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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jorveza

International non-proprietary name: budesonide

Procedure No. EMA/X/0000257468

Note

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
ADR	Adverse drug reaction
AE	Adverse event
AGA	American Gastroenterological Association
AIH	Autoimmune hepatitis
ATC	Anatomical Therapeutic Chemical
$AUC_{0-\infty}$	Area under the curve, from the first time point (t = 0) extrapolated to infinity
AUC_{0-12h}	Area under the curve from 0 to 12 hours
$AUC_{0-tlast}$	AUC vs. time curve from dosing time to the last measurement time point
BID	Twice daily
BMI	Body mass index
BUL	Budesonide orodispersible tablets
BUU	Budesonide oral suspension
BUU-H	High-dose BUU
BUU-L	Low-dose BUU
CD	Crohn's Disease
CHMP	Committee for Medicinal Products for Human Use (of EMA)
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed plasma concentration
COC	Collagenous colitis
COPD	Chronic obstructive pulmonary disease
CSCR	Central serous chorioretinopathy
CSR	Clinical study report
CV	Coefficient of variation
CYP	Cytochrome P450
DB	Double blind
ECG	Electrocardiogram
ECP	Eosinophil cationic protein
EEA	European Economic Area
EMA	European Medicines Agency
EndoFLIP	Endolumenal functional lumen imaging probe (EndoFLIP®)
EoE	Eosinophilic oesophagitis
EoEHSS	Eosinophilic Oesophagitis Histological Scoring System
eos	Eosinophils
EREFS	Endoscopic reference score
EU	European Union

Term	Explanation
FAS	Full analysis set
FU	Follow-up
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
hpf	High-power field
IgE	Immunoglobulin E
IMP	Investigational medicinal product
LOCF	Last observation carried forward
MA	Marketing authorisation
MAA	Marketing Authorisation Application
MAH	Marketing authorisation holder
MBq	Megabecquerel
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NMT	Not more than
NRS	Numerical Rating Scale
OD	Once daily
ODT	Orodipersible tablet
OLE	Open-label extension
OLI	Open-label induction
OLRI	Open-label re-induction
OS	Oral solution
PatGA	Patient's Global Assessment
ParGA	Parent's Global Assessment
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamic(s)
PedsQL	Paediatric Quality of Life Inventory
PK	Pharmacokinetic(s)
PP	Per-protocol
PPI	Proton-pump-inhibitor
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient reported outcome
PSUSA	Periodic safety update single assessment
PT	Preferred term
QoI	Quality of Life
SAE	Serious adverse event
SAF	Safety analysis set
SD	Standard deviation
SE	Standard error

Term	Explanation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TAP	Tapering phase
TEAE	Treatment-emergent adverse event
Th2	T-helper cell type 2
T_{max}	Time to reach maximum plasma concentration
vs.	versus

1. Administrative/regulatory information and recommendations on the procedure

1.1. Submission of the dossier

On 5 March 2025, Dr Falk Pharma submitted an extension of the marketing authorisation.

The MAH applied for a new pharmaceutical form associated with a new strength intended for a paediatric indication.

1.2. Legal basis

The legal basis for this application refers to: The legal basis for this application refers to Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) points (c) (d) - Extensions of marketing authorisations.

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

1.3. Scientific advice and protocol assistance

Not applicable.

1.4. Information on paediatrics

Not applicable.

1.5. Information on orphan market exclusivity

Jorveza 0.2 mg/mL oral suspension was designated as an orphan medicinal product EU/3/13/1181 on 05 August 2013 in the following condition: treatment of EoE.

1.6. Similarity with authorised orphan medicinal products

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

1.7. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur:	Dr Janet Koenig

The application was received by the EMA on	05 March 2025
The procedure started on	27 March 2025
The CHMP Rapporteur's first Assessment Report was received on	17 June 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	24 June 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 July 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	24 July 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	09 October 2025
The CHMP Rapporteur circulated the Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	06 November 2025
The PRAC Rapporteur's Assessment Report on the responses to the List of Questions was added to the Rapporteur's report and circulated to all PRAC and CHMP members on	10 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP Rapporteur circulated the updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	04 December 2025
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	11 December 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	23 January 2026
The CHMP Rapporteur circulated the Rapporteur's Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 February 2026
The CHMP Rapporteur circulated the updated Rapporteur's Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	18 February 2026
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 February 2026

1.8. CHMP outcome

1.8.1. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of the oral suspension 0.2 mg/mL of Jorveza is favourable in the following indication(s):

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.

The CHMP therefore recommends the extension of the marketing authorisation for Jorveza subject to the conditions described in the following sections.

1.8.2. Conditions or restrictions regarding supply and use

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

1.8.3. Other conditions and requirements of the marketing authorisation

1.8.3.1. Periodic safety update reports

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

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

1.8.4.1. 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.

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

Not applicable.

2. Introduction

Therapeutic Context

Disease Definition and Clinical Characteristics

Eosinophilic oesophagitis (EoE) is a chronic, immune-mediated, antigen-triggered inflammatory disease of the oesophagus characterized by symptoms of oesophageal dysfunction and histologically by eosinophil-predominant inflammation. In children, the clinical manifestations of EoE are age-dependent: feeding difficulties are most common in infants and toddlers, vomiting and abdominal pain are more frequently observed in school-aged children, while adolescents typically present with dysphagia and food impaction.

Natural History and Disease Subtypes

EoE typically follows a chronic, relapsing-remitting course. If left untreated, persistent eosinophilic inflammation can lead to progressive tissue remodelling, including subepithelial fibrosis and oesophageal strictures. The disease can transition from an inflammatory to a fibrostenotic phenotype over time. This progression underscores the importance of early and effective anti-inflammatory treatment to prevent long-term complications.

Population Affected and Epidemiology

EoE affects both children and adults, with a higher prevalence in males. A systematic review and meta-analysis estimated a pooled prevalence of approximately 34.4 cases per 100,000 population, with incidence rates of 6.6 per 100,000 person-years in children and 7.7 in adults. Despite increasing awareness, underdiagnosis remains a concern, particularly in younger patients who may exhibit non-specific symptoms.

Diagnosis and Diagnostic Methods

Diagnosis of EoE requires a combination of clinical, endoscopic, and histological assessments. Histologically, the presence of ≥15 eosinophils per high-power field in oesophageal biopsies is a key criterion. Endoscopic findings may include linear furrows, white plaques, oedema, rings, strictures, and narrowing. Additional investigations, including pH monitoring and imaging, are used to exclude differential diagnoses such as gastroesophageal reflux disease (GERD).

Impact on Daily Life and Patient Perspective

EoE significantly impacts quality of life. Children may experience failure to thrive, anxiety around eating, and social limitations due to dietary restrictions. Adolescents and adults report food impactions requiring emergency intervention and adapt their eating habits to cope with symptoms. Delayed diagnosis can further exacerbate emotional and physical burden due to the risk of complications and the chronic nature of the disease.

Current Treatment Approaches in the EU

Standard therapies in the EU include dietary elimination strategies, proton-pump inhibitors (PPIs), and topical corticosteroids. Elemental and empirical six-food elimination diets are effective but are often difficult to maintain and associated with reduced quality of life. Budesonide, a topically acting corticosteroid, is the most commonly used pharmacological therapy, traditionally administered as off-label preparations (e.g., swallowed nebulized solutions). Since 2018, Jorveza® (budesonide orodispersible tablets) has been approved in the EU for adults, and clinical guidelines now recommend topical corticosteroids as first-line therapy.

In 2023, dupilumab (Dupixent®) received EU approval for use in EoE for patients ≥12 years weighing ≥ 40 kg, with recent label extension to children ≥1 year weighing ≥15 kg. However, this therapy is limited to selected patient populations and has a distinct safety profile.

Unmet Needs and Treatment Gaps

Prior to this application, no medicinal product for first-line treatment (topical corticosteroids) was authorised in the EU specifically for paediatric EoE. Off-label use of inhaled corticosteroids in liquid or slurry form lacks regulatory oversight and standardisation, raising concerns about safety, efficacy, and dosing accuracy.

There is a clear need for a paediatric formulation that ensures optimal oesophageal delivery, is well tolerated, and offers predictable pharmacokinetics and therapeutic outcomes.

2.1. Aspects of development

The clinical development programme for budesonide 0.2 mg/mL oral suspension was designed to support the proposed indication: "*Treatment of eosinophilic oesophagitis (EoE) in paediatric patients aged 2 to 17 years*".

The development programme includes nonclinical studies and a clinical programme comprising pharmacokinetic (PK), pharmacoscintigraphic, and efficacy/safety studies. It was tailored to the specific therapeutic context of EoE, a localized oesophageal condition requiring targeted mucosal delivery of anti-inflammatory treatment.

The budesonide oral suspension was developed as a child-friendly, viscous formulation intended to optimise oesophageal mucosal exposure.

Clinical Studies Supporting This Application

The application is supported by the following clinical studies:

- Study BUL-007/BIO: A Phase I, open-label pharmacoscintigraphic and PK study in healthy adults comparing oesophageal transit and systemic exposure of budesonide oral suspension versus orodispersible tablets.
- Study BUU-008/BIO: A two-part, open-label study in healthy adults assessing the pharmacokinetics of single and multiple doses of budesonide oral suspension under fasting and fed conditions.
- Study BUU-5/EEA: A pivotal Phase II/III, double-blind, randomised, placebo-controlled trial in paediatric patients (2–17 years) with active EoE. The study assessed efficacy and safety over a 12-week induction phase, followed by optional open-label induction (12 patients) and extension (24 patients) phases.

In addition, a population PK analysis was conducted using data from BUU-5/EEA and earlier adult studies (including BUU-1/BIO and BUL-6/BIO) to characterise budesonide exposure across age groups and support the dose selection in children.

During the development of budesonide oral suspension for the treatment of EoE in paediatric patients, no formal Protocol Assistance or EMA Scientific Advice was sought by the applicant.

No Paediatric Investigation Plan (PIP) was required or agreed with the Paediatric Committee (PDCO), and no waiver or deferral was issued, as the product falls outside the scope of mandatory paediatric obligations.

2.2. Description of the product

The product is a viscous oral suspension containing budesonide at a concentration of 0.2 mg/mL. It is specifically formulated to adhere to the oesophageal mucosa, enhancing topical exposure in the treatment of eosinophilic oesophagitis (EoE). The formulation includes well-established excipients that meet pharmacopoeial standards and is intended for age-appropriate, weight-based dosing in the paediatric population. The viscosity of the suspension prolongs oesophageal contact time relative to non-viscous liquids, supporting its therapeutic objective.

Budesonide is a synthetic glucocorticoid with high topical anti-inflammatory activity and low systemic bioavailability due to extensive first-pass hepatic metabolism. In EoE, it suppresses local immune-mediated inflammation by inhibiting cytokine production and inflammatory cell activation in the oesophageal mucosa.

Budesonide orodispersible tablets (Jorveza®) are authorised in the EU for use in adults with EoE. The oral suspension formulation submitted here is not yet approved in any market and represents the first application for its use in the paediatric population.

Proposed Indication (SmPC Section 4.1)

Jorveza 0.2 mg/mL oral suspension is indicated for the treatment of eosinophilic oesophagitis (EoE) in children and adolescents aged 2 to 17 years.

Proposed Posology (SmPC Section 4.2)

Children aged 2 to 11 years: Low dose: 0.5 mg once daily, high dose: 0.5 mg twice daily.

Adolescents aged 12 to 17 years: Low dose: 1.0 mg once daily, high dose: 1.0 mg twice daily.

Treatment duration is generally 12 weeks for induction of remission, with optional continuation under clinical supervision for maintenance of effect.

2.3. Inspection issues

Not applicable.

3. Quality aspects

Introduction

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). This line extension concerns addition of a new strength and pharmaceutical form; a liquid multidose preparation (oral suspension) to support the extension of indication to age groups 2-17 years.

The finished product is presented as an oral suspension containing 0.2 mg/ml of budesonide as active substance.

Other ingredients are sucrose, purified water, sodium benzoate (E211), disodium edetate, citric acid, methylcellulose [1500 mPa*s] and blackcurrant flavour.

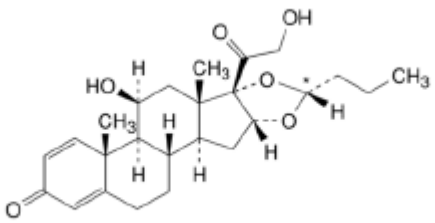
The product is available in a 200 ml amber glass bottle (type III glass) with a child resistant white plastic closure consisting of a ribbed screw cap (PP) with a colourless screw closure (HDPE) and an internal colourless flow limiter (LDPE), co-packaged with a CE-certified oral syringe consisting of a colourless barrel (PP) with six printed graduations (1.0 mL, 2.0 mL, 2.5 mL, 3.0 mL, 4.0 mL and 5.0 mL) and a white plunger (HDPE).

3.1. Active substance

3.1.1. General information

The chemical name of budesonide is 16α, 17α-[(R,S)Butylidenedioxy]-11β,21-dihydroxypregna-1,4-diene-3,20-dione corresponding to the molecular formula C25H34O6. It has a relative molecular mass of 430.5 g/mol and the following structure:

Structural formula:



And epimer at C*

As there is a monograph of budesonide in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for budesonide which has been provided within the current Marketing Authorisation Application.

3.1.2. Manufacture, characterisation, and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

3.1.3. Specification

The active substance specification includes tests for appearance, solubility, identity (IR, TLC, colour reaction), related substances (HPLC), epimer A (Ph. Eur.), loss on drying (Ph. Eur.), assay (Ph. Eur.), particle size (Laser Light Diffraction) and residual solvents (GC).

The applicant confirms that the quality of the active substance is controlled in accordance with the Ph. Eur. monograph. In addition, the substance is tested for the solvents methanol, acetone and butyraldehyde, as specified in the CEP. The active substance is micronised and a specification for the particle size is presented. The analytical procedures are performed according to the current monograph of the European Pharmacopoeia for budesonide with exception of the in-house method for the solvents and particle size determination. All additional methods have been adequately validated and described according to ICH Q2.

The active substance manufacturer and finished product manufacturer each submit three certificates of analysis for three identical batches. All results comply with proposed active substance specification. No upward or downward trend is noticeable. Batch analysis demonstrates consistency from batch to batch and presented data indicates that process is under control.

Adequate information (including all declarations of compliance) is provided for proposed container closure system. The composition of LDPE and the laminated aluminium bags comply with Regulation (EU) No 10/2011.

3.1.4. Stability

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

The parameters tested are the same as for release (with exception of solubility, residual solvents and particle size distribution). The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications. The proposed retest period of 60 months in the proposed container with no specified storage conditions is acceptable.

3.2. Finished medicinal product

3.2.1. Description of the product and pharmaceutical development

The finished product is an oral suspension. It is a whitish, viscous suspension with a characteristic cassis aroma. Budesonide 0.2 mg/mL oral suspension is presented in a multidose container (200 ml amber glass bottle) and is administered by means of a 5 mL oral syringe (graduated for 2.5 mL or 5 mL dose).

The suspension contains micronised budesonide with defined characteristics in terms of crystallinity and particle size distribution as the dispersed inner phase and an aqueous-based, viscosity-increased outer phase that ensures the physical and chemical stability of the preparation. The aqueous formulation contains an antimicrobial preservative to prevent proliferation or to limit microbial contamination. A homogeneous suspension is obtained upon shaking that should be remain stable to enable correct dosing by means of an oral syringe.

The physicochemical and biological properties of the active substance have been adequately discussed. The applicant has described the excipients, justified the choice of these excipients, and discussed the quantity used in the product. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of the in-house blackcurrant flavour. For this excipient an appropriate specification has been presented. The excipients are appropriate in view of the proposed paediatric population. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The formulation contains a preservative (sodium benzoate) and efficacy of antimicrobial preservation was demonstrated during the development in line with Ph. Eur. requirements and considering the intended in-use period.

The development of the prototype formulation of budesonide 0.4 mg/mL oral suspension is described. An aqueous based (vehicle: purified water), thixotropic and highly viscous (syrup-like) oral suspension was considered. Relevant parameters are the pH value of the vehicle, the redispersibility and the rheological properties. The early formulation of budesonide oral suspension was tested in the clinical Phase 2a study BUU-2/EEA. This trial was designed as a placebo-controlled, proof-of-concept, formulation selection and dose finding study comparing the efficacy and safety of Budesonide 0.4 mg/mL oral suspension with Budesonide 1 mg and 2 mg orodispersible tablets.

The proposed/final formulation of Budesonide 0.2 mg/mL oral suspension was tested in the pivotal clinical Phase 3 study BUU-5/EEA. Prior to the start of the clinical trial the formulation was optimised. The Phase 3 study was designed as a double-blind, randomised, placebo-controlled, dose-ranging Phase 3 trial testing the efficacy and tolerability of budesonide in comparison with placebo in children and adolescents (2 to 18 years of age) with EoE. The patients were stratified by age and randomized (1: 1: 1) to receive a 12-week double blind oral treatment of different doses of budesonide. The Phase 3 study was supplied using the proposed formulation of Budesonide 0.2 mg/mL oral suspension in the final multidose container.

Manufacturing process development is presented. Scale-up studies are described. Critical parameters are identified. The development of a dissolution test method was described. The in vitro dissolution method was not implemented as a routine test for release and stability testing of the finished product as the method lacks pharmacopeial compliance and was not considered necessary as the product is intended to act locally on the oesophageal mucosa in the treatment of EoE.

The primary container corresponds to the specification of the Ph. Eur. concerning a multi-dose container for aqueous preparations for non-parenteral use. It consists of the following components:

- A 200 mL amber glass bottle of blow moulded type III glass.
- A child resistant white plastic closure consisting of a ribbed screw cap with an internal colourless flow limiter. After first opening, the flow limiter remains in the bottle neck and enables the insertion of the syringe for removal of the suspension.

