# EU Risk Management Plan for

# Jorveza® 0.5 mg / 1 mg orodispersible tablets (budesonide)
# Jorveza® 0.2 mg/mL oral suspension (budesonide)

**RMP version to be assessed as part of this application:**

RMP Version number: 3.2

Data lock point for this RMP: 03 Jan 2025

Date of final sign off: 25 Sep 2025

Rationale for submitting an updated RMP: procedure EMA/X/0000257468 (EMEA/H/C/004655/X/0030)

Summary of significant changes in this RMP:

- oral suspension (0.2 mg/mL) added as new pharmaceutical form
- new indication for children of 2 to 17 years of age for oral suspension
- inclusion of additional results of BUU-5/EEA, BUL-007/BIO and BUU-008/BIO (Part II, Module SIII)
- inclusion of available post-authorisation experience (Part II, Module SV)
- corresponding update of Part II, Module SVII

QPPV name: Dr. Carsten Wieser

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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# Part I: Product(s) Overview

Table Part I.1 – Product Overview

| | |
|---|---|
| **Active substance(s)**<br>**(INN or common name)** | Budesonide |
| **Pharmacotherapeutic group(s) (ATC Code)** | A07EA06 |
| **Marketing Authorisation Applicant** | Dr. Falk Pharma GmbH |
| **Medicinal products to which this RMP refers** | 3 |
| **Invented name(s) in the European Economic Area (EEA)** | Jorveza® 0.5 mg / 1mg orodispersible tablets<br>Jorveza® 0.2 mg/mL oral suspension |
| **Marketing authorisation procedure** | centralised |
| **Brief description of the product** | Chemical class: antidiarrheals, intestinal anti-inflammatory agents, corticosteroids acting locally (ATC code A07EA06) |
| | Summary of mode of action:<br>Budesonide, as all glucocorticoids, acts primarily via the glucocorticoid receptor. In the cytoplasm, the ligand bound receptor can interact with signalling pathways involving PI3K, JNK, 14-3-3 proteins and components of the T-cell receptor signalling complex, and thereby modulate pro-inflammatory gene expression.<br>Data from clinical pharmacology studies and controlled clinical trials indicate that topical budesonide acts locally due to its affinity to the tissue and its high grade first pass liver metabolism. |
| | Important information about its composition<br>The particular advantage of budesonide in the form of orodispersible tablets is in its pharmaceutical form. The production of saliva is stimulated a few seconds after the drug is placed on the tip of the tongue. The viscosity of the saliva dampens the effervescence of the tablet supporting the release of the active ingredient. The viscous saliva/budesonide mixture is continuously swallowed. This specific mode of release of the active ingredient results in low systemic bioavailability and simultaneously in a high local anti-inflammatory effect.<br>The particular advantage of budesonide in the form of an oral suspension is that it can be administered in an individual dose appropriate to the age of children/adolescents and that it can be |

| | |
|---|---|
| | administered to children of an age when the use of orodispersible tablets is not possible. |
| **Hyperlink to the Product Information** | product information Jorveza® 0.2 mg/mL oral suspension |
| **Indication(s) in the EEA** | Current for orodispersible tablet:<br>- Jorveza® is indicated for the treatment of eosinophilic esophagitis (EoE) in adults (older than 18 years of age) |
| | Proposed for oral suspension only:<br>- Jorveza 0.2 mg/mL oral suspension is indicated for the treatment of eosinophilic esophagitis (EoE) in paediatric patients 2 to 17 years of age. |
| **Dosage in the EEA** | Current for orodispersible tablet:<br>Induction of remission<br>The recommended daily dose is 2 mg budesonide as one 1 mg tablet in the morning and one 1 mg tablet in the evening.<br>The usual duration of induction treatment is 6 weeks. For patients who are not appropriately responding during 6 weeks, the treatment can be extended to up to 12 weeks.<br>Maintenance of remission<br>The recommended daily dose is 1 mg budesonide as one 0.5 mg tablet in the morning and one 0.5 mg tablet in the evening or 2 mg budesonide as one 1 mg tablet in the morning and one 1 mg tablet in the evening, depending on the individual clinical requirement of the patient.<br>The duration of maintenance therapy is determined by the treating physician. |
| | Proposed for oral suspension only:<br>Induction of remission<br>Children 2 to 11 years of age:<br>The recommended daily dose is 1 mg budesonide to be administered as one dose of 2.5 mL suspension (corresponding to 0.5 mg budesonide) in the morning and one dose of 2.5 mL suspension (corresponding to 0.5 mg budesonide) in the evening.<br>Adolescents 12 to 17 years of age:<br>The recommended daily dose is 2 mg budesonide to be administered as two separate doses per day: one dose of 5 mL suspension (corresponding to 1 mg budesonide) in the morning and one dose of 5 mL suspension (corresponding to 1 mg budesonide) in the evening. |

| | |
|---|---|
| | The usual duration of induction treatment is 12 weeks. For patients who areappropriately responding within 12 weeks, the treatment can be extended to up to 24 weeks.<br><br>Maintenance of remission<br>Children 2 to 11 years of age:<br>The recommended daily dose is 0.5 mg budesonide to be administered as one dose of 2.5 mL suspension (corresponding to 0.5 mg budesonide) in the morning, depending on the individual clinical requirement of the patient.<br>A maintenance dose of 0.5 mg budesonide twice daily is recommended for patients with a long-standing disease history and/or high extent of oesophageal inflammation in their acute disease state, see also section 5.1 of the SmPC.<br><br>Adolescents 12 to 17 years of age:<br>The recommended daily dose is 1 mg budesonide to be administered as one dose of 5 mL suspension (corresponding to 1 mg budesonide) in the morning, depending on the individual clinical requirement of the patient.<br>A maintenance dose of 1 mg budesonide twice daily is recommended for patients with a long-standing disease history and/or high extent of oesophageal inflammation in their acute disease state, see also section 5.1 of the SmPC.<br>The duration of maintenance therapy is determined by the treating physician. |
| **Pharmaceutical form(s) and strengths** | Current: orodispersible tablet, 0.5 mg /1 mg |
| | Proposed for oral suspension only:<br>oral suspension, 0.2 mg/mL |
| **Is/will the product be subject to additional monitoring in the EU?** | No |

# Part II: Safety specification

## Part II: Module SI - Epidemiology of the indication(s) and target population(s)

**Indication: Treatment of eosinophilic oesophagitis (EoE) in adults (older than 18 years of age) and in paediatric patients 2 to 17 years of age.**
**Incidence:** EoE is believed to occur mainly in developed countries; it affects both adults and children with a general higher prevalence in adults than in children. It shows a male predominance (10). There is an increasing trend in newly diagnosed cases per year worldwide. The incidence of clinically diagnosed EoE increased significantly over the last 3 decades. Seasonal incidence is greatest in late summer and fall. EoE also appears to be a relapsing-remitting disease in a substantial proportion of patients (7)(8).

In 2005, Straumann and Simon (9) reported an average incidence of 1.438 cases of EoE per 100,000 inhabitants over a 16-year observational period in Switzerland. A marked increase in newly diagnosed cases was noted in most recent years of the study. Since EoE is a chronic condition, this increased incidence reflected increased prevalence. The authors of this study also suggested that this trend reflects a true increase in incidence and not just an increased awareness of the disease.

**Prevalence:** Mean overall (children and adults) population-based prevalence of EoE in Europe is approximately 1.6 per 10,000 persons (10).

An increased prevalence of EoE has been observed in patients with coeliac disease (11).

