of the PK and PD of the compound. This limitation is based on the fact that the active substance budesonide is well known, and effects of glucocorticosteroids do clearly not need to be characterised any further. The development programme therefore partly relies on extrapolation of the known properties of the active substance from other available budesonide containing medicinal products, which is considered an overall reasonable strategy.

As part of the present application, the MAH submitted the results of a recently completed open-label, randomised, 3-period, 3-sequence, single dose change over trial in healthy volunteers (BUL-6/BIO). The study evaluated dose-proportionality of the new dose-strength 0.5 mg to the previously licensed strength 1 mg. The study also determined the disintegration kinetics of the orodispersible tablets.

The statistical evaluation of the dose-adjusted PK data indicates a similar relative bioavailability of Jorveza 0.5 mg tablet vs. Jorveza 1 mg tablet by means of systemic exposure ($AUC_{0\ inf}$, $AUC_{0\text{-}tlast}$) and a similar maximum exposure (C_{max}). Considering the difference in dose, Jorveza 0.5 mg tablet vs. Jorveza 1 mg tablet demonstrated bioequivalence, although this was not an objective of this trial. Similar results were obtained for the two main metabolites of budesonide. Thus, based on the comparative PK data dose proportionality of the systemic exposure (C_{max} and AUC) from 0.5 mg orodispersible tablets to 1 mg orodispersible tablets has been demonstrated. This is reflected in section 5.2 of the SmPC.

Furthermore, both dosage forms demonstrated comparable oral disintegration kinetics, i.e. similar median and mean disintegration times and numbers of swallowing actions. The individual oral disintegration time was variable, but none of the subjects showed a disintegration time below 2 minutes.

The effects of topically acting glucocorticosteroids on the inflamed oesophageal mucosa of EoE patients has also extensively been described in the literature, 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.

The conducted PK-study BUU-1/BIO reviewed at time of initial MAA has also included a limited amount of investigations into the primary and secondary pharmacology of the compound.

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.

In addition, during study BUU-1/BIO, the MAH 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. However, a theoretical potential for the influence of the compound on the HPA-axis has been demonstrated and is reflected in the section 4.4 of the SmPC.

2.4.5. Conclusions on clinical pharmacology

The limited PK/PD data presented in this application do not bring new information on the pharmacology profile of budesonide. The results of the recently completed PK study (BUL-6/BIO) demonstrated dose proportionality of the systemic exposure from the new strength 0.5 mg orodispersible tablets to the already authorised strength 1 mg orodispersible tablets. The new strength is therefore approvable from the pharmacology point of view.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

No dose response study was conducted in support of the present application. A supportive and dose-response study, Study BUU-2/EEA, was submitted at time of initial MAA. This was a double-blind, double-dummy, randomised, placebo-controlled phase II study on the efficacy and tolerability of a 14-day treatment with budesonide orodispersible tablets (formerly called 'budesonide effervescent tablets for orodispersible use') vs. viscous budesonide suspension vs. placebo in patients with eosinophilic esophagitis. The assessment of this study can be found in the EPAR for Jorveza.

2.5.2. Main study on long-term treatment - Study BUL-2/EER

Methods

Study BUL-2/EER was a randomised, multi-centre, placebo-controlled, comparative, phase III study evaluating the efficacy and tolerability of a long-term treatment with two different doses of budesonide orodispersible tablets vs. placebo for maintenance of clinico-pathological remission in adult patients with eosinophilic esophagitis.

The study comprised 6 phases:

- Screening phase (1 to 6 weeks);

- Open-label induction (OLI) phase: with treatment with budesonide orodispersible tablets (BUL) 1 mg, twice daily (BID) for 6 weeks;
- Double-blind (DB) phase with 1:1:1 randomisation and treatment with BUL 0.5 mg BID, BUL 1 mg BID, or placebo BID for 48 weeks;
- Open-label re-induction (OLRI) phase: for patients who experienced relapse during the DB phase. Treatment was given with BUL 1 mg BID (up to 6 weeks);
- Open-label extension (OLE) phase: for patients in remission at the end of the DB phase or OLRI phase. Treatment with BUL 0.5 mg BID (with optional escalation to 2xBUL 0.5 mg BID (up to 96 weeks);
- Follow-up (FU) phase: 4-week safety FU after last treatment visit in any phase of the trial.

The data reported in this submission do not (yet) comprise the OLRI, OLE and FU phases of the trial.

It is expected that the final study report, including the full evaluation of the OLRI, OLE, and FU phases of the trial are reported as soon as available.

Study Participants

Main inclusion criteria in the DB phase of the study:

- Patients (aged 18-75 years) had to have a confirmed clinico-pathological diagnosis of EoE according to the established criteria[17] ;
- Patients in clinico-pathological remission at end of treatment (EOT) visit of study BUL-1/EEA or EOT visit of the OLI phase of study BUL-2/EER were included, if the following two criteria were fulfilled at the EOT visit: histological remission (i.e. peak eos < 16 eos/mm² hpf) and resolution of symptoms (i.e. no or only minimal problems) defined as dysphagia ≤ 2 on a 0-10-point numerical rating scale (NRS) and pain during swallowing ≤ 2 on 0-10 NRS on each day of the last 7 days prior to the EOT visit

Main exclusion criteria in the DB phase of the study:

- Patients who were clinically and endoscopically suspected to have gastroesophageal reflux disease, achalasia, scleroderma oesophagus or systemic sclerosis;
- History of oesophageal surgery at any time or of oesophageal dilation procedures within the last 8 weeks prior to DB visit 1;
- Any relevant systemic diseases (e.g. acquired immune deficiency syndrome, active tuberculosis);
- Other clinically evident causes than EoE for oesophageal eosinophilia, any concomitant oesophageal disease and relevant gastro-intestinal disease, upper gastrointestinal bleeding within 8 weeks prior to DB baseline visit, abnormal hepatic or renal function;
- A history of cancer in the last 5 years (except for non-metastatic cancers, e.g. basalioma);
- Treatment with systemic therapies (including concomitant treatment with ethinylestradiol in a dose of more than 30 µg/d) and treatment with topical therapies that could have affected assessment of the primary or secondary endpoints;

[17] Liacouras CA, Furuta GT, Hirano I et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011 Jul;128(1):3-20.e6

- Other non-EoE disease-related exclusion criteria included cardiovascular disease, diabetes mellitus, osteoporosis, active peptic ulcer disease, glaucoma, cataract, or infection.

Treatments

During study BUL-2/EER, the patients received one of the following treatments:

- Group A ('BUL 0.5mg BID'): Budesonide 0.5 mg orodispersible tablet twice daily (BID);
- Group B ('BUL 1mg BID'): Budesonide 1 mg orodispersible BID;
- Group C ('Placebo'): Placebo orodispersible tablet BID.

One orodispersible tablet had to be taken in the morning and one in the evening after the meal. The orodispersible tablet had to be placed on the tongue which allowed rapid disintegration. The orodispersible tablet was to dissolve rapidly and to be swallowed with saliva little by little.

Objectives

The primary objective of the DB phase of the study was:

- To assess the efficacy of a 48-week treatment with 2 x 0.5 mg/d or 2 x 1 mg/d of budesonide orodispersible tablets vs. placebo for the maintenance of clinico-pathological remission in adult patients with EoE.

The secondary objectives were:

- To study the safety and tolerability in the form of adverse events (AEs) and laboratory parameters;
- To assess patients' quality of life (QoL).

Further objectives were defined for the OLRI phase and the OLE phase of the study, which are, however, currently not (yet) reported.

Outcomes/endpoints

The primary efficacy variable of the DB phase was defined as follows:

Rate (%) of patients free of treatment failure at week 48 or EOT visit, whereby treatment failure was defined as one of the following criteria that occurred at any time during the DB treatment:

- Clinical relapse, i.e. experiencing dysphagia or pain during swallowing in the past seven days (7-day recall period) of a severity of ≥4 points on a 0-10 Numerical Rating Scale (NRS) for dysphagia or pain during swallowing, respectively, confirmed by a severity of ≥4 points on at least 1 day during the subsequent week on the respective 0-10 NRS for dysphagia or pain during swallowing (24-hours recall period) (any of the visits);
- Histological relapse, i.e. a peak of ≥48 eos/mm^2 hpf at DB week 48/EOT;
- Experiencing a food impaction which needed endoscopic intervention;
- Need for an endoscopic dilation;
- Premature withdrawal for any reason.

Similar criteria as for the "regular" clinical relapse were also applied for any "extra visit" during the DB treatment phase.

Histological relapse was defined as a peak of ≥48 eos/mm^2 hpf. The peak number of eos/mm^2 hpf was derived from the evaluation of a total of 6 hpfs obtained from 6 oesophageal biopsies (two from the proximal, two from the mid and two from the distal part of the oesophagus).

The secondary endpoints were the following:

The following variables were analysed as *a priori* ordered key secondary efficacy variables:

1) Rate of patients with histological relapse, defined as a peak of ≥48 eos/mm^2 hpf at DB week 48/EOT;
2) Change in the peak eos/mm² hpf from DB baseline to DB week 48/EOT;
3) Rate of patients with a clinical relapse, have experienced a food impaction, which needed endoscopic intervention, or needed an endoscopic dilation during the DB treatment phase;
4) Rate of patients with a total weekly Eosinophilic Oesophagitis Activity Index – Patient-Reported Outcome (EEsAI-PRO) score of ≤20 at DB week 48/EOT;
5) Rate of patients in deep disease remission, i.e., deep clinical, deep endoscopic, and histological remission (based on the peak number of eos per hpf), at DB week 48/EOT.

Of these 5 variables, the first four were included in the study protocol, whereas the fifth was added only in the statistical analysis plan (SAP).

Further exploratory secondary efficacy variables were evaluated, comprising a list of 38 different endpoints.

All efficacy evaluations of the OLI phase of the study are also included as exploratory endpoints.

Sample size

The sample size for the pivotal study was calculated based on the primary endpoint and taking into account expected remission rates from the literature.

Randomisation and blinding (masking)

Patients who gave their written consent and met the respective inclusion criteria at the screening visit, or at baseline visit for patients coming from BUL-1/EEA, were uniquely identified by a 5-digit enrolment (i.e. screening) number, consisting of a unique 3-digit centre number followed by a 2-digit screening number.

Once the subject was considered qualified for entry into the DB treatment phase of the study, i.e., the patient met all inclusion criteria and did not fulfil any of the exclusion criteria at DB visit 1, a randomisation number was allocated to the patient via the interactive web-response system (IWRS), integrated in the electronic code of federal regulations (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 DB phase of the trial, by means of a computer-generated randomisation list. Randomisation was performed using randomly permuted blocks. No stratification of randomised treatment assignment based on centre, age, sex, or other characteristics was performed.

The study was fully blinded with regard to the appearance of the study medication, and the amount of study drug to be administered.

Statistical methods

The evaluation of primary and secondary efficacy variables for the DB phase was performed for the full analysis set of the double-blind phase (FAS-DB; intention-to-treat [ITT] analysis) and for the per-protocol analysis set (per-protocol [PP] analysis). The primary analysis set for efficacy analyses was the FAS-DB.

The evaluation of 'other' variables (further exploratory secondary endpoints) relevant for the OLI phase was performed for the full analysis set for the OLI phase (FAS-OLI).

The safety analysis set for the DB phase (SAF-DB) was used for the evaluation of safety during the DB phase, the safety analysis set for the OLI phase (SAF-OLI) was used for the evaluation of safety during the OLI phase.

The primary efficacy variable (and the a priori ordered key secondary efficacy variables) were subjected to a confirmatory statistical analysis. Hypothesis testing (one-sided) was performed for both budesonide treatment arms separately at Bonferroni adjusted significance level of 0.0125. The Bonferroni adjustment was applied to account for the multiple budesonide groups. The primary hypotheses to be tested were:

• H0: $\pi_{PLA} \geq \pi_{Eff1}$ vs. H1: $\pi_{PLA} < \pi_{Eff1}$

· H0: $\pi_{PLA} \geq \pi_{Eff2}$ vs. H1: $\pi_{PLA} < \pi_{Eff2}$,

where π_{PLA}, π_{Eff1} and π_{Eff2} (π_{Eff1}: BUL 0.5 mg BID; π_{Eff2}: BUL 1 mg BID) denote the rate of patients who are not treatment failures after 48 weeks of double-blind treatment in each treatment group. These hypotheses were tested at a one-sided Bonferroni adjusted type I error rate level of 0.0125 using the normal approximation tests for the comparison of rates. For estimating the treatment effect compared to placebo, two-sided 97.5% (Bonferroni correction) confidence intervals (CI) for the difference of rates were provided.

Comparisons between the budesonide groups, which were performed on the primary efficacy endpoint using the test as specified above, were not interpreted in a confirmatory manner.

A sensitivity analysis was planned in the CSP using the FAS-DB and 'a logistic regression model for the treatment failure rate with treatment group as a factor and baseline peak number of eos/mm² hpf, baseline dysphagia NRS and baseline pain during swallowing NRS of the preceding induction phase (either BUL-1/EEA or BUL-2/EER OLI-phase) as covariates'.

In case the actual number of treatment failures did not allow a joint model containing these variables, separate sensitivity analyses were to be performed by entering each covariate separately.

A subgroup analysis was performed, differentiating the patients by their path to remission.

The evaluation of the secondary efficacy variables for the DB phase was performed for the FAS-DB (intention-to-treat analysis) and for the PP set. The evaluation of 'other' variables (further exploratory secondary endpoints) for the OLI phase was performed for the FAS-OLI.

Efficacy significance testing was continued in hierarchical fashion in support of labelling claims for five key secondary efficacy endpoints as given above, until the first of these comparisons of BUL 0.5mg BID versus placebo or BUL 1mg BID versus placebo showed a one-sided p-value >0.0125 (FAS-DB).

Once a non-significant p-value occurred all subsequent significance tests were considered exploratory in nature. Both streams were tested independently from each other, such that key secondary efficacy variables were tested in a confirmatory fashion for each active treatment group only if the primary

efficacy variable showed significance for that treatment group. Conversely, non-significance in a key secondary efficacy variable for one of the active treatment groups did not imply stopping the hierarchical testing in the other treatment group.

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

• Dichotomous key secondary endpoints (key secondary endpoints no. 1, 3, 4 and 5) were analysed using the normal approximation test for rates (test for superiority, one-sided alpha level of 0.0125 for confirmatory analyses). The denominator was all patients included in the respective analysis set, the numerator was all patients with 'yes'. Dichotomous key secondary endpoints with a corresponding baseline measurement (key secondary endpoints no. 1 and 4) were in addition analysed using logistic regression including the screening/baseline value(s) of the preceding induction phase in addition to treatment group:

For key secondary endpoint no. 1 the peak number of eos/mm^2 hpf at screening was used as covariate, for key secondary endpoint no. 4 the weekly EEsAI-PRO score at baseline of the preceding induction phase was used as covariate.