The bottles are packed together with the leaflet and the measuring device into suitably labelled, non-functional secondary packaging material (e.g. folding carton). The provided measuring device is a CE-certified plastic syringe consisting of a colourless barrel with six printed graduations (1.0 mL, 2.0 mL, 2.5 mL, 3.0 mL, 4.0 mL and 5.0 mL) and a white plunger is used for oral administration.

3.2.2. Manufacture of the product and process controls

For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The manufacturing process consists of seven main steps preparation of excipient solutions, mixing, addition of active substance, homogenisation, mixing, filling and packaging. Due to the low content of the active substance (0.02%), the manufacturing process is classified as a non-standard process. During the procedure, a major objection (MO) was raised on the level of detail provided about the manufacturing process. In response, the applicant provided the necessary detail in terms of appropriate process parameters along with their target values or ranges. The flow chart and narrative description were updated, and the MO was considered to be resolved.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Major steps of the manufacturing process have been validated. The process validation study considered the manufacturing and primary packaging process of Budesonide 0.2 mg/mL suspension. Three commercial batches have been produced during this study. Routine release testing was performed according to valid testing instructions, and all validation batches were well within the specification. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

3.2.3. Specification

The finished product specifications include appropriate tests for this kind of dosage form; appearance (visual), clarity (Ph. Eur.), odour (Ph. Eur.), pH (Ph. Eur.), density (Ph. Eur.), viscosity (Ph. Eur.), resuspendability (HPLC), uniformity and accuracy of delivered doses from multidose containers (Ph. Eur.), filling volume, particle size (microscopic), identity (UV), assay (HPLC), related substances (HPLC), tightness of closure, microbiological quality (Ph. Eur.).

The selected test parameters are appropriate to ensure consistent finished product quality. All acceptance criteria are justified and considered acceptable.

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.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The batch results of three commercial batches confirm consistency and uniformity of the finished product and demonstrate that the process is under control.

3.2.4. Stability of the product

Stability data from one clinical batch and three commercial scale batches of finished product stored for 12-24 months under long term conditions (25 ºC / 60% ± 5% RH), 12 months under intermediate conditions (30 °C / 75 ± 5% 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 are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

All analysed stability samples were stored in inverted position (upside down) to demonstrate that contact between the suspension and the child resistant closure does not impair the quality and stability of the suspension and that the closure system is leak-proof.

Samples were tested in line with the shelf-life specifications. The analytical procedures used are stability indicating. No out of specification results or significant trends have been observed.

As a limited amount of stability data is available to date and considering that temperature- and time-dependent formation of impurities (5-HMF and Impurity D) was observed in development batches stored at intermediate and accelerated storage conditions, a precautionary storage condition of below 25°C is applied.

A photostability study has been performed. Based on the available data, as long as the finished product is stored in the proposed primary container closure (amber glass bottle (type III)), there is no change due to light exposure.

The shelf-life of 24 months with the storage recommendation 'Do not store above 25°C' is considered acceptable.

A stability study was conducted to define the storage recommendation after first opening. The first in-use evaluation was started after 6 months long-term storage. The second in-use evaluation was started after 18 months storage. The quality of the product can be confirmed for an opened container for 6 weeks. The in-use shelf life "After first opening: use within 6 weeks" is stated in SmPC section 6.3.

3.2.5. Post-approval change management protocol(s)

Not applicable.

3.2.6. Adventitious agents

No materials of human or animal origin are used.

3.3. Discussion on chemical, pharmaceutical and biological aspects

The information provided on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

The manufacturing process for the suspension is classified as a non-standard process due to the low active substance content. During the procedure, a MO was raised requesting further detail on the manufacturing process and controls, which was provided by the applicant.

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.

3.4. Conclusions on 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.

3.5. Recommendation(s) for future quality development

Not applicable.

4. Non-clinical aspects

Apart from an updated ERA, no new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

4.1.1. Ecotoxicity/environmental risk assessment

For the present extension of application, the ERA was updated to the revised guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.), including new $PEC_{surface\ water}$ calculations, considering the new additional indication (minors 2-17 years) and consequently an updated risk characterisation for the surface and groundwater compartment as well as for the STP.

Table 1: Summary of main study results: Phase I

Substance (INN/Invented Name):	Budesonide		
CAS-number (if available):	51333-22-3		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Kow	OECD107	3.23 at pH 6.2 (water w/o buffer)	Potential PBT: N
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	log Kow	3.23 at pH 6.2	potentially B
	BCFssl	9 L/kg_{ww}	Not B
Persistence	Ready biodegradability	N	potentially P
	$DT_{50,sediment}$ at 12°C	62.6 d	not P
Toxicity	$NOEC_{aquatic}$	0.000032 mg/L	T
PBT/vPvB statement:	Budesonide is considered to be not PBT, nor vPvB		

Phase I			
Parameter	**Value**	**Unit**	**Conclusion**
PEC_{sw}, refined (prevalence)	0.00137	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)	Potential Endocrine Disruptor		Y

Table 2: Summary of main study results: Phase II

Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Result**			**Remarks**
Adsorption-Desorption Soil 1 = Clay	OECD 106				No correlation with OC OC Soil 1 = 1.3 %
Soil 2 = Silt Loam		$K_{F, soil\ 1}$ = 41 L/kg$_{oc}$			OC Soil 2 = 3.7 %
Soil 3 = Loam		$K_{F, soil\ 2}$ = 22 L/kg$_{oc}$			OC Soil 3 = 3.45 %
Soil 4 = Silt		$K_{F, soil\ 3}$ = 19 L/kg$_{oc}$			OC Soil 4 = 1.55 %
Soil 5 = Loamy Sand		$K_{F, soil\ 4}$ = 17 L/kg$_{oc}$			OC Soil 5 = 9.25 %
Ready Biodegradability Test	OECD 301F	$K_{F, soil\ 5}$ = 31 L/kg$_{oc}$			OC Soil 5 = 9.25 %
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 'River' = loamy sand	OECD 308	0 % (28 d) not readily biodegradable			
Sediment 2 'Pond' = silt loam		$DT_{50, water\ 1}$ = 6.5 d $DT_{50, sediment\ 1}$ = 22.7 d $DT_{50, whole\ system\ 1}$ = 12.5 d CO_2 = 86.2 % NER_{total} = 9.3 % $NER_{type\ I}$ = n/d			21.2 °C CO_2 and NER values at test end
		$DT_{50, water\ 2}$ = 6.9 d $DT_{50, sediment\ 2}$ = 29.4 d $DT_{50, whole\ system\ 2}$ = 18.1 d CO_2 = 54.8 % NER_{total} = 14.7 % $NER_{type\ I}$ = n/d			21.2 °C CO_2 and NER values at test end (98 d)
Phase II Aquatic effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ Pseudokirchneriella subcapitata	OECD 201	NOEC	⩾ 7900	µg/L	growth rate
Daphnia sp. Reproduction Test/ Daphnia magna	OECD 211	NOEC LOEC EC10 EC50	3360 6950 3990 5300	µg/L	mortality of offspring
Fish, FFLC/ Danio rerio	OECD 240 (conducted bevor adoption of GL)	NOEC LOEC	0.032 0.1	µg/L	28 d survival of F1 generation
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	10^6	µg/L	total respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/n/a			n/d	mg/kg$_{dw}$	No sediment dwelling organism test required due to specific work mechanism of Budesonide
Phase II Secondary poisoning					
Bioaccumulation Test/ Cyprinus carpio Test 1 = 0.3 µg/L Test 2 = 3.0 µg/L	OECD 305	$BCF_{ssL, 1}$ $BCF_{ssL, 2}$	8 9	L/kg L/kg	Measured BCF at steady state. No depurination stage included in test due to low BCF value. 5% lipid normalization of BCF.

Risk characterisation				
Compartment	**PEC**	**PNEC**	**RQ**	**Conclusion**
STP	0.0137 µg/L	10^6 µg/L	1.37×10^{-7}	No risk
Surface water	0.00137 µg/L	0.0032 µg/L	0.43	No risk
Groundwater	7.16×10^{-8} µg/L	0.00032 µg/L	2.24×10^{-4}	No risk
Sediment	0.037 mg/kg_{dw}	n/d	<1	No risk (cf. comment on sediment study

Considering the above data of the definitive hazard assessment, budesonide is not a PBT or vPvB substance. Considering the above data from Phase I and Phase II, budesonide is not expected to pose a risk to the environment.

5. Clinical aspects

Introduction

This submission concerns the introduction of a new strength and age-appropriate formulation (0.2 mg/mL oral suspension) for the "treatment of eosinophilic esophagitis (EoE) in paediatric patients 2 to 17 years of age". Budesonide 0.2 mg/mL oral suspension is presented in a multidose container and is administered by means of a 5 mL oral syringe (single dose: 2.5 mL respectively 5 mL).

Data are presented from the following studies:

- Study BUL-007/BIO: A two-period, sequential, open-label phase I study in healthy subjects to compare budesonide orodispersible tablets and budesonide oral suspension using pharmacoscintigraphic imaging.
- Study BUU-008/BIO: An open-label, single-centre, two-part trial in healthy subjects to assess the food effect and the pharmacokinetics (PK) of single and multiple doses of budesonide 0.2 mg/mL oral suspension.
- 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.
- Population PK Analysis of Budesonide oral suspension in the Paediatric Population.

In addition, the MAH refers to another study (study BUL-6/BIO) comparing the oral suspension vs the already approved two dose strengths (0.5 mg and 1 mg orodispersible tablets). This study has been already submitted and assessed within the scope of extension EMEA/H/C/004655/X/0007/G.

The population PK analysis was conducted using data from study BUU-5/EEA and earlier studies with the orodispersible tablets (including BUU-1/BIO and BUL-6/BIO) to characterise budesonide exposure across age groups and support the dose selection in children. Study BUU-1/BIO has been already submitted and assessed within the scope of the initial MAA.

No other new PK, or pharmacodynamics (PD) data are submitted, however, 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 extension (studies BUL-007/BIO and BUU-008/BIO, the population PK analysis as well as a summary of study BUL-6/BIO and study BUU-5/EEA).

5.1.1. GCP aspects

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.

5.1.2. Tabular overview of clinical trials

Table 3: Tabular overview of pivotal clinical study BUU-5/EEA

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
BUU-5EEA	The study was conducted from 03.09.2019 to 07.08.2023. 76 patients were randomized. The planned sample size was 69 FAS patients	DB, RD, PC, parallel group trial. The DB treatment phase included two active (high and low dose) treatment arms and 1 placebo arm.	12weeks placebo controlled phase, followed by 12 weeks OL induction for eligible patients and 24 weeks OL extension. 3 weeks tapering and 4 weeks follow-up. Oral administration of high and low-dose budesonide suspension	Paed. patients from 2 to < 18 yrs. with symptomatic clinic-histological EoE

RD = randomised; DB = double blind; PC = placebo controlled; EoE = eosinophilic esophagitis; OL =open label; yrs = years

5.2. Clinical pharmacology

Budesonide 0.2 mg/mL oral suspension is intended to act locally on the oesophageal mucosa in the treatment of EoE. As such, the focus is on achieving local efficacy with minimal systemic absorption. Systemic exposure is considered minimal, and PK data support this local mechanism of action. Budesonide undergoes extensive first-pass metabolism in the liver via CYP3A4, leading to low systemic concentrations of the parent compound. After oral administration most of the drug acts locally in the oesophagus and is swallowed and metabolized before reaching systemic circulation. The main metabolites, 6β-hydroxybudesonide (6β-OH-budesonide) and 16α-hydroxyprednisolone (16α-OH-prednisolone), are considered pharmacologically inactive and do not contribute to the therapeutic effect.

5.2.1. Methods

Summary of Analytical Methods

The quantification of budesonide and its metabolites in clinical studies supporting this application was conducted using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. These assays were developed and validated by Nuvisan GmbH and ACC GmbH for use in plasma and

urine samples, with performance characteristics aligned to ICH guidelines for bioanalytical method validation.

Table 4: Summary of Analytical Methods and Key Characteristics

Method	Analytes	Matrix	Validation Site	Studies Applied
UX030	Budesonide, 6β-OH-budesonide, 16α-OH-prednisolone	Plasma	Nuvisan GmbH	BUU-1/BIO
UX031	Budesonide, 6β-OH-budesonide, 16α-OH-prednisolone	Urine	Nuvisan GmbH	BUU-1/BIO
UX032	Cortisol	Plasma/Urine	Nuvisan GmbH	BUU-1/BIO
014B19-Val	Budesonide, 6β-OH-budesonide, 16α-OH-prednisolone	Plasma	ACC GmbH	BULU-6/BIO
011B20-Val	Budesonide, 6β-OH-budesonide, 16α-OH-prednisolone	Plasma	ACC GmbH	BUL-007/BIO, BUU-008/BIO

Table 5: Method Usage per Study

Study	Matrix	Method ID	Bioanalytical Laboratory
BUU-1/BIO	Plasma & Urine	UX030 / UX031 / UX032	Nuvisan GmbH
BUU-6/BIO	Plasma	014B19-Val	ACC GmbH
BUL-007/BIO	Plasma	011B20-Val	ACC GmbH
BUU-008/BIO	Plasma	011B20-Val	ACC GmbH

Incurred Sample Reanalysis

Incurred sample reanalysis was performed in accordance with EMA bioanalytical method validation guidance. ISR confirmed assay reproducibility, with results meeting predefined acceptance criteria (≥67% of ISR samples within ±20% of original values).

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

Budesonide 0.2 mg/mL oral suspension is intended to act locally on the oesophageal mucosa in the treatment of EoE. As such, the focus is on achieving local efficacy with minimal systemic absorption. Systemic exposure is considered minimal, and PK data support this local mechanism of action.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population Pharmacokinetics

The adult model was built on limited data of EoE patients (n=12), patients had a different clearance (46.5% lower) than healthy volunteers (n=48). Several changes were necessary when applying the adult model to the paediatric population (addition of an allometric body weight scaling effect on CL with a fixed exponent of 0.75, removing IOV on F1, and estimating F1 (36.3% of adult estimate) along with IIV on F1 (178%) separately for children). The cause of the big difference in F1 could not be

explained, according to the company, it remains unclear whether this was study specific or revealed a real difference between adults and paediatrics. Adult patients had taken orodispersible tablets whereas paediatric patients took budesonide as suspension. Even if the final model did not describe a difference in F between formulations, the plots in figure 2 showed that after administration of suspension, concentrations tend to be lower. This might in part explain the differences between age groups.

The target for paediatric dose definition was not completely clear. Exposures in paediatric patients were not related to adult efficacious and safe exposures but only compared within the paediatric age groups.

Adolescent patients received the same dose as adults, all paediatric patients aged 2-11 years received half of the adult dose, without further adjustment to body weight. Resulting exposures show that younger children (2-<6 years) in the mean have higher exposure but are still in the same range as older children and adolescents. Due to high inter-individual variability (178%) in bioavailability and the limited number of paediatric patients investigated in this age range (n=7), also keeping in mind that one third of exposures were simulated (placebo group) and not observed, it remains uncertain, whether exposures in a larger population of 2-5 year-olds will still be in an acceptable range or might be safety-relevant. Exact numbers of patients treated in the different randomisation groups (high/low dose or placebo) are requested as well as additional plots clearly separating between high dose, low dose and without simulated data from the placebo group.

5.2.2.2.2. Physiology based pharmacokinetic model

N/A

5.2.2.3. Absorption

Following administration of Jorveza, budesonide is rapidly absorbed. Pharmacokinetic data following administration of single doses of 1 mg budesonide to fasted healthy adult subjects in two different PK studies (BUU-1/BIO and BUU-6/BIO) 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 adult 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.

Adult patients showed a 35% increase in peak plasma concentrations and a 60% increase in AUC_{0-12} compared to healthy adult 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 in study BUU-6/BIO.

Study BUL-7/BIO

Study BUL-007/BIO was a single-centre, open-label, sequential, single-dose (1 mg) two-period scintigraphic imaging trial conducted in 11 healthy male participants, 10 of whom completed both treatment regimens as per protocol. The primary aim of the study was to assess the oesophageal transit of the budesonide orodispersible tablet (ODT;'Test') and budesonide oral suspension (OS) using scintigraphic techniques. Secondary objectives included the evaluation of the pharmacokinetics (PK) of

budesonide and its metabolites following administration of each formulation, along with assessments of safety and tolerability. Each dose of budesonide was administered under fasting conditions and radiolabelled with no more than (NMT) 1 MBq of 111In (indium-111).

Each study period was separated by a minimum washout interval of 48 hours. Scintigraphic imaging of the head and thorax was performed from immediately before dosing up to 40 minutes post-dose. Imaging included 10 minutes of dynamic acquisition, followed by 10 minutes of continuous static imaging (25-second frames taken continuously with minimal interruption to allow subject repositioning), and finally 20 minutes of static imaging at approximately 2-minute intervals. Blood samples were collected at scheduled time points up to 24 hours after dosing to determine plasma concentrations of budesonide, 6β-hydroxy-budesonide, and 16α-hydroxy-prednisolone using validated analytical assays. Safety assessments comprised monitoring of adverse events (AEs), laboratory evaluations (including hematology, clinical chemistry, and urinalysis), vital signs, electrocardiograms (ECGs), body weight, and physical examination findings.

Scintigraphic results

Administration of Budesonide OS resulted in a mean total esophageal transit time of 8.7 minutes (range: 0.20–35.63 min), compared to a markedly longer average of 83.7 minutes (range: 9.23–119.77 min) for the ODT. Median transit times were 3.7 minutes for the OS and 106.9 minutes for the ODT—approximately a 30-fold increase with the latter. High inter-subject variability was observed for both formulations: 128.7% for the OS (reduced to 0.20–14.10 min when excluding one outlier) and 53.7% for the ODT. In five ODT-treated subjects, residual radioactivity remained detectable in the mouth and esophagus at 120 minutes, potentially leading to slight underestimation of their transit times. However, these findings highlight a clear and substantial difference in esophageal transit between the two formulations.