**Risk factors for the disease:**

EoE disease risk is multifactorial and involves genetic, immunologic and environmental factors.

There are indications that EoE may be associated with changes in the gut microbiota in early life potentially resulting from changes in diet, antibiotic exposure, Cesarean deliveries and reduced exposure to microbial disease ("hygiene hypothesis") (54).

Climatic and seasonal variation in presentation of EoE can be noted throughout the whole year (13)(14)(15)(16). Most of the available studies showed an increase in new cases of EoE during the months when air pollens are active.

An inverse association between EoE and Heliobacter pylori infection has been reported. Decrease in H. pylori has been associated with the increase of atopic conditions, including EoE (55).

**The main existing treatment options:**

Elimination diet
Dietary changes are usually more effective in children than adults.

Topical corticosteroids
Treatment with locally acting corticosteroids intended for the treatment of asthma, such as fluticasone and budesonide, were shown to be efficacious and safe in the management of EoE in many clinical trials, mainly for the induction but also for the maintenance of clinical, endoscopic and histological responses or remission of EoE.

Prednisone

Systemic corticosteroids may be useful in the management of EoE when topical corticosteroids are not effective or in patients who require rapid symptoms improvement.

Endoscopic treatment

Oesophageal dilation, if approached conservatively, may be used as an effective therapy in symptomatic EoE patients with strictures that persist in spite of pharmacologic or dietary therapy (3). Dilation successfully addresses the luminal narrowing that can complicate EoE but does not treat the underlying inflammatory process (19).

To date, it is unknown whether any treatment will impact the long-term outcome of the disease. Treatments for EoE under investigation include acid suppression, oesophageal dilatation, administration of leukotriene receptor antagonists and mast cell stabilisers, and various dietary therapies; some biologics have shown promising results, notably anti-interleukin-5 monoclonal antibodies (20)(1).

**Natural history of the indicated condition in the untreated population, including mortality and morbidity:**

The clinical presentation of EoE is strongly depending on the patient's age. In children suffering from EoE, the symptom pattern can be rather unspecific including dyspepsia, heartburn or abdominal pain as the most common symptoms. However, paediatric patients may also complain about nausea, regurgitation, chest pain or sialorrhea. Also decreased appetite, food avoidance, failure to thrive, sleep disturbances or respiratory complaints may be associated with paediatric EoE. (57) In younger children and infants, the most common symptoms reported are reflux-like symptoms, vomiting, abdominal pain, food refusal, and failure to thrive.

In the adult population, EoE is a chronic and potentially progressive condition with no significant impact on mortality (21). However, EoE and its symptoms have significant impact on patients' health-related quality of life'. Symptoms range from intermittent dysphagia for solids, food impaction, chest pain, reflux-like symptoms to decreased elasticity due to oesophageal fibrosis and stricture formation. The presence of oesophageal strictures was found to correlate with the duration of untreated disease (5).

No increased risk of malignancy was found and no eosinophilic gastroenteritis was documented (21).

**Important co-morbidities:**

Disease is more frequently associated with various atopic diseases (5), including allergic rhinitis; asthma or eczema and various food allergies (more common in children).
The incidence of atopic diseases is constantly increasing worldwide. These diseases represent the most common chronic conditions in childhood. The increasing incidence is probably dictated by the scientific and technological revolution, urbanisation and modern lifestyle (20). Mainly external factors must be considered when explaining the rapid increase in the prevalence of asthma and allergy, typical representatives of atopic diseases (21).
EoE has been associated with coeliac disease, but the evidence is still weak and more investigation is required (56).

# Part II: Module SII - Non-clinical part of the safety specification

The pharmacological, pharmacokinetic and toxicological properties of budesonide are well-known. The body of evidence published in the scientific literature was supplemented by the original studies conducted by the applicant for the development programme of other authorised formulations of budesonide. All relevant data are summarised in the Non-clinical Overview for budesonide (eCTD Module 2.4).

## Table SII.0-1 Key safety findings from non-clinical development programme

| Key Safety findings (from non-clinical studies) | Relevance to human usage |
|---|---|
| **Developmental toxicity**<br>(based on the eCTD Module 2.4, Non-clinical Overview)<br>No observed effects level (NOEL) for maternal toxicity ($F_0$ animals) was 4 µg/kg/day prior to and in the initial stages of gestation and 0.8 µg/kg/day at the late stages of gestation in rats.<br>In rabbits, the NOEL for maternal toxicity during gestation was <5 µg/kg/day.<br>Budesonide did not show a teratogenic effect but exerted a dose-dependent retardation of intrauterine growth and ossification. The NOEL for abnormalities in embryonic and neonatal development of the offspring ($F_1$ generation) was 4 µg/kg/day in rats and <5 µg/kg/day in rabbits. The abnormalities in foetal development observed in rats and rabbits are likely to be associated with the pronounced maternotoxic effects and/or the typical growth retardation and disruption that steroids are known to exert on the bone matrix structure in embryos. | Abnormalities in foetal development have been observed in animals. The relevance for human use remains unclear, but cannot be completely excluded.<br>Therefore, the use in pregnancy should be avoided unless the potential benefit justifies the potential risk of the foetus. |
| **Carcinogenicity**<br>(based on the eCTD Module 2.4, Non-clinical Overview)<br>Male rats treated with either budesonide, prednisolone, or triamcinolone acetonide in drinking water for up to 104 weeks developed a slightly increased incidence of basophilic foci and a significantly increased incidence of combined hepatocellular adenomas/carcinomas compared to controls. The same increase in incidence of liver tumours was seen after a 2-year treatment with prednisolone and triamcinolone acetonide, indicating a class-effect of corticosteroids that appears to result from the known promotion of spontaneously occurring preneoplastic liver foci by steroid hormones. | Tumours noted in non-clinical studies are most likely due to the specific steroid receptor action, increased metabolic burden and anabolic effects on the liver, effects which are also known from other corticosteroids studies in rats. Based on the available non-clinical data, no increased risk of carcinogenicity for the users of locally acting corticosteroids has been identified. Increased incidence of tumours in animal species was associated with the systemic and long-term treatment that is not expected with budesonide orodispersible tablets. |

## Part II: Module SIII - Clinical trial exposure

The clinical development program for EoE includes the following completed or ongoing clinical studies:

- Completed Study BUU-1/BIO – a phase I pharmacokinetic study of budesonide orodispersible (formerly called effervescent) tablets in EoE patients and healthy volunteers (38);
- Completed Study BUL-6/BIO - a phase I pharmacokinetic study of budesonide 0.5 mg/1 mg orodispersible tablets and budesonide 0.2 mg/mL oral suspension;
- Completed study BUL-007/BIO – a phase 1, two-period, sequential, open-label study in healthy subjects to evaluate budesonide orodispersible tablets and budesonide oral suspension using pharmacoscintigraphic imaging;
- Completed study BUU-008/BIO - an open-label, single-center, two-part trial in healthy subjects to assess the food effect and the pharmacokinetics of single and multiple doses of budesonide 0.2 mg/mL oral suspension;
- Completed Study BUL-1/EEA – a pivotal phase III randomised, double-blind, placebo-controlled, multicentre study, investigating the efficacy and tolerability of a 6-week treatment with budesonide effervescent tablets vs. placebo in adult patients with active EoE;
- Completed Study BUL-2/EER – a phase III randomised, double-blind, placebo-controlled study on the efficacy and tolerability of a 48-week treatment with two different doses of budesonide effervescent tablets vs. placebo for the maintenance of remission in adult patients with EoE;
- Completed Study BUU-2/EEA – a phase IIa randomised, double-blind, double-dummy, placebo-controlled study on the efficacy and tolerability of a 14-day treatment with budesonide effervescent tablets vs. viscous budesonide suspension in adult patients with active EoE;
- Completed Study BUU-5/EEA – a double-blind, randomized, placebo-controlled, phase II/III trial on the efficacy and tolerability of treatment with budesonide oral suspension vs. placebo in children and adolescents with eosinophilic esophagitis (58);
- Ongoing study BUL-3/EER – a double-blind, randomized phase III trial in adult and adolescent patients with eosinophilic esophagitis to prove superiority compared to placebo of an episodic and/or a continuous 48-week treatment with budesonide orodispersible tablets for maintaining clinical-histological remission;
- Ongoing study BUL-5/ESD – a double-blind, randomised, placebo-controlled, phase IIa trial on the efficacy and tolerability of an 8-week treatment with two different doses of budesonide orodispersible tablets vs. placebo for prevention of oesophageal strictures in adult patients after endoscopic submucosal dissection;
- Ongoing study BUL-8/EEA – a double-blind, double-dummy, randomized, parallel-group, non-inferiority phase III trial on the efficacy and tolerability of 2 mg once daily vs. 1 mg twice daily budesonide orodispersible tablets for induction of histological remission in adults with eosinophilic esophagitis.

**Table SIII.1: Overall extent of exposure in clinical trials in this submission**

| Clinical study | Number of subjects / patients treated | |
|---|---|---|
| | **Budesonide** | **Placebo** |
| **Clinical pharmacology study BUU-1/BIO** | **12** | **NA** |
| Healthy subjects | 12 | NA |
| Patients | 12 | NA |
| **Clinical pharmacology study BUL-6/BIO** | **18** | **NA** |
| Healthy subjects | 18 | NA |
| **Clinical pharmacology study BUL-007/BIO** | **11** | **NA** |
| Healthy subjects | 11 | NA |
| **Clinical pharmacology study BUU-008/BIO** | **18** | **NA** |
| Healthy subjects | 18 | NA |
| **Pivotal clinical study BUL-1/EEA** | **87** | **29** |
| DB phase | 59 | 29 |
| OLI phase | 28[a] | – |
| **Pivotal clinical study BUL-2/EER** | **244** | **68** |
| OLI-phase | 181[b] | – |
| DB phase | 92[c] | 68 |
| OLRI phase | 82[d] | NA |
| OLE1 phase (48-week OLE phase) | 186[e] | NA |
| OLE2 phase (96-week, prolonged OLE phase) | 166[f] | NA |
| **Supportive clinical study BUU-2/EEA** | **57** | **19** |
| Patients | 57[g] | 19 |
| **Pivotal paediatric study BUU-5/EEA** | **75** | **24** |
| DB-phase | 52 | 24 |
| OLI phase | 45[h] | NA |
| OLE phase | 62[i] | NA |
| **TOTAL** | **534** | **140** |

Only counts in **bold** letters are counted for total patient numbers

BID: twice daily; BUL: budesonide orodispersible tablet; BUU: budesonide viscous suspension; DB: double-blind; NA: not applicable; OLE: open-label extension; OLI: openlabel induction; OLRI: open-label re-induction.

[a] patients who received Placebo in the DB phase and received budesonide (ODT in study BUL-7/EEA or oral suspension in BUU-5/EEA) 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 BUL2/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] patients who received BUL 1.0 mg BID in the OLRI phase. Of these, 15 patients previously received BUL 0.5 mg BID and 10 patients previously received BUL 1.0 mg BID in the DB phase, and are not counted twice in the total. The remaining 57 patients who received Placebo in the DB phase and BUL1 mg BID in the OLRI phase are added to the total.

[e] patients who received BUL 0.5 mg BID or BUL 1 mg BID (for patients with dose escalation) in the OLE1. Note: These 186 patients have already received budesonide treatment in the DB and/or OLRI phases of the study and are not counted twice in the total.

[f] patients who received BUL 0.5 mg BID or BUL 1 mg BID (for patients with dose escalation) in the OLE2. Note: These 166 patients have already received budesonide treatment in OLE1 phase and are not counted twice in the total.

[g] all patients who received BUL (budesonide orodispersible tablets) or BUU (budesonide viscous suspension)

[h] of the 45 patients in the OLI phase, 22 received budesonide oral suspension in the DB phase and are not counted twice in the total.

[i] These patients received budesonide oral suspension in the DB and/or OLI phase and are not counted twice in the total.

Source: BUU-1/BIO (5.3.3.1), Section 10.1; BUL-6/BIO (5.3.3.1), Section 10.1; BUL-007/BIO (5.3.3.1), Section 12.1; BUU-008/BIO (5.3.3.1), Section 12.1; BUL-1/EEA (5.3.5.1) Appendix 8.2.1, Table 1.1.1.1; BUL2/EER v2.0 (5.3.5.1) Appendix 8.2.1, Table 1.1.1.1 (ALL); BUU-2/EEA (5.3.5.1), Appendix 8.2, Table 1-3; BUU-5/EEA v1.0 (5.3.5.1) Section 4.3.1

**Table SIII.2: Exposure by demographic characteristics- BUU-1/BIO**

| | | Healthy Subjects (n = 13) | Healthy Subjects[a] (n = 12) | Patients (n = 12) |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | n (%) | 6 (46.2%) | 6 (50.0%) | 10 (83.3%) |
| Female | n (%) | 7 (53.8%) | 6 (50.0%) | 2 (16.7%) |
| **Ethnic origin** | | | | |
| Caucasian | n (%) | 13 (100%) | 12 (100%) | 12 (100%) |
| **Age [years]** | Mean (SD) | 43.8 (6.7) | 44.9 (5.7) | 39.3 (13.2) |
| | Range | 31 – 53 | 34 - 53 | 20 – 62 |
| **Height [cm]** | Mean (SD) | 171.9 (7.8) | 171.3 (7.7) | 175.2 (8.9) |
| | Range | 159 - 183 | 159 - 183 | 160 – 192 |
| **Weight [kg]** | Mean (SD) | 69.53 (9.41) | 68.54 (9.09) | 79.08 (12.27) |
| | Range | 54.9 – 83.9 | 54.9 – 83.9 | 57.0 – 37.1 |
| **Body mass index [kg/m²]** | Mean (SD) | 23.43 (1.73) | 23.28 (1.73) | 25.92 (4.68) |
| | Range | 20.5 – 25.8 | 20.5 – 25.8 | 17.4 -37.1 |

n: number of healthy subjects/patients; SD: standard deviation.
[a] pharmacokinetic/pharmacodynamic (PK/PD) population only

**Table SIII.3: Exposure by demographic characteristics from study BUL-6/BIO**

| Parameter | age [years] | height [m] | weight [kg] | BMI [kg/m²] |
|---|---|---|---|---|
| N | 18 | 18 | 18 | 18 |
| Arithmetic Mean | 43.7 | 1.744 | 75.50 | 24.75 |
| Standard Deviation | 12.3 | 0.103 | 11.15 | 2.55 |
| Minimum | 20 | 1.58 | 54.0 | 20.6 |
| Median | 49.0 | 1.705 | 77.35 | 24.10 |
| Maximum | 57 | 1.90 | 99.6 | 30.0 |

| sex | | | | | | |
|---|---|---|---|---|---|---|
| female | | male | | missing | | |
| N | [%] | N | [%] | N | [%] | N total |
| FAS | | | | | | |
| 8 | 44.44 | 10 | 55.56 | 0 | 0.00 | 18 |
| PPS | | | | | | |
| 8 | 44.44 | 10 | 55.56 | 0 | 0.00 | 18 |