• Change in the peak eos/mm^2 hpf was analysed using the Wilcoxon rank sum test. [The following is stated in CSP Section 9.3.2.: 'Quasi-continuous target variables (change in the peak eos/mm^2 hpf) will be analysed by fitting a linear least squares model with treatment effect and baseline value(s) as covariate(s) if warranted by the number of parameter values actually observed; alternatively, a Wilcoxon test may be appropriate.' As preliminary blinded data suggested peak eos/mm^2 hpf values of 0 for almost all patients at baseline and around half of the patients at the end of the DB phase, it was planned in the SAP to use the Wilcoxon rank sum test for the analysis of this endpoint.]

All tests for key secondary endpoints were done on a one-sided alpha level of 0.0125 (Bonferroni correction) with the intent to show the superiority of active treatment over placebo in the context of the hierarchical testing procedure.

Results

Participant flow

In total, 297 patients were included in the study: 66 patients were former participants of the BUL-1/EEA trial and were all randomised for the DB treatment phase; and 231 patients were screened for this trial without previous participation in BUL-1/EEA. One of the 231 screened patients was a screening failure following his/her first screening visit and was subsequently screened a second time, but counted only once. A total of 50 patients of the 231 screened patients were screening failures and were not included in the OLI phase of this trial, 181 patients were included in the OLI phase and received at least one dose of OLI investigational medicinal product (IMP). Of these, 138 patients were considered for transition into the DB phase of the trial. Hence a total of 204 patients were randomised for the DB phase, and all of these received at least one dose of the investigational product, and were thus included in the FAS-DB population.

Of note, at the time of submission of the Day120 responses by the applicant, from the 204 patients treated in the DB treatment phase, 82 patients entered the 6-weeks open-label re-induction phase (OLRI); 186 entered the OLE phase (first 48 weeks; either by switch from DB or from OLRI phase), and 159 continued from OLE into the OLE 2 phase (up to 96 weeks treatment). In the OLE phases, the majority of patients was treated with BUL 0.5mg BID.

So far, 114 of 204 patients from the DB phase have completed the study and are included into the FU phase. Of the 186 patients from the OLE (48 weeks) phase, so far 168 patients have completed this phase and only 10 patients were prematurely withdrawn, of whom 8 withdrawals were due to lack of patient's cooperation and 2 due to intolerable AEs, but none due to lack of efficacy.

The participants flow is shown in the following Figure 2.

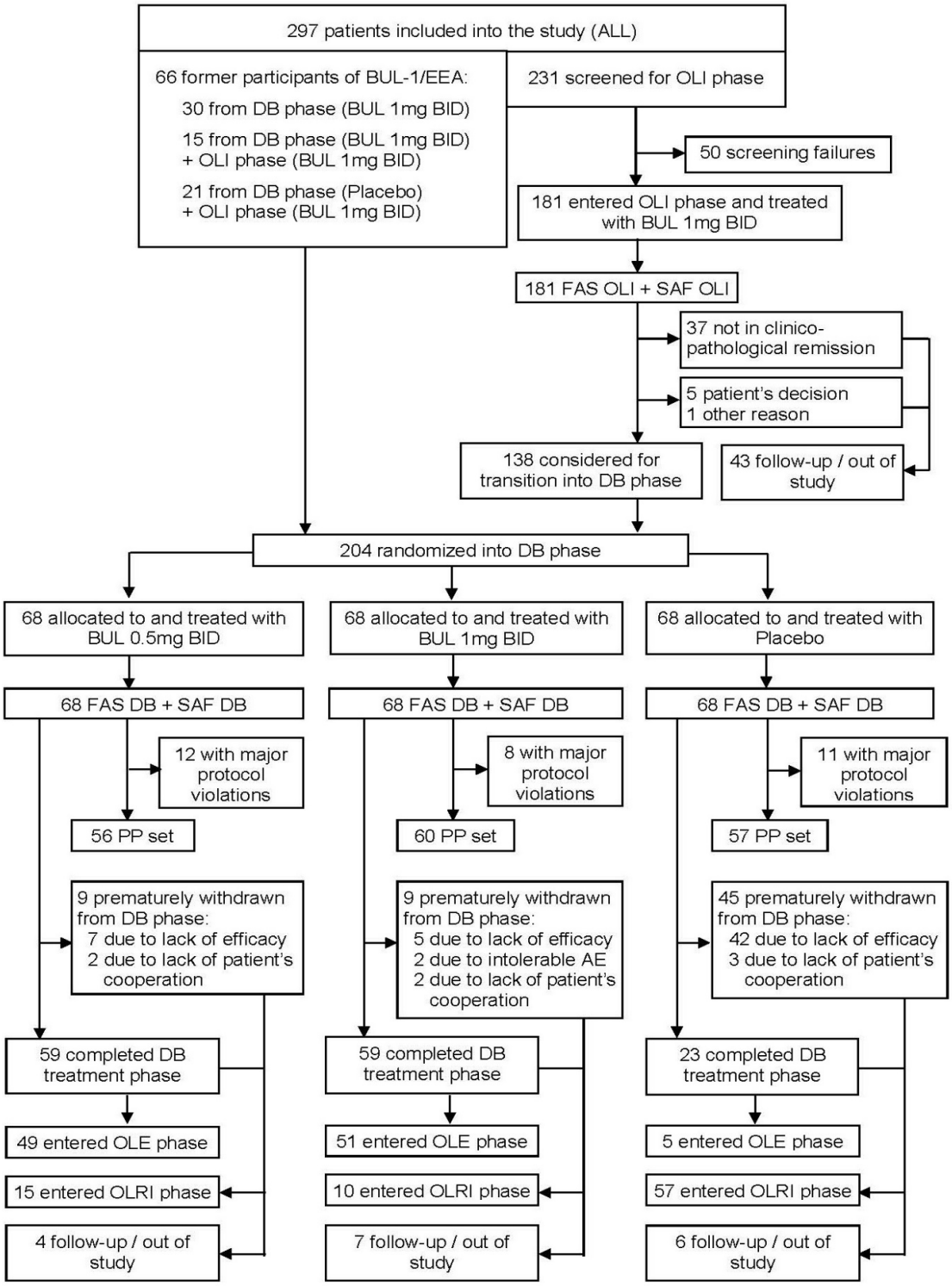

Figure 2 Participants flow in study BUL-2/EER

Recruitment

The date of first randomisation into this study was 29 January 2016, and the last patient which completed the DB phase was on 28 November 2018. As reported above, the recruitment into the trial was faster than expected, and the planned interim analysis was not conducted due to this fast recruitment. At the time of submission of the data, a final study report is not available due to the fact that OLRI, as well as OLE and FU phases were ongoing at the time of submission.

Conduct of the study

Major protocol violations leading to exclusion from the PP set included violations of major in-/ exclusion criteria, insufficient compliance with respect to intake of IMP during the DB phase, use of prohibited concomitant medication, premature discontinuation from DB treatment phase – unless the reason for discontinuation was lack of efficacy, or intolerable AE with at least possible causal relationship with the IMP, or intolerable AE which was a deterioration of study disease, change of concomitant treatment with PPIs during the DB phase, DB EOT/withdrawal visit more than seven days after last IMP intake during the DB treatment phase, and administration of IMP during the DB phase for less than 28 days. Major protocol violations leading to exclusion from the PP set are presented in Table 6.

Table 6 Major protocol violations (reasons) leading to exclusion from the PP set

Protocol violations		0.5 mg BUL		1 mg BUL		Placebo	
Patients with at least one protocol violation		N	%	N	%	N	%
Major	Number of protocol violations	17	34.0	14	34.1	21	40.4
	Inclusion criterion violated	2	4.0	2	4.9	2	3.8
	Exclusion criterion violated	1	2.0	1	2.4	1	1.9
	Prohibited concomitant medication	3	6.0	1	2.4	3	5.8
	IMP intake less than 28 days or not assessable	0	0	1	2.4	2	3.8
	DB treatment phase not completed	2	4.0	2	4.9	3	5.8
	Insufficient or not assessable compliance (DB IMP)	4	8.0	2	4.9	3	5.8
	DB EOT visit > 7 days after last IMP intake or not assessable	0	0	2	4.9	2	3.8
	Change of concomitant treatment with PPIs during DB phase	3	6.0	1	2.4	3	5.8
	Other protocol violation	2	4.0	2	4.9	2	3.8

Baseline data

The main baseline demographics and disease characteristics of the DB population is given in Table 7 and Table 8.

Table 7 Demographics (FAS-DB)

	Statistic	BUL 0.5 mg BID (N = 68)	BUL 1 mg BID (N = 68)	Placebo (N = 68)	Total (N = 204)
Sex					
Male	n (%)	57 (83.8%)	57 (83.8%)	55 (80.9%)	169 (82.8%)
Female	n (%)	11 (16.2%)	11 (16.2%)	13 (19.1%)	35 (17.2%)
Race					
White	n (%)	68 (100%)	68 (100%)	68 (100%)	204 (100%)
Smoking habits					
Current	n (%)	8 (11.8%)	3 (4.4%)	2 (2.9%)	13 (6.4%)
Former	n (%)	7 (10.3%)	9 (13.2%)	8 (11.8%)	24 (11.8%)
Never	n (%)	53 (77.9%)	56 (82.4%)	58 (85.3%)	167 (81.9%)
Age (years)	Mean (SD)	36 (10.9)	37 (11.1)	36 (9.9)	36 (10.6)
	Range	19 – 69	18 – 64	18 – 64	18 – 69
Height (cm)	Mean (SD)	177 (7.6)	177 (8.7)	177 (8.5)	177 (8.2)
	Range	160 – 196	156 – 193	155 – 206	155 – 206
Weight (kg)	Mean (SD)	76 (11.6)	80 (14.2)	77 (15.2)	78 (13.8)
	Range	49 – 98	53 – 120	42 – 123	42 – 123
BMI (kg/m^2)	Mean (SD)	24.1 (3.02)	25.4 (4.22)	24.4 (4.12)	24.7 (3.85)
	Range	18.0 – 30.4	17.9 – 40.9	17.6 – 41.5	17.6 – 41.5

Table 8 Demographics and anamnestic disease characteristics (FAS-DB):

Disease characteristic	Statistic	BUL 0.5 mg BID (N = 68)	BUL 1 mg BID (N = 68)	Placebo (N = 68)	Total (N = 204)
Duration since diagnosis (years)	Mean (SD) Median (Range)	4.3 (3.47) 4.1 (0.2-15.7)	4.2 (4.04) 2.6 (0.2-19.2)	3.3 (2.85) 2.1 (0.2-11.7)	3.9 (3.50) 3.0 (0.2-19.2)
Duration since first symptoms (years)	Mean (SD) Median (Range)	12.6 (8.50) 10.4 (0.3-35.7)	11.8 (9.37) 9.5 (1.0-42.7)	9.6 (8.22) 7.0 (1.0-37.6)	11.4 (8.76) 9.2 (0.3-42.7)
Previous oesophageal surgeries (yes)	n (%)	-	-	-	-
Previous oesophageal dilations (yes)	n (%)	13 (19.1%)	8 (11.8%)	4 (5.9%)	25 (12.3%)
Conducted PPI trial (previous or during screening)	n (%)	68 (100%)	68 (100%)	68 (100%)	204 (100%)
Clinical response	n (%)	8 (11.8%)	8 (11.8%)	5 (7.4%)	21 (10.3%)
Pathological response	n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Previous [1] EoE treatment					
PPI	n (%)	46 (67.6%)	45 (66.2%)	46 (67.6%)	137 (67.2%)
Topical budesonide	n (%)	11 (16.2%)	11 (16.2%)	14 (20.6%)	36 (17.6%)
Topical fluticasone	n (%)	29 (42.6%)	26 (38.2%)	16 (23.5%)	71 (34.8%)
Systemic steroids	n (%)	1 (1.5%)	4 (5.9%)	0 (0%)	5 (2.5%)
Other	n (%)	3 (4.4%)	0 (0%)	1 (1.5%)	4 (2.0%)
Endoscopic dilation	n (%)	13 (19.1%)	8 (11.8%)	4 (5.9%)	25 (12.3%)
Elemental diet	n (%)	0 (0%)	0 (0%)	2 (2.9%)	2 (1.0%)
Directed elimination diet (based on allergy test)	n (%)	3 (4.4%)	6 (8.8%)	6 (8.8%)	15 (7.4%)
Non-directed elimination diet	n (%)	28 (41.2%)	21 (30.9%)	24 (35.3%)	73 (35.8%)
History of allergic disease	n (%)	54 (79.4%)	55 (80.9%)	50 (73.5%)	159 (77.9%)

1) Treatment options used in patient's history prior to enrolment into the study program of BUL-1/EEA and BUL-2/EER.

The disease characteristics at baseline (expressed as with symptomatic NRS scales, the EEsAI-PRO instrument, QoL scales, and histology) indicated that requested state of remission in all treatment groups was fulfilled.

Numbers analysed

The final analysis was performed on a total of 204 FAS-DB and 173 per-protocol patients. The allocation of patients to the per-protocol set for the final analysis was performed before unblinding. The reason for non-inclusion of patients into the PP set are given in Table 8 above.

Outcomes and estimation

Primary outcome:

In the FAS-DB, rates of patients free of treatment failure at week 48 were comparable between the two dose groups (BUL 0.5 mg BID group: 73.5%; BUL 1 mg BID group: 75.0%) and higher compared with the Placebo group (4.4% of patients). The difference between BUL 0.5 mg BID and Placebo groups with respect to the rate of patients free of treatment failure at week 48 was 69.1% (97.5% CI: [55.89%; 82.34%]), with one-sided p-value resulting from the normal approximation test < 0.0001, demonstrating the highly significant superiority of BUL 0.5 mg BID to Placebo for maintenance of clinico-pathological remission in adult patients with EoE. Likewise, the estimated difference between BUL 1 mg BID and Placebo groups of 70.6% (97.5% CI: [57.56%; 83.61%, one-sided p-value < 0.0001) was also statistically significant and demonstrated the superiority of BUL 1 mg BID to Placebo.

The outcome of the primary evaluation is shown in Table 9.

Table 9 Rate of patients free of treatment failure after 48 weeks of double blind treatment – study BUL-2/EER (FAS-DB and PP)

	Number (%) of patients free of treatment failure			Difference between proportions[a] [97.5% CI][b]		Testing of H_0[c]	
	BUL 0.5 mg BID	BUL 1 mg BID	Placebo	BUL 0.5 mg BID	BUL 1 mg BID	BUL 0.5 mg BID	BUL 1 mg BID
FAS-DB	50/68 (73.5%)	51/68 (75.0%)	3/68 (4.4%)	69.1% [55.89%; 82.34%]	70.6% [57.56%; 83.61%]	< 0.0001	< 0.0001
PP	45/56 (80.4%)	48/60 (80.0%)	3/57 (5.3%)	75.1% [61.47%; 88.72%]	74.7% [61.40%; 88.08%]	< 0.0001	< 0.0001

a Difference between proportions (π_{Eff} - π_{Pla}), π_{Eff}: BUL 0.5 mg BID or BUL 1 mg BID.
b Bonferroni correction.
c Testing of H_0 ($\pi_{Pla} \geq \pi_{Eff}$) by means of the one-sided normal approximation test, Bonferroni adjusted alpha = 0.0125.