Table 6: Arithmetic mean, median (arithmetic CV%) quantitative oesophageal transit rate parameters (Study BUL-007/BIO)

Treatment	Summary Statistic	T10%* (min)	T50% (min)	T90%* (min)	T_{max*} (min)	T-90%* (min)
Regimen A ^{111}In-Budesonide OS [N=10]	Mean Median CV%	0.007 0.005 (76.7%)	0.021 0.022 (36.6%)	0.061 0.044 (71.1%)	0.063 0.050 (97.5%)	3.539 0.248 (271.9%)
Regimen B ^{111}In-Budesonide ODT [N=10]	Mean Median CV%	4.650 4.184 (59.0%)	7.170 5.938 (61.5%)	22.404 13.227 (121.6%)	9.585 11.267 (56.3%)	10.218 11.481 (54.4%)

*Data from n=9 for Regimen B
T10%: Time at which 10% radiolabel has arrived in the oesophagus from the mouth (90% left in mouth)
T50%: Time at which 50% radiolabel has arrived in the oesophagus from the mouth (50% left in mouth)
T90%: Time at which 90% radiolabel has arrived in the oesophagus from the mouth (10% left in mouth)
T-90%: Time at which 90% radiolabel present at Tmax has left the oesophagus and arrived in the stomach (10% peak left in oesophagus)
T_{max}: Time at which the amount of radiolabel present in the oesophagus peaks
All subjects were planned to receive a single dose of 1 mg [^{111}In]-Budesonide OS and a single dose of 1 mg [^{111}In]-Budesonide ODT across Periods 1 and 2.
Source: Table 7, CSR BUL-007/BIO (Module 5.3.3.1)

Arithmetic mean radioactivity levels in the mouth, oesophagus, and stomach (measured at 30-second intervals) for 111In-Budesonide OS and ODT are shown in Figure 1 and Figure 2. Median overall exposure (AUC) in the mouth was less than 1% for the OS compared to the ODT, largely due to the ODT's slow disintegration and sustained release of budesonide. Over half of the oral exposure with the ODT was linked to the presence of undissolved tablet core. In the oesophagus, median exposure (AUC) with the ODT was approximately 1.9 times higher during dynamic imaging and 3.3 times higher over the full 40-minute imaging period compared to the OS.

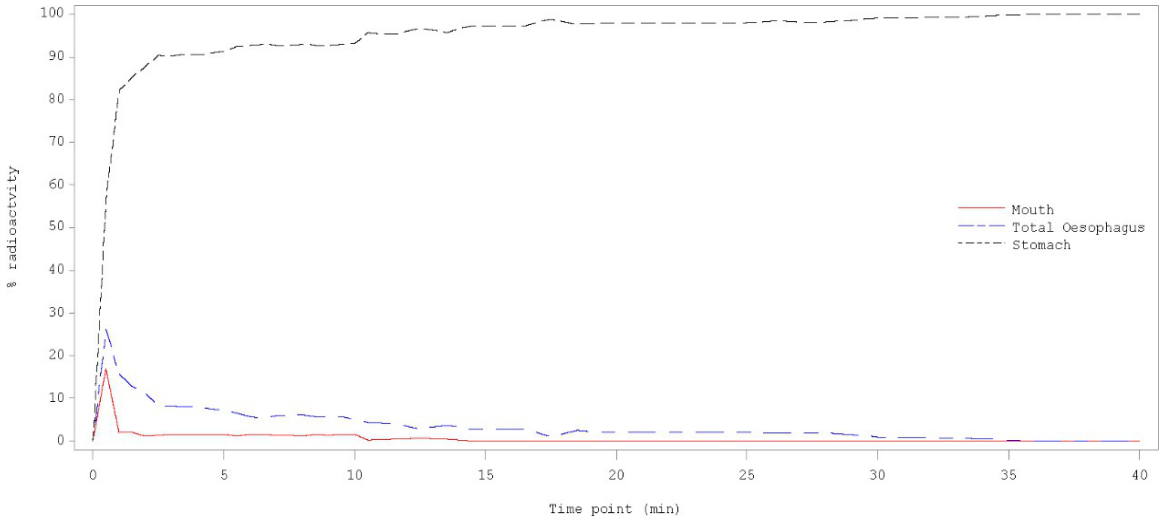


Figure 1: Arithmetic Mean Percent Radioactivity (30-sec interval) Present in Mouth, Total Oesophagus and Stomach Following Oral Administration of 111In-Budesonide OS (Linear/Linear): Scintigraphic Analysis Set (Study BUL-007/BIO), Source: Figure 2, CSR BUL-007/BIO (Module 5.3.3.1)

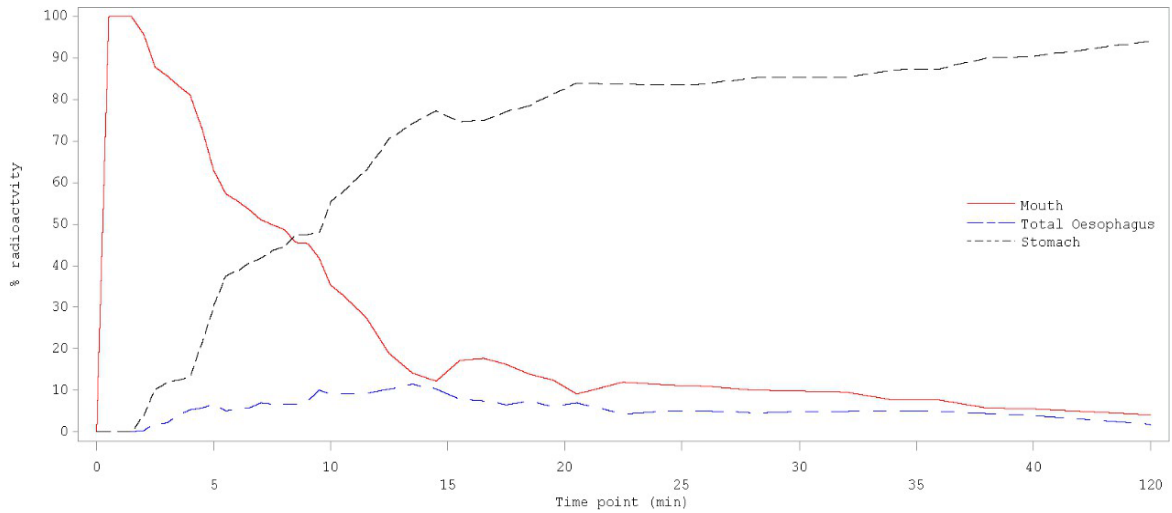


Figure 2: Arithmetic Mean Percent Radioactivity (30-sec interval) Present in Mouth, Total Oesophagus and Stomach Following Oral Administration of 111In-Budesonide ODT (Linear/Linear): Scintigraphic Analysis Set (Study BUL-007/BIO), Source: Figure 2, CSR BUL-007/BIO (Module 5.3.3.1)

Pharmacokinetic results

Budesonide was absorbed more rapidly from the OS than the ODT, with median tmax values of 1.0 and 1.375 hours, respectively. Peak plasma concentrations (Cmax) were similar for both, but overall exposure (AUC_0–last and AUC_0–inf) was significantly higher with the ODT ($p < 0.05$). Budesonide was quickly metabolized to 6β-hydroxy-budesonide and 16α-hydroxy-prednisolone, with comparable tmax values across formulations. Cmax values for both metabolites were lower with the ODT, reaching statistical significance for 6β-hydroxy-budesonide ($p = 0.02$), though AUC values were similar between formulations. Notably, metabolite-to-parent ratios (MPRs) for Cmax and AUCs were significantly lower with the ODT ($p < 0.05$). Plasma half-lives for budesonide and its metabolites were consistent across both formulations.

Study BUU-8/BIO

Study BUU-008/BIO was a single-centre, open-label, two-part trial conducted in 18 healthy male and nonpregnant female subjects. The aim was to evaluate the pharmacokinetics of budesonide oral suspension following both single and multiple doses, and to investigate the effect of food on its pharmacokinetic profile after single-dose administration.

In Part I, participants received a single 5 mL dose of budesonide 0.2 mg/mL oral suspension under three conditions: fasting (Treatment A), after a high-fat, high-calorie meal (Treatment B), and after a moderate meal (Treatment C). The study followed a three-period, three-sequence crossover design, with doses administered on Days 1, 4, and 7, each separated by a 72-hour washout. In each period, 25 blood samples were collected to assess concentrations of budesonide and its metabolites, 6β-hydroxy-budesonide and 16α-hydroxy-prednisolone.

Part II involved multiple-dose administration of 5 mL of the same suspension twice daily (BID) once in the morning and once in the evening for seven consecutive days. From Days 9 to 14, doses were given after a standard breakfast and dinner, spaced 12 ± 1 hours apart. On Day 15, dosing occurred 30 minutes after the start of a moderate meal, again 12 hours apart. Pre-dose samples were taken on Days 12 to 15, with 33 additional post-dose samples collected after the morning dose on Day 15.

Pharmacokinetic results Part I

Following administration of budesonide oral suspension with food (high-fat-high-calorie or moderate meal), Cmax decreased by approximately 36–41%, and tmax was delayed by 0.9 to 1.25 hours compared to fasting, indicating slower absorption (Table *7*). A similar food effect was observed for metabolites. However, the extent of absorption remained unaffected, as systemic exposure (AUC_0–t and $AUC_{0-\infty}$) was comparable across fed and fasted conditions. Geometric mean ratios and 90% confidence intervals for ln-transformed AUC values remained within the 80–125% bioequivalence range.

Table 7: Summary Statistics of the Pharmacokinetic Parameters for Budesonide Following Single Dose Administration of Budesonide Under Fasting (Treatment A) and Under Fed (With a High-Fat-High-Calorie Meal [Treatment B] and a Moderate Meal [Treatment C]) Conditions (Study BUU-008/BIO)

Parameter (unit)	Treatment A (n=18)	Treatment B (n=18)	Treatment C (n=18)
C_{max} (pg/mL)	385.770 (72.04%)	228.630 (52.65%)	247.438 (57.45%)
T_{max} (h)	1.000 (0.500 - 1.750)	2.250 (0.500 - 5.500)	1.750 (0.500 - 5.000)
T_{lag} (h)	0.000 (0.000 - 0.250)	0.000 (0.000 - 0.250)	0.000 (0.000 - 0.250)
C_{last} (pg/mL)	6.156 (54.01%)	6.804 (65.08%)	6.448 (52.86%)
T_{last} (h)	18.010 (18.000 - 24.000)	24.000 (18.000 - 24.030)	21.000 (18.000 - 24.020)
AUC_{0-t} (pg.h/mL)	1428.170 (64.56%)	1472.189 (47.20%)	1362.518 (50.85%)
AUC_{0-12} (pg.h/mL)	1310.494 (62.78%)	1256.592 (45.88%)	1221.838 (48.64%)
AUC_{0-24} (pg.h/mL)	1443.662 (63.27%)	1477.272 (46.35%)	1375.579 (49.74%)
$AUC_{0-\infty}$ (pg.h/mL)	1468.472 (64.16%)	1527.264 (47.70%)	1395.193 (52.58%)[#]
$\%AUC_{extrap}$ (%)	2.448 (54.07%)	2.980 (68.52%)	2.408 (64.48%)[#]
λ_z (1/h)	0.1713 (22.51%)	0.1494 (23.21%)	0.1797 (28.23%)[#]
$t_{1/2}$ (h)	4.046 (22.51%)	4.638 (23.12%)	3.857 (28.19%)[#]

n - Number of Subjects
Values are geometric mean (Gmean) with geometric coefficient of variation (GCV%) between parenthesis
Tmax, Tlag and Tlast values are median with range between parentheses
#For AUC0-∞, %AUC extrap, λz, t1/2, n=17 for Treatment C
Source: Table E1, CSR BUU-008/BIO

Pharmacokinetic results Part II

Following twice-daily dosing of budesonide oral suspension over seven days, steady state was achieved. On Day 15, budesonide showed ~15% accumulation in exposure (AUC_{0}–24,ss) compared to a single dose, consistent with the mean elimination rate constant (0.17 h^{-1}). No accumulation was observed for the metabolites. Steady-state and single-dose comparisons indicated linear pharmacokinetics for budesonide and its metabolites (6β-OH-budesonide and 16α-OH-prednisolone). Metabolic ratios normalized by molecular weight were similar between dosing regimens, confirming linearity. Additionally, 16α-OH-prednisolone exposure was approximately ten times higher than 6β-OH-budesonide. PK profiles are shown in Figure 3.

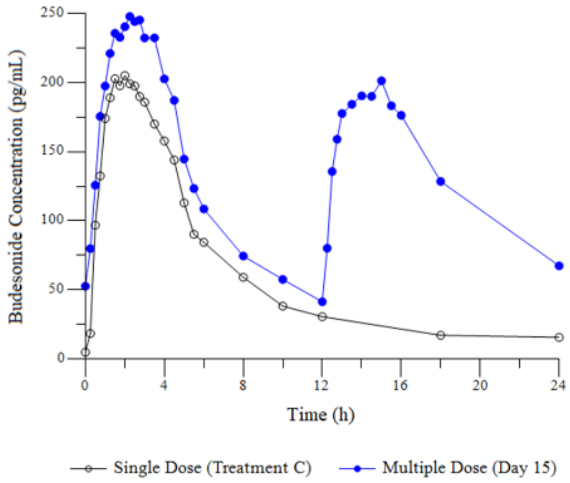


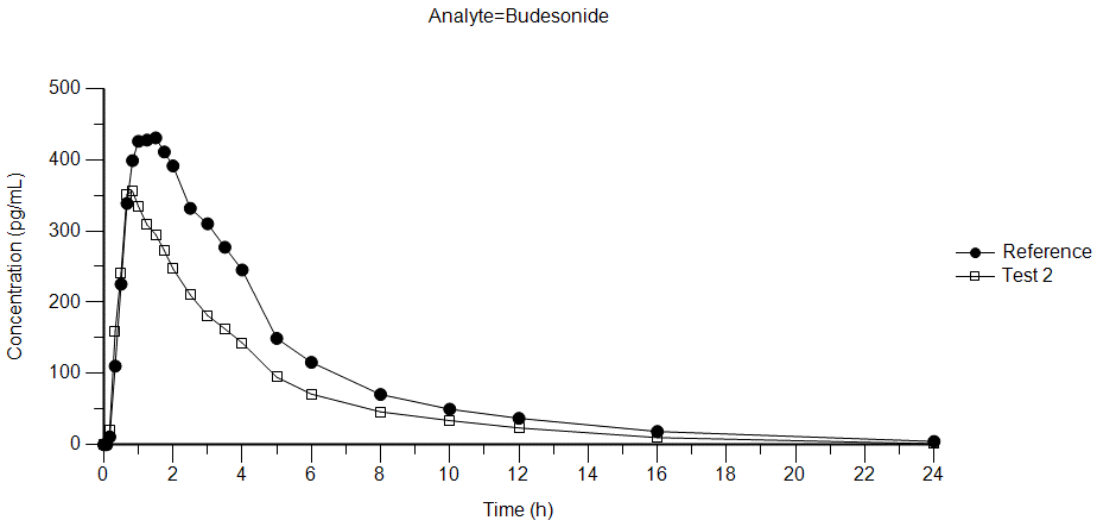
Figure 3: Geometric Mean Plasma Concentration Versus Time Profiles for Budesonide Following Single dose (Treatment C) and Twice a Day Administration of Budesonide at Steady State (Day 15) – Linear Scale (Study BUU-008/BIO), Source: Figure 2.5-2 Module 2.5

5.2.2.4. Bioequivalence

Study BUL-6/BIO

Table 8: Parametric point estimates and 90 % confidence intervals determined for the secondary pharmacokinetic parameters of budesonide; comparison of Test 2 (oral suspension) vs. Reference (orodispersible tablet)

Parameter	Observations	Point Estimate	90 % confidence interval		CV_{ANOVA} (%)
			Lower Limit (%)	Upper Limit (%)	
$AUC_{0\text{-inf}}$	36	66.42	58.51	75.39	21.93
$AUC_{0\text{-tlast}}$	36	65.76	57.52	75.18	23.21
C_{max}	36	82.33	71.6	94.68	24.26



5.2.2.5. Distribution

No new data has been provided.

The apparent volume of distribution following oral administration of 1 mg budesonide to healthy adult 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%.

5.2.2.6. Metabolism

No new data has been provided.

Metabolism of budesonide is decreased in EoE adult patients compared to healthy adult 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.

5.2.2.7. Elimination

No new data has been provided.

The median elimination half-life is 2 - 3 hours in healthy adult subjects (receiving 1 mg budesonide) and 4 - 5 hours in EoE adult patients (receiving 4 mg budesonide). Clearance of budesonide is about 13 – 15 L/hour/kg in healthy adult subjects and 6.54 ± 4.4 L/hour/kg in EoE adult patients. Budesonide is eliminated only in marginal if any amounts by the kidney. No budesonide, but only budesonide metabolites were detected in urine.

5.2.2.8. Dose proportionality and time dependency

No new data has been provided.

Dose proportionality of the systemic exposure (Cmax and AUC) from 0.5 mg orodispersible tablets to 1 mg orodispersible tablets has been demonstrated in study BUU-6/BIO.

5.2.2.9. Pharmacokinetics in the target population

In Study BUU-5/EEA, PK data were collected; however, these data were not submitted.

5.2.2.10. Special populations

No new data has been provided.

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[1,2,3,4].

[1] Edsbäcker S and T Andersson: Pharmacokinetics of Budesonide (Entcort TM EC) capsules for Crohn's Diesease. Clin Pharmacol 2003, 43: 803-821.
[2] 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.
[3] Rautiainen H et al: Pharmacokinetics and bone effects of budesonide in primary biliary cirrhosis. Aliment Pharmacol Ther 2006; 24: 1545-1552.
[4] 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.