**Table SIII.4: Exposure by demographic characteristics from study BUL-007/BIO**

| | | OVERALL (N=11) |
|---|---|---|
| Age (years) | n | 11 |
| | Mean | 48.6 |
| | SD | 12.4 |
| | Median | 51.0 |
| | Min | 30 |
| | Max | 63 |
| Ethnicity n (%) | NOT HISPANIC OR LATINO | 11 ( 100) |
| Race n (%) | WHITE | 11 ( 100) |
| Sex n (%) | Male | 11 ( 100) |
| Height (cm) | n | 11 |
| | Mean | 175.1 |
| | SD | 5.3 |
| | Median | 175.0 |
| | Min | 168 |
| | Max | 186 |
| Weight (kg) | n | 11 |
| | Mean | 83.74 |
| | SD | 12.57 |
| | Median | 80.00 |
| | Min | 68.8 |
| | Max | 107.2 |
| BMI (kg/m²) | n | 11 |
| | Mean | 27.23 |
| | SD | 3.15 |
| | Median | 26.60 |
| | Min | 22.9 |
| | Max | 31.1 |

**Table SIII.5: Exposure by demographic characteristics from study BUU-008/BIO**

| | | **Total (n = 18)** |
|---|---|---|
| **Sex** | | |
| Male | n (%) | 11 (61.11%) |
| Female | n (%) | 7 (39.89%) |
| **Race** (White) | n (%) | 14 (77.78%) |
| Black or Afro American | | 1 (5.6%) |
| Multiple | | 3 (16.67%) |
| **Age [years]** | Mean (SD) | 35.1 (8.3) |
| | Range | 22 – 53 |
| **Height [cm]** | Mean (SD) | 172.8 (8.8) |
| | Range | 158 - 186 |
| **Weight [kg]** | Mean (SD) | 75.59 (8.3) |
| | Range | 66.1 – 95.4 |
| **BMI [kg/m²]** | Mean (SD) | 25.34 (2.27) |
| | Range | 19.8 – 29.1 |

n: number of patients; SD: standard deviation

**Table SIII.6: Exposure by demographic characteristics from study BUL-1/EEA**

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

BID: twice daily; BMI: body mass index; BUL: budesonide orodispersible tablet; DB: double blind; FAS: full analysis set; n: number of patients; SD: standard deviation.
Source: BUL-1/EEA (5.3.5.1)

**Table SIII.7: Exposure by demographic characteristics from study BUL-2/EER (FAS-DB)**

| | | BUL 0.5 mg BID (n = 68) | BUL 1 mg BID (n = 68) | Placebo BID (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/m²]** | 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 |

BID: twice daily; BMI: body mass index; BUL: budesonide orodispersible tablet; DB: double blind; FAS: full analysis set; n: number of patients; SD: standard deviation.
Source: BUL-2/EER

**Table SIII.8: Exposure by demographic characteristics- BUU-2/EEA**

| | | BUL 1 mg BID (n = 19) | BUL 2 mg BID (n = 19) | BUU 2 mg BID (n = 19) | Placebo (n = 19) | Total (n = 76) |
|---|---|---|---|---|---|---|
| **Sex** | | | | | | |
| Male | n (%) | 17 (89.5%) | 16 (84.2%) | 14 (73.7%) | 16 (84.2%) | 63 (82.9%) |
| Female | n (%) | 2 (10.5%) | 3 (15.8%) | 5 (26.3%) | 3 (15.8%) | 13 (17.1%) |
| **Race** | | | | | | |
| White | n (%) | 19 (100.0%) | 18 (94.7%) | 19 (100.0%) | 19 (100.0%) | 75 (98.7%) |
| Asian | n (%) | --- | 1 (5.3%) | --- | --- | 1 (1.3%) |
| **Age [years]** | Mean (SD) | 38.9 (12.6) | 37.2 (13.9) | 46.5 (14.1) | 36.3 (9.9) | 39.7 (13.1) |
| | Median Range | 36 (22–61) | 35 (18–69) | 47 (26–70) | 34 (23–60) | 36 (18–70) |
| **Weight [kg]** | Mean (SD) | 83.0 (16.2) | 80.7 (13.6) | 82.0 (11.7) | 75.4 (13.2) | 80.2 (13.8) |
| | Median Range | 81.8 (56.0–120.0) | 84.0 (50.0–103.0) | 82.1 (63.0–109.7) | 75.0 (55.0–97.0) | 80.0 (50.0–120.0) |
| **Height [cm]** | Mean (SD) | 180.0 (8.7) | 181.8 (9.3) | 177.7 (9.2) | 178.0 (9.9) | 179.4 (9.2) |
| | Median Range | 179 (158–195) | 182 (162–196) | 178 (161–193) | 176 (153–196) | 179 (153–196) |
| **BMI [kg/m²]** | Mean (SD) | 25.5 (4.41) | 24.3 (2.79) | 25.9 (2.35) | 23.7 (3.16) | 24.8 (3.34) |
| | Median Range | 24.3 (19.2–36.7) | 24.6 (19.1–29.2) | 25.7 (22.9–30.0) | 23.8 (19.7–31.3) | 24.4 (19.1–36.7) |

BID: twice daily; BMI: body mass index; BUL: budesonide orodispersible tablet; BUU: budesonide viscous suspension; FAS: full analysis set; n: number of patients; SD: standard deviation..