Secondary outcomes:

The first key secondary endpoint was the rate of patients with histological relapse, defined as a peak of ≥48 eos/mm² hpf at DB end of treatment. The results are shown in table 10.

Table 10 Histological relapse at double blind end of treatment – (FAS-DB and PP)

		Number (%) of patients with histological relapse at DB EOT		
		BUL 0.5 mg BID	**BUL 1 mg BID**	**Placebo**
FAS-DB	Yes	9/68 (13.2%)	7/68 (10.3%)	61/68 (89.7%)
	No	57/68 (83.8%)	58/68 (85.3%)	4/68 (5.9%)
	Not evaluable	2/68 (2.9%)	3/68 (4.4%)	3/68 (4.4%)
PP	Yes	4/56 (7.1%)	5/60 (8.3%)	53/57 (93.0%)
	No	52/56 (92.9)	55/60 (91.7%)	3/57 (5.3%)
	Not evaluable	0/56 (0.0%)	0/60 (0.0%)	1/57 (1.8%)

The second key secondary endpoint was the change from baseline in peak eos/mm² hpf at the end of DB treatment. The results are shown in Table 11.

Table 11 Change from baseline in peak eos/mm² hpf at the end of DB treatment – (FAS-DB and PP)

	Mean change (SD) [95% CI] from baseline in peak eos/mm² hpf at DB EOT			Testing of H_0*	
	BUL 0.5 mg BID	**BUL 1 mg BID**	**Placebo**	**BUL 0.5 mg BID**	**BUL 1 mg BID**
FAS-DB	38 (112.6) [10.0, 65.3] n = 66	21 (64.0) [5.0, 36.7] n = 65	262 (216.3) [208.4, 315.5] n = 65	< 0.0001	< 0.0001
PP	30 (114.7) [-1.1, 60.4] n = 56	17 (56.5) [1.9, 31.1] n = 60	270 (226.8) [209.1, 330.6] n = 56	< 0.0001	< 0.0001

*Comparison between budesonide and placebo groups by means of the one-sided Wilcoxon rank sum test (p-value); Bonferroni adjusted alpha = 0.0125.

The third key secondary endpoint was the rate of patients with a clinical relapse, have experienced a food impaction, which needed endoscopic intervention, or needed an endoscopic dilation during the DB treatment phase. The results of this analysis are shown in Table 12.

Table 12 Clinical relapse during the double blind phase - (FAS-DB and PP)

	Number (%) of patients with clinical relapse during the DB phase					
	FAS-DB			**PP**		
	BUL 0.5 mg BID	**BUL 1 mg BID**	**Placebo**	**BUL 0.5 mg BID**	**BUL 1 mg BID**	**Placebo**
Not suspected	60/68 (88.2%)	60/68 (88.2%)	21/68 (30.9%)	48/56 (85.7%)	54/60 (90.0%)	17/57 (29.8%)
Suspicion resolved	1/68 (1.5%)	1/68 (1.5%)	5/68 (7.4%)	1/56 (1.8%)	0/60 (0%)	4/57 (7.0%)
Yes	7/68 (10.3%)	5/68 (7.4%)	41/68 (60.3%)	7/56 (12.5%)	4/60 (6.7%)	36/57 (63.2%)
Suspected but not assessable	0/68 (0.0%)	2/68 (2.9%)	1/68 (1.5%)	0/56 (0.0%)	2/60 (3.3%)	0/57 (0.0%)

The fourth key secondary endpoint was the rate of patients with a total weekly EEsAI-PRO score of ≤20 at DB week48/EOT. This evaluation is shown in Table 13.

Table 13 Rates of patients with a total weekly EEsAI-PRO score ⩽ 20 at the end of double blind treatment – (FAS-DB)

	Patients(%) with total weekly EEsAI-PRO score ≤ 20 at DB EOT			Difference between proportions[a] [97.5% CI][b]		Testing of H_0[c]	
	BUL 0.5 mg BID	BUL 1 mg BID	Placebo	BUL 0.5 mg BID	BUL 1 mg BID	BUL 0.5 mg BID	BUL 1 mg BID
FAS-DB	49/68 (72.1%)	50/68 (73.5%)	14/68 (20.6%)	51.5% [35.1%; 67.9%]	52.9% [36.7%; 69.2%]	< 0.0001	< 0.0001

a Difference between proportions (π_{Eff} - π_{Pla}), π_{Eff}: BUL 0.5 mg BID or BUL 1 mg BID.
b Bonferroni correction.
c Testing of H_0 ($\pi_{Pla} \geq \pi_{Eff}$) by means of the one-sided normal approximation test, Bonferroni adjusted alpha = 0.0125.

The fifth key secondary endpoint was the rate of patients in deep disease remission, i.e., deep clinical, deep endoscopic, and histological remission (based on the peak number of eos per hpf), at DB week 48/EOT. The results are shown in Table 14.

Table 14 Rate of patients in deep disease remission at the end of double-blind treatment – (FAS-DB)

	Patients (%) with deep disease remission at DB week 48/EOT			Difference between proportions[a] [97.5% CI][b]		Testing of H_0[c]	
	BUL 0.5 mg BID	BUL 1 mg BID	Placebo	BUL 0.5 mg BID	BUL 1 mg BID	BUL 0.5 mg BID	BUL 1 mg BID
FAS-DB	27/68 (39.7%)	36/68 (52.9%)	0/68 (0.0%)	39.7% [26.4%; 53.0%]	52.9% [39.4%; 66.5%]	< 0.0001	< 0.0001

a Difference between proportions (π_{Eff} - π_{Pla}), π_{Eff}: BUL 0.5 mg BID or BUL 1 mg BID.
b Bonferroni correction.
c Testing of H_0 ($\pi_{Pla} \geq \pi_{Eff}$) by means of the one-sided normal approximation test, Bonferroni adjusted alpha = 0.0125.

A selection of the results of the pre-planned exploratory endpoints is shown in Table 15.

Table 15 Further exploratory efficacy endpoints (FAS-DB)

		BUL 0.5mg BID (n = 68)	BUL 1mg BID (n = 68)	Placebo (n = 68)
Physician's Global Assessment of EoE Activity (0-10)*				
DB Baseline, Mean (SD)		1 (0.8)	1 (1.0)	1 (0.9)
DB EOT, Mean (SD)		1 (1.8) n=66	1 (1.4) n=67	5 (2.4) n=66
Absolute change from DB Baseline to DB EOT, Mean (SD)		0 (1.8) n=66	0 (1.7) n=67	4 (2.4) n=66
Patient's Global Assessment of EoE Severity (0-10)*				
DB Baseline, Mean (SD)		1 (0.8)	1 (0.8)	1 (0.9) n=67
DB EOT, Mean (SD)		1 (1.8) n=66	1 (1.7) n=67	4 (2.6) n=64
Absolute change from DB Baseline to DB EOT, Mean (SD)		0 (2.0) n=66	0 (1.8) n=67	3 (2.7) n=63
Rate of patients with an increase of ≥ 3 points from DB Baseline to DB EOT, n (%)		5 (7.4%)	7 (10.3%)	34 (50.0%)
Rate of patients with PatGA NRS ≤ 2 points at DB EOT, n (%)		60 (88.2%)	58 (85.3%)	22 (32.4%)
Dysphagia NRS (0-10; 7-day recall period) in the week prior to a visit*				
DB Baseline, Mean (SD)#		1 (0.9)	1 (0.9)	1 (0.8)
DB EOT, Mean (SD)		1 (1.8) n=66	1 (1.7) n=67	4 (2.7) n=65
Absolute change from DB Baseline to DB EOT, Mean (SD)#		0 (2.0) n=66	0 (1.8) n=67	3 (2.9) n=65
Pain during swallowing NRS (0-10; 7-day recall period) in the week prior to a visit*				
DB Baseline, Mean (SD)#		1 (0.9)	1 (1.0)	0 (0.8)
DB EOT, Mean (SD)		1 (1.6) n=66	0 (1.4) n=67	2 (2.6) n=65
Absolute change from DB Baseline to DB EOT, Mean (SD)#		0 (1.8) n=66	0 (1.6) n=67	2 (2.7) n=65
Blood eosinophil (abs.) counts [/cmm]				
DB Baseline, Mean (SD)		205 (141.2) n=67	186 (175.6) n=68	170 (156.8) n=68
DB EOT, Mean (SD)		209 (129.3) n=65	222 (175.7) n=66	386 (245.9) n=64
Absolute change from DB Baseline to DB EOT, Mean (SD)		7 (154.2) n=64	40 (207.2) n=66	223 (299.7) n=64
Rate of patients with a clinical relapse during the DB phase				
n (%)		7 (10.3%)	5 (7.4%)	41 (60.3%)
Rate of patients experiencing a food impaction which needed endoscopic intervention at any time during the DB treatment phase				
n (%)		0 (0.0%)	0 (0.0%)	1 (1.5%)
Rate of patients with need for endoscopic dilation at any time during the DB treatment phase				
n (%)		0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient's global satisfaction at the end of the DB treatment phase				
DB EOT, n (%)	Extremely satisfied	39 (57.4%)	49 (72.1%)	28 (41.2%)
	Satisfied	23 (33.8%)	15 (22.1%)	18 (26.5%)
	Neither satisfied nor dissatisfied	1 (1.5%)	2 (2.9%)	8 (11.8%)
	Dissatisfied	3 (4.4%)	0 (0.0%)	9 (13.2%)
	Extremely dissatisfied	0 (0.0%)	0 (0.0%)	1 (1.5%)
Time in DB phase [weeks]§				
Mean (SD)		44 (12.3)	44 (11.2)	23 (18.8)
Time to relapse (clinical or histological), experiencing a food impaction which needed endoscopic intervention, or need for an endoscopic dilation (DB Phase) [days] $				
Median [Q25%; Q75%]		336 [333; 340]	335 [332; 339]	86 [29; 333]
Time to treatment failure [days] +				
Median [Q25%; Q75%]		336 [333; 340]	335 [332; 339]	86 [29; 333]
Time to first occurrence of clinical relapse [days] +				
Median [Q25%; Q75%]		336 [333; 340]	335 [332; 339]	86 [29; 333]

Ancillary analyses

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:

- Path to remission (i.e., BUL-1/EEA or BUL-2/EER OLI-phase);
- Localisation of the inflammation at screening of either BUL-1/EEA or BUL-2/EER (unique categories):
  - Proximal (yes/no), median (yes/no), and distal (yes/no) 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 treatment phase,

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

- History of allergic diseases (yes/no, as documented in the eCRF at DB V1),
- Patient's Global Assessment (PatGA) at baseline of induction phase (Baseline visit of BUL-1/EEA or OLI Baseline visit of BUL-2/EER),

For the stratified analysis PatGA was categorised into 4 groups: '0 to 2', '3 to 5', '6 to 8', and '9 to 10'. An additional stratified post-hoc analysis was performed with PatGA categorised into 2 groups: '≤5' and '>5'.

- Time interval since first symptoms of EoE at DB Baseline (years):

< median (years) and ≥ median (years).

Table 16 shows the results according to these criteria.

Table 16 Freedom of treatment failure after 48 weeks of double blind treatment - stratified analysis (FAS-DB and PP)

Criteria for stratified analysis	Number (%) of patients free of treatment failure after 48 weeks of treatment					
	FAS-DB			PP		
	BUL 0.5 mg BID N = 68	BUL 1 mg BID N = 68	Placebo N = 68	BUL 0.5 mg BID N = 56	BUL 1 mg BID N = 60	Placebo N = 57
Country						
Germany	17/24 (70.8%)	20/28 (71.4%)	2/33 (6.1%)	15/19 (78.9%)	19/24 (79.2%)	2/28 (7.1%)
Switzerland	10/14 (71.4%)	11/14 (78.6%)	0/5 (0.0%)	9/11 (81.8%)	10/13 (76.9%)	0/5 (0.0%)
Spain	20/26 (76.9%)	17/22 (77.3%)	1/26 (3.8%)	18/22 (81.8%)	17/21 (81.0%)	1/21 (4.8%)
Other (BE/NL/UK)	3/4 (75.0%)	3/4 (75.0%)	0/4 (0.0%)	3/4 (75.0%)	2/2 (100.0%)	0/3 (0.0%)

Criteria for stratified analysis	Number (%) of patients free of treatment failure after 48 weeks of treatment					
	FAS-DB			PP		
	BUL 0.5 mg BID N = 68	BUL 1 mg BID N = 68	Placebo N = 68	BUL 0.5 mg BID N = 56	BUL 1 mg BID N = 60	Placebo N = 57
Centre						
Centre 101	5/9 (55.6%)	4/8 (50.0%)	0/13 (0.0%)	4/5 (80.0%)	4/6 (66.7%)	0/12 (0.0%)
Centre 103	5/6 (83.3%)	2/3 (66.7%)	0/9 (0.0%)	4/5 (80.0%)	2/3 (66.7%)	0/6 (0.0%)
All other DE centres pooled	7/9 (77.8%)	14/17 (82.4%)	2/11 (18.2%)	7/9 (77.8%)	13/15 (86.7%)	2/10 (20.0%)
All CH centres pooled	10/14 (71.4%)	11/14 (78.6%)	0/5 (0.0%)	9/11 (81.8%)	10/13 (76.9%)	0/5 (0.0%)
Centre 401	12/15 (80.0%)	12/16 (75.0%)	0/15 (0.0%)	12/14 (85.7%)	12/16 (75.0%)	0/14 (0.0%)
All other ES centres pooled	8/11 (72.7%)	5/6 (83.3%)	1/11 (9.1%)	6/8 (75.0%)	5/5 (100.0%)	1/7 (14.3%)
All centres from other countries (BE/NL/UK) pooled+	3/4 (75.0%)	3/4 (75.0%)	0/4 (0.0%)	3/4 (75.0%)	2/2 (100.0%)	0/3 (0.0%)
Path to remission						
BUL-1/EEA	20/22 (90.9%)	18/22 (81.8%)	0/22 (0.0%)	19/21 (90.5%)	18/22 (81.8%)	0/20 (0.0%)
BUL-2/EER OLI-phase	30/46 (65.2%)	33/46 (71.7%)	3/46 (6.5%)	26/35 (74.3%)	30/38 (78.9%)	3/37 (8.1%)
Localisation of inflammation at screening of either BUL-1/EEA or BUL-2/EER						
Proximal oesophagus						
No	11/11 (100.0%)	9/12 (75.0%)	1/7 (14.3%)	11/11 (100.0%)	8/11 (72.7%)	1/7 (14.3%)
Yes	39/57 (68.4%)	42/56 (75.0%)	2/61 (3.3%)	34/45 (75.6%)	40/49 (81.6%)	2/50 (4.0%)
Mid oesophagus						
Not evaluable	-	-	0/1 (0.0%)	-	-	0/1 (0.0%)
No	10/11 (90.9%)	6/8 (75.0%)	0/3 (0.0%)	9/9 (100.0%)	5/7 (71.4%)	0/3 (0.0%)
Yes	40/57 (70.2%)	45/60 (75.0%)	3/64 (4.7%)	36/47 (76.6%)	43/53 (81.1%)	3/53 (5.7%)
Distal oesophagus						
Not evaluable	-	0/1 (0.0%)	0/1 (0.0%)	-	-	0/1 (0.0%)
No	2/3 (66.7%)	3/5 (60.0%)	0/1 (0.0%)	1/1 (100.0%)	3/5 (60.0%)	0/1 (0.0%)
Yes	48/65 (73.8%)	48/62 (77.4%)	3/66 (4.5%)	44/55 (80.0%)	45/55 (81.8%)	3/55 (5.5%)
Extent of inflammation at screening: Number of oesophageal segments affected						
1	7/7 (100.0%)	6/7 (85.7%)	0/3 (0.0%)	7/7 (100.0%)	5/6 (83.3%)	0/3 (0.0%)
2	9/11 (81.8%)	6/12 (50.0%)	1/7 (14.3%)	7/7 (100.0%)	6/11 (54.5%)	1/7 (14.3%)
3	34/50 (68.0%)	39/49 (79.6%)	2/58 (3.4%)	31/42 (73.8%)	37/43 (86.0%)	2/47 (4.3%)
Concomitant use of PPIs during the DB phase						
No	37/52 (71.2%)	42/56 (75.0%)	2/59 (3.4%)	36/47 (76.6%)	40/50 (80.0%)	2/53 (3.8%)
Yes	13/16 (81.3%)	9/12 (75.0%)	1/9 (11.1%)	9/9 (100.0%)	8/10 (80.0%)	1/4 (25.0%)
History of allergic diseases						
No	9/14 (64.3%)	10/13 (76.9%)	1/18 (5.6%)	9/13 (69.2%)	10/11 (90.9%)	1/13 (7.7%)
Yes	41/54 (75.9%)	41/55 (74.5%)	2/50 (4.0%)	36/43 (83.7%)	38/49 (77.6%)	2/44 (4.5%)