Regarding 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.

5.2.2.11. Pharmacokinetic interaction studies

As already 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[5,6].

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[7] . 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 about 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 BUU-1/BIO 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 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 studies BUU-6/BIO and BUU-8/BIO investigating the novel oral solution. This is in agreement with literature data for other budesonide formulations, and no further information is requested.

5.2.3. 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.

[5] Jönsson G et al: Budesonide is metabolized by cytochrome P450 3A (CYP3A) enzymes in human liver; Drug Metab Dispos 1995; 23: 137-142.
[6] 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.
[7] 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.

In the context of the initial MAA, study BUU-1/BIO has also investigated the influence of EoE symptoms in the adult 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.

5.2.3.1. 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.

5.2.3.2. Primary and secondary pharmacology

The effects of topically acting glucocorticosteroids on the inflamed oesophageal mucosa of EoE adult patients have also extensively been described in the literature[8,9], 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 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 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 adult subjects, as well as in EoE adult patients. This was also reflected in the urinary excretion of cortisol, which also showed a relevant decrease after multiple-dose administration.

5.2.4. Overall discussion and conclusions on clinical pharmacology

5.2.4.1. Discussion

The MAH conducted only limited investigations into the pharmacokinetics (PK) and pharmacodynamics (PD) of budesonide, relying on the well-established profile of the active substance. Given the known class effects of glucocorticosteroids, further characterisation was not deemed necessary. Similarly to the PK development programme, this is based on the fact that the substance budesonide is well known

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

and effects of glucocorticosteroids do not need to be further characterised. The development strategy therefore included extrapolation from existing budesonide-containing medicinal products, which is considered reasonable overall.

In the present application, the MAH submitted results from two newly conducted PK studies:

- **Study BUL-7/BIO**: An open-label, sequential, single-dose (1 mg = 5 mL) two-period scintigraphic imaging trial.
- **Study BUL-8/BIO**: An open-label, two-part trial evaluating the PK of budesonide oral suspension after single (1 mg) and multiple doses (1 mg BID), including the effect of food on its PK profile following single-dose administration.

In addition, the MAH referred to previously submitted data from **Study BUL-6/BIO**, assessed under extension EMEA/H/C/004655/X/0007/G:

- **Study BUL-6/BIO**: An open-label randomised, three-period, three-sequence, single-dose crossover trial comparing the PK of the oral suspension (1 mg = 5 mL) with the already approved 0.5 mg and 1 mg budesonide orodispersible tablets (ODT, Jorveza).

The combined results from studies BUL-6/BIO, BUL-7/BIO, and BUL-8/BIO provide a comprehensive assessment of the oral suspension (OS) formulation, particularly in terms of esophageal transit behavior and pharmacokinetics. Through studies, the OS demonstrated physicochemical and absorption characteristics relevant to local esophageal delivery.

Study BUL-6/BIO revealed notable PK differences between the OS and ODT formulations. The OS showed lower systemic exposure and higher metabolic clearance, likely reflecting differences in absorption sites. While the ODT may enable more direct absorption via the esophageal mucosa, potentially bypassing first-pass hepatic metabolism, the OS appears to be primarily absorbed in the upper small intestine, where it is subject to greater pre-systemic metabolism. The PK differences for similar doses, however, are not of concern, due to the fact that own clinical data for this formulation are expected to be generated in the clinical studies in children and adolescents.

Study BUL-008/BIO showed that food intake delayed absorption and reduced Cmax, without affecting overall exposure (AUC). Based on these findings and consistent with the administration in the pivotal efficacy study the applicant proposes that the OS should be taken after a meal. Multiple-dose data indicated limited accumulation (~15%) and linear pharmacokinetics for budesonide and its metabolites, supporting dose predictability under repeated administration.

In **Study BUL-007/BIO**, the oral suspension demonstrated longer-than-expected esophageal transit for a non-viscous liquid, which may support local therapeutic potential. However, significant inter-subject variability reduces the robustness of this finding. Compared with the ODT, the OS exhibited shorter mucosal contact time and lower esophageal exposure, which may be relevant when assessing clinical efficacy.

The **paediatric popPK model** including allometric scaling (with exponents 0.75 for clearances and 1 for volumes) revealed higher average exposure in the youngest age group (2-5 years). Observed data were quite limited, especially in the youngest age group (n=7 devided in high, low and placebo group) and interindividual variability was very high and number of BLQ samples was very high.

After multiple-dose administration, the endogenous cortisol levels were clearly lowered (compared to the single-dose reference intake), both in healthy adult subjects, as well as in EoE adult 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 also in children and adolescents and is outlined in 4.4 of the SmPC.

5.2.4.2. Conclusions

The newly submitted PK studies provide a reasonable characterisation of the oral suspension formulation, demonstrating appropriate oesophageal delivery and predictable systemic exposure. However, notable formulation-related PK differences exist and paediatric data particularly in the 2–5-year age group, remain limited and variable. Clarification on patient numbers per dose group and plots excluding simulated data were requested to further support the paediatric assessment. These data and figures were provided and results were considered acceptable.

5.3. Clinical efficacy

5.3.1. Dose response study

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.

5.3.2. Main study(ies)

5.3.2.1. Study BUU-5/EEA

5.3.2.1.1. Study title

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.

5.3.2.1.2. Study design

Study BUU-5/EEA was a double-blind, randomized, multicenter, placebo-controlled, comparative, Phase II/III clinical trial in children and adolescents with EoE, ≥2 to <18 years of age. The trial comprises three treatment groups with parallel group comparison to compare a 12-week oral treatment with different daily doses of budesonide oral suspension (high dose and low dose) vs. placebo for the treatment of active EoE. 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, a 3-week tapering phase, and a 4-week follow-up period after the patient's last end of treatment visit. The trial enrolled paediatric patients. with symptomatic clinico-histological EoE. Patients were randomized in two age strata (Stratum 1: 2 to 11yrs., Stratum 2: 12 to< 18yrs.).

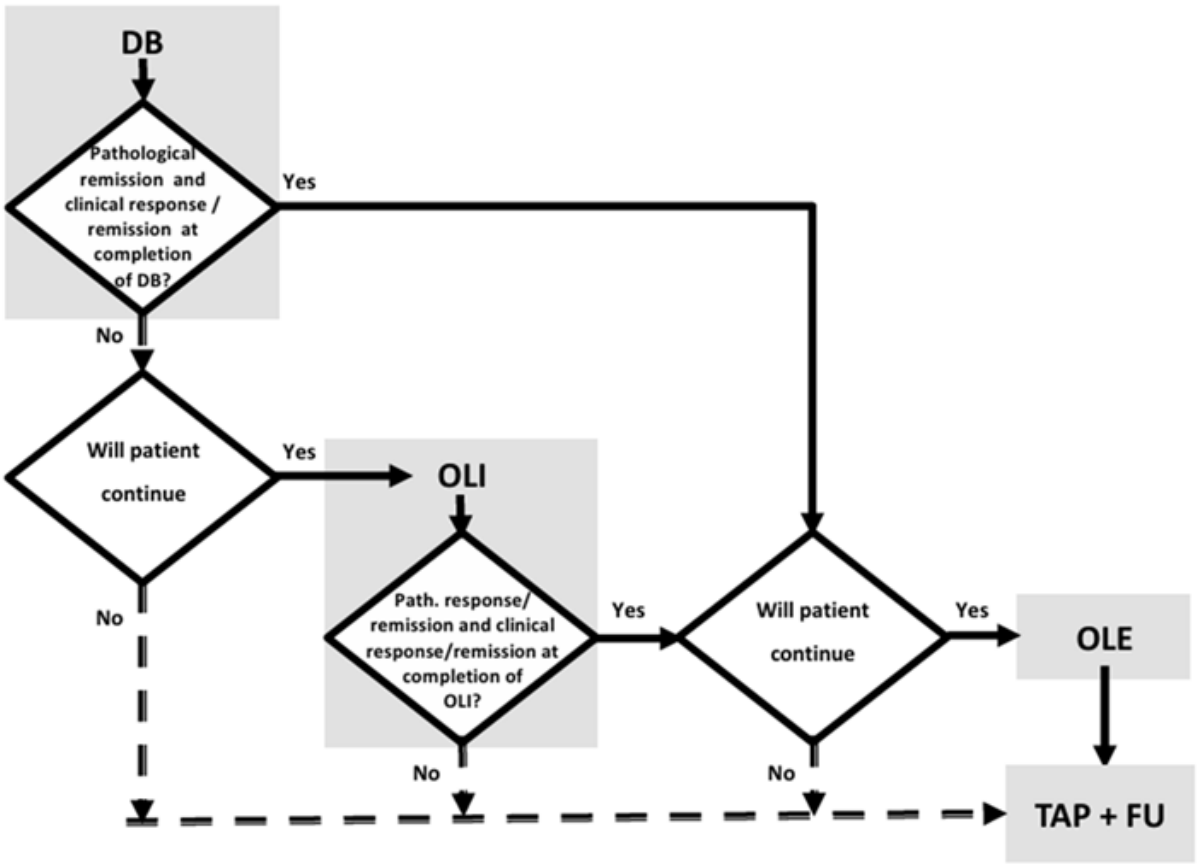


Figure 4: Patient trial flow
DB: double-blind; OLI: open-label induction phase (optional); OLE open-label extension phase (optional);
TAP tapering phase; FU follow-up phase

5.3.2.1.2.1. Treatment

The trial evaluated two dose levels per age stratum in the double-blind treatment phase.

Table 9: Dosing Scheme Stratum I and Stratum II Double-Blind Phase

DB Dosing Scheme (Stratum I: Age 2 to 11 years at DB V1)

	Group	Morning budesonide / placebo dose	Evening budesonide / placebo dose	Total daily budesonide dose [mg]	Total budesonide dose / DB phase 12 weeks [mg]
	Study phase	DB V1 – DB V4 / EOT			
A	Low-Dose ("BUU-L")	0.5 mg budesonide/ 2.5 ml	placebo/ 2.5 ml	0.5	42.0
B	High-dose ("BUU-H")	0.5 mg budesonide/ 2.5 ml	0.5 mg budesonide/ 2.5 ml	1.0	84.0
C	Placebo	placebo/ 2.5 ml	placebo/ 2.5 ml	0.0	0.0

DB Dosing Scheme (Stratum II: Age 12 to <18 years at DB V1)

	Group	Morning budesonide / placebo dose	Evening budesonide / placebo dose	Total daily budesonide dose [mg]	Total budesonide dose / DB phase 12 weeks [mg]
	Studyphase	DB V1 – DB V4 / EOT			
A	Low-dose ("BUU-L")	1.0 mg budesonide/ 5.0 ml	placebo/ 5.0 ml	1.0	84.0
B	High-dose ("BUU-H")	1.0 mg budesonide/ 5.0 ml	1.0 mg budesonide/ 5.0 ml	2.0	168.0
C	Placebo	placebo/ 5.0 ml	placebo/ 5.0 ml	0.0	0.0

The patients with insufficient response after 12 weeks had the option to enrol in an open label induction phase (OLI), where they received the higher dose level for another 12 weeks.

For the open label extension (OLE) phase, patients were treated on the low dose level for 24 additional weeks, unless the investigator chose to put the patient on an "escalated dose" corresponding to the higher dose level.

5.3.2.1.2.2. Randomisation

Patients were stratified by their age at baseline visit: Stratum I (Age 2 to 11 years) and Stratum II (age 12 < 18 years). Patients were centrally randomized 1:1:1 to receive a 12-week, double-blind treatment (with the possibility of early termination after 8 weeks of treatment in case of lack of efficacy) either with budesonide low dose or budesonide high dose or placebo.

5.3.2.1.2.3. Blinding

BUU-5/EEA was a double-blind study. The placebo oral suspension was identical in appearance and taste to the active substance oral suspension.

5.3.2.1.2.4. Patient population

The study enrolled patients from 2 to < 18 yrs. of age. with confirmed clinic- histological EoE (active histological EoE confirmed by central pathologist and defined as peak eosinophils ≥65/mm2 hpf in at least 1 hpf, out of a total of 6 hpfs derived from six oesophageal biopsy specimens at screening

endoscopy). Active symptomatic EoE was determined based on results from the Pediatric Eosinophilic Esophagitis (EoE) Symptom Score (PEESS) Version 2.0 (parent report for patients < 12 yrs. of age, and self-report for adolescents).

5.3.2.1.3. Objectives and estimands

5.3.2.1.3.1. Primary objective

The primary objective of the trial was to evaluate the superior efficacy of two doses of budesonide oral suspension compared to placebo for the induction of pathological remission and clinical response at DB week 12 (LOCF) in children and adolescents with EoE.

5.3.2.1.3.2. Estimands for the primary objective

Table 10: Estimands for primary objective

Population	Children and adolescents with active symptomatic EoE, ≥2 to <18 years of age
Treatment condition<s>	Two budesonide treatment regimens (low dose and high dose) compared to placebo ○ High dose budesonide treatment [1,0 mg/day for patients with age 2 to 11 years at DB V1 and 2,0 mg/day for patients with age 12 to <18 years at DB V1] for 12 weeks Low dose budesonide treatment [0,5 mg/day for patients with age 2 to 11 years at DB V1 and 1,0 mg/day for patients with age 12 to <18 years at DB V1] for 12 weeks
Endpoint (variable)	Pathological remission and clinical response at DB week 12 (LOCF) [yes or no], defined as fulfilling both criteria: - Histological remission, i.e., peak of <16 eos/mm^2 hpf at DB week 12 (LOCF), AND - Clinical response defined as: Stratum I: Age 2 to 11 years at DB V1: ≥ 30% drop in the total score of PEESS Version 2.0 – parent reported for children and teens (ages 2-18) from baseline to DB week 12 (LOCF), Stratum II: Age 12 to < 18 years at DB V1: ≥ 30% drop in the total score of PEESS Version 2.0 – children and teens report (ages 8-18) from baseline to DB week 12 (LOCF). Patients who experienced either a food impaction which needed endoscopic intervention, or who needed an endoscopic dilation at any time during the DB treatment phase, or who were prematurely withdrawn due to lack of efficacy after at least 8 patients of DB treatment and who showed no change or a deterioration in the Global Assessment Score (ParGA/PatGA) compared to baseline at their last visit in the DB treatment phase (DB V4 EOT/ withdrawal DB), were assessed as treatment failures, and thus did not fulfil by definition the 'pathological remission and clinical response' criterion.

Population-level summary	Difference in the proportions of patients with pathological remission and clinical response at DB week 12 (LOCF) between each budesonide treatment regimen (low dose or high dose) and placebo
Intercurrent events and strategy to handle them	
Premature withdrawal from DB treatment phase due to lack of efficacy with no change or a deterioration in the Patient's/Parent's Global Assessment [PatGA/ParGA] compared to baseline after ≥8 patients treatment	The composite variable strategy was applied, i.e., such premature discontinuation was counted as 'no'.
Other premature discontinuations	The while on treatment strategy was applied as far as data were available from the DB EOT visit. In case no post-baseline endoscopy was performed, the composite variable strategy was applied, i.e., such missing data were counted as 'no'.
Non-compliance with IMP intake, use of prohibited concomitant therapies and other protocol violations	The treatment policy strategy was applied, i.e., data were included in the analysis even if collected after occurrence of such an intercurrent event.

The clinical question of interest targets the effects of two budesonide treatment regimens compared to placebo in children and adolescents with active symptomatic EoE (refer to the detailed inclusion and exclusion criteria) in inducing pathological remission and clinical response at DB week 12 (LOCF) [refer to the detailed definition of the primary endpoint], regardless of actual eligibility according to inclusion and exclusion criteria, regardless of duration of and compliance with IMP intake, regardless of the use of prohibited concomitant therapies and regardless of other protocol violations. Patients who experienced either a food impaction which needed endoscopic intervention, or who needed an endoscopic dilation at any time during the DB treatment phase, or who were prematurely withdrawn due to lack of efficacy after at least 8 patients of DB treatment and who showed no change or a deterioration in the Global Assessment Score (ParGA/PatGA) compared to baseline at their last visit in the DB treatment phase (DB V4 EOT/ withdrawal DB), were assessed as treatment failures, and thus did not fulfil by definition the 'pathological remission and clinical response' criterion.

Statistical methods for estimation and sensitivity analysis on primary estimands

For the DB phase, efficacy evaluation was based on the FAS-DB [primary analysis set for efficacy analyses; all randomized patients (as randomized) who received at least one dose of IMP during the

DB phase] and on the per-protocol (PP) set (all patients of the FAS-DB, except for patients with major protocol violations).

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 adverse event with at least possible causal relationship with the IMP, or intolerable adverse event which was a deterioration of study disease, change of concomitant treatment with PPIs during the DB phase, DB V4/EOT (EOT/withdrawal DB 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 14 days.

The primary efficacy endpoint (and the a priori ordered key secondary efficacy endpoints) was subjected to a confirmatory statistical analysis (α=0.025, one-sided testing) with Bonferroni correction to account for multiple testing introduced by the evaluation of two budesonide groups. Confirmatory testing (one-sided) was performed for each budesonide treatment arm separately at Bonferroni adjusted significance level of 0.0125. The null hypotheses of a lower or equal percentage of patients in pathological remission and with clinical response at DB week 12 (LOCF) in each budesonide group compared to the placebo group were tested on a global one-sided significance level of 0.025 using Fisher's exact test (test for superiority). As described above, for each comparison of budesonide with placebo Bonferroni correction i.e., a one-sided significance level of 0.0125 was used. This enabled subsequent confirmatory testing of the key secondary endpoints in hierarchical fashion for each budesonide group with significant results for the primary endpoint, independently from the results for the other budesonide group. Two-sided 97.5% confidence intervals for the difference in remission rates were calculated.

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 an (exact) logistic regression taking the age strata into account, if warranted by the distribution of the data. Adjustment for the screening peak number of eos/mm^2 hpf and the baseline PEESS total score was also considered in this context.