**Table SIII.9: Exposure by demographic characteristics from study BUU-5/EEA**

| | | BUU-L (n = 26) | BUU-H (n = 26) | Placebo (n = 24) | Total (n = 76) |
|---|---|---|---|---|---|
| **Sex** | | | | | |
| All patients | | | | | |
| Male | n (%) | 18 (69.2%) | 23 (88.5%) | 18 (75.0%) | 59 (77.6%) |
| Female | n (%) | 8 (30.8%) | 3 (11.5%) | 6 (25.0%) | 17 (22.4%) |
| Stratum I: age 2 to 11 years | | **(n = 12)** | **(n = 12)** | **(n = 11)** | **(n = 35)** |
| Male | n (%) | 10 (83.3%) | 10 (83.3%) | 9 (81.8%) | 29 (82.9%) |
| Female | n (%) | 2 (16.7%) | 2 (16.7%) | 2 (18.2%) | 6 (17.1%) |
| Stratum II: age 12 to <18 years | | **(n = 14)** | **(n = 14)** | **(n = 13)** | **(n = 41)** |
| Male | n (%) | 8 (57.1%) | 13 (92.9%) | 9 (69.2%) | 30 (73.2%) |
| Female | n (%) | 6 (42.9%) | 1 (7.1%) | 4 (30.8%) | 11 (26.8%) |
| **Race** | | | | | |
| All patients | | | | | |
| White | n (%) | 26 (100%) | 23 (88.5%) | 24 (100%) | 73 (96.1%) |
| Asian | n (%) | 0 (0%) | 2 (7.7%) | 0 (0%) | 2 (2.6%) |
| Other | n (%) | 0 (0%) | 1 (3.8%) | 0 (0%) | 1 (1.3%) |
| Stratum I: age 2 to 11 years | | **(n = 12)** | **(n = 12)** | **(n = 11)** | **(n = 35)** |
| White | n (%) | 12 (100%) | 9 (75%) | 11 (100%) | 32 (91.4%) |
| Asian | n (%) | 0 (0%) | 2 (16.7%) | 0 (0%) | 2 (5.7%) |
| Other | n (%) | 0 (0%) | 1 (8.3%) | 0 (0%) | 1 (2.9%) |
| Stratum II: age 12 to <18 years | | **(n = 14)** | **(n = 14)** | **(n = 13)** | **(n = 41)** |
| White | n (%) | 14 (100%) | 14 (100%) | 13 (100%) | 41 (100%) |
| **Smoking habits at Screening** | | | | | |
| All patients | | | | | |
| Not available | n (%) | 1 (3.8%) | 1 (3.8%) | 0 (0%) | 2 (2.6%) |
| Former | n (%) | 0 (0%) | 1 (3.8%) | 0 (0%) | 1 (1.3%) |
| Never | n (%) | 25 (96.2%) | 24 (92.3%) | 24 (100%) | 73 (96.1%) |
| Stratum I: age 2 to 11 years | | **(n = 12)** | **(n = 12)** | **(n = 11)** | **(n = 35)** |
| Not available | n (%) | 1 (8.3%) | 1 (8.3%) | 0 (0%) | 2 (5.7%) |
| Never | n (%) | 11 (91.7%) | 11 (91.7%) | 11 (100%) | 33 (94.3%) |
| Stratum II: age 12 to <18 years | | **(n = 14)** | **(n = 14)** | **(n = 13)** | **(n = 41)** |
| Former | n (%) | 0 (0%) | 1 (7.1%) | 0 (0%) | 1 (2.4%) |
| Never | n (%) | 14 (100%) | 13 (92.9%) | 13 (100%) | 40 (97.6%) |
| **Age [years]** | | | | | |
| All patients | Mean (SD) | 12.3 (3.8) | 11.2 (4.5) | 11.7 (3.8) | 11.7 (4.0) |
| | Range | 3 - 17 | 2 - 17 | 2 - 17 | 2 - 17 |
| Stratum I: age 2 to 11 years | | **(n = 12)** | **(n = 12)** | **(n = 11)** | **(n = 35)** |
| | Mean (SD) | 8.8 (2.3) | 7.0 (2.9) | 8.3 (2.7) | 8.0 (2.7) |
| | Range | 3 - 11 | 2 - 11 | 2 - 11 | 2 - 11 |
| Stratum II: age 12 to <18 years | | **(n = 14)** | **(n = 14)** | **(n = 13)** | **(n = 41)** |
| | Mean (SD) | 15.4 (1.1) | 14.7 (1.7) | 14.5 (1.7) | 14.9 (1.5) |
| | Range | 14 - 17 | 12 - 17 | 12 - 17 | 12 - 17 |
| **Pubertal stage at Screening** | | | | | |
| All patients | | | | | |
| Not available | n (%) | 1 (3.8%) | 0 (0.0%) | 0 (0.0%) | 1 (1.3%) |
| Pre-puberty | n (%) | 7 (26.9%) | 10 (38.5%) | 11 (45.8%) | 28 (36.8%) |
| In puberty | n (%) | 14 (53.8%) | 14 (53.8%) | 10 (41.7%) | 38 (50.0%) |
| Post-puberty | n (%) | 4 (15.4%) | 2 (7.7%) | 3 (12.5%) | 9 (11.8%) |

| | | BUU-L (n = 26) | BUU-H (n = 26) | Placebo (n = 24) | Total (n = 76) |
|---|---|---|---|---|---|
| Stratum I: age 2 to 11 years | | **(n = 12)** | **(n = 12)** | **(n = 11)** | **(n = 35)** |
| Not available | n (%) | 1 (8.3%) | 0 (0.0%) | 0 (0.0%) | 1 (2.9%) |
| Pre-puberty | n (%) | 7 (58.3%) | 9 (75.0%) | 10 (90.9%) | 26 (74.3%) |
| In puberty | n (%) | 4 (33.3%) | 3 (25.0%) | 1 (9.1%) | 8 (22.9%) |
| Post-puberty | n (%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Stratum II: age 12 to <18 years | | **(n = 14)** | **(n = 14)** | **(n = 13)** | **(n = 41)** |
| Not available | n (%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Pre-puberty | n (%) | 0 (0.0%) | 1 (7.1%) | 1 (7.7%) | 2 (4.9%) |
| In puberty | n (%) | 10 (71.4%) | 11 (78.6%) | 9 (69.2%) | 30 (73.2%) |
| Post-puberty | n (%) | 4 (28.6%) | 2 (14.3%) | 3 (23.1%) | 9 (22.0%) |
| **Height [cm] at Screening** | | | | | |
| All patients | Mean (SD) | 152 (23.9) | 152 (27.2) | 153 (23.9) | 152 (24.7) |
| | Range | 93 - 187 | 98 - 187 | 89 - 192 | 89 - 192 |
| Stratum I: age 2 to 11 years | | **(n = 12)** | **(n = 12)** | **(n = 11)** | **(n = 35)** |
| | Mean (SD) | 131 (17.3) | 128 (19.2) | 133 (18.5) | 131 (17.9) |
| | Range | 93 - 154 | 98 - 157 | 89 - 157 | 89 - 157 |
| Stratum II: age 12 to <18 years | | **(n = 14)** | **(n = 14)** | **(n = 13)** | **(n = 41)** |
| | Mean (SD) | 169 (10.7) | 172 (11.3) | 170 (11.5) | 171 (10.9) |
| | Range | 144 - 187 | 148 - 187 | 152 - 192 | 144 - 192 |
| **Weight [kg] at DB baseline** | | | | | |
| All patients | Mean (SD) | 47 (20.1) | 46 (20.6) | 46 (16.8) | 46 (19.0) |
| | Range | 14.7 - 83.3 | 14.7 - 78.7 | 11.8 - 75.0 | 11.8 - 83.3 |
| Stratum I: age 2 to 11 years | | **(n = 12)** | **(n = 12)** | **(n = 11)** | **(n = 35)** |
| | Mean (SD) | 30 (11.2) | 28 (12.7) | 32 (10.7) | 30 (11.4) |
| | Range | 14.7 – 53.6 | 14.7 – 54.5 | 11.8 – 48.7 | 11.8 – 54.5 |
| Stratum II: age 12 to <18 years | | **(n = 14)** | **(n = 14)** | **(n = 13)** | **(n = 41)** |
| | Mean (SD) | 61 (13.4) | 61 (12.0) | 57 (11.2) | 60 (12.1) |
| | Range | 37.6 – 83.3 | 43.0 – 78.7 | 42.1 – 75.0 | 37.6 – 83.3 |
| **BMI [kg/m$^2$] at Screening** | | | | | |
| All patients | Mean (SD) | 19.1 (4.4) | 18.4 (3.4) | 18.4 (2.6) | 18.7 (3.5) |
| | Range | 12.0 - 30.0 | 13.1 - 26.1 | 14.0 - 23.7 | 12.0 - 30.0 |
| Stratum I: age 2 to 11 years | | **(n = 12)** | **(n = 12)** | **(n = 11)** | **(n = 35)** |
| | Mean (SD) | 16.6 (3.2) | 16.2 (3.0) | 17.1 (2.1) | 16.6 (2.7) |
| | Range | 12.0 - 22.4 | 13.1 - 22.4 | 14.0 - 19.8 | 12.0 - 22.4 |
| Stratum II: age 12 to <18 years | | **(n = 14)** | **(n = 14)** | **(n = 13)** | **(n = 41)** |
| | Mean (SD) | 21.3 (4.2) | 20.4 (2.5) | 19.6 (2.6) | 20.4 (3.2) |
| | Range | 16.5 - 30.0 | 16.9 - 26.1 | 16.5 - 23.7 | 16.5 - 30.0 |
| **Time since first diagnosis [years]** | Mean (SD) | 3.7 (2.8) | 2.1 (2.5)[1] | 3.1 (2.9) | 3.0 (2.8)[1] |
| | Median (Range) | 3.2 (0.1-9.1) | 1.6 (0.0-9.1) | 2.9 (0.2-9.5) | 2.0 (0.0-9.5) |
| **Time since first symptoms (Duration of disease) [years]** | Mean (SD) | 6.0 (3.8) | 4.2 (3.7) | 5.0 (2.5) | 5.1 (3.4) |
| | Median (Range) | 6.6 (0.1-14.5) | 2.6 (0.9-15.8) | 4.7 (1.0-9.3) | 4.3 (0.1-15.8) |
| **Previous esophageal surgeries** | n (%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Previous EoE treatment** | | | | | |
| PPI* | n (%) | 21 (80.8%) | 21 (80.8%) | 22 (91.7%) | 64 (84.2%) |
| Topical budesonide | n (%) | 7 (26.9%) | 5 (19.2%) | 6 (25.0%) | 18 (23.7%) |
| Topical fluticasone | n (%) | 8 (30.8%) | 6 (23.1%) | 7 (29.2%) | 21 (27.6%) |
| Systemic corticosteroids | n (%) | 0 (0.0%) | 0 (0.0%) | 1 (4.2%) | 1 (1.3%) |
| Other | n (%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Endoscopic dilation | n (%) | 0 (0.0%) | 1 (3.8%) | 1 (4.2%) | 2 (2.6%) |