Criteria for stratified analysis	Number (%) of patients free of treatment failure after 48 weeks of treatment					
	FAS-DB			PP		
	BUL 0.5 mg BID N = 68	BUL 1 mg BID N = 68	Placebo N = 68	BUL 0.5 mg BID N = 56	BUL 1 mg BID N = 60	Placebo N = 57
PatGA at baseline of OLI phase (categorized into 4 groups)						
0 to 2	-	-	-	-	-	-
3 to 5	19/28 (67.9%)	25/34 (73.5%)	1/32 (3.1%)	18/23 (78.3%)	22/27 (81.5%)	1/27 (3.7%)
6 to 8	28/35 (80.0%)	20/28 (71.4%)	2/34 (5.9%)	24/29 (82.8%)	20/27 (74.1%)	2/29 (6.9%)
9 or 10	3/5 (60.0%)	6/6 (100.0%)	0/2 (0.0%)	3/4 (75.0%)	6/6 (100.0%)	0/1 (0.0%)
PatGA at baseline of OLI phase (categorized into 2 groups: *post-hoc* analysis)						
⩽ 5	19/28 (67.9%)	25/34 (73.5%)	1/32 (3.1%)	18/23 (78.3%)	22/27 (81.5%)	1/27 (3.7%)
> 5	31/40 (77.5%)	26/34 (76.5%)	2/36 (5.6%)	27/33 (81.8%)	26/33 (78.8%)	2/30 (6.7%)
Time since first symptoms of EoE at DB baseline[1)]						
Not evaluable	-	-	0/2 (0.0%)	-	-	0/1 (0.0%)
< median (9.2 years)	21/27 (77.8%)	23/33 (69.7%)	2/41 (4.9%)	19/22 (86.4%)	21/27 (77.8%)	2/34 (5.9%)
⩾ median(9.2 years)	29/41 (70.7%)	28/35 (80.0%)	1/25 (4.0%)	26/34 (76.5%)	27/33 (81.8%)	1/22 (4.5%)

[1] Median of time interval since first symptoms of EoE at DB Baseline is 9.2 years and was calculated based on FAS-DB patients.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17 Summary of efficacy for trial BUL-2/EER

Title: Double- blind, randomised, placebo-controlled, phase III study on the efficacy and tolerability of a 48-week treatment with two different doses of budesonide effervescent tablets vs. placebo for maintenance of clinico-pathological remission in adult patients with eosinophilic esophagitis		
Study identifier	BUL-2/EER EudraCT No.: 2014-001485-99/ Acronym: EOS-2	
Design	Double-blind, randomised, placebo-controlled multi-centre, phase III study	
	Duration of main phase:	First patient enrolled: 29 Jan 2016 Last patient completed double-blind treatment phase:28 Nov 2018
	Duration of open-label induction phase:	6 weeks
	Duration of double-blind treatment phase:	48 weeks
	Duration of open-label extension phase:	96 weeks (ongoing)

Hypothesis	Superiority of a 48-week treatment with 2 x 0.5 mg/d or 2 x 1 mg/d budesonide orodispersible tablets vs. placebo for the maintenance of clinico-pathological remission in adult patients with eosinophilic esophagitis (EoE).		
Treatment groups	BUL 0.5 mg BID: 0.5 mg budesonide orodispersible tablet BID		48-week DB: n=68
	BUL 1 mg BID: 1 mg budesonide orodispersible tablet BID		48 weeks DB; n=68
	Placebo: Placebo orodispersible tablet		48 weeks DB; n= 68
Endpoints and definitions	Primary endpoint	Rate of patients free of treatment failure after 48 weeks of treatment.	Treatment failure after 48 weeks of treatment was "yes", if at least one of the following criteria was met at any time during the DB treatment phase: - Clinical relapse, i.e., experiencing dysphagia or pain during swallowing in the past seven days (7 day recall period) of a severity of ≥4 points on a 0–10 NRS for dysphagia or pain during swallowing, respectively, confirmed by a severity of ≥4 points on at least 1 day during the subsequent week on the respective 0-10 NRS for dysphagia or pain during swallowing (24-hour recall period). - Histological relapse, i.e., a peak of ≥48 eos/mm^2 hpf at DB V6/EOT, - Experiencing a food impaction which needed endoscopic intervention, - Need for an endoscopic dilation, - Premature withdrawal for any reason
	Key secondary endpoint 1	Histological relapse	Rate of patients with histological relapse, defined as peak of ≥48 eos/mm^2 hpf at DB V6/EOT,
	Key secondary endpoint 2	Change in peak eos	Change in the peak eos/mm^2 hpf from DB V1 to DB V6/EOT,
	Key secondary endpoint 3	Clinical relapse	Rate of patients with a clinical relapse, having experienced a food impaction which needed endoscopic intervention, or needed an endoscopic dilation during the DB treatment phase
	Key secondary endpoint 4	EEsAI-PRO score	Rate of patients with a total weekly Eosinophilic Esophagitis Activity Index (EEsAI) – Patient-Reported Outcome (EEsAI-PRO) score of ≤20 at DB V6/EOT
	Key secondary endpoint 5	Deep remission	Rate of patients in deep disease remission, i.e., deep clinical, deep endoscopic and histological remission (based on the peak number of eos per hpf), at DB V6/EOT
Database lock	22.01.2019		
<u>Results and Analysis</u>			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Intent to treat At week 48/end of treatment (EOT)			
Descriptive statistics and estimate variability	Treatment group	BUL 0.5 mg BID:	BUL 1 mg BID:	Placebo
	Number of subject	68	68	68
	Free of treatment failure	50/68 (73.5%)	51/68 (75.0%)	3/68 (4.4%)
	Histological relapse	9/68 (13.2%)	7/68 (10.3%)	61/68 (89.7%)
	Change in eos (mean; SD)	38 (112.6)	21 (64.0)	262 (216.3)
	Clinical relapse etc.	7/68 (10.3%)	5/68 (7.4%)	41/68 (60.3%)
	Total weekly EEsAI-PRO ≤20	49/68 (72.1%)	50/68 (73.5%)	14/58 (20.6%)
	Deep remission	27/68 (39.7%)	36/68 (52.9%)	0/68 (0.0%)

Effect estimate per comparison		**1 mg BID vs. Placebo**	**0.5 mg BID vs. Placebo**
	Primary endpoint	Difference between proportions	Difference between proportions
		70.6% [57.56%; 83.61%]	69.1% [55.89%; 82.34%]
		P-value (1-sided): <0.0001	P-value (1-sided) <0.0001
	Key secondary EP 1; Rate of histological relapse	Difference between proportions	Difference between proportions
		-79.4% [-91.1%; -67.7%]	-76.5% [-88.8%; -64.1%]
		P-value (1-sided): <0.0001	P-value (1-sided) <0.0001
	Key secondary EP 2: Change in peak eos	Comparison of mean change	Comparison of mean change
		P-value (1-sided): <0.0001	P-value (1-sided) <0.0001
	Key secondary EP 3 Rate of patients	Difference between proportions	Difference between proportions

	with clinical relapse or food impaction needing endoscopic intervenstion or dilatation.	-52.9% [-68.0%; -37.9%]	50.0% [-65.7%; -34.3%]
		P-value (1-sided): <0.0001	P-value (1-sided) <0.0001
	Key secondary EP 4 Rate of patients with a total weekly EEsAI-PRO score of ≤20 at DB V6/EOT	Difference between proportions	Difference between proportions
		52.9% [36.7%; 69.2%]	51.5% [35.1%; 67.9%]
		P-value (1-sided): <0.0001	P-value (1-sided) <0.0001
	Key secondary EP 5 Rate of patients in deep disease remission, i.e., deep clinical, deep endoscopic and histological remission (based on the peak number of eos per hpf, i.e., <15 eos/hpf), at DB V6/EOT*	Difference between proportions	Difference between proportions
		52.9% [39.4%; 66.5%]	39.7% [26.4%; 53.0%]
		P-value (1-sided): <0.0001	P-value (1-sided) <0.0001

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

No pooled data were presented.

Clinical studies in special populations

No studies in special populations were conducted. A subgroup analysis according to age (cut-off: median age; but also patients> 60 years of age) and gender is presented in Table 18**.**

Table 18 Primary endpoint by age (median and categorical) and gender (FAS-DB)

Patients free of treatment failure after 48 weeks of treatment	**BUL 0.5mg BID (n=68)**	**BUL 1mg BID (n=68)**	**Placebo (n=68)**
Age at DB Baseline < median (i.e. 36 yr)			
n (%)	23/35 (65.7%)	25/33 (75.8%)	2/32 (6.3%)
Difference between proportions (BUL vs. Placebo)[+] [97.5% CI][§]	59.5% [39.1%; 79.9%]	69.5% [50.0%; 88.8%]	---
Testing of H_0 (BUL vs. Placebo): One-sided p-value[#]	<0.0001	<0.0001	---
Age at DB Baseline >= median (i.e. 36 yr)			
n (%)	27/33 (81.8%)	26/33 (74.3%)	1/36 (2.8%)
Difference between proportions (BUL vs. Placebo)[+] [97.5% CI][§]	79.0% [62.8%; 95.3%]	71.5% [53.9%; 89.2%]	---
Testing of H_0 (BUL vs. Placebo): One-sided p-value[#]	<0.0001	<0.0001	---

Patients free of treatment failure after 48 weeks of treatment	BUL 0.5mg BID (n=68)	BUL 1mg BID (n=68)	Placebo (n=68)
Age at DB Baseline <= 60 yr			
n (%)	49/67 (73.1%)	50/66 (75.8%)	3/67 (4.5%)
Difference between proportions (BUL vs. Placebo)+ [97.5% CI]§	68.7% [55.3%; 82.1%]	71.3% [58.2%; 84.4%]	---
Testing of H_0 (BUL vs. Placebo): One-sided p-value#	<0.0001	<0.0001	---
Age at DB Baseline > 60 yr			
n (%)	1/1 (100.0%)	1/2 (50.0%)	0/1 (0.0%)
Difference between proportions (BUL vs. Placebo)+ [97.5% CI]§	Number of patients with age >60 years at DB Baseline was very low. Therefore, the normal approximation test to compare the difference in proportions between each budesonide group and Placebo and between the two budesonide groups was not calculated for this subgroup.		
Testing of H_0 (BUL vs. Placebo): One-sided p-value#			
Male			
n (%)	43/57 (75.4%)	43/57 (75.4%)	3/55 (5.5%)
Difference between proportions (BUL vs. Placebo)+ [97.5% CI]§	70.0% [55.5%; 84.5%]	70.0% [55.5%; 84.5%]	---
Testing of H_0 (BUL vs. Placebo): One-sided p-value#	<0.0001	<0.0001	---
Female			
n (%)	7/11 (63.6%)	8/11 (72.7%)	0/13 (0.0%)
Difference between proportions (BUL vs. Placebo)+ [97.5% CI]§	63.6% [31.1%; 96.2%]	72.7% [42.6%; 100.0%]	---
Testing of H_0 (BUL vs. Placebo): One-sided p-value#	=0.0003	<0.0001	---

For this analysis not evaluable results were set to 'No'.
Normal approximation test was used for testing. Testing of H_0 ($\pi_{Pla} \geq \pi_{Eff}$) by means of the one-sided normal approximation test, Bonferroni adjusted alpha = 0.0125.
+ Difference between proportions (π_{Eff} - π_{Pla}), π_{Eff}: BUL 0.5mg BID or BUL 1mg BID, π_{Pla}: Placebo
§ Bonferroni correction

Supportive study

The results of the OLI (=introductory phase) of study BUL-2/EER are presented in this section.

The number of patients recruited and evaluated have already been shown above. As reported, the FAS-OLI comprised 181 patients.