Missing values of the efficacy parameters at the EOT/withdrawal DB visit were replaced by the last measurement (last measured week, if appropriate) obtained during DB treatment (last observation carried forward; LOCF). This means that baseline values were carried forward for patients who provide no post-baseline data. This approach is justified by the facts that the patients have been off systemic anti-inflammatory or EoE-specific treatment, or dietary restrictions for ≥4 patients and off topical anti-inflammatory or EoE-specific treatment for ≥ 2 patients prior to the screening assessments, meaning that no worsening after baseline is to be expected on one hand, and that spontaneous remissions are highly unlikely to occur. Patients without a post-baseline endoscopy were considered non-responders with regard to the primary endpoint.

5.3.2.1.3.3. Secondary objectives

The secondary objectives were:

• To further assess efficacy of budesonide oral suspension in children and adolescents with eosinophilic esophagitis (EoE),

• To study safety and tolerability of budesonide oral suspension in children and adolescents with eosinophilic esophagitis (EoE).

5.3.2.1.3.4. Estimands for the secondary objectives

No estimands for secondary objectives were described in the CSP or SAP. The a priori key secondary efficacy EPs (DB phase) were:

1.) Rate of patients with histological remission, defined as a peak of <16 eos/mm2 hpf at DB week 12 (LOCF),

2.) Change in the peak eos/mm2 hpf from screening to DB week 12 (LOCF),

3.) Rate of patients with clinico-pathological remission defined as:

Histological remission, i.e., peak of <16 eos/mm2 hpf at DB week 12 (LOCF), and

Clinical remission (i.e., no or only minimal problems) defined as clinical response (≥ 30% drop in the total score of PEESS Version 2.0 from baseline to DB week 12 [LOCF]) AND

Stratum I: Age 2 to 11 years at DB V1: PEESS Version 2.0 – parent report for children and teens (ages 2-18)

· ≤4 points in each of the subdomains GERD/nausea-vomiting/pain, and

· ≤7 points in the subdomain dysphagia,

Or

≤5 points in the total score and ≥2 subdomains with a drop of at least 50% compared to baseline at DB week 12 (LOCF),

Stratum II: Age 12 to <18 years at DB V1: PEESS Version 2.0 – children and teens report (ages 8-18)

· ≤4 points in each of the subdomains GERD/nausea-vomiting/pain, and

· ≤7 points in the subdomain dysphagia,

or

· ≤5 points in the total score and ≥2 subdomains with a drop of at least 50% compared to baseline at DB week 12 (LOCF),

4.) Rate of patients with clinical remission (i.e., no or only minimal problems) defined as above (clinical remission component of the endpoint clinico-pathological remission) at DB week 12 (LOCF),

5.) Rate of patients with clinical response at DB week 12 (LOCF), defined as

Stratum I: Age 2 to 11 years at DB V1:

≥ 30% drop in the total score of PEESS Version 2.0 - parent report for children and teens (ages 2-18) from baseline to DB week 12 (LOCF),

Stratum II: Age 12 to <18 years at DB V1:

≥ 30% drop in the total score of PEESS Version 2.0 - children and teens report (ages 8-18) from baseline to DB week 12 (LOCF)

6.) In the subgroup of patients with ≥ 4 points in NRS for dysphagia on the day of the baseline visit (only

patients of Stratum II: Age 12 to <18 years at DB V1), the rate of patients with resolution of dysphagia symptom (i.e., no or only minimal problems). Resolution of dysphagia symptom is defined as a severity of ≤2 points on 0 to 10-point (0-10) NRS on each day in the week prior to DB week 12 (LOCF).

Secondary safety EPs included morning cortisol, ACTH tests, assessments to identify cases of candidiasis and monitoring of growth.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

Dichotomous key secondary endpoints (key secondary endpoints no. 1, 3, 4, 5, 6) were analyzed using the one-sided Fisher's exact test (test for superiority, one-sided alpha level of 0.0125 for confirmatory analyses). The denominator was all patients included in the respective analysis set. For key secondary endpoint no.6 the denominator was the subgroup of patients in the respective analysis set with ≥4 points in NRS for dysphagia on the day of the DB baseline visit (only patients of Stratum II: Age 12 to <18 years at DB V1). The numerator was all patients with 'yes'.

Change in the peak eos/mm^2 hpf was analyzed 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 was appropriate. Linear least squares models including age stratum were also considered if warranted by the distribution of the data.

5.3.2.1.3.5. Tertiary objectives

The tertiary objectives were:

• To evaluate the **pharmacokinetics (PK)** of budesonide oral suspension via a population PK approach,

• To further evaluate histological parameters and patient reported outcomes (PROs),

• To evaluate efficacy parameters at end of OLI/OLE phase,

• To assess acceptance of study medication

5.3.2.1.3.6. Estimands for the tertiary objectives

No estimands for tertiary objectives were described in the CSP or SAP.

Tertiary endpoints (selection)**:**

- Population pharmacokinetic under steady-state condition

• Rate of patients with histological healing of esophagitis, defined as peak of 0 eos/mm2 hpf at DB week 12 (LOCF),

• Course and change from screening in the modified endoscopic reference score (EREFS),

• Course and change from screening in the 'inflammatory signs' subscore of the modified EREFS,

• Course and change from screening in the 'fibrotic signs' subscore of the modified EREFS,

• Rate of patients with grade 0 for all major and minor modified EREFS features at screening and at DB week 12 (LOCF),

- Assessment of acceptance of the study medication by investigator and patient/parent

Further tertiary endpoints (OLI phase):

• Rate of patients with pathological remission and clinical response at OLI week 12 (LOCF), whereby clinical response is defined relative to baseline of the OLI phase,

• Rate of patients with histological remission, defined as a peak of <16 eos/mm2 hpf at OLI week 12 (LOCF),

• Rate of patients with clinical response at OLI week 12 (LOCF), whereby clinical response is defined relative to baseline of the OLI phase

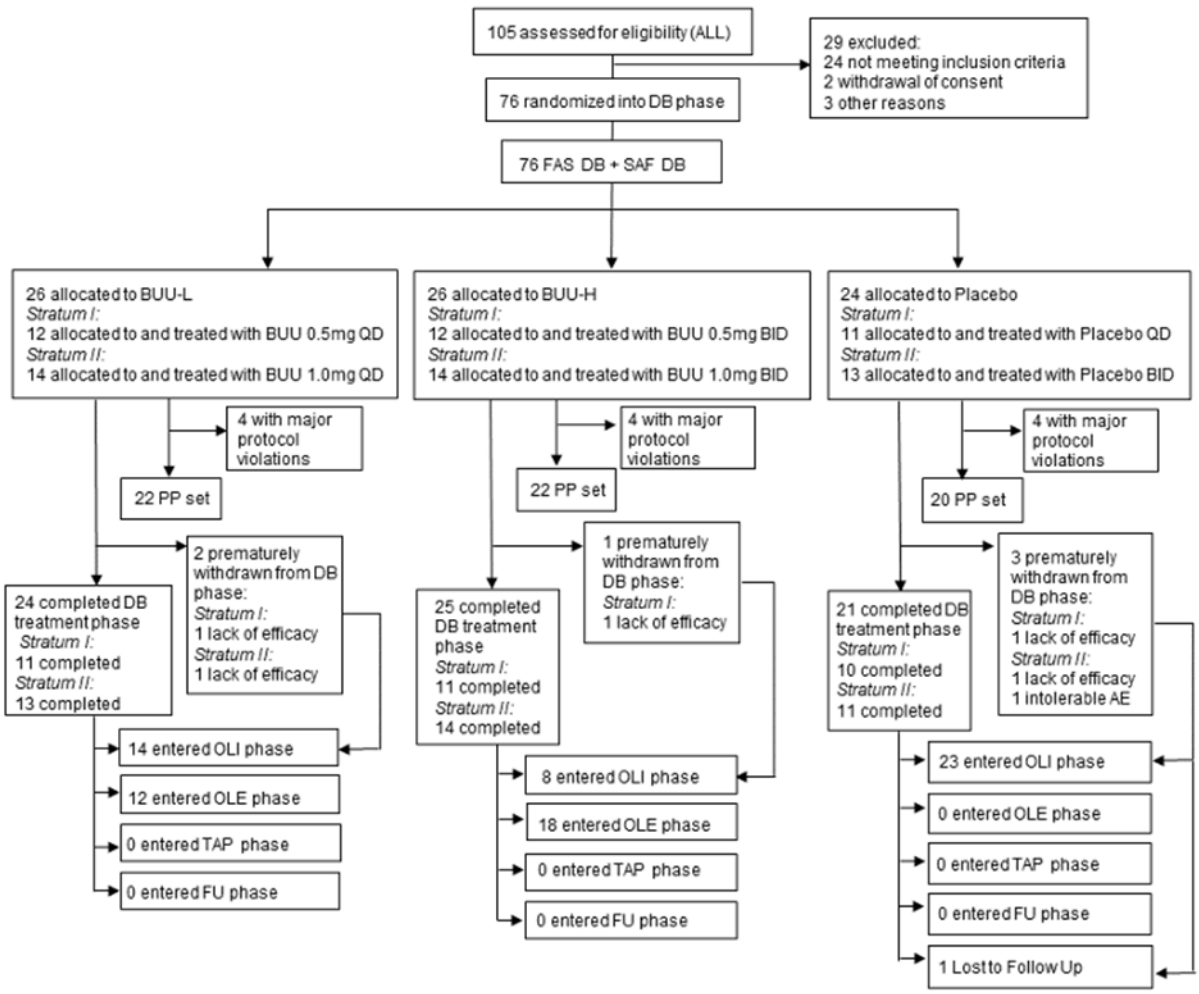
Further tertiary endpoints (OLE phase):

• Rate of patients with clinical remission (i.e., no or only minimal problems defined based on PEESS) at each OLE visit.

5.3.2.1.4. Results

5.3.2.1.4.1. Participant flow and numbers analysed

Figure 5: Participant Flow



The trial was conducted from 03.09.2019 to 07.08.2023 in 15 centers : 1 center in Australia (AU), 2 centers in Greece (GR), 2 centers in Israel (IL), 3 centers in Portugal (PT), 3 centers in Spain (ES), 2 centers in The Netherlands (NL), 1 center in Turkey (TR) and 1 center in the United Kingdom (UK).

5.3.2.1.4.2. Deviations from study plan

Six amendments including four local amendments took place. These did not result in major changes to the study conduct likely to influence the results.

14 major protocol violations (in 12 patients) were categorized into the following types of violations:

Prohibited concomitant medication (3 violations [1.2%]), Administration of DB IMP for less than 14 days (1 violation [0.4%]), insufficient compliance concerning administration of DB IMP (8 violations [3.2%]), and other violations (2 violations [0.8%]).

6 patients prematurely withdrew from the DB phase (2 patients in the BUU-L, 1 pt. in the BUU-H and 3 patients in the placebo group), all for lack of efficacy.

5.3.2.1.4.3. Baseline data

Overall, in each treatment group and in both age strata, most patients were male, ranging from approximately 60% to 90%. Male preponderance is known in EoE. Most of the patients were white. The majority of patients suffered from a panesophatitis with a gradient of inflammation declining from distal to proximal parts of the oesophagus, similar as observed in adult EoE patients.

There were some minor imbalances in baseline characteristics, that are unlikely to have influenced the outcomes in a relevant way.

5.3.2.1.4.4. Outcomes and estimation

PEP:

Table 11: Rate of patients with histological remission and clinical response at DB Week 12 (LOCF) (FAS-DB/PP)

	Treatment group		
	BUU-L	**BUU-H**	**Placebo**
FAS-DB			
Number (%) of patients with histological remission and clinical response at DB Week 12 (LOCF)	12/26 (46.2%)	18/26 (69.2%)	0/24 (0.0%)
Difference between proportions (%) (BUU vs. Placebo)* [98.75% CI]**	46.2% [21.73; 70.57]	69.2% [46.62; 91.84]	--
Testing of H_0 (BUU vs. Placebo)*** One-sided p-value Fisher's exact test	<0.0001	<0.0001	--
Difference from BUU-H (%) (BUU-L vs. BUU-H) [95% CI]	23.1% [-3.04; 49.19]	--	--
Testing of BUU-L vs. BUU-H **** Two-sided p-value Fisher's exact test	0.1599	--	--
PP (sensitivity analysis)			
Number (%) of patients with histological remission and clinical response at DB Week 12 (LOCF)	9/22 (40.9%)	16/22 (72.7%)	0/20 (0.0%)
Difference between proportions (%) (BUU vs. Placebo)* [98.75% CI]**	40.9% [14.73; 67.09]	72.7% [49.01; 96.44]	--
Testing of H_0 (BUU vs. Placebo)*** One-sided p-value Fisher's exact test	0.0011	<0.0001	--
Difference from BUU-H (%) (BUU-L vs. BUU-H) [95% CI]	31.8% [4.10; 59.54]	--	--
Testing of BUU-L vs. BUU-H **** Two-sided p-value Fisher's exact test	0.0666	--	--

For this analysis 'not assessable' results were set to 'No'.
*Difference between proportions ($\pi_{Eff} - \pi_{Pla}$), π_{Eff}: BUU-L or BUU-H
**Bonferroni correction
***Testing of H_0 ($\pi_{Pla} \geq \pi_{Eff}$) by means of the one-sided Fisher's exact test, Bonferroni adjusted alpha = 0.0125.
****Exploratory p-value was calculated based on two-sided Fisher's exact test. 95%-CI was calculated based on normal approximation.
Source: Appendix 8.2.2., Table 1.1.1 (FAS-DB) and 1.1.1 (PP).

For the pEP, both active groups showed highly significantly better results compared to placebo. The results in the BUU-H group were clinically relevant better compared to the BUU-L group, but statistical significance was not reached.

Key sEPs:

Table 12: A priori ordered key secondary endpoints (FAS-DB)

A priori ordered key secondary endpoints:	BUU-L (n=26)	BUU-H (n=26)	Placebo (n=24)
1. Rate of patients with histological remission at Week 12 (LOCF)*			
n (%)	16/26 (61.5%)	23/26 (88.5%)	0/24 (0.0%)
Difference between proportions (BUU vs. Placebo)+ [98.75% CI]§	61.5% [37.7%; 85.4%]	88.5% [72.8%; 100.0%]	--
Testing of H_0 (BUU vs. Placebo): One-sided p-value#	<0.0001	<0.0001	--
2. Change in the peak eos/mm² hpf from Screening to Week 12 (LOCF)			
LSMean (SE)^	-165.7 (25.0) n=26	-230.3 (25.5) n=25	-11.4 (27.2) n=22
Differences of LSMeans (SE) to Placebo [95% CI]	-154.3 (36.9) [-228.0; -80.6]	-218.9 (37.3) [-293.3; -144.5]	--
Pr|t| value	<0.0001	<0.0001	--
3. Rate of patients with clinico-histological remission at Week 12 (LOCF)*			
n (%)	7/26 (26.9%)	9/26 (34.6%)	0/24 (0.0%)
Difference between proportions (BUU vs. Placebo)+ [98.75% CI]§	26.9% [5.2%; 48.7%]	34.6% [11.3%; 57.9%]	--
Testing of H_0 (BUU vs. Placebo): One-sided p-value#	0.0066	0.0012	--
4. Rate of patients with clinical remission at Week 12 (LOCF)*			
n (%)	11/26 (42.3%)	10/26 (38.5%)	12/24 (50.0%)
Difference between proportions (BUU vs. Placebo)+ [98.75% CI]§	-7.7% [-42.8%; 27.5%]	-11.5% [-46.4%; 23.4%]	--
Testing of H_0 (BUU vs. Placebo): One-sided p-value#	0.7964	0.8657	--

A priori ordered key secondary endpoints:	BUU-L (n=26)	BUU-H (n=26)	Placebo (n=24)
5. Rate of patients with clinical response at Week 12 (LOCF)*			
n (%)	18/26 (69.2%)	20/26 (76.9%)	17/24 (70.8%)
Difference between proportions (BUU vs. Placebo)+ [98.75% CI]§	-1.6% [-34.0%; 30.8%]	6.1% [-24.9%; 37.1%]	--
Testing of H_0 (BUU vs. Placebo): One-sided p-value#	0.6663	0.4328	--
6. In subgroup of patients with ≥4 points in NRS for dysphagia on the day of baseline visit, the rate of stratum II patients with resolution of dysphagia symptom at Week 12 (LOCF)*			
n (%)	2/5 (40.0%)	3/5 (60%)	2/8 (25%)
Difference between proportions (BUU vs. Placebo)+ [98.75% CI]§	15.0% [-51.8%; 81.8%]	35.0% [-31.8; 100.0%]	--
Testing of H_0 (BUU vs. Placebo): One-sided p-value°	0.2843	0.1035	--

* For this analysis 'not evaluable' results were set to 'No'.
^ Linear least square model with treatment effect, age stratum and baseline values as covariates.
# Fisher's exact test was used for testing.
§ Risk difference test was used for testing.
+ Difference between proportions ($\pi_{Eff} - \pi_{Pla}$), π_{Eff}: BUU-L or BUU-H, π_{Pla}: Placebo
° Bonferroni correction
Source: Appendix 8.2.2, Table 1.2.1.1 (FAS-DB), Table 1.2.2.1 (FAS-DB), Table 1.2.3.1 (FAS-DB), Table 1.2.4.1 (FAS-DB), Table 1.2.5.1 (FAS-DB) and Table 1.2.6.1 (FAS-DB).

Efficacy significance testing continued in hierarchical fashion for the six key secondary endpoints defined until the first of these comparisons of BUU-L versus Placebo or BUU-H 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 had shown 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. As the fourth key secondary efficacy endpoint did not reach statistical significance in any of the BUU treatment groups compared to placebo, all further testings were only performed on an exploratory level.