| | | BUU-L (n = 26) | BUU-H (n = 26) | Placebo (n = 24) | Total (n = 76) |
|---|---|---|---|---|---|
| Elemental diet | n (%) | 1 (3.8%) | 0 (0.0%) | 1 (4.2%) | 2 (2.6%) |
| Directed elimination diet (based on allergy test) | n (%) | 7 (26.9%) | 4 (15.4%) | 4 (16.7%) | 15 (19.7%) |
| Non-directed elimination diet | n (%) | 13 (50.0%) | 14 (53.8%) | 8 (33.3%) | 35 (46.1%) |
| **History of allergic disease** | n (%) | 22 (84.6%) | 22 (84.6%) | 22 (91.7%) | 66 (86.8%) |

* For three patients the question "Did the patient receive PPI treatment for EoE in the past?" was answered in the eCRF with "yes". However, no PPI treatment was entered in the next form "Previous medical treatment of EoE". After review of the relevant query resolution and the concomitant medication information Appendix 8.2.1, Table 1.3.5.7 (FAS-DB) was determined to be the correct source for this information.

Source: Clinical study report Appendix 8.2.1, Tables 1.3.1 (FAS-DB), 1.3.4.2 (FAS-DB), 1.3.5.1 (FAS-DB) to 1.3.5.2 (FAS-DB), 1.3.5.5 (FAS-DB) to 1.3.5.6 (FAS-DB), 1.3.5.7 (FAS-DB) and 1.3.5.9 (FAS-DB).

# Part II: Module SIV – Populations not studied in clinical trials

## SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

**Clinical signs and/or endoscopic signs of gastroesophageal reflux disease (GERD)**

Reason for exclusion: The exclusion of GERD patients ensures proper inclusion of the targeted patient population to allow for an unbiased efficacy assessment in this target group.

Is it considered to be included as missing information?: No

Rationale: Exclusion of GERD is integral part of standard medical practice for confirmation of the diagnosis eosinophilic esophagitis.

**PPI-responsive oesophageal eosinophilia**

Reason for exclusion: The exclusion of patients with PPI-responsive esophageal eosinophilia ensures proper inclusion of the targeted patient population to allow for an unbiased efficacy assessment in this target group.

Is it considered to be included as missing information?: No

Rationale: There is growing evidence that PPI-RRE and EoE exhibit overlapping phenotypic, genetic and mechanistic features. The exclusion of patient with PPI-RRE is therefore not relevant outside the scope of clinical trial settings.

**Achalasia, scleroderma oesophagus or systemic sclerosis**

Reason for exclusion: Patients suffering from one of these oesophageal disorders have been excluded in order not to confound the results of the clinical trial.

Is it considered to be included as missing information?: No

Rationale: In rare cases, an association of EoE and oesophageal disorders like achalasia, scleroderma esophagus or systemic sclerosis with a negative impact on the course of disease has been reported. However, there is no need to exclude such patients outside the scope of clinical trial settings.

**Other clinically evident causes for esophageal eosinophilia**

Reason for exclusion: Patients suffering from respective disorders (e.g. Crohn's disease, eosinophilic gastroenteritis, graft-versus-host disease) have been excluded in order not to confound the results of the clinical trial.

Is it considered to be included as missing information?: No

Rationale: Exclusion of other possible causes for esophageal eosinophilia is part of standard medical practice for confirmation of the diagnosis eosinophilic esophagitis.

**If careful monitoring is not ensured: cardiovascular disease, diabetes mellitus, osteoporosis, active peptic ulcer disease, glaucoma, cataract or infection are potential side effects**

Reason for exclusion: These effects are well-known class effects associated with the use of glucocorticosteroids.

Is it considered to be included as missing information?: No

Rationale: The events are well-known and therefore adequately addressed by routine clinical practice. Additional warnings are included under section 4.4 of both SmPCs (orodispersible tablets and oral suspension).

**ALT or ALP > 2.5 x upper limit of normal, liver cirrhosis or portal hypertension**

Reason for exclusion: A severely impaired hepatic function may possibly lead to an increased systemic availability of budesonide associated with an increased risk for systemic side effects.

Is it considered to be included as missing information?: No

Rationale: A warning with regard to impaired liver function is included in section 4.4 of both SmPCs.

**Installation of dietary restrictions within 4 weeks prior to baseline visit or during treatment**

Reason for exclusion: This criterion has been implemented in order to allow for an unbiased assessment of the efficacy of study medication.

Is it considered to be included as missing information?: No

Rationale: Outside the clinical trial setting, treatment with budesonide orodispersible tablets may well be combined with dietary restrictions depending on the clinical need of the patient.