Overall, efficacy of BUL 1mg BID was shown independently of the outcome parameter used (clinico-pathological remission rate, resolution of symptoms rate, PatGA, PRA, and patient's global satisfaction). At OLI Week 6 (LOCF), 126 of 181 patients (69.6%) were in clinico-pathological remission. The number of patients who were extremely satisfied at OLI Week 6 (LOCF) was 95 of 181 (52.5%). The main results of this part of the trial are shown in Table 19:

Table 19 Evaluation of the OLI phase of trial BUL-2/EER

		BUL 1mg BID (n = 181)
Rate of patients with clinico-pathological remission at OLI Week 6 (LOCF)	n (%)	126 (69.6%)
Rate of patients with resolution of symptoms in the week prior to OLI Week 6 (LOCF)+	n (%)	136 (75.1%)
Physician's Global Assessment of EoE activity in the course of the OLI phase#		
OLI Baseline	Mean (SD)	6 (1.6)
OLI Week 6 (LOCF)	Mean (SD)	1 (1.6)
Absolute change from OLI Baseline to OLI Week 6 (LOCF)	Mean (SD)	-5 (2.2)

Total modified EEsAI endoscopic instrument score		BUL 1mg BID (n = 181)
Total modified EEsAI endoscopic instrument Score*		
Screening	Mean (SD)	4 (1.6)
OLI Week 6 (LOCF)	Mean (SD)	1 (1.3) n=176
Absolute change from Screening to OLI Week 6 (LOCF)	Mean (SD)	-3 (1.9) n=176
Rate of patients with all features graded as 0#		
Screening	n (%)	1 (0.6%)
OLI Week 6 (LOCF)	n (%)	72 (39.8%)

		BUL 1mg BID (n = 181)
Rate of patients with histological remission defined as a peak of <16 eos/mm² hpf at OLI Week 6 (LOCF)	n (%)	163 (90.1%)
Rate of patients with deep histological remission, defined as a peak of 0 eos/mm² hpf, at OLI Week 6 (LOCF)	n (%)	153 (84.5%)
Change in the peak eos/mm² hpf from OLI Baseline to OLI Week 6 (LOCF)	Mean (SD)	-283 (270.9)

The rate of clinico-pathological remission observed in the OLI phase is in full accordance with the results of the DB phase of study BUL-1/EEA. This is taken as a further confirmation of the results of this earlier induction trial.

Currently, for the OLRI and OLE extension phases, only interim results are available (data lock point 29 Oct 2019).

In the OLRI phase, a total of 76 of 82 patients (92.7%) showed resolution of their symptoms (i.e., no or only minimal problems), qualifying them to be enrolled in the optional OLE phase. Treatment success did not depend on the previous treatment received (success rates 80%, 100%, and 93% in those previously treated with low-dose, high-dose, and placebo, respectively).

The OLE phases of the trial, both for those patients switching from the double-blind treatment, as well as from the OLRI phase, the documented relapse rates are very low, overall confirming the results from the double-blind treatment phase. However, the full interpretation of the data is currently hampered by the incomplete reporting, especially for the extended open-label phase, which is intended to provide an extended follow-up up to 96 weeks of treatment.

2.5.3. Discussion on clinical efficacy

The discussion on clinical efficacy, and the further chapters, mainly refer to the newly submitted data from the long-term study BUL-2/EER.

Clinical efficacy for short term treatment had already been shown at the time of initial approval and can be found in the EPAR for Jorveza.

Design and conduct of clinical studies

The MAH, in order to document long-term efficacy of Jorveza in the treatment of EoE in adults, has presented a well-conducted, and well-planned clinical study of 1-year duration.

The study was a randomised, placebo-controlled, double-blind phase III clinical study (BUL-2/EER) including 204 adult patients with EoE in clinico-pathological remission. Patients were randomised to treatment with 0.5 mg budesonide twice daily (BID), 1 mg budesonide BID, or placebo (all given as orodispersible tablets) for 48 weeks. The primary endpoint was the rate of patients free of treatment failure with treatment failure defined as clinical relapse (severity of dysphagia or pain during swallowing of ≥4 points on a 0-10 numerical rating scale, respectively), and/or histological relapse

(peak of ≥ 48 eosinophils/mm^2 high power field), and/or food impaction requiring endoscopic intervention, and/or need of an endoscopic dilation, and/or premature withdrawal for any reason.

The design of the study has been drawn up according to the advice given by CHMP. The investigation of a 48-week treatment period is considered adequate, and it was also fully reasonable to investigate a lower dose of the investigational agent for the long-term treatment once remission had been achieved.

The population included is considered fully adequate considering the disease history, and the previous inclusion in either the DB trial evaluated earlier, or – as shown in the evaluation of the long-term trial – in a short-term open-label induction trial, as part of the long-term trial. All patients (with very few exceptions) were in full remission at the time of inclusion.

The chosen control group is considered fully acceptable at a time with no other medicinal product being licensed for the long-term treatment of EoE.

The choice of the trial endpoints has been according to the protocol assistance given, and according to the scientific consensus of the learned societies, that both, symptoms as well as histological and endoscopic appearance should be included for the demonstration of efficacy. The primary endpoint combined symptomatic and histological evaluation, and the key secondary endpoints were different aspects of these components, which is considered fully adequate. Additional aspects have been tested with established symptoms as well as quality of life scales, and with endoscopic assessment of the oesophageal mucosa. All of these evaluations appeared to be in full accordance.

No concerns are raised with regard to the study design, the mode of evaluation, as well as the results of the analyses conducted. Additional analyses requested with regard to the influence of age and gender on efficacy results did not reveal relevant differences with regard to these categories, although – reflecting the epidemiology of the disease – truly "elderly" patients were not included in the studies.

Efficacy data and additional analyses

This newly submitted long-term study on the maintenance of remission in adult patients with EoE has convincingly demonstrated superiority of both doses (0.5 mg and 1 mg) of budesonide orodispersible tablets over placebo. Significantly more patients in the 0.5 mg BID (73.5%) group and the 1 mg BID (75.0%) group were free of treatment failure at week 48 compared to placebo (4.4%).

The results of almost all endpoints used (both the primary, the confirmatory evaluated secondary (histological relapse, change in peak eos, clinical relapse, EEsAI PRO score, deep remission) as well as the exploratory secondary) have shown highly statistically significant superiority over placebo for both doses of the investigational compound. As far as evaluated, all results not only demonstrate statistical significance, but also a high level of clinical relevance with a huge magnitude of effect against placebo.

The results have also shown a vast robustness with regard to the evaluation of subgroups, based on several disease characteristics at baseline, and region/country of conduct of the study. 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 (and those to potentially be presented in addition from the long-term data), an influence of gender and age on the rates of relapses appears unlikely.

An effect on the long-term sequelae of EoE, namely stricture formation (as assessed by endoscopy) or the occurrence of food impaction events could not be demonstrated but might be due to a relevantly longer time needed for observation for this type of endpoint. Similarly, the effects of the compound – even in the 48-week treatment – on the alteration of eating behaviour appear to be clinically not fully relevant, although some effect could be detected, in the relevant subscores of the EEsAI-PRO.

The data are in accordance with the protocol assistance given during early development and considering results on histological remission and the fact that patients did not only maintain a state of being free of symptoms in a high rate, but also had a relevant superior experience of their quality of life in the long-term, as compared to the patients treated with placebo the efficacy of Jorveza for the long-term treatment can be considered demonstrated.

The most stringent secondary endpoint "deep disease remission", i.e., deep clinical, deep endoscopic and histological remission showed a clinically relevant higher efficacy in the 1 mg BID group (52.9%) compared to the 0.5 mg BID group (39.7%), indicating that a higher dose of budesonide is of advantage to achieve and maintain deep disease remission. A maintenance dose of 1 mg budesonide twice daily is recommended for patients with a long-standing disease history and/or high extent of esophageal inflammation in their acute disease state because relevantly higher rates of being free from treatment failure were achieved in these subgroups (80% vs 70%, and 80% vs 68%).

The open-label extension of the study (as well as the open-label re-treatment in part of the patient population) was ongoing at the time of submission of the presented evaluation. Currently, the duration of maintenance therapy is determined by the treating physician which is acceptable. As final data from this study (BUL-2/EER) could however add relevant information to the prescriber, the marketing authorisation holder is recommended to submit the final study report for regulatory assessment once available.

The applicant has committed to further investigate the compound also in children, which was, however, not the subject of the current submission. The applicant is, however, encouraged to further engage into the development in children.

2.5.4. Conclusions on the clinical efficacy

Clinical efficacy of the compound – while being demonstrated already for the short-term treatment up to 12 weeks, in order to achieve a state of remission – has now also been convincingly demonstrated for the long-term treatment (at either 0.5 mg BID or 1 mg BID depending on individual clinical requirement), showing that patients in remission can be kept in such state for at least 1 year in a high proportion. Available data from long-term open-label extension studies beyond 1 year support the conclusion that remission can be kept up for even relevantly longer duration.

As stated already in the assessment of the initial marketing authorisation there is a high unmet medical need for the development of an age appropriate pharmaceutical formulation in children. The MAH is recommended to further engage in this development.

2.6. Clinical safety

This submission mainly concerns a line extension, and a change in posology with extension of the treatment duration (unlimited). The documentation of safety for the short-term treatment, as previously submitted, is therefore not relevantly altered.

Patient exposure

In the clinical trials in this submission (both short-term, as well as long-term studies), 368 subjects of patients with EoE (i.e. 31 healthy subjects and 337 patients) received at least 1 dose of budesonide; of those, 318 patients with EoE were exposed to budesonide orodispersible tablets. The numbers are displayed in Table 20, however, this table excludes the numbers from study BUL-6/BIO.

Table 20 Overall extent of exposure in clinical trials in this submission (excluding study BUL-6/BIO)

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]	–
Pivotal clinical study BUL-2/EER		
OLI-phase	181[b]	–
DB phase	92[c]	68
Supportive clinical study BUU-2/EEA	57[d]	19
TOTAL	**350**	**116**

BID: twice daily; BUL: budesonide orodispersible tablet; BUU: budesonide viscous suspension; DB: double blind; OLI: open-label induction; NA: not applicable.
[a] patients who received Placebo in the DB phase and received BUL 1 mg BID in the OLI phase
[b] 181 patients received BUL 1 mg BID in the OLI phase. Of these, 138 continued to randomisation in the DB phase. A further 66 patients from study BUL-1/EEA were randomised to the DB phase of study BUL-2/EER.
[c] patients who received BUL 0.5 mg or BUL 1.0 mg in BUL-2/EER study without previous participation in BUL-1/EEA (an additional 44 patients treated with BUL in BUL-1/EEA continued to BUL-2/EER study). Note: These 92 patients are already counted in the 181 patients of the OLI phase and are not counted twice in the total.
[d] all patients who received BUL (budesonide orodispersible tablets) or BUU (budesonide viscous suspension)

For the DB phase of the newly submitted study BUL-2/EER, the exposure was relevantly different between the active treatment groups and the placebo group. BUL 0.5mg BID was administered on average on 308 days (SD: 87.0 days, median: 337 days), BUL 1mg BID was administered on average on 310 days (SD: 80.3 days, median: 336 days), and placebo medication was administered on average on 164 days (SD: 132.9 days, median: 97 days) in the FAS-DB.

From the overall number of 204 patients from the DB phase, 82 patients entered the OLRI phase. The exposure in the OLE phase of study BUL-2/EER with the data lock-point 29 October 2019 comprises 186 patients from the 3 groups of the DB phase during the first year (OLE 1), and 159 patients for the second year (OLE 2). The mean duration of IMP intake during OLE 1 phase was 328 days. At the time of the data lock-point, 94 patients have already completed the OLE-2 phase.

Adverse events

Adverse events (AEs) during OLI Phase of Study BUL-2/EER:

All of the following analyses are based on the safety analysis set OLI phase (SAF-OLI): In total, 300 AEs occurred in 123 patients (68.0%); 52 AEs in 35 patients (19.3%) were classified as pre-OLI treatment AEs, 5 AEs in 4 patients (2.2%) were classified as post-OLI treatment AEs, and 243 AEs in 112 patients (61.9%) were classified as OLI treatment emergent adverse events (TEAEs).

A total of 95 AEs in 60 patients (33.1%) were rated as adverse drug reactions (ADRs), as a causal relationship with budesonide was considered at least possible. All reported ADRs were OLI treatment emergent ADRs.

Table 21 shows the display of AEs during OLI phase according to SOC.

Table 21 Patients with at least one OLI treatment-emergent AE by SOC

System Organ Class	Number (%) of patients with at least one OLI TEAE BUL 1mg BID (n = 181)
Blood and lymphatic system disorders	2 (1.1%)
Cardiac disorders	1 (0.6%)
Ear and labyrinth disorders	1 (0.6%)
Eye disorders	3 (1.7%)
Gastrointestinal disorders	40 (22.1%)
General disorders and administration site conditions	13 (7.2%)
Infections and infestations	41 (22.7%)
Injury, poisoning and procedural complications	2 (1.1%)
Investigations	8 (4.4%)
Metabolism and nutrition disorders	1 (0.6%)
Musculoskeletal and connective tissue disorders	11 (6.1%)
Nervous system disorders	31 (17.1%)
Psychiatric disorders	7 (3.9%)
Renal and urinary disorders	5 (2.8%)
Reproductive system and breast disorders	2 (1.1%)
Respiratory, thoracic and mediastinal disorders	14 (7.7%)
Skin and subcutaneous tissue disorders	4 (2.2%)
Vascular disorders	1 (0.6%)

OLI TEAE: open-label induction treatment-emergent adverse event

The next table shows the AEs according to preferred term (PT) when occurring in at least 3 patients:

Table 22 Patients with at least one OLI treatment-emergent AE by PT (SAF-OLI - only PTs occurring in at least 3 patients)

Preferred term	Number (%) of patients with at least one OLI TEAE BUL 1mg BID (n = 181)
Abdominal pain	4 (2.2%)
Abdominal pain upper	3 (1.7%)
Dyspepsia	6 (3.3%)
Gastritis erosive	3 (1.7%)
Gastroesophageal reflux disease	9 (5.0%)
Nausea	4 (2.2%)
Esophageal food impaction	3 (1.7%)
Toothache	3 (1.7%)
Vomiting	3 (1.7%)
Condition aggravated (EoE)	5 (2.8%)
Nasopharyngitis	11 (6.1%)
Suspected candidiasis adverse event*	24 (13.3%)
Esophageal candidiasis	16 (8.8%)
Oral candidiasis	2 (1.1%)
Oral fungal infection	1 (0.6%)
Oropharyngeal candidiasis	8 (4.4%)
Vulvovaginal candidiasis	1 (0.6%)
Blood cortisol decreased	4 (2.2%)
Lipase increased	3 (1.7%)
Back pain	5 (2.8%)
Pain in extremity	3 (1.7%)
Dysgeusia	3 (1.7%)
Headache	28 (15.5%)
Cough	3 (1.7%)
Dry throat	3 (1.7%)
Oropharyngeal pain	6 (3.3%)

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 "Suspected candidiasis adverse event" category.

Adverse events during DB phase of Study BUL-2/EER

In total, including post-induction pre-DB AEs and DB TEAEs, 259 AEs occurred in 57 patients (83.8%) taking BUL 0.5mg BID, 227 AEs occurred in 59 patients (86.8%) taking BUL 1mg BID, and 168 AEs occurred in 61 patients (89.7%) taking Placebo. A total of 34 AEs in 22 patients (32.4%) taking BUL 0.5mg BID, 34 AEs in 22 patients (32.4%) taking BUL 1mg BID, and 3 AEs in 3 patients (4.4%) taking Placebo were rated as ADRs, as a causal relationship with DB investigational medicinal product (IMP) was considered at least possible. An overview on AE occurrence and ADRs is given in Table 23 **Overview of adverse events in the DB phase – BUL-2/EER (SAF-DB)**.