In the FAS-DB, the first three a priori ordered key secondary endpoints showed a clinically relevant and statistically significant superiority of BUU-L and BUU-H over Placebo as well as a numerically better outcome under BUU-H compared to BUU-L treatment. As the fourth key secondary efficacy endpoint did not reach statistical significance in any of the BUU treatment groups compared to placebo, all further testings were only performed on an exploratory level.

The analyses in the PP confirmed the analyses in the FAS.

The 4th and 5th key sEP on clinical remission/response showed high response rates in all groups (high placebo effect). Results in the active treatment groups were not better compared to the placebo group. The difference between the budesonide and the placebo group in the pEP seems to be mainly driven by the histological response. The applicant explains the results of the 4th and 5th key sEP, stating that : *"Although the PEESS score has been validated in its component content, so far, no validation on its response to treatment has been performed and its minimal clinically meaningful difference is still unknown. As PEESS assessment was performed in the majority of the patients by the parents, these clinical outcomes might also be biased due to the high expectation by the parents as during the study conduct no drug for the treatment of paediatric population was available. As the clinical symptoms are in addition highly variable, especially in younger children, further bias might have been introduced, which might have contributed to the extreme high placebo clinical remission/response rates."* (p. 202 of the CSR). Table 23 of the CSR provides results for the change in the total PEESS for the two age strata separately. It seems that the results for the adolescent patients, who did the self-assessments do not clearly indicate a superior effect of the two active treatments over placebo, but the applicant is welcome to provide additional analysis.

Additional relevant efficacy results

Table 13: Tertiary endpoints – Endoscopy (FAS-DB)

(of note, that the first column always presents the results of the BUU-L, the second column presents the results of the BUU-H and the third column presents the results of the placebo group):

	BUU-L (n =26)	BUU-H (n = 26)	Placebo (n = 24)
Change from screening in the modified endoscopic reference score (EREFS)*			
Screening, Mean (SD)	3.6 (1.4) n=25	3.2 (1.0) n=24	3.2 (1.8)
DB Week 12 (LOCF), Mean (SD)	1.2 (1.3)	0.9 (1.2) n=25	3.5 (1.6) n=22
Absolute change from Screening to DB Week 12 (LOCF), Mean (SD)	-2.4 (1.7) n=25	-2.2 (1.5) n=23	0.4 (2.0) n=22
Change from screening in the 'inflammatory signs' subscore of the modified EREFS+			
Screening, Mean (SD)	2.9 (1.0) n=25	2.8 (1.1) n=24	2.5 (1.1)
DB Week 12 (LOCF), Mean (SD)	0.9 (1.2)	0.8 (1.2) n=25	2.6 (0.9) n=22
Absolute change from Screening to DB Week 12 (LOCF), Mean (SD)	-1.9 (1.4) n=25	-2.0 (1.6) n=23	0.2 (1.1) n=22
Change from screening in the 'fibrotic signs' subscoreof the modified EREFS+			
Screening, Mean (SD)	0.6 (0.9)	0.3 (0.6) n=24	0.5 (0.7)
DB Week 12 (LOCF), Mean (SD)	0.3 (0.5)	0.1 (0.3) n=25	0.7 (1.0) n=22
Absolute change from Screening to DB Week 12 (LOCF), Mean (SD)	-0.3 (0.7)	-0.2 (0.4) n=23	0.2 (1.0) n=22
Physician's Global Assessment of EoE Activity (0-10)^			
DB Baseline, Mean (SD)	6.1 (1.3) n=25	6.8 (1.2)	6.4 (1.4)
DB Week 12 (LOCF), Mean (SD)	2.5 (2.6)	2.2 (2.1)	5.5 (2.4)
Absolute change from DB Baseline to DB Week 12 (LOCF), Mean (SD)	-3.6 (2.7) n=25	-4.6 (2.1)	-0.9 (2.2)
Central Pathologist's Global Assessment of EoE Activity (0-10)^			
Screening, Mean (SD)	6.5 (2.3)	7.0 (2.3)	7.9 (1.2)
DB Week 12 (LOCF), Mean (SD)	2.3 (3.4)	0.5 (1.5) n=25	7.8 (1.4) n=22
Absolute change from Screening to DB Week 12 (LOCF), Mean (SD)	-4.2 (3.4)	-6.6 (2.3) n=25	-0.1 (1.7) n=22
Assessment of acceptance of the study medication by patient: General attitude towards the study medication (age stratum II)			
DB Week 12 (LOCF)	Unacceptable	0/14 (0.0%)	0/14 (0.0%)	0/13 (0.0%)
	Partially acceptable	1/14 (7.1%)	1/14 (7.1%)	0/13 (0.0%)
	Acceptable	5/14 (35.7%)	5/14 (35.7%)	4/13 (30.8%)
	Very acceptable	7/14 (50.0%)	8/14 (57.1%)	8/13 (61.5%)
	Missing	1/14 (7.1%)	0/14 (0.0%)	1/13 (7.7%)

(of note, the first column always presents the results of the BUU-L, the second column presents the results of the BUU-H and the third column presents the results of the placebo group):

Rate of patients with no or only minimal problems (0 - 2) in dysphagia on each day in the week prior to a visit by visit for subset of patients with NRS>=3 of the symptom at DB baseline

Stratum I (age 2 to 11 years)			
DB week 12, n(%)	2/5 (40.0 %)	3/8 (37.5 %)	4/8 (50.0 %)
Difference between proportions (%) (BUU vs. Placebo)* [95% CI]**	-10.00 % [-65.18; 45.18]	-12.50 % -60.73; 35.73]	--
Testing of BUU vs. Placebo** Two-sided p-value (Fisher's exact test)	>0.9999	>0.9999	--
Stratum II: age 12 to <18 years			
DB week 12, n(%)	3/7 (42.9%)	4/7 (57.1%)	2/10 (20.0%)
Difference between proportions (%) (BUU vs. Placebo)* [95% CI]**	22.86% [-21.40; 67.11]	37.14 % [-7.11; 81.40]	--
Testing of BUU vs. Placebo** Two-sided p-value (Fisher's exact test)	0.5928	0.1618	--

Rate of patients with histological healing of oesophagitis, i.e., peak of 0 eos/mm^2 hpf at DB Week 12 (LOCF)

DB Week 12 (LOCF), n (%)	14/26 (53.8%)	22/26 (84.6%)	0/24 (0.0%)

Results of tertiary EPs from the OLI:

A total of 23 of the 24 patients who had received placebo and 14 of the 26 patients who had received BUU-L during the DB treatment phase took part in the optional 12-week OLI treatment phase. Due to the high rate of histological remission and clinical response/remission seen for the BUU-H group in the DB treatment phase, only 8 of the 26 patients from this group were included in the OLI treatment phase. The outcome of the OLI treatment phase was assessed as a tertiary efficacy evaluation of the study.

The endpoint 'histological remission and clinical response' was achieved in 13/23 patients (56.5%) previously on placebo and 11/14 patients (78.6%) previously on BUU-L who received BUU-H for 12 patients in the OLI treatment phase, and in 4/8 patients (50%) of patients who continued BUU-H for a further 12 patients during OLI (i.e., a total of 24 patients at this dose). The respective rates of clinical response at OLI week 12 were 69.6% (former placebo group), 92.9% (former BUU-L group) and 62.5% (former BUU-H group). The rates of histological remission at OLI week 12 were 87.0% (former placebo group), 85.7% (former BUU-L group) and 87.5% (former BUU-H group). The results for other tertiary clinical endpoints (OLI phase) were in line with the above, including physician rating scales, patient symptom scores and EREFS, as were QoL endpoints.

Results from the OLE:

Histological data were not collected in this phase of the study, which is a major shortfall of the program, especially as the standard dose in the OlE was the BUU-L dose level which showed inferior results to the BUU-H dose.

Results for the clinical endpoints assessed in the OLE phase showed that a 24-week open-label treatment with 1 x 0.5 mg/d budesonide (or with an escalated dose of 2 x 0.5 mg/d budesonide) for stratum I (age 2 to 11 years) or with 1 x 1 mg/d budesonide (or with an escalated dose of 2 x 1 mg/d budesonide) for stratum II (age 12 to <18 years) was effective in maintaining and deepening the clinical remission achieved during DB and/or OLI phase treatment.

For the PedsQL for parents of teens, children, young children and toddlers, a maintenance of the scale score was observed from OLE Baseline to OLE Week 24 for the majority of the outcome parameters, both overall and per age stratum. The same pattern was seen in the PedsQL for patients.

Table 14: Rate of patients with clinical remission - DB and OLI phase

	BUU-L DB >BUU OLE (n = 12)	BUU-H DB >BUU OLE (n = 18)	BUU-H OLI > BUU OLE (n = 32)	OLE Total (n=62)
Rate of patients with clinical remission by visit				
OLE baseline, n (%)	7/12 (58.3)	9/18 (50)	23/32 (71.9)	39/62 (62.9)
OLE EOT, n (%)	8/12 (66.7)	10/18 (55.6)	24/32 (75.0)	42/62 (67.7)

5.3.2.1.4.5. Pre-defined and post-hoc subgroup analyses

The most relevant sub-group analyses are the analyses of the different doses and the different age strata. The pre-specified subgroup analyses of the primary endpoint related to age supported the outcome (stratum I/n=35: BUU-H [66.7%], BUU-L [41.7%], placebo [0.0%]; stratum II/n=41: BUU-H [71.4%], BUU-L [50.0%]; placebo [0.0%]; FAS-DB).

5.3.2.1.4.6. Pre-defined and post-hoc sensitivity analyses

Results for the pEP and the key sEPs in the FAS were confirmed by the analyses in the PP.

5.3.3. Overall discussion and conclusions on clinical efficacy

5.3.3.1. Discussion

The applicant requests to extend the indication for the treatment of eosinophilic esophagitis to paediatric patients (patients) from 2 years of age. With this regard they have conducted a single efficacy and safety study that comprises a 12-week double blind randomised placebo-controlled phase that evaluates two dose levels of topical budesonide administered as 0.2mg/ml suspension compared to placebo. Eligible patients, basically patients with an inadequate response, could enrol in an additional 12-week open label induction phase. Patients who had adequately responded during the double-blind phase had the option to enrol in a 24-week open label extension followed by 3-week tapering period and a 4-week follow-up.

Patients from 2 to < 18 yrs. of age with confirmed symptomatic clinico-histological EoE were eligible to enrol in the trial. The trial enrolled 76 randomized patients in the three treatment arms, who were eligible for the primary analysis in the FAS (64 patients in the PP population). Overall, the study design as well as the chosen endpoints for the double-blind phase as well as for the OLI are considered acceptable.

The justification of the chosen doses is mainly based on recommendations in published guideline. As the higher dose level resulted in clinically relevant superior results and therefore unnecessary overexposure can be excluded, the applicant's choice is considered acceptable.

The study showed highly statistically significant results for the pEP "Rate of patients with pathological and clinical response at DB week 12". Results of the high and the low dose group were not statistically

significantly different but the higher portion of patients who achieved responder status as well as the higher portion of patients with histological remission/healing in the BUU-H group are considered clinically relevant. Of note, 14/26 (53.8%), 22/26 (84.6%) and 0/24 (0.0%) of the patients in the BUU-L, BUU-H and the placebo group showed histological healing, respectively. None of the patients in the placebo group achieved histological remission at week 12 (1. key sEP) compared to 61.5% and 88.5 % in the BUU-L and the BUU-H group, respectively. Endoscopy EPs as well as the Physician's and the Central Pathologist's Global assessment of EoE activity favoured the active treatments over placebo. Generally, the higher dose level, proposed in the dosing recommendations of the SmPC for the induction phase, showed better results, providing re-assurance that the higher dose is not expected to provide unnecessary overexposure.

The 4th and 5th key sEP on clinical remission/response showed high response rates in all groups (high placebo effect). Results in the active treatment groups were not better compared to the placebo group. In fact, the rate of patients with clinical remission at Week 12 was the highest in the placebo group, indicating that symptoms did not reliably predict the histological outcome. The difference in the pEP between the budesonide and the placebo group seems to be mainly driven by the histological response, which was not achieved by any pt. in the placebo group. The applicant explains the results of the 4th and 5th key sEP, stating that: "Although the PEESS score has been validated in its component content, so far, no validation on its response to treatment has been performed and its minimal clinically meaningful difference is still unknown. As PEESS assessment was performed in most of the patients by the parents, these clinical outcomes might also be biased due to the high expectation by the parents as during the study conduct no drug for the treatment of paediatric population was available. As the clinical symptoms are in addition highly variable, especially in younger children, further bias might have been introduced, which might have contributed to the extreme high placebo clinical remission/response rates."

In addition, the applicant also claims that the 6th key sEP, (in subgroup of patients with ≥4 points in NRS for dysphagia on the day of baseline visit), the rate of stratum II patients with resolution of dysphagia symptom at Week 12" is of special interest "as it mimics the clinical endpoint used in the Jorveza EoE adult program, where dysphagia is the leading clinical symptom, and which has shown statistical superiority over placebo and which also led to marketing authorization of budesonide 1mg orodispersible tablets (Jorveza). In the current study, a tendency for numerically higher efficacy in the BUU-H (60%) and BUU-L group (40%) was shown compared to the placebo group (25%). Also, the BUU-H dose group showed a clinically relevant better outcome compared to the BUU-L group. Moreover, the BUU-H results (60%) are in a comparable range as being observed with budesonide 1mg BID orodispersible tablets [(37 of 59 patients (62.7%) versus placebo (4 of 29 patients (13.8%) after 6-patients of treatment in adult EoE patients]. In conclusion, due to the small sample size, it can be agreed that no firm conclusion could be drawn." It is agreed that this outcome can be regarded as supportive, but caution needs to be taken as the numbers analysed are very low.

The acceptability of the formulation was self-assessed and only in the adolescent group. It is encouraging that more than 80% of the adolescents rate the formulation "acceptable" or "very acceptable". This is in line with the rating of the caregivers, indicating that no major issues occurred with the administration of the product.

Additional patients who were either switched to high-dose budesonide or continued the treatment on this dose level in the OLI achieved responder status indicating that longer induction periods might be needed for some patients. This was the case for 4/8 patients who switched from the BUU-H group in the OLI, indicating that for some patients a prolonged induction treatment is beneficial. The applicant has considered a longer disease duration, extended histological inflammation and higher baseline

histological and clinical disease activity as risk factors for the need for a prolonged induction period. This is agreed and the information has been included in the SmPC section 4.2.

The results of the OLE are difficult to interpret as information on the dose (standard vs. escalated) is missing. Generally, it seems that clinical remission status was at least maintained in the OLE. The lack of histological data is a limitation, in addition to the lack of a randomised comparison of different dose levels, of the extension period. Data from the DB treatment phase showed that symptoms did not fully reliably predict the histological status. This can however be acceptable to CHMP and recommendations for follow up are included in the SmPC according to current clinical guidelines.

The applicant proposed a lower dose for the maintenance phase (0.5 mg children, 1 mg adolescents) compared to the induction phase (1mg children, 2 mg adolescents) as standard maintenance dose and histological results from the DB phase showed clinically relevant better results for the BUU-H compared to the BUU-L group. This proposal is agreed. The applicant justified the proposed maintenance doses stating that these doses correspond to the adult dose, which resulted in disease control. In addition, the results from the controlled study phase were comparable between adults and paediatric patients. As data demonstrating that the reduced doses were sufficient for a sustained response in paediatric patients are missing and as symptoms did not reliably predict the histological outcome, the SmPC has been updated recommending performing control endoscopies if symptoms persist or return. In addition, follow-up endoscopies are recommended in line with current clinical guidelines as symptoms may not reliably predict histological disease activity.

5.3.3.2. Conclusions on the clinical efficacy

It is concluded that the pivotal study established efficacy, especially for the higher dose level. The efficacy is mainly based on histological endpoints which is acceptable.

5.4. Clinical safety

5.4.1. Safety data collection

Adverse events were collected during each visit. Vital signs, auxological measures, physical examination and laboratory assessments were conducted as specified in the study report.

Patient exposure

Table 15: Patient exposure (cut off)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
Blinded studies (placebo-controlled)	76	76	52 patients were treated with budesonide in the DB phase, 45 patients in the OLI and 62 patients in the OLE.	unclear
Blinded studies (active -controlled)				
Open studies				
Post marketing				
Compassionate use				

* Received at least 1 dose of active treatment
** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

12 patients - DB phase:

In the BUU-L group, budesonide was administered in average on 92 days (SD: 10.8 days, median: 93 days), and in the BUU-H group in average on 95 days (SD: 14.8 days, median: 93 days).

12 patients – OLI phase:

OLI IMP was administered on average on 93 days (SD: 8 days) and the median duration of OLI IMP intake was 93 days

24 patients. OLE:

OLE IMP was administered on average on 169.4 days (SD: 24 days) and the median duration of OLE IMP intake was 169.5 days.

The number of patients with 48 weeks exposure (the ones who completed the DB phase, OLI and OLE) was only 11 patients from the DB BUU-L group completed and 4 patients from the BUU-H group (three phases completed).

5.4.2. Adverse events

DB Phase:

Table 16: Patients with at least one DB treatment-emergent AE by preferred term (SAF-DB – only preferred terms occurring in at least 3 patients in one treatment group) – BUU-5/EEA

Preferred term	Number (%) of patients with at least one DB TEAE		
	BUU-L (n = 26)	BUU-H (n = 26)	Placebo (n = 24)
Abdominal pain	3 (11.5%)	4 (15.4%)	--
Abdominal pain upper	3 (11.5%)	--	4 (16.7)
Dyspepsia	--	--	3 (12.5%)
Vomiting	5 (19.2%)	3 (11.5%)	1 (4.2%)
Corona virus infection	1 (3.8%)	3 (11.5%)	1 (4.2%)
Nasopharyngitis	3 (11.5%)	5 (19.2%)	5 (20.8%)
Pharyngitis	1 (3.8%)	3 (11.5%)	4 (16.7)
Headache	5 (19.2%)	5 (19.2%)	3 (12.5%)
Cough	--	2 (7.7%)	3 (12.5%)
Oropharyngeal pain	4 (15.4%)	2 (7.7%)	1 (4.2%)

DB double blind treatment phase
Source: BUU-5/EEA (5.3.5.1), In-text Table 42 (CSR Appendix 8.2.3, Table 1.1.3 (SAF-DB)).