### SIV.2 Limitations to ADR detection common to clinical trial development programmes

| Ability to detect adverse reactions | Limitation of trial programme | Discussion of implications for target population |
|---|---|---|
| Which are rare/very rare | Only limited number of patients were exposed to budesonide orodispersible tablets or oral viscous suspension over the whole clinical development programme; therefore, the ability to detect specific rare adverse reactions in EoE population could have been affected. | Budesonide is well-established drug with known safety profile. Other dosage forms are authorised and marketed since 1980s and are used for the management of various diseases in different patient populations. Even though any disease-specific adverse reactions cannot be excluded in the EoE patients, the limitations in their detection are not expected to have any impact of the target population. |
| Due to prolonged exposure<br>Due to cumulative effects<br>Which have a long latency | In the double-blind phase study BUL-2/EER patients have been treated for 48 weeks.<br>In the double blind phase II/III study BUU-5/EEA, the up to 4-week screening period was followed by a 12-week double-blind (DB) treatment period, an optional 12-week open-label induction (OLI) treatment for eligible patients, an optional 24-week open-label extension (OLE) treatment with budesonide oral suspension for eligible patients and a 3-week tapering phase (58).<br>However, there may still be the potential for cumulative effects or | Budesonide is well-established drug with known safety profile which is not expected to significantely differ in patients with EoE. The available safety data over a 48-weeks exposure show an overall favourable safety profile.<br>However, safety data over a longer period of exposure are still not available. |

| | | |
|---|---|---|
| | effects with long latency over yet longer periods of time. | |

## SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

| Type of special population | Exposure |
|---|---|
| Pregnant women | Not included in the clinical development program<br>Although data on the use of inhaled budesonide in a large number of exposed pregnancies indicate no adverse effect, the maximal concentration of budesonide in plasma has to be expected to be higher in the treatment with Jorveza® 0.5 mg/1mg compared to inhaled budesonide. In pregnant animals, budesonide, like other glucocorticosteroids, has been shown to cause abnormalities of fetal development. The relevance of this to men has not been established. |
| Breastfeeding women | No data of lactating women are available from clinical trials.<br>Budesonide is excreted in human milk (data on excretion after inhalative use is available).<br>However, only minor effects on the breast-fed child are anticipated with Jorveza® 0.5 mg/1 mg intake within the therapeutic range. |
| Patients with relevant comorbidities:<br>• Patients with severe hepatic impairment<br>• Patients with a history of cancer within the last five years | <br>• Not included in the clinical development program<br>• Not included in the clinical development program |
| Population with relevant different ethnic origin | Patients and subjects participating in the clinical trial program were predominantly Caucasian. One patient of Asian origin has been included. However, budesonide is a well-known substance and there is no evidence of a different mode of action or metabolism in populations of different ethnic origins. |
| Subpopulations carrying relevant genetic polymorphisms | No information on such subpopulations was reported from clinical development program |
| Other: Paediatric population | Results for patients 2 to 17 years of age are available from BUU-5/EEA. Results of study do not show any population-based risk besides known risks for the adult population. |

# Part II: Module SV - Post-authorisation experience

Jorveza® 1mg orodispersible tablets were first granted marketing authorisation in the EU on 08 Jan 2018. On 20 May 2020 marketing authorisation for the additional strength Jorveza® 0.5 mg orodispersible tablets has been granted in the EEA.

Outside the EEA, marketing authorisation for Jorveza® 1 mg has been obtained in Switzerland (25 May 2018), Canada (06 Nov 2019), Israel (30 Dec 2019), Australia (07 Sep 2020).

Marketing authorisation for Jorveza® 0.5 mg has been obtained in Switzerland (15 Apr 2021), Canada (16 Mar 2021), Israel (22 Mar 2023) and Australia (30 Aug 2021).

Additionally, marketing authorisation for both strengths has been obtained in Nothern Ireland (08 Jan 2018), Great Britain (01 Jan 2021), the United Arab Emirates (05 Jul 2021), Serbia (23 Dec 2021) and New Zealand (23 Jun 2022).

A marketing authorisation has been applied for in South Korea. For Saudi Arabia a Temporary Import Authorisation (SIoZ) has been issued for Jorveza 1mg only.

The product is currently marketed in the following EEA countries: Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Slovenia, Spain, Sweden and in the following countries outside the EEA: Australia, Canada, the United Arab Emirates, Israel, Switzerland and the United Kingdom.

## SV.1 Post-authorisation exposure

### SV.1.1 Method used to calculate exposure

Since no data on the detailed indication (induction or maintenance of remission) and the duration of treatment are available to the MAH, calculation of exposure data has been based on the following considerations:

1 mg orodispersible tablets are predominantly used for induction of maintenance, with a recommended daily dose of 2 orodispersible 1 mg tablets over 6 weeks, equaling 84 single doses per treatment cycle.

0.5 mg orodispersible tablets are predominantly used for maintenance of remission, with a recommended daily dose of 2 orodispersible 0,5 mg tablets. Duration of treatment is at the discretion of the treating physician and defined in line with the clinical requirement of the individual patient, but assumed to be 24 weeks in average. A daily dose of 2 orodispersible 0.5 mg tablets over 24 weeks equals 336 single doses per treatment cycle.

### SV.1.2 Exposure

**Total distribution of Jorveza® 1 mg orodispersible tablets (number of tablets)**

| Time frame | Germany | Export | Total |
|---|---|---|---|
| Jan 2018 - Jul 2021 | 4 267 060 | 4 450 760 | 8 727 820 |
| Jan 2021 - Jul 2021 | 787 420 | 981 990 | 1 769 410 |
| Jul 2021 - Jul 2022 | 1 684 930 | 3 002 810 | 4 687 740 |
| Jul 2022 - Jul 2023 | 1 891 880 | 4 342 230 | 6 234 110 |

| | | | |
|---|---|---|---|
| Jul 2023 - Jul 2024 | 2 301 570 | 9 466 370 | 11 767 940 |
| | | | **33 187 020** |

**Total distribution of Jorveza® 0.5 mg orodispersible tablets (number of tablets)**

| Time frame | Germany | Export | Total |
|---|---|---|---|
| Jan 2018 - Jul 2021 | 270 770 | 107 580 | 378 350 |
| Jan 2021 - Jul 2021 | 235 970 | 107 580 | 343 550 |
| Jul 2021 - Jul 2022 | 806 010 | 936 600 | 1 742 610 |
| Jul 2022 - Jul 2023 | 1 172 770 | 1 654 520 | 2 827 290 |
| Jul 2023 - Jul 2024 | 1 871 490 | 2 895 170 | 4 766 660 |
| | | | **10 058 460** |

**Cumulative patient exposure** to Jorveza® 1 mg used for induction of remission is estimated as **395.083 patient treatment cycles**, based on 33 187 020 orodispersible tablets (total doses distributed) divided by 84 orodispersible tablets (doses per patient treatment cycle).

**Cumulative patient exposure** for Jorveza® 0.5 mg for maintenance of remission is estimated as 29.936 **patient treatment cycles**, based in 10 058 460 orodispersible tablets (total doses distributed) divided by 336 orodispersible tablets (doses per patient treatment cycle).

# Part II: Module SVI - Additional EU requirements for the safety specification

### Potential for misuse for illegal purposes

The potential for misuse for illegal purposes is not consistent with the pharmacological profile of budesonide. However, administration of the medicinal product, budesonide orodispersible tablets, can lead to positive results in doping tests. It is believed that the potential for such activities is very low.

# Part II: Module SVII - Identified and potential risks

### SVII.1 Identification of safety concerns in the initial RMP submission

In study BUL-2/EER 17 suspected ADRs of candidiasis were reported in 12 patients (17.6%) in the BUL 0.5mg BID treatment group and 13 suspected ADRs of candidiasis in 9 patients (13.2%) in the BUL 1mg BID treatment group.

Local fungal infections are common (≥1/100 to <1/10; oral and/or oropharyngeal candidiasis) undesirable effects of budesonide orodispersible tablets.

In study BUL-2/EER, overall numbers of double-blind treatment-emergent adverse events (DB TEAEs) were higher under treatment with budesonide, the proportion of DB TEAEs were similar between treatment groups.

Four serious AEs (SAEs) were reporting in 3 patients (4.4%) taking BUL 0.5mg BID and one SAE in 1 patient (1.5%) taking BUL 1 mg BID and no SAE under Placebo. All SAE were treatment-emergent and assessed by the investigator as not related to IMP.