Table 23 Overview of adverse events in the DB phase – BUL-2/EER (SAF-DB)

	Number (%) of patients experiencing at least one AE or ADR		
	BUL 0.5 mg BID (n = 68)	BUL 1 mg BID (n = 68)	Placebo BID (n = 68)
AEs total	57 (83.8%)	59 (86.8%)	61 (89.7%)
ADRs[a]	22 (32.4%)	22 (32.4%)	3 (4.4%)
DB TEAE	57 (83.8%)	59 (86.8%)	61 (89.7%)
DB TE ADR	22 (32.4%)	22 (32.4%)	3 (4.4%)
Post-OLI pre DB-treatment AE	1 (1.5%)	1 (1.5%)	5 (7.4%)

[a] Causal relationship with IMP assessed as at least possible by the investigator.

Table 24 gives an overview on the AEs according to system organ class (SOC).

Table 24 Patients with at least one treatment-emergent adverse event in the double blind phase by SOC – study BUL-2/EER (SAF-DB)

System Organ Class	Number (%) of patients with at least one DB TEAE		
	BUL 0.5 mg BID (n = 68)	BUL 1 mg BID (n = 68)	Placebo (n = 68)
Any TEAE	**57 (83.8%)**	**59 (86.8%)**	**61 (89.7%)**
Blood and lymphatic system disorders	1 (1.5%)	---	---
Cardiac disorders	---	1 (1.5%)	---
Ear and labyrinth disorders	1 (1.5%)	---	---
Eye disorders	5 (7.4%)	5 (7.4%)	7 (10.3%)
Gastrointestinal disorders	19 (27.9%)	23 (33.8%)	10 (14.7%)
General disorders and administration site conditions	17 (25.0%)	14 (20.6%)	45 (66.2%)
Hepatobiliary disorders	1 (1.5%)	---	---
Immune system disorders	1 (1.5%)	1 (1.5%)	1 (1.5%)
Infections and infestations	40 (58.8%)	38 (55.9%)	23 (33.8%)
Injury, poisoning and procedural complications	6 (8.8%)	4 (5.9%)	3 (4.4%)
Investigations	4 (5.9%)	2 (2.9%)	---
Metabolism and nutrition disorders	1 (1.5%)	2 (2.9%)	---
Musculoskeletal and connective tissue disorders	8 (11.8%)	5 (7.4%)	7 (10.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.5%)	1 (1.5%)	---
Nervous system disorders	17 (25.0%)	14 (20.6%)	6 (8.8%)
Psychiatric disorders	4 (5.9%)	1 (1.5%)	2 (2.9%)
Renal and urinary disorders	3 (4.4%)	1 (1.5%)	---
Reproductive system and breast disorders	---	3 (4.4%)	2 (2.9%)
Respiratory, thoracic and mediastinal disorders	4 (5.9%)	6 (8.8%)	2 (2.9%)
Skin and subcutaneous tissue disorders	2 (2.9%)	3 (4.4%)	2 (2.9%)
Surgical and medical procedures	2 (2.9%)	3 (4.4%)	1 (1.5%)
Vascular disorders	1 (1.5%)	4 (5.9%)	1 (1.5%)

Clear imbalances for the rates of occurrence of AEs to the disadvantage for active treatment according to SOC can be detected for gastrointestinal disorders, infections and infestations, and for nervous system disorders, whereas an imbalance to the disadvantage of placebo is seen in the SOC general disorders and administration site conditions.

The following Table 25 shows the AEs displayed according to PT occurring in at least 3 patients.

Table 25 Patients with at least one treatment-emergent adverse event in the double blind phase by PT – study BUL-2/EER (SAF-DB - only PTs occurring in at least 3 patients in one treatment group)

MedDRA PT	Number (%) of patients with at least one DB TEAE		
	BUL 0.5 mg BID (n = 68)	BUL 1 mg BID (n = 68)	Placebo (n = 68)
Any TEAE	57 (83.8%)	59 (86.8%)	61 (89.7%)
Blepharitis	3 (4.4%)	2 (2.9%)	1 (1.5%)
Diarrhoea	5 (7.4%)	2 (2.9%)	---
Dyspepsia	3 (4.4%)	7 (10.3%)	3 (4.4%)
Dysphagia	7 (10.3%)	---	2 (2.9%)
Oesophageal food impaction	---	3 (4.4%)	2 (2.9%)
Chest pain	4 (5.9%)	2 (2.9%)	1 (1.5%)
Condition aggravated	11 (16.2%)	8 (11.8%)	44 (64.7%)
Bronchitis	1 (1.5%)	4 (5.9%)	---
Gastroenteritis	3 (4.4%)	5 (7.4%)	1 (1.5%)
Influenza	3 (4.4%)	3 (4.4%)	2 (2.9%)
Nasopharyngitis	25 (36.8%)	20 (29.4%)	19 (27.9%)
Suspected candidiasis adverse event[a]	13 (19.1%)	10 (14.7%)	---
Balanitis candidas	1 (1.5%)	---	---
Genital candidiasis	1 (1.5%)	---	---
Oesophageal candidiasis	7 (10.3%)	3 (4.4%)	---
Oral candidiasis	7 (10.3%)	4 (5.9%)	---
Oropharyngeal candidiasis	3 (4.4%)	4 (5.9%)	---
Vulvovaginal candidiasis	---	1 (1.5%)	---
Pharyngitis	3 (4.4%)	2 (2.9%)	1 (1.5%)
Urinary tract infection	3 (4.4%)	4 (5.9%)	---
Back pain	3 (4.4%)	1 (1.5%)	1 (1.5%)
Headache	14 (20.6%)	10 (14.7%)	5 (7.4%)
Anxiety	3 (4.4%)	1 (1.5%)	---
Asthma	4 (5.9%)	4 (5.9%)	---

[a] Patients with more than one candidiasis AE may appear several times in different subcategories, but are counted only once in the "Suspected candidiasis adverse event" category.

The display of the causality assessment evaluation, and thus the ADR table is shown in the following Table 26.

Table 26 Number of adverse drug reactions (considered possibly related to study medication by the investigator) in the double blind phase by SOC and PT – study BUL-2/EER (SAF-DB)

System Organ Class MedDRA PT	Number of adverse drug reactions (at least possible causal relationship to IMP)		
	BUL 0.5 mg BID	BUL 1 mg BID	Placebo
Total number ADRs	**34**	**34**	**3**
Eye disorders	**1**	**1**	**1**
Blepharitis	1	---	---
Cataract nuclear	---	---	1
Dry eye	---	1	---
Gastrointestinal disorders	**5**	**5**	---
Dry mouth	1	1	---
Dyspepsia	1	1	---
Dysphagia	2	---	---
Gastric ulcer	---	1	---
Glossodynia	---	1	---
Hypoaesthesia oral	---	1	---
Tongue disorder	1	---	---
General disorders and administration site conditions	**2**	**2**	---
Chest discomfort	1	---	---

System Organ Class MedDRA PT	Number of adverse drug reactions (at least possible causal relationship to IMP)		
	BUL 0.5 mg BID	**BUL 1 mg BID**	**Placebo**
Chest pain	---	1	---
Fatigue	---	1	---
Sensation of foreign body	1	---	---
Infections and infestations	**18**	**14**	**1**
Gastrointestinal viral infection	---	---	1
Oesophageal candidiasis	6	3	---
Oral candidiasis	7	6	---
Oropharyngeal candidiasis	4	4	---
Pharyngitis	1	---	---
Retinitis	---	1	---
Investigations	**3**	**2**	---
Blood cortisol decreased	2	2	---
Vitamin D decreased	1	---	---
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	---	**1**	---
Lipoma	---	1	---
Nervous system disorders	**3**	**3**	---
Disturbance in attention	---	1	---
Dysgeusia	---	1	---
Headache	2	1	---
Migraine	1	---	---
Reproductive system and breast disorders	---	**1**	**1**
Adipomastia	---	1	---
Vulvovaginal pruritus	---	---	1
Respiratory, thoracic and mediastinal disorders	---	**1**	---
Oropharyngeal pain	---	1	---
Skin and subcutaneous tissue disorders	**2**	**3**	---
Angioedema	1	---	---
Dermatitis allergic	---	1	---
Eczema	---	1	---
Erythema	---	1	---
Urticaria	1	---	---
Vascular disorders	---	**1**	---
Hypertension	---	1	---

Suspected candidiasis AEs affected overall 13 patients (19.1%) in the BUL 0.5mg BID group, 10 patients (14.7%) in the BUL 1mg BID group, and no patients in the Placebo group. Some patients had more than one candidiasis infection in different subcategories. The balanitis candidiasis, genital candidiasis and vulvovaginal candidiasis were assessed by the investigator as not related to the IMP, one oesophageal candidiasis and one oral candidiasis AE were assessed as unlikely related to the IMP, all other candidiasis AEs were assessed with at least possible relationship to the IMP. During the initial application, the applicant has claimed that the rate of candidiasis events was reported high also due to the fact that all investigators had been instructed to search for the respective events, and that any deterioration was also leading to the suspicion of – besides the deterioration of the underlying disease –oesophageal candidiasis. This has indeed been confirmed in additional analyses submitted. Nevertheless, oesophageal candidiasis remains the most important ADR also in long-term treatment with a rate of 6.6% in the double-blind phase of study BUL-2/EER, and a rate of 14% in the open-label extension phase, as reported by the presented interim analyses.

Serious adverse events/deaths/other significant events

In the SAF-OLI, which includes pre-OLI, on OLI, and post-OLI-FU events, 3 serious adverse events (SAEs) occurred in 3 patients (1.7%). One SAE occurred pre-OLI treatment (SAE PT: depression), and 2 SAEs were OLI treatment-emergent (SAE PTs: fibula fracture, viral tracheitis). All 3 SAEs were assessed by investigator as not related to IMP, and the reason for classifying the AE as serious was hospitalisation. There was also one SAE in a screening failure patient. This patient experienced Mallory-Weiss-Syndrome.

All events were assessed as not related and were resolved at the time of last reporting.

In the SAF-DB period of study BUL-2/EER, which includes post-induction pre-DB, on DB, post-DB pre-OL, and post-DB-FU events, 4 SAEs occurred in 3 patients (4.4%) in the BUL 0.5mg BID group (SAE PTs: cartilage injury, upper limb fracture, sinusitis, inguinal hernia), one SAE occurred in one patient (1.5%) in the BUL 1mg BID group (SAE PT: skull fracture), and no SAE occurred in the Placebo group. All 5 SAEs were DB treatment-emergent and assessed by investigator as not related to IMP.

Table 27 Serious adverse events – BUL-2/EER (SAF-DB)

Patient No.	Sex	Age (years) categorized [a]	SAE (preferred term)	Severity	Causality	Time (days) since start of DB treatment[b]	Premature termination[c] (reason)
BUL 0.5 mg BID							
	m	31-35	Cartilage injury	Moderate	Not related	Not evaluable	No
	m	51-55	Upper limb fracture	Moderate	Not related	230	No
	m	66-70	Sinusitis	Moderate	Not related	255	No
	m	66-70	Inguinal hernia	Mild	Not related	Not evaluable	No
BUL 1 mg BID							
	f	26-30	Skull fracture	Severe	Not related	201	No
Placebo							
---	---	---	---	---	---	---	---

a Age at baseline
b Start date of AE was considered, not start date of seriousness
c From DB treatment phase

Note: All SAEs were treatment-emergent in the DB phase and included post-induction pre-DB, on DB, post-DB pre-OL, and post-DB-FU events

The assessment of causality is agreed with after review of the case narratives.

There were no deaths during the study.

The interim evaluation of the open-label extension phase of study BUL-2/EER submitted during the evaluation phase showed the occurrence of the following SAEs (Table 28):

Table 28 OLE treatment-emergent serious adverse events by SOC and PT (SAF-OLE) - DLP 29 Oct 2019

		Treatment group		
		Total		
		Entries (N)	Patients (N)	Patients (%)
System Organ Class (SOC)	**Preferred term (MedDRA)**			
	Number of Patients at Risk		186	100.0
Ear and labyrinth disorders	Deafness unilateral	1	1	0.5
	Total	1	1	0.5
Gastrointestinal disorders	Oesophageal food impaction	1	1	0.5
	Total	1	1	0.5
Infections and infestations	Appendicitis	1	1	0.5
	Cellulitis staphylococcal	1	1	0.5
	Sinusitis	1	1	0.5
	Total	3	3	1.6
Injury, poisoning and procedural complications	Hand fracture	1	1	0.5
	Ligament rupture	1	1	0.5
	Total	2	2	1.1
Nervous system disorders	Intracranial pressure increased	1	1	0.5
	Nervous system disorder	1	1	0.5
	Total	2	2	1.1
Respiratory, thoracic and mediastinal disorders	Pleurisy	1	1	0.5
	Total	1	1	0.5
Surgical and medical procedures	Surgery	1	1	0.5
	Total	1	1	0.5
Total	Total	11	10	5.4

Due to the interim character of the submitted data, and the fact that only single events were reported, a final conclusion on causality could not be drawn at this point of time.

Laboratory findings

The applicant provided listings and tables of statistics of laboratory values with regard to means/mean changes from baseline, frequencies of values within, above, and below the normal range, as well as shift tables for changes. As seen in the previously conducted studies, the most pronounced effects were seen on eosinophil counts.

There was also a slight imbalance for the decrease of cortisol, especially for morning cortisol. The applicant presented a detailed analysis of patients who showed shifts towards low cortisol (below the lower limit of normal (LLN; i.e., 6.2 µg/dL) during the OLI and DB phase of study BUL-2/EER. Although some discrepancies in the analysis were noted, it is agreed with the applicant that most of cases of reduced cortisol do show levels very close to normal (between 5-6 µg/dl), and there is only 1 case in each of the trial phases for which a level at or below 1 µg/dl was shown (and both cases received the

high dose). Overall, in the clear majority of the observed morning (8:00-9:00 a.m.) serum cortisol level values below the LLN were assessed by the investigator as being not clinically relevant.

The parameters measuring bone metabolism did not show relevant changes.

Safety in special populations

No analyses in relevant subpopulations or special populations are presented. An analysis of AEs in patients with older age (those above 65, 75, or even 85) appeared not sensible for the initial submission, and is also not considered sensible for the later submission of the long-term study, because the overall number of such patients was too low (in fact the oldest patient was 69 years of age). The applicant has analysed an age cut-off at 35 years for the initial submission. 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 initial clinical development programme 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

For the newly submitted data the number of AEs attributed to the SOC "immune system disorders" was one in each of the treatment arms and there was no event in this SOC for the evaluation of ADRs.

Some regrouping and a re-evaluation of the frequency of events has been proposed for the SmPC/PL, which is acceptable.

Safety related to drug-drug interactions and other interactions

No drug-drug interactions study was performed in support of this application.

With regard to potential changes in the safety profile by drug-drug interactions, the MAH referred, in the context of the initial MAA, to theoretical considerations only and the data from pharmacovigilance with their capsule formulations used in inflammatory bowel disease (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 AEs reported for these cases were also mostly related to the endoscopic procedures performed. A conclusion with regard to the causation of AEs by concomitant medication cannot be drawn.