Table 17: Adverse drug reactions (SAF-DB)

SOC Preferred term	Number of adverse drug reactions* (at least possible causal relationship to IMP)		
	BUU-L	BUU-H	Placebo
Gastrointestinal disorders	**1**	**1**	**3**
Abdominal pain upper	1	--	1
Dyspepsia	--	--	1
Gastrooesophageal reflux disease	--	--	1
Vomiting	--	1	--
General disorders and administration site conditions	--	--	**1**
Chest pain	--	--	1
Infections and infestations	**1**	**1**	--
Herpes ophthalmic	1	--	--
Oesophageal candidiasis	--	1	--
Investigations	--	**1**	**2**
Cortisol decreased	--	1	1
Lymphocyte count decreased	--	--	1
Metabolism and nutrition disorders	**1**	--	--
Decreased appetite	1	--	--
Respiratory, thoracic and mediastinal disorders	--	--	**2**
Cough	--	--	2
Total	**3**	**3**	**8**

* None of the reported ADRs were serious.
Coded with MedDRA version 22.1.
Source: Appendix 8.2.3, Table 1.1.6 (SAF-DB).

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OLI:

Table 18: Patients with at least one OLI treatment-emergent AE by preferred term (SAF-OLI – only preferred terms occurring in at least 2 patients)

	Number (%) of patients with at least one OLI/TAP TEAE
Preferred term	**Total (n =45)**
Abdominal pain	5 (11.1%)
Abdominal pain upper	2 (4.4%)
Fatigue	2 (4.4%)
Pyrexia	3 (6.7%)
COVID-19	5 (11.1%)
Nasopharyngitis	11 (24.4%)
Oesophageal candidiasis	4 (8.9%)
Pharyngitis	2 (4.4%)
Upper respiratory tract infection	2 (4.4%)
Musculoskeletal stiffness	2 (4.4%)
Headache	7 (15.6%)
Dysmenorrhoea	3 (6.7%)
Heavy menstrual bleeding	2 (4.4%)
Cough	2 (4.4%)
Epistaxis	2 (4.4%)

OLI TEAE: open-label induction treatment-emergent adverse event
Source: Appendix 8.2.3, Table 2.1.2 (SAF-OLI).

Table 19: Adverse drug reactions (SAF-OLI)

	Number of adverse drug reactions* (at least possible causal relationship to IMP)
SOC Preferred term	**Entries (N)**
Endocrine disorders	**2**
Adrenal insufficiency	1
Adrenal suppression	1
Infections and infestations	**5**
Gastointestinal candidiasis	1
Oesophageal candidiasis	4
Investigations	**1**
Lymphocyte count decreased	1
Total	**8**

*None of the reported ADRs were serious.
Coded with MedDRA version 26.0
Source: Appendix 8.2.3, Table 2.1.4 (SAF-OLI).

OLE:

Table 20: Patients with at least one OLE treatment-emergent AE by preferred terms (SAF-OLE – only preferred terms occurring in at least 3 patients on one treatment group) – BUU-5/EEA

Preferred term	Number (%) of patients with at least one OLE TEAE			
	BUU-L DB> BUU OLE (n = 12)	BUU-H DB> BUU OLE (n = 18)	BUU-H OLI> BUU OLE (n=32)	Total (n=62)
Vomiting	1 (8.3%)	3 (16.7%)	3 (9.4%)	7 (11.3%)
Condition aggravated (EoE)	1 (8.3%)	--	3 (9.4%)	4 (6.5%)
COVID-19	0 (0%)	2 (11.1%)	5 (15.6%)	7 (11.3%)
Gastroenteritis	2 (16.7%)	1 (5.6%)	5 (15.6%)	8 (12.9%)
Nasopharyngitis	--	5 (27.8)	9 (28.1%)	14 (22.6%)
Headache	3 (25.0%)	2 (11.1%)	4 (12.5%)	9 (14.5%)
Dysmenorrhoea	--	--	5 (15.6%)	5 (8.1%)
Cough	1 (8.3%)	1 (5.6%)	3 (9.4%)	5 (8.1%)
Oropharyngeal pain	1 (8.3%)	--	3 (9.4%)	4 (6.5%)

OLE TEAE: open-label extension treatment-emergent adverse event
Source: BUU-5/EEA (5.3.5.1), In-text Table 55 (CSR Appendix 8.2.3, Table 3.1.2 (SAF-OLE)).

Table 21: Adverse drug reactions (SAF-OLE)

SOC Preferred term	Number of adverse drug reactions (at least possible causal relationship to IMP)			
	BUU-L DB> BUU OLE	BUU-H DB> BUU OLE	BUU-H OLI> BUU OLE	Total
Gastrointestinal disorders	--	--	**1**	**1**
Vomiting	--	--	1	1
Infections and infestations	--	--	**2**	**2**
Oropharyngeal candidiasis	--	--	2	2
Investigations	--	**1**	**1**	**1**
Blood cortisol decreased	--	1	--	1
White blood cell count increased	--	--	1	1
Musculoskeletal and connective tissue disorders	--	**1**	--	**1**
Joint swelling	--	1	--	1
Total	**0**	**2**	**4**	**6**

Coded with MedDRA version 26.0
Source: Appendix 8.2.3, Table 3.1.4 (SAF-OLE).

Table 22: Patients with at least one BUU treatment-emergent AE by preferred term (SAF-BUU only preferred terms occurring in at least 3 patients) – BUU-5/EEA

Preferred term	Number (%) of patients with at least one BUU TEAE Any BUU (n = 75)
Abdominal pain	14 (18.7%)
Abdominal pain upper	6 (8.0%)
Constipation	3 (4.0%)
Diarrhoea	4 (5.3%)
Dyspepsia	4 (5.3%)
Nausea	5 (6.7%)
Vomiting	13 (17.3%)
Chest pain	3 (4.0%)
Condition aggravated	10 (13.3%)
Fatigue	3 (4.0%)
Pyrexia	6 (8.0%)
Hypersensitivity	3 (4.0%)
COVID-19	17 (22.7%)
Ear infection	3 (4.0%)
Gastroenteritis	12 (16.0%)
Nasopharyngitis	26 (34.7%)
Oesophageal candidiasis	4 (5.3%)
Pharyngitis	9 (12.0%)
Tonsilitis	3 (4.0%)
Upper respiratory tract infection	5 (6.5%)
Viral infection	3 (4.0%)
Fall	4 (5.3%)
Cortisol decreased	3 (4.0%)
Vitamin D deficiency	5 (6.7%)
Arthralgia	3 (4.0)
Back pain	5 (6.7%)
Myalgia	3 (4.0%)
Dizziness	4 (5.3%)
Headache	20 (26.7%)
Dysmenorrhea	5 (6.7%)
Cough	8 (10.7%)
Epistaxis	4 (5.3%)
Oropharyngeal pain	10 (13.3%)
Rash	5 (6.7%)

Source: BUU-5/EEA (5.3.5.1), In-text Table 61 (CSR Appendix 8.2.3, Table 5.1.3 [SAF-BUU]).

Table 23: Adverse drug reactions (SAF-BUU)

SOC Preferred term	Number of adverse drug reactions (at least possible causal relationship to IMP) Any BUU
Endocrine Disorders	**2**
Adrenal insufficiency	1
Adrenal suppression	1
Gastrointestinal disorders	**3**
Abdominal pain upper	1
Vomiting	2
Infections and infestations	**9**
Gastrointestinal candidiasis	1
Herpes ophthalmic	1
Oesophageal candidiasis	5
Oropharyngeal candidiasis	2
Investigations	**4**
Blood cortisol decreased	2
Lymphocyte count decreased	1
White blood cell count increased	1
Metabolism and nutrition disorders	**1**
Decreased appetite	1
Musculoskeletal and connective tissue disorders	**1**
Joint swelling	1
Total	20

Coded with MedDRA version 26.0
Source: Appendix 8.2.3, Table 5.1.4 (SAF-BUU).

The SAF-BUU includes all the patients during the trial who ever received even one dose of budesonide.

Adverse drug reactions

Summary of the safety profile

Children and adolescents 2-17 years of age

The applicant reported that in the paediatric clinical study PEDEOS 1 (BUU-5/EEA) with Jorveza 0.2 mg/mL oral suspension, local fungal infection (candidiasis, confirmed by histology) occurred in 10.5% of patients across all budesonide dosage groups, with no dose effect. All cases were non-serious, generally of mild intensity, did not generally interfere with normal daily activities, and did not impact the treatment effect.

Adverse reactions observed in clinical studies with Jorveza 0.5 mg and 1 mg orodispersible tablets and 0.2 mg/mL oral suspension are listed in the table below, by MedDRA system organ class and frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).

Table 24: List of Adverse Reactions in clinical studies with Jorveza orodispersible tablets and oral suspension

MedDRA system organ class	Very common	Common	Uncommon
Infections and infestations	Esophageal candidiasis, oral and/or oropharyngeal candidiasis		Nasopharyngitis, pharyngitis
Immune system disorders			Angioedema
Psychiatric disorders		Sleep disorder	Anxiety, agitation
Nervous system disorders		Headache, dysgeusia	Dizziness
Eye disorders		Dry eyes	
Vascular disorders			Hypertension
Respiratory, thoracic and mediastinal disorders			Cough, dry throat, oropharyngeal pain
Gastrointestinal disorders		Gastroesophageal reflux disease, nausea, oral paraesthesia, dyspepsia, upper abdominal pain, dry mouth, glossodynia tongue disorder, oral herpes	Abdominal pain, abdominal distension, dysphagia, erosive gastritis, gastric ulcer, lip edema, gingival pain
Skin and subcutaneous tissue disorders			Rash, urticaria
General disorders and administration site conditions		Fatigue	Sensation of foreign body
Investigations		Blood cortisol decreased	Osteocalcin decreased, weight increased

5.4.3. AEs of special interest, serious adverse events and deaths, other significant events

DB Phase:

No death occurred.

Table 25: Patients experiencing SAEs (SAF-DB)

Patient	Sex	Age (years) categorized*	SAE (preferred term)	Severity	Causality	Onset	Time (days) since start of DB treatment**	Premature termination*** (reason)
BUU-L								
0078	m	2-11	Seizure	Moderate	Unlikely	DB treatment-emergent	87	No
BUU-H								
0004	m	12-17	Arthroscopy	Mild	Not related	DB treatment-emergent	69	No
0085	m	2-11	Hypersensitivity	Moderate	Not related	DB treatment-emergent	68	No
Placebo								
0093	m	12-17	Neck mass	Mild	Not related	DB treatment-emergent	32	No

* Age at baseline ** Start date of AE was considered, not start date of seriousness *** of DB treatment phase
Sex: f = female, m = male.
Source: Appendix 8.3.1, Listing 3.1 and Listing 1.2, and Appendix 8.3.3, Listing 1.2.

The outcome for all SAEs was recovered/resolved.

In total, 3 AESI occurred in 3 patients (11.5%) in the BUU-H group and 1 AESI occurred in 1 patient (4.2%) in the Placebo group. The 3 AESI reported in the BUU-H group were esophageal candidiasis, cortisol decreased and insomnia. The AESI reported in the Placebo group was cortisol decreased. Esophageal candidiasis occurred in 1 patient (3.8%) of age stratum I in the BUU-H treatment group. The event was non-serious, considered of moderate severity and with a probable/likely causality to the IMP. Esophageal candidiasis had recovered/resolved at the time of the DB phase database lock. This event of esophageal candidiasis was considered an ADR.

OLI:

No death or SAE occurred during the OLI and the follow-up.

Table 26: Adverse Events of Special Interest in OLI treatment groups by Preferred Term (SAF-OLI)

Preferred term	Treatment group		
	BUU-L > BUU-H (n = 14)	BUU-H > BUU-H (n = 8)	Placebo > BUU-H (n = 23)
Gastrointestinal candidiasis	0 (0%)	0 (0%)	1 (4.3%)
Oesophageal candidasis	0(0%)	2 (25.0%)	2 (8.7%)
Cortisol decreased	1 (7.1%)	0 (0%)	0 (0%)
Total	**1 (7.1%)**	**2 (25.0%)**	**3 (13.0%)**

Source: Appendix 8.2.3, Table 2.1.20 (SAF-OLI).

OLE:

No death occurred during the OLE. One SAE, which led to hospitalization, occurred:

Table 27: Patients experiencing SAEs (SAF-OLE)

Patient	Sex	Age (years) categorized*	SAE (preferred term)	Severity	Causality	Onset	Time (days) since start of first intake of study medication **	Premature termination (reason)
BUU-H DB >BUU OLE								
0034^	m	2-11	Pneumonia	Severe	Not related	OLE treatment-emergent	229	No

* Age at baseline ** Start date of AE was considered, not start date of seriousness
^ Patients was on regular dose (0.5mg OD) and after 3 months was changed to escalated dose (0.5mg BID) due to increase in eosinophils and symptoms.
Sex: f = female, m = male.
Source: Appendix 8.3.1, Listings 1.2 and 3.1, and Appendix 8.3.3, Listing 1.2.

Table 28: Patients with suspected candidiasis ADRs (SAF-BUU)

Preferred term	Number (%) of patients with at least one suspected candidiasis ADR
	BUU (n = 75)
Clinically manifested suspected candidiasis ADR	**6 (8.0%)**
Gastrointestinal candidiasis	1 (1.3%)
Oesophageal candidiasis	4 (5.3%)
Oropharyngeal candidiasis	2 (2.7%)
Histologically confirmed clinically manifested candidiasis ADR	
Esophageal candidiasis	4 (5.3%)

Source: Appendix 8.2.3, Table 5.1.25.1 (SAF-BUU) to 5.1.28.2 (SAF-BUU).

The presentation of AEs regarding effects on the HPA is unclear and the applicant is asked to provide a summary of the cases discussing the age rage, dose, onset, resolution/outcome and clinical relevance of the cases.

5.4.4. Discontinuation due to adverse events

DB Phase:

3 AEs (abdominal pain upper, chest pain, cough) in 1 patient in the Placebo group, led to discontinuation of DB IMP.

OLI:

No patient withdrew due to an AE.

OLE:

One patient was withdrawn from the OLE due to an TEAE in the OLI of adrenal suppression (based on the result of the ACTH test). The AE was rated non-serious and the outcome recovered/resolved.

5.4.5. Safety in special populations

Apart from the paediatric data discussed above, no new data is available.

5.4.6. Vital signs and laboratory findings

DB Phase:

A small decrease in serum cortisol as well as serum cortisol measured between 7 a.m. and 9 a.m. was seen from Screening/DB Baseline to DB Week 12 in the BUU-L and BUU-H groups in age stratum I. In age stratum II, a small decrease in serum cortisol was seen in the BUU-L and BUU-H groups when serum cortisol was measured in the morning between 7 a.m. and 9 a.m. In contrast, a small increase was observed in serum cortisol in stratum II of the BUU-L group. Serum cortisol level was unchanged or slightly increased in the Placebo group.

Table 29: ACTH test DB phase (SAF-DB)

	BUU-L (n = 26)	BUU-H (n = 26)	Placebo (n = 24)	Total (n = 76)
Peak serum cortisol [µg/dl] approximately 30-60 min after Synacthen application by visit				
Screening, Mean (SD)	22.5 (8.5) n=25	21.4 (3.4)	24.0 (4.6) n=22	22.5 (6.0) n=73
DB Week 12 (LOCF) Mean (SD)	21.5 (5.4) n=24	19.4 (4.3) n=25	22.4 (3.1) n=21	21.0 (4.6) n=70
Change of serum cortisol [µg/dl] from initial measurement to peak measurement by visit				
Screening, Mean (SD)	10.2 (5.0) n=25	11.0 (5.1)	13.0 (4.5) n=22	11.3 (5.0) n=73
DB Week 12 (LOCF) Mean (SD)	10.5 (4.2) n=24	11.0 (4.6) n=25	12.4 (4.9) n=21	11.2 (4.6) n=70

Source: Appendix 8.2.3, Table 1.3.38.1 and Table 1.3.38.2 (SAF-DB).

Table 30: ACTH test results by months of any BUU treatment (SAF-BUU)

	3 months (n = 6)	6 months (n = 7)	9 months (n = 47)	12 months (n = 15)
Peak serum cortisol [µg/dl] approximately 30-60 min after Synacthen application				
Visit prior BUU initiation Mean (SD)	22.3 (3.4) n=5	20.3 (4.3)	22.2 (6.6) n=46	22.4 (3.0) n=14
EOT visit Mean (SD)	21.1 (7.1) n=2	14.4 (4.3) n=5	22.5 (4.9) n=38	24.0 (7.1) n=11
Change of serum cortisol [µg/dl] from initial measurement to peak measurement by visit				
Visit prior BUU initiation Mean (SD)	11.0 (4.4) n=5	12.3 (5.0)	10.8 (5.4) n=46	11.9 (4.0) n=14
EOT visit Mean (SD)	15.8 (1.6) n=2	6.5 (4.7) n=5	10.7 (5.0) n=38	11.5 (4.3) n=11

Source: Appendix 8.2.3, Tables 5.2.1.2 to 5.2.4.3 (SAF-BUU).

Bone alkaline phosphatase and osteocalcin were measured to detect a possible osteoporosis promoting effect of budesonide. For bone alkaline phosphatase, a decrease in mean (SD) from Screening/DB Baseline to DB Week 12 (LOCF) was seen in the BUU-L and BUU-H treatment groups, respectively, whereas a small increase was seen for the Placebo group. For osteocalcin, a decrease in mean (SD) from Screening/DB Baseline to DB Week 12 (LOCF) was seen in all three groups. Overall, the

laboratory values did not indicate an increased bone resorption after a 12-week treatment with BUU-L or BUU-H. Overall, results of the laboratory measurements did not raise safety concerns.