The nature and frequency of adverse events observed in the budesonide treatment groups were consistent with the known safety profile of topical budesonide.

## SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

**Reason for not including an identified or potential risk in the list of safety concerns in the RMP:**

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

The following ADRs in clinical studies assessed by the investigator were few, usually mild or moderate, and transient. The ADRs are sorted by SOCs. The frequency of these ADRs was low.

- *Gastrointestinal disorders*: (Upper) abdominal pain, abdominal distension, dry mouth, dyspepsia, dysphagia, glossodynia, erosive gastritis, gastric ulcer, lip edema, gingival pain, tongue disorder, oral herpes, nausea, oral discomfort, oral paresthesia
- *General disorders and administration site disorders:* fatigue, sensation of foreign body
- *Infection and infestations:* nasopharyngitis, pharyngitis
- *Nervous system disorders:* Headache, dysgeusia, dizziness
- *Psychiatric disorders:* Sleep disorders, anxiety, agitation
- *Eye disorders:* dry eyes
- *Respiratory, thoracic and mediastinal disorders:* Cough, dry throat, oropharyngeal pain
- *Skin and subcutanous tissue disorders:* rash, urticaria
- *Vascular disorders:* hypertension

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

<u>Interactions with CYP3A4 Inhibitors</u>

The potential for interaction with CYP3A4 inhibitors is described in detail in section 4.5 of both SmPCs and thus in the awareness of the treating physician.

<u>Adverse reactions known to be associated with the therapeutic class (corticosteroids) including Cushing's syndrome, growth retardation in children, adrenal suppression, various psychiatric effects, myalgia osteoposis, hypokalaemia, hyperglycaemia, glaucoma, cataract, CSCR:</u>

These risks listed in section 4.8 of both SmPCs are well-known to health care professionals.

In clinical study BUU-5/EEA ACTH test results did not indicate any concern regarding adrenal suppression with long-term budesonide treatment of 9 and 12 months. There was also no indication for any risk of growth retardation and change of z-score from screening visit (V0) to follow-up visit did not reveal any significant discrepancy between the different treatment groups of BUU-L, BUU-H and Placebo over all age groups.

Therefore guidance for growth monitoring in context of routine clinical practice and follow up via routine pharmacovigilance is considered appropriate.

Gastric ulcer

The adverse reaction is a well-known class effect associated with the use of glucocorticosteroids. A corresponding warning is included in section 4.4 of both SmPCs.

Gastroesophageal reflux disease (GERD)

Cases of GERD so far observed in the clinical development programs were all non-serious and mild of nature.
According to current relevant guidelines, GERD and EoE often coexist in a single patient, but do not necessarily interact. Awareness of this possible overlap of the two disease entities in a single patient has led to respective treatment strategies as part of standard clinical practice.

Oesophageal/oral/oropharyngeal candidiasis

Fungal infections of the mouth, pharynx and/or oesophagus associated with the use of topical glucocorticosteroids have been extensively described in literature and are listed as common adverse reaction in section 4.8 of both SmPCs. During the clinical trial program, patients often recovered under continued treatment without any corrective measures. If needed, treatment with antifungals of the azole-type is standard clinical practice. This advice is also included in both SmPCs in section 4.4.

Blood cortisol decreased

In the clinical studies no clinically relevant changes in the serum cortisol as well as the morning serum cortisol levels were observed in any treatment group. Decreased blood cortisol was reported in single patients receiving BUL or placebo as non serious event. The severity was mainly mild to moderate, no measures were taken and the outcome was recovered/resolved.

“Blood cortisol decreased” is listed as an ADR in section 4.8 of both SmPCs and is a known class effect associated with the use of glucocorticosteroids and therefore adequately addressed by routine clinical practice.

Angioedema

In total six cases of angioedema with different severity have been observed during the clinical development and post-marketing exposure with Jorveza®. Based on a plausible time correlation and mechanistic considerations a causal relationship between the use of Jorveza® and the event angioedema is at least reasonably possible.
The event has therefore been included in section 4.8 of both SmPCs in the scope of PSUSA procedure EMEA/H/C/PSUSA/00010664/202101.

The signal "hypersensitivity reactions including angioedema" remains under close monitoring by the MAH.

No additional pharmacovigilance actions are currently considered necessary.

Use in patients with severe renal impairment

There are only limited data in patients with renal impairment. Treatment of patients with severe renal impairment is explicitly not recommended (section 4.2 of both SmPCs). Therefore, no additional pharmacovigilance activities are required to address this risk.

### SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

None.

### SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The currently approved RMP for Jorveza® 0.5mg/1mg orodispersible tablets (version 3.0, Data lock point: 15 Dec 2021; date of final sign off: 14 Feb 2022) has been updated to include results of the meanwhile completed clinical studies BUU-5/EEA, BUL-007/BIO and BUU-008/BIO and to add a new pharmaceutical formulation: 0.2 mg/mL oral suspension for paediatric use.

There were no deaths, SAEs, nor discontinuations due to TEAEs reported in study BUU-008/BIO or BUL-007/BIO.

No new safety concerns have been identified.

### SVII.3 Details of important identified risks, important potential risks, and missing information

Not applicable.

### SVII.3.2. Presentation of the missing information

Not applicable

## Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | None |

## Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

### III.1 Routine pharmacovigilance activities

There are no routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

### III.2 Additional pharmacovigilance activities

None.

### III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

# Part IV: Plans for post-authorisation efficacy studies

No imposed post-authorisation efficacy studies are on-going or planned.

# Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Not applicable.

## V.1. Routine Risk Minimisation Measures

Not applicable.

## V.2. Additional Risk Minimisation Measures

Not applicable.

## V.3 Summary of risk minimisation measures

Not applicable.

# Part VI: Summary of the risk management plan for Jorveza® 0.5 mg / 1 mg orodispersible tablets and 0.2 mg/mL oral suspension

This is a summary of the risk management plan (RMP) for Jorveza® 0.5 mg / 1mg orodispersible tablets and 0.2 mg/mL oral suspension. The RMP details important risks of Jorveza® 0.5 mg / 1 mg orodispersible tablets and 0.2 mg/mL oral suspension, how these risks can be minimised, and how more information will be obtained about risks and uncertainties (missing information) associated with the use of the product.

Jorveza® 0.5 mg / 1 mg orodispersible tablet's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Jorveza® 0.5 mg / 1 mg orodispersible tablets should be used.

Jorveza® 0.2 mg/mL oral suspension's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Jorveza® 0.2 mg/mL oral suspension should be used.

## I. The medicine and what it is used for

Jorveza® 0.5 mg / 1 mg orodispersible tablets are authorised for the treatment of eosinophilic esophagitis (EoE) in adults (older than 18 years of age).

Jorveza® 0.2 mg/mL oral suspension is authorised for the treatment of eosinophilic esophagitis (EoE) in paediatric patients (2 to 17 years of age).

It contains budesonide as the active substance, and it is given by oral route of administration.

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Jorveza® 0.5 mg / 1 mg orodispersible tablets and 0.2 mg/mL oral suspension, together with measures to minimise such risks and the proposed study for learning more about Jorveza®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on medicine's packaging;
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

## II.A List of important risks and missing information

None.

## II.B Summary of important risks

None.

## II.C Post-authorisation development plan

### II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Jorveza® 0.5mg/1mg orodispersible tablets.

### II.C.2 Other studies in post-authorisation development plan

Not applicable.

# Part VII: Annexes

# Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

# Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.