Discontinuation due to adverse events

Overall, 7 AEs in 7 patients (10.3%) in the BUL 0.5mg BID group, 9 AEs in 8 patients (11.8%) in the BUL 1mg BID group, and 43 AEs in 42 patients (61.8%) in the Placebo group led to discontinuation of DB IMP. The AEs leading to withdrawal are displayed in the following table:

Table 29 Patients with AEs leading to discontinuation of study medication during the double blind treatment phase – study BUL-2/EER (SAF-DB)

	Number of AEs leading to withdrawal of DB IMP		
System Organ Class MedDRA PT	**BUL 0.5 mg BID (n = 68)**	**BUL 1 mg BID (n = 68)**	**Placebo (n = 68)**
Patients with any AE leading to discontinuation	**7**	**9**	**43**
Gastrointestinal disorders	---	---	**2**
Oesophageal food impaction	---	---	2
General disorders and administration site conditions	**7**	**6**	**41**
Chest pain	---	1	---
Condition aggravated	7	5	41
Infections and infestations	---	**1**	---
Retinitis	---	1	---
Respiratory, thoracic and mediastinal disorders	---	**1**	---
Oropharyngeal pain	---	1	---
Skin and subcutaneous tissue disorders	---	**1**	---
Dermatitis allergic	---	1	---

N = number of patients

Withdrawals were mainly related to the aggravation of the underlying condition. Other events leading to withdrawal were only singular in occurrence, and conclusions are therefore difficult to take.

Post marketing experience

The MAH included two PSURs into the submission.

In the period from 08 January 2018 to 07 January 2019 (i.e. in the periods covered by PSUR 2018 from 08 January 2018 to 07 July 2018 and PSUR 2019, (08 July 2018 to 07 January 2019)), budesonide orodispersible tablets were used for an estimated 7,917 patient treatment cycles.

In the periods covered by both PSURs, there were no changes to the reference safety information of Jorveza.

During the period covered by the most recent PSUR 2019, a total of 182 suspected ADRs in 83 patients associated with intake of budesonide (all budesonide dosage forms, i.e. Jorveza 1mg orodispersible tablets, Budenofalk 3 mg gastro-resistant capsules, 9 mg gastro-resistant granules and 2 mg rectal foam) were reported to the MAH. A total of 152 ADRs in 69 patients were related to the intake of Budenofalk (all three dosage forms), whereas 30 ADRs in 14 patients were related to the intake of Jorveza. Of the ADRs reported for Jorveza, 1 reaction (PT: angioedema) was serious and unlisted, 1 reaction (PT: rash generalised) serious and listed. In addition, 22 non-serious, unlisted and 6 non-serious, listed ADRs have been documented. No reports on deaths were received.

Most frequently, ADRs relating to the use of Jorveza were reported in the SOC Respiratory, thoracic and mediastinal disorders (7 ADRs in 4 patients), followed by Gastrointestinal disorders (6 suspected

ADRs in 4 patients), and Infections and infestations (4 ADRs in 4 patients). There were 6 reports of off-label use.

The safety information reviewed in the PSURs are in line with the known safety profile of Jorveza and did not change the benefit-risk profile.

2.6.1. Discussion on clinical safety

In support of the present application, the applicant has filed a new study (BUL-2/EER), documenting the long-term treatment over a duration of 48 weeks. The study also included an open-label induction part, with the documentation of short-term treatment for 6 weeks in 181 additional patients, which exceeds already the total number of patients assessed during the initial submission.

A total of 138 patients from the OLI phase of the study were included into the following double-blind part of study BUL-2/EER, documenting long-term treatment for the prevention of relapse. The study also included a number of 66 patients transferred from the short-term efficacy trial BUL-1/EEA.

The DB phase of the study included a total of 204 patients treated (as scheduled) for 48 weeks, and therefore relevantly extending the documented length of exposure. The number of patients with a documentation of long-term treatment does not fully comply with the ICH guideline E1[18] (at least 300 patients for 6 months, and at least 100 patients for 1 year). However, this is considered acceptable based on the orphan disease status of the product.

During the DB phase of the newly submitted study BUL-2/EER, the mean days on investigational compound was significantly different between the active treatment groups, and the placebo group, with about only half of the time spent on study drug for the placebo group.

Although a full evaluation of safety is somewhat hampered by the fact that the OLI phase was not controlled, the OLI phase of the study BUL-2/EER very closely reflects the observations of the earlier short-term studies, in terms of nature, frequency, and severity of AEs.

In similar way, the number and type of AEs observed during long-term treatment, at least for those events occurring more frequently than only once or twice, largely resemble the observations of the short-term treatment studies.

The main type of AEs occurs in the SOC "gastrointestinal disorders", with a wide range of "functional" complaints, but also with uncommon occurrence of erosive gastritis and gastric ulcer. Consequently, the following ADRs have been added in the SmPC with a frequency uncommon: abdominal pain, dry mouth, dysphagia, erosive gastritis, gastric ulcer, glossodynia and lip edema. Dyspepsia is added with a frequency common and upper abdominal pain moved from frequency common to uncommon.

The highest frequency of AEs is again observed in the SOC "infections and infestations" with oral, pharyngeal, and oesophageal candidiasis taking the highest share of AEs in the actively treated population, while no such events were observed in the placebo group. During the long-term treatment (both DB and OLE phases) the investigators were not instructed to search for (especially oesophageal) candidiasis events with the same rigour as in the short-term study. Nevertheless, the fact that the overall frequency of such events is not increased despite the most relevantly longer observation period of study BUL-2/EER compared with the previously submitted data is considered reassuring.

[18] Guideline ICH E1 Population exposure: the extent of population exposure to assess clinical safety (CPMP/ICH/375/95)

Otherwise, common AEs were also observed for headache (which had also been observed in the short-term studies), and there was a couple of additional uncommon events such as sleep disorder, dizziness, dysgeusia, dry eye, cough, dry throat, rash, urticaria and sensation of foreign body. These uncommon ADRs have been added in section 4.8 of the SmPC.

Also a number of AE cases were observed relating to the potential systemic action of corticosteroids, such as "cortisol decreased". As reported, again, no indication is seen that systemic glucocorticosteroid effects would occur in clinically relevant numbers. Blood cortisol decreased is an already known ADR listed as common in the SmPC.

Most of the AEs (and ADRs) observed were of mild intensity, and only a couple of serious AEs occurred during the course of the OLI and DB phases of the new trial submitted. After review of the details of these cases, it is concluded that in none of these cases a clear conclusion on relatedness to the study drug can be drawn. There were no deaths during the newly submitted study.

Overall, the laboratory evaluations were unremarkable, with the most pronounced effect relating to the eosinophil count, rather reflecting pharmacodynamics activity/efficacy (or the lack thereof) than any safety related issue. Small decreases in serum cortisol were observed overall, and the number of patients with shifts towards low cortisol values was consistently higher in the active treatment groups. From the data submitted, however, the clinical relevance of these events appears doubtful. There appear to be no consistent effects on markers of bone turnover.

During the reporting period of PSUR 2019, no changes to the reference safety information have been made, and questions arose with regard to the occurrence of especially SAEs from clinical trials. These concerns have adequately been addressed, especially with regard to the additional submission of the updated safety analysis of the ongoing long-term extension study. Furthermore the marketing authorisation holder is recommended to submit the final evaluation from the OLRI and OLE phases of study BUL-2/EER for regulatory assessment as soon as available.

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

Assessment of paediatric data on clinical safety

No paediatric data are available at this time point.

2.6.2. Conclusions on the clinical safety

The submission of the long-term study BUL-2/EER has broadened the safety database for the compound under evaluation in relevant way. Both phases of the trial that have been presented (the OLI and the DB phase) have largely confirmed the overall acceptable safety profile of the compound, being unlikely to exert the typical "systemic" effects of corticosteroids. However, the known potential to cause a relevant number of fungal infections of the upper GI tract has also been confirmed, but the fear of relevantly increased rates of these infections in long-term treatment could not be verified. To the contrary, the rate of occurrence of these events appeared to be in the same level as in the short-term studies submitted previously and can be adequately managed with existing wordings in the product information. 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. A couple of other events have also been detected, either being identified as ADR by the investigators, or occurred more frequently in the placebo group, as compared to the active group. The SmPC is updated to reflect these ADRs as uncommon.

Overall, as for other formulations of budesonide to be administered in the gastrointestinal tract, the safety profile is considered 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. This is adequately reflected in the product information.

Although the safety profile and specific risks associated with the administration of budesonide (glucocorticosteroids) are considered known and thoroughly described in the literature, the marketing authorisation holder is recommended to provide the safety data from the two subsequent phases of study BUL-2/EER for regulatory assessment as soon as available.

2.7. Risk Management Plan

Safety concerns

The applicant justified the removal of all the safety concerns initially included in the RMP following an update to align to GVP V rev2. All risks have been removed based on the fact that these are appropriately described in the SmPC and that health professionals are already aware of such risks and have the appropriate measures implemented as part of clinical practice.

Therefore, no safety concerns remain in the RMP.

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable as there are no relevant changes in the wording of the package leaflet that would impact the readability of the product information.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Jorveza (budesonide) is indicated for the treatment of eosinophilic oesophagitis (EoE) in adults (older than 18 years of age). The current recommended posology is a daily dose of 2 mg of budesonide as 1-mg tablet in the morning and 1-mg tablet in the evening. The usual duration of treatment is 6 weeks. For patients who are not appropriately responding during 6 weeks the treatment can be extended to up to 12 weeks.

In the present application, a new additional strength (0.5 mg orodispersible tablet) is introduced. In addition, the previously restricted treatment duration (6-12 weeks maximum) is proposed to be extended to infinite duration (at the discretion of the treating physician).

The condition Eosinophilic Oesophagitis had not been subject of a MAA for a medicinal product before 2017. 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 with budesonide 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.

Recent research has also more clearly clarified than at the time of submission of the initial MAA that the condition most likely needs a continuous treatment, and the tendency to relapse is high in most patients.

The aim of therapy is therefore foremost the treatment and prevention of the inflammatory changes within the oesophagus, and the reduction (or cure) of the associated symptoms. Long-term treatment is aimed to keep the oesophagus inflammation free, and prevent symptoms from re-occurring.

The long-term consequences of ongoing inflammation and symptoms are the development of fibrotic changes in the oesophageal lining, narrowing of the oesophageal lumen, and formation of strictures.

The consequences for the patients are modification of eating behaviour, avoiding of certain types of food, and finally oesophageal obstruction, and need for endoscopic disimpaction, and dilatation treatment. However, the current application has not specifically aimed at demonstrating an influence on these long-term consequences.

3.1.2. Available therapies and unmet medical need

The treatment modalities available before the approval of Jorveza relied on one part on the off-label use of available medicinal products. These comprised proton-pump inhibitors, which can be used to treat EoE patients, as well as 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. This unmet medical need has been met by the introduction of the compound with the strength of 1 mg, to be used in short-term up to 12 weeks of duration.

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.

With this application, the applicant has submitted a long-term maintenance trial, documenting the need for long-term treatment. This need for long-term treatment was not fully clear at the time of filing the initial MAA, and study supporting that indeed a high rate of and usually quite fast occurrence of relapse is regularly part of the disease spectrum have only been published in the years 2018 and 2019. The application with the intent to include recommendations for an infinite treatment duration is therefore meeting an unmet medical need, which had not (yet) been addressed by the initial MA.

3.1.3. Main clinical studies

For the initial MAA, the MAH had presented study BUL-1/EEA as the one and only pivotal efficacy safety study. The study was a randomised, placebo-controlled parallel-group, multi-centre double-blind study in patients with EoE being unresponsive to PPIs to evaluate the efficacy and safety of the compound.

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.

For this grouped variation, the applicant has presented the results of study BUL-2/EER. This study was also a randomised, placebo-controlled, multi-centre, parallel-group study. It included patients brought into remission during the previous study BUL-1/EEA, but also included an open-label induction phase, in which patients similar to the study BUL-1/EEA were included, and treated with Jorveza 1 mg orodispersible tablets for 6 weeks. Patients in remission from these two "feeder studies" were then randomised 1:1:1 into treatment with 0.5 mg budesonide orodispersible tablets BID, 1 mg budesonide orodispersible tablets BID, or placebo BID. The duration of this phase of the study was 48 weeks.

The patients were observed at regular study visits for the recurrence of symptoms, and, in case such was observed, also for the recurrence of the endoscopic and histological changes in the oesophagus (at the time of the visit, or, in case no clinical deterioration was observed, at the end of the treatment period). The included patients had previously – similarly to the short-term study – partially already been treated with other treatment modalities (PPIs and dietary).

The open-label induction phase of the study comprised 181 patients (of which 126 entered the DB phase), and the DB phase of the study comprised 204 patients. The objectives of the trial were again the evaluation of efficacy as well as safety. The endpoint chosen was the occurrence of "treatment failure", consisting of either clinical relapse, histological relapse, or the occurrence of food impaction, need for endoscopic dilation, or premature withdrawal for any reason. The single components of this were defined as secondary, along with (other) evaluations of histology and or a PRO scale. These endpoints are also considered to be in accordance with the recommendations given by the CHMP.

3.2. Favourable effects

For the long-term study BUL-2/EER, the primary endpoint of being free of treatment failure was reached by more than 70% of the patients in the two active treatment groups, while only 4.4% of the patients treated with placebo remained free of treatment failure. This effect was highly statistically significant ($p<0.0001$ one-sided), with the lower boundary of the 97.5% CI for the difference showing an at least 55%-57% superiority of active treatment over placebo.

The study included a range of 5 key secondary endpoints which were tested in hierarchical manner. All of these endpoints also demonstrated high statistical significance (p-value<0.0001 one-sided) in fully consistent manner for both doses. These comprised the occurrence of histological relapse (observed in 89% in the placebo group, and 10 and 13% in the active treatment groups), the change in eosinophil infiltration (assessed by high-power field in microscopy as eos/mm^2 hpf), which showed 262 eos/hpf in the placebo group, and 38 and 21 eos/hpf in the 0.5 mg and 1 mg active treatment groups. The endpoint clinical relapse showed a rate of 10 and 7% in the 0.5 mg and 1 mg treatment groups, compared to a 60.3% relapse rate for the placebo group. The rate of "maintenance of remission" according to the EEsAI-PRO (with the criterion EEsAI-PRO≤20) was 72 and 73% for the 0.5 mg and 1 mg active treatment groups, and 20% for the placebo group. The rate of patients being in "deep remission" (=being in deep clinical, deep endoscopic, as well as histological remission) was 39 and 53% for the 0.5 mg and 1 mg active treatment groups, but 0.0% for placebo.

Similar to the short-term study, the results of the long-term study appeared to be extremely robust with regard to the demonstration of efficacy in subgroups (e.g., country, centre, path to remission, localisation and extent of inflammation at screening, history of allergic disease, and the time since the first symptoms of the disease). Subgrouping with regard to age and sex were presented as far as sensible, but did not reveal relevant differences. Further evaluations with regard to the extent of inflammation within the oesophagus, and with regard to the disease duration indicated the need for treatment recommendations with regard to dose, with the recommendation to use the higher dose in those patients with a long-standing disease history, and with more extensive inflammatory changes.

The study also showed that the median time to relapse was only 86 days for the patients in the placebo group (compared to more than 330 days in the active treatment groups), demonstrating that more than 50% of the patients can be expected to have a relapse within 3 months.

In addition, the MAH evaluated a numerous range of exploratory secondary endpoints, ranging from scales of global well-being, single symptoms, time-related evaluations, endoscopy-based evaluations, subscores of the EEsAI-PRO, as well as quality of life scores, which almost all showed highly relevant and statistically significant results.

Besides the long-term efficacy results, the OLI phase of the trial confirmed in a relatively high number of patients (181 patients included as opposed to 59 for which short-term efficacy was documented previously) that about 70% of the patients can be brought into remission within 6 weeks. This result is considered to be reassuring with regard to the earlier documentation of short-term efficacy.

Interim data available from the OLRI and OLE studies also support the above conclusions.

3.3. Uncertainties and limitations about favourable effects

As it 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 the conducted studies. This is true for the short-term treatment trial, but also for the long-term prevention trial where on the respective subscales of the EEsAI-PRO scale only minor differences in favour of active treatment were found.

Similarly, the effect on prevention of complications of the disease could not be directly evaluated, because only one patient (in the placebo group) during the course of the short-term study developed a food impaction. A similar result was observed in the long-term prevention study, where also only one patient in the placebo group developed this complication.

There are subgroups of patients for which the available information is relatively limited which relates to the female gender (only 15 patients included in the initial pivotal short-term trial were female, whereas 35 female patients were included in the long-term trial), and to elderly patients (the oldest patient included into the phase III studies was 69). However, overall, the influence of age on efficacy has been found to be negligible. Explorative evaluations of the pharmacokinetic data at the time of initial licensing 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 AEs appears unlikely.

While the initial small study conducted was not designed 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, it now appears that even 1-year data are not fully suitable to document such an effect, at least not in a population that had been in remission at the start of the observation period. The number of patients with food impaction which needed endoscopic intervention was 1 patient in the placebo group only, and none in the active treatment groups, while in the AE reporting, food impaction (without endoscopic intervention) was noted in 2 patients in the placebo group, and 3 patients in the 1 mg active dosing group, while no such case was reported for the low-dose active treatment group. Furthermore, the presented data do not directly address the question whether the long-term treatment would alter the disease course as a "disease modifying" agent including long term positive influence on the fibrotic changes in the oesophagus, and prevention of food impaction, and/or need for dilation. However, considering the clinically relevant results provided based on the primary and numerous secondary endpoints of the pivotal study this is not considered decisive for the conclusion on risk-benefit ratio in this orphan disease. The need for ongoing maintenance treatment, has therefore been sufficiently demonstrated.

3.4. Unfavourable effects

In the initial submission from the short-term data, 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 previous placebo treatment, and the rate seems to be little lower in those previously treated with active medication.

During the long-term study, however, the rate of observed (suspected and confirmed) cases of candidiasis was not relevantly further increased, and appeared to be overall rather lower than observed in the initial study, with a rate of 10.3% of oesophageal candidiasis, and of 4.4% of oropharyngeal candidiasis.

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 (5%-10% in the long-term study). The orodispersible tablets also induce the known effects of budesonide in some patients (e.g. such as headache with about 7% in short term, and 20% in the long-term), and the adverse effects "blood cortisol decreased" and hypertension (up to 5%, but at lower rates in the long-term study), which relate to the known systemic effects of all glucocorticosteroids. In the short-term study, none of any other observed AE 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.

In the long-term study, additional AEs/ADRs were identified by the applicant, relating to sleep disorder, dizziness, dysgeusia, dry eye, cough, dry throat, abdominal pain, dry mouth, dysphagia, erosive gastritis, gastric ulcer, glossodynia, lip edema, rash, urticaria and sensation of foreign body which now complement the listed ADRs in the product information. In addition, based on the evaluation of differential frequencies, biological plausibility, as well as previous inclusion in product information of other oral dosage forms of budesonide products anxiety was included as ADR in the product information with a frequency uncommon.

The vast majority of AEs 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 AEs during the short-term controlled trial, and the serious events that occurred during the OLI or DB phase of the long-term trial have been assessed as not or unlikely be related to the study drug intake. There were no deaths during the course of any of the studies.

As far as available at this point of time, the safety evaluation of the long-term extension phase of the trial BUL-2/EER confirmed the safety profile of the short-term studies, and of the double-blind phase but the MAH is recommended to present the final evaluation of the open-label extension phase of the trial BUL-2/EER as soon as available.

3.5. Uncertainties and limitations about unfavourable effects

During the short-term trial submitted for the initial MAA, for the main identified unfavourable effects, the fungal infections, the MAH 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 related to a real effect, because no culture (or other microbiological method, e.g. PCR-based methods) had been performed to exclude fungal infection, and because the biopsy specimens only covered 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. Different instructions have been given to investigators during the long-term trial, and only those events related to clinical symptoms have been reported as AEs.

The causation of upper GI symptoms such as nausea, dyspepsia and reflux complaints (and some of the additional ADRs identified in the long-term study) 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, for the time being, the events are labelled as adverse reactions.

Also, whether the few cases of hypertension are indications of systemic effects will remain uncertain, similar to the clinical meaningfulness of the "investigation-based" AEs of "cortisol decreased", and the singular cases of gastric erosions and ulcer. However, a theoretical potential for the influence of the compound on the HPA-axis is reflected in the section 4.4 of the SmPC which is considered adequate.

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 (and those to potentially be presented in addition from the long-term data), an influence of gender and age on the rates of AEs 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 of the short-term study.

Since the duration of treatment and posology is not limited in the proposed SmPC, the submitted data from the 48-week clinical trial does not describe the long-term safety of budesonide beyond one year. Whilst the submitted data base is considered to sufficiently support the proposed label, the marketing authorisation holder is recommended to submit results from the two subsequent phases of study BUL-2/EER.

3.6. Effects Table

The effect table for the short-term treatment with Jorveza in Study BUL-1/EEA can be found in the Jorveza EPAR.

The below table shows the results for the long-term treatment in the study submitted in this application, Study BUL-2/EER.

Table 30 Effects Table for the long-term treatment with Jorveza

Effect	Short Description	Unit	Treatment 0.5 mg/1 mg	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Rate of patients free of treatment failure after 48 weeks of treatment	Treatment failure was "yes", if one of the following criteria was: - Clinical relapse (see below), Histological relapse (see below), - food impaction needing endoscopic intervention, - Need for an endoscopic dilation, - Premature withdrawal for any reason	%	73.5%/75.0%	4.4%	Evidence strong High statistical significance High clinical relevance, no uncertainties	BUL-2/EER

Effect	Short Description	Unit	Treatment 0.5 mg/1 mg	Control	Uncertainties/ Strength of evidence	References
Histological relapse	Rate of patients with histological relapse, defined as peak of ≥48 eos/mm^2 hpf at DB V6/EOT	%	13.2%/10.3%	89.7%	Evidence strong High statistical significance, clinical relevance for patient well-being unclear Hence some uncertainty	BUL-2/EER
Change in peak eos	Change in the peak eos/mm^2 hpf from DB V1 to DB V6/EOT,	mean change (no.)	38/21	262	Evidence strong High statistical significance, clinical relevance for patient well-being unclear Hence some uncertainty	BUL-2/EER
Clinical relapse	- Clinical relapse, i.e., experiencing dysphagia or pain during swallowing in the past seven days (7 day recall period) of a severity of ≥4 points on a 0–10 NRS for dysphagia or pain during swallowing, respectively, confirmed by a severity of ≥4 points on at least 1 day during the subsequent week on the respective 0 10 NRS for dysphagia or pain during swallowing (24-hour recall period). - food impaction which needing endoscopic intervention, - Need for an endoscopic dilation,	%	10.3%/7.4%	60.3%	Evidence strong High statistical significance High clinical relevance, uncertainties relating to the components "food impaction needing endoscopic intervention" and "need for dilatation"	BUL-2/EER
EEsAI-PRO remission maintained	Rate of patients with a total weekly Eosinophilic Esophagitis Activity Index (EEsAI) – Patient-Reported Outcome (EEsAI-PRO) score of ≤20 at DB V6/EOT	%	72.1%/73.5%	20.6%%	Evidence strong High statistical significance High clinical relevance, no uncertainties	BUL-2/EER
Deep remission	Rate of patients in deep disease remission, i.e., deep clinical, deep endoscopic and histological remission (based on the peak number of eos per hpf), at DB V6/EOT	%	39.7%/52.9%	0.0%	Evidence strong High statistical significance High clinical relevance, no uncertainties	BUL-2/EER

Effect	Short Description	Unit	Treatment 0.5 mg/1 mg	Control	Uncertainties/ Strength of evidence	References
Time to clinical relapse	Median days until clinical relapse (see above)	Days	336/335	86	Evidence strong High statistical significance High clinical relevance, no uncertainties	BUL-2/EER
Unfavourable Effects						
Fungal infection of the oesophagus	Endoscopic diagnosis	%	4.4% (high dose) 10.3% (low dose)	0.0%	Evidence strong, final frequency to be clarified, clinical meaningfulness to be clarified	BUL-2/EER
Fungal infection of the mouth and pharynx	Endoscopic diagnosis	%	14.7% (low dose) 11.8% (high dose)	0.0%	Evidence strong, final frequency to be clarified, clinical meaningfulness to be clarified	BUL-2/EER
Upper GI tract complaints Nausea, dyspepsia, GERD etc.	Symptoms reported by patients	%	22.1% (low dose) 13.2% (high dose)	7.3%	Evidence strong, final frequency to be clarified, clinical meaningfulness moderate	BUL-2/EER
Systemic adverse effects of cortisol	Laboratory measurement/physical sign	n	<3,<3 (both doses) (<=<4%)	0	Evidence moderate, frequency rare, clinical meaningfulness unclear	BUL-2/EER
Headache	Symptoms reported by patients	%	20.6 % (low dose) 14.7% (high dose)	7.4%	Evidence strong (known effect of budesonide), frequency obvious, clinical meaningfulness moderate	BUL-2/EER
Immunological events (rash, erythema urticarial)	Skin efflorescences notified by patients (symptoms) or by physician	n	<3/<3 in both doses (<=<4%)	0	Evidence moderate (to be counted with lip oedema events in short-term trial as "immunological effect". Frequency rare, clinical meaningfulness unclear	BUL-2/EER

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 across relevant subgroups could be shown, which indicates an unexpected high robustness of the results.

The results of this controlled short-term trial have been confirmed with the open-label induction phase of the trial BUL-2/EER, achieving similar rates of remission (similarly defined as in the controlled study) for a considerably higher number of patients. However, no control group was included.

The DB phase of study BUL-2/EER was able to demonstrate that patients having been brought into remission with a 6- or 12-week course of orodispersible tablets 1 mg BID, can be reliably maintained in clinical and histological remission for a prolonged time with both doses of the product. At one year, the rates of remission were highly statistically significantly superior compared to placebo treatment, and a most clinically relevant superiority could be seen, both for the prevention of recurrence of symptoms, as well as for the endoscopic, and histological sequelae of the disease. The time to relapse was most relevantly shorter for the placebo treated group, as compared to the active treatment group. There was no statistically significant difference, or clinically relevant difference between the two doses investigated in this trial. The patients not only maintained a state of being free of symptoms in a high rate, but also had a relevant superior experience of their quality of life in the long-term, as compared to the patients treated with placebo.

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 after short term treatment, 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.

The long-term study has confirmed the positive influence on the histological picture of the EoE, demonstrating that a mucosa without relevant infiltration of eosinophils, or without eosinophil infiltration at all can be prevented in a high percentage of patients, while almost no patients under placebo did have no eosinophil infiltration at the end of the observation period.

The long-term extension study – as far as available and although open-label in trial design – could confirm the maintenance of the effects with regard to symptoms and well-being, as well as with regard to histology and endoscopy.

However, even during the long-term study, an effect on the long-term consequences of the disease could not be shown, because the number of events, such as food impaction or oesophageal dilation due to stricture formation were too low. Despite this long-term study having investigated a relevantly longer time period, this potential benefit of the treatment could not be established, which could be due to the fact that – due to the need for rescue treatment once symptom and histological relapse was confirmed – the patients were included in an open-label re-induction trial, and thus the observation period on placebo was too short.

During the short-term trial, the course of the symptom severity in the placebo group during the first 6 weeks of treatment has 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 was limited at the initial time of MA. However, even at that time, the evaluation of the safety database did not reveal completely unexpected findings, but confirmed the known AE/reaction profile of the substance budesonide. The phase II as well as the phase III 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.

This result has been confirmed with the additional trial BUL-2/EER, both in the short-term open-label treatment phase, as well as in the long-term treatment phase. While the rate of fungal infections observed can be assumed to have been mostly diagnosed on symptoms, the overall rate did not relevantly increase over time, despite the relevantly longer treatment period.

According to the currently available data on the long-term extension beyond 1 year, the safety profile appears to be similar during long-term extension also.

Other adverse reactions 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. The SmPC takes due account of all reported adverse reactions.

3.7.2. Balance of benefits and risks

The demonstrated benefits with the high superiority against the placebo 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 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 and can be addressed with routine risk minimisation measures.

3.8. Conclusions

The overall benefit risk balance of Jorveza 0.5 mg/ 1 mg orodispersible tablet is positive in the maintenance of remission of eosinophilic esophagitis in adults.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Jorveza 0.5 mg orodispersible tablet is positive in the following indication:

- Treatment of eosinophilic esophagitis (EoE) in adults (older than 18 years of age).

The CHMP therefore recommends the extension of the marketing authorisation for Jorveza subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of PSURs 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.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.

In addition, CHMP recommends the variations to the terms of the marketing authorisation, concerning the following changes:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	I, IIIA, IIIB and A

- Extension of indication to include the maintenance of remission for Jorveza (0.5 mg and 1 mg orodispersible tablets); as a consequence, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated to reflect the recommended daily dose and duration of treatment of Jorveza for the maintenance of remission, to update the list of adverse reactions and the clinical efficacy and safety information based on the results of the phase III clinical study BUL-2/EER. The relevant sections of the package leaflet are updated accordingly. In addition, a revised RMP (version 2.1) has been submitted to reflect the results of this study and to align with the GVP Module V (rev 2) template. The MAH also took the opportunity to bring the product information in line with the latest QRD template (version 10.1).

- To add a new pack-size of 200 x 1 orodispersible tablets (unit dose) in a blister for Jorveza 1 mg orodispersible tablet (EU/1/17/1254/006)

Appendix

None