Table 31: Patients with a change in laboratory values from normal to abnormal from DB baseline to DB week 12 (LOCF) – only laboratory parameters with a change to low or high in at least 10% of patients with normal baseline value in at least one treatment group (SAF-DB)

	Number (%) of patients with a change in laboratory values from normal to abnormal from DB Baseline to DB Week 12 (LOCF)					
	BUU-L (n = 26)		BUU-H (n = 26)		Placebo (n = 24)	
	To low	To high	To low	To high	To low	To high
Erythrocytes	0/23 (0.0%)	0/23 (0.0%)	1/24 (4.2%)	5/24 (20.8%)	0/22 (0.0%)	0/22 (0.0%)
Haemoglobin	0/22 (0.0%)	0/22 (0.0%)	3/22 (13.6%)	4/22 (18.2%)	1/21 (4.8%)	0/21 (0.0%)
Leukocytes	0/22 (0.0%)	1/22 (4.5%)	1/22 (4.5%)	1/22 (4.5%)	3/22 (13.6%)	2/22 (9.1%)
Neutrophils rel.	1/20 (5.0%)	0/20 (0.0%)	2/18 (11.1%)	0/18 (0.0%)	2/21 (9.5%)	2/21 (9.5%)
Neutrophils abs.	1/19 (5.3%)	0/19 (0.0%)	1/20 (5.0%)	1/20 (5.0%)	4/18 (22.2%)	1/18 (5.6%)
Eosinophils rel.	0/5 (0.0%)	2/5 (40.0%)	0/5 (0.0%)	0/5 (0.0%)	0/7 (0.0%)	4/7 (57.1%)
Eosinophils abs.	0/10 (0.0%)	2/10 (20.0%)	0/15 (0.0%)	2/15 (13.3%)	0/14 (0.0%)	2/14 (14.3%)
Basophils abs.	0/24 (0.0%)	0/24 (0.0%)	0/23 (0.0%)	0/23 (0.0%)	0/21 (0.0%)	3/21 (14.3%)
Lymphocytes abs.	0/22 (0.0%)	1/22 (4.5%)	0/22 (0.0%)	3/22 (13.6%)	1/21 (4.8%)	2/21 (9.5%)
AST (SGOT)	3/24 (12.5%)	0/24 (0.0%)	0/25 (0.0%)	2/25 (8.0%)	0/22 (0.0%)	0/22 (0.0%)
gGT	0/22 (0.0%)	0/22 (0.0%)	0/23 (0.0%)	1/23 (4.3%)	4/21 (19.0%)	0/21 (0.0%)
Potassium (K^+)	0/21 (0.0%)	2/21 (9.5%)	0/21 (0.0%)	5/21 (23.8%)	0/20 (0.0%)	4/20 (20.0%)
Phosphate	0/22 (0.0%)	2/22 (9.1%)	0/19 (0.0%)	1/19 (5.3%)	0/19 (0.0%)	2/19 (10.5%)
25-Hydroxyvitamin D3	3/3 (100.0%)	0/3 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)
Serum cortisol*	1/12 (8.3)	1/12 (8.3)	4/16 (25.0%)	0/16 (0.0%)	1/17 (5.9%)	2/17 (11.8%)
Morning serum cortisol (7 a.m. to 9 a.m.)	0/4 (0.0%)	0/4 (0.0%)	0/5 (0.0%)	0/5 (0.0%)	0/6 (0.0%)	1/6 (16.7%)

*Serum cortisol was often measured in the afternoon due to ACTH test.
For each laboratory parameter, patients with values within the reference range at DB Baseline and with valid values at DB Week 12 (LOCF) are included.
AST (SGOT): Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); gGT: γ-Glutamyltransferase.
Source: Appendix 8.2.3, Table 1.9 (SAF-DB).

OLI:

There was no clinically relevant change in serum cortisol as well as serum cortisol measured between 7 a.m. and 9 a.m. from OLI Baseline to OLI Week 12. Parameters like bone alkaline phosphatase and osteocalcin were measured to detect a possible osteoporosis-promoting effect of budesonide, but showed mostly no relevant changes to baseline after a 12-week treatment with BUU. The mean (SD) osteocalcin value at OLI Week 12 (LOCF) 67.4 (39.46) ng/ml was slightly lower compared to the OLI Baseline value 77.2 (43.13) ng/ml. Overall, the laboratory values did not indicate an increased bone resorption after a 6-week treatment with OLI treatment. For all other measured laboratory parameters, no remarkable changes from OLI Baseline to OLI Week 12 (LOCF) were observed.

OLE:

A slight clinically non-relevant decrease in mean serum cortisol measured between 7 a.m. and 9 a.m (-0.04 [SD: 1.43] µg/dl) from OLE Baseline to OLE Week 24 (LOCF) could be observed. In total 5/40 patients changed to low levels.

Parameters like bone alkaline phosphatase and osteocalcin that were measured to detect a possible osteoporosis-promoting effect of budesonide, showed no relevant changes from OLE baseline after a 24-week treatment with budesonide. Overall, the laboratory values did not indicate an increased bone resorption after a 24-week treatment with budesonide during the OLE phase.

Vital signs and weight:

DB Phase:

Table 32: Vital signs, body temperature, body weight, and BMI at DB Baseline and at DB week 12 (LOCF) (SAF-DB)

	Mean (SD) vital signs, body temperature, body weight, and BMI					
	BUU-L (n = 26)		BUU-H (n = 26)		Placebo (n = 24)	
	DB Baseline	DB Week 12 (LOCF)	DB Baseline	DB Week 12 (LOCF)	DB Baseline	DB Week 12 (LOCF)
Systolic blood pressure [mmHg]	104 (12.8)	111 (14.2)	108 (11.0)	113 (12.0)	106 (17.0)	111 (13.9)
Diastolic blood pressure [mmHg]	64 (9.2)	67 (9.7)	62 (7.6)	64 (10.8)	62 (7.8)	67 (6.8)
Heart rate [beats/min]	79 (20.3)	77 (17.1)	82 (18.1)	79 (20.5)	76 (13.1)	85 (15.4)
Body temperature [°C]	36.2 (0.59)	36.2 (0.52)	36.1 (0.80)	36.1 (0.49)	36.0 (0.48)	36.3 (0.51)
Body weight [kg]	47.0 (20.10)	47.5 (20.42)	45.7 (20.55)	45.8 (20.46)	45.6 (16.75)	46.1 (16.64)
BMI*	19.1 (4.40)	19.4 (4.38)	18.4 (3.39)	18.4 (3.51)	18.4 (2.63)	18.4 (2.57)

*BMI assessed at screening and DB Week 12 (LOCF).
Source: Appendix 8.2.3, Tables 1.2.1 (SAF-DB) to 1.2.6 (SAF-DB).

OLI:

Vital signs, body temperature, body weight, and BMI did not show any relevant changes from OLI Baseline to OLI Week 12.

OLE:

Vital signs, body temperature, body weight, and BMI did not show any relevant changes from OLE Baseline to OLE Week 24

Physical examination:

At the EOT DB visit newly abnormal or worsened findings were observed in 2/26 patients (7.7%) in the BUU-L group, in 2/26 patients (7.7%) in the BUU-H group, and in 1/24 patients (4.2%) in the Placebo group. All newly abnormal or worsened findings were documented as AEs.

OLI:

At the OLI EOT visit newly abnormal or worsened findings since screening / OLI Baseline visit were observed in 4/35 patients. All newly abnormal or worsened findings were documented as AEs.

OLE:

At the OLE V4 EOT visit newly abnormal or worsened findings since DB EOT visit or OLRI EOT visit were observed in 1/62 patients (1.6%). All newly abnormal or worsened findings were documented as AEs.

5.4.7. Post marketing experience

During the most recent reporting period of 08 Jul 2023 to 07 Jul 2024, a total of 504 ADRs (228 cases, including 190 reported by health care practitioners) related to the use of Jorveza® 0.5 mg and Jorveza® 1 mg orodispersible tablets were reported. Of the 504 ADRs, 7 ADRs were serious and unlisted and 322 ADRs were non-serious and unlisted from spontaneous/authority sources.

Use in children or adolescents (age 3 to 17 years) was reported in 58 cases of Jorveza, of which 51 cases were classified as special situation without adverse events. In 7 of 58 cases, adverse events were reported; 3 of these 7 cases were serious and associated with the events (PT) herpes simplex oesophagitis, herpes simplex pharyngitis, osteoporosis, skin swelling and Cushing´s syndrome (isolated cases only).

Non-serious cases were associated with the following events (PT), which occurred as isolated cases only: oral candidiasis; vomiting; burning sensation; mouth injury.

5.4.8. Overall discussion and conclusions on clinical safety

5.4.8.1. Discussion

EoE is a rare disease in the paediatric population. The safety database for the product mainly consists of the data from the single pivotal trial which enrolled 76 patients. Therefore, the safety data generated with the product is rather limited. On the other hand, budesonide is a drug with a well-known safety profile and topical budesonide products have been licensed in the paediatric population for other indications since a long time. PK data are relevant to look at the safety profile of the oral suspension into perspective and better define the risk for systemic adverse reactions. Generally, the observed safety data provided is in line with what is expected for topical budesonide. Cases of local candidiasis as well as negative effects on the HPA axis (cortisol decreased, adrenal insufficiency/suppression) were reported in the DB phase as well as the OLI and the OLE as ADRs. None of these events was classified as SAE, which is re-assuring, however one case of adrenal insufficiency (based on ACTH test) led to withdrawal of one patient in the OLE phase. The AE was rated non-serious and the outcome recovered/resolved.

Corticosteroids including topical corticosteroids can have negative effects on growth. This issue is specific to paediatric patients and it is already reflected in Section 4.8 of the proposed SmPC. The study design with a short placebo-controlled treatment phase cannot fully assess effects on growth. Measures that can detect effects on the growth plate even with short-term treatment like knemometry have not been included in the trial and would have been helpful to better characterise the effect on the growth plate. In conclusion, a warning related to growth and a recommendation to monitor growth has been included in the SmPC section 4.4.

The applicant proposed to use the same ADR table in section 4.8 as for the adult formulations. Regarding AEs concerning the HPA axis, only blood cortisol was listed, while cases of adrenal sufficiency/suppression were reported during the clinical study. This had been added to the SmPC section 4.8.

5.4.8.2. Conclusions on clinical safety

Generally, the safety profile is consistent with the well-known safety profile of budesonide, which has been used in the paediatric population for a long time.

6. Risk management plan

6.1. Safety specification

The proposed safety specifications are agreed.

Table 33: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

The applicant did not propose any additional pharmacovigilance activities.

6.2.2. Discussion on the Pharmacovigilance Plan

The proposed pharmacovigilance plan is acceptable as no safety concerns have been identified.

6.3. Plans for post-authorisation efficacy studies

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

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Not applicable.

6.5. PRAC Outcome

PRAC endorsed the PRAC assessment of the RMP and its conclusions, without further additions.

6.6. Overall conclusion on the Risk Management Plan

The PRAC consider that the updated risk management plan version 3.2 is acceptable.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

7. Pharmacovigilance

Pharmacovigilance system

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

7.1. 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.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The proposed wording for the therapeutic indication "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" is considered acceptable.

8.1.2. SmPC section 5.1 justification

The applicant has provided a rather concise summary of the paediatric clinical trial. Additional information on the outcome of the clinical symptoms endpoints and the lack of histological data at the end of the OLE have been included upon CHMP request.

8.2. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Jorveza adult formulations. The bridging report submitted by the MAH has been found acceptable.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

Eosinophilic Oesophagitis (EoE) 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 to induce a rapid reduction of the inflammatory changes in the mucosa.

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. The current application is not aiming at demonstrating an influence on these long-term consequences.

Currently Jorveza (budesonide) 0.5 mg and 1mg orodispersible tablets are indicated for the "treatment of eosinophilic esophagitis (EoE) in adults (older than 18 years of age)".

This submission concerns the introduction of a new strength and age-appropriate paediatric formulation (0.2 mg/mL oral suspension) for the "treatment of eosinophilic esophagitis (EoE) in paediatric patients 2 to 17 years of age".

For *induction of remission*, the following posology is proposed:

Children 2 to 11 years of age

The recommended daily dose is 1 mg budesonide to be administered as two separate doses per day: 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.

Adolescents 12 to 17 years of age

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.

For *maintenance of remission*, a reduction of the posology is proposed as follows:

Children 2 to 11 years of age

A recommended daily dose of 0.5 mg depending on the individual clinical requirement of the patient.

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.

Adolescents 12 to 17 years of age

A recommended daily dose of 1 mg depending on the individual clinical requirement of the patient.

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.

The duration of maintenance therapy is determined by the treating physician.

9.1.2. Available therapies

Paediatric EoE is a rare disease with a high unmet need and limited licensed treatment options. PPIs, empiric elimination diets and topical steroids are all options for first-line induction treatments according to the ESPGHAN GL. The high need for licensed treatments is also evidenced by the off-label use, e.g. of topical corticosteroid preparations licensed for other indications. Of note, dupilumab has recently been licensed for the treatment of EoE in children aged 1 year and older and weighing at least 15 kg who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy (second line indication).

9.2. Main clinical studies

The MAH has submitted an application for the treatment of eosinophilic esophagitis (EoE) to paediatric patients from 2 years of age. To support this, a single efficacy and safety study was conducted, consisting of a 12-week double-blind, randomized, placebo-controlled phase comparing two dose levels of topical budesonide (0.2 mg/mL suspension) to placebo: high dose (2 to 11 years: 0.5 mg budesonide twice daily; 12 to 17 years: 1.0 mg budesonide twice daily); low dose (2 to 11 years: 0.5 mg budesonide once daily in the morning; 12 to 17 years: 1.0 mg budesonide once daily in the morning). Patients with an inadequate response were eligible for a 12-week open-label induction phase (OLI). Those who responded adequately during the double-blind phase could enter a 24-week open-label extension (OLE), followed by a 3-week tapering period and a 4-week follow-up. The study enrolled patients aged 2 to <18 years with confirmed symptomatic clinico-histological EoE. A total of 76 patients were randomized across the three treatment arms, with 64 included in the per-protocol population. The study design and chosen endpoints for both the double-blind phase and the OLI are considered acceptable.

9.3. Favourable effects

The study BUU-5/EEA showed statistically significant results for the primary endpoint "Rate of patients with pathological and clinical response at DB week 12". 46,2% of patients in BUU-Low dose and 69,2% of patients in BUU-High dose achieved clinical and histological remission with Jorveza compared to one in the placebo group (p value 0<0001 for both high and low doses comparisons). Both budesonide groups showed numerically better outcomes in key endoscopic, pathological, and disease activity endpoints, with the high-dose group generally performing better than the low-dose group. Clinical symptoms improved across all groups, including placebo. The higher portion of patients who achieved responder status as well as the higher portion of patients with histological remission/healing in the high-dose group are considered clinically relevant. Additional patients achieved a response after extended treatment in the open-label induction phase, and clinical remission was maintained during the open-label extension.

9.3.1. Uncertainties and limitations about favourable effects

The difference in primary efficacy between the high-dose and low-dose budesonide groups was clinically relevant but not statistically significant. Clinical symptoms improved across all groups, largely due to a strong placebo effect, resulting in no meaningful difference between treatment and placebo. Symptom improvement did not reliably predict overall clinical outcome. While clinical remission was maintained during the open-label extension, it remains unclear whether histological remission was sustained.

9.4. Unfavourable effects

The overall safety database is limited, due to the rarity of the condition with reported cases of local candidiasis and effects on the HPA axis, including decreased serum cortisol and adrenal suppression, one of which led to trial withdrawal. The short placebo-controlled treatment period in the study is not optimal for assessing growth effects, and sensitive methods like knemometry were not used. Generally, the safety profile is consistent with the well-known safety profile of budesonide, which has been used in the paediatric population for a long time (e.g. inhalation products). It appears also largely consistent with the known safety profile of the orodispersible tablet formulation in adults.

9.4.1. Uncertainties and limitations about unfavourable effects

Paediatric PK data, particularly in the 2–5-year age group, are limited and variable, leaving uncertainties around exposure and potential safety concerns in this population.

Long-term safety data demonstrating a positive impact on EoE complications are missing. The long-term safety will be further characterised in the post marketing setting.

9.5. Effects Table

Table 34: Effects Table

Effect (short description)	Treatment		Control	Uncertainties/ Strength of evidence	Ref
Favourable Effects					
BUU-5/EEA	*BUU-L*	*BUU-H*	*Placebo*		
pEP (rate of patients with histological remission and clinical response at weeks 12 DB	12/26 (46.2%)	18/26 (69.2%)	0/24 (0)	P< 0.0001 for both active groups vs. placebo	*Study BUU-5/EEA*
Rate of patients with histological remission at DB weeks 12	16/26 (61.5%)	23/26 (88.5%)	0/24 (0%)	P< 0.0001 for both active groups vs. placebo	
Rate of patients with histological healing at DB weeks 12 (LOCF)	14/26 (53.8%)	22/26 (84.6%)	0/24 (0%)	No statistical testing provided (Study BUU-5/EEA)	
Change from screening to DB weeks 12 in EREFS	-2.4	-2.2	0.4	No statistical testing provided (Study BUU-5/EEA)	
Unfavourable Effects					
SAF-BUU population (number of events)	ADR (Table 64, CSR)	SAE			
Local candidiasis (gastrointestinal, esophagus, oropharyngeal)	8	0			
HPA effects (serum cortisol decreased, adrenal insufficiency/suppression)	4	0		Clinical relevance still unclear	

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; sBA: serum bile acids;PELD: paediatric end-stage liver disease; MELD: model for end-stage liver disease score; SBD: surgical biliary diversion; OLT: orthotopic liver transplantation; PE: primary endpoint; SE: secondary endpoint; OR: odds ratio.

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

The pivotal study BUU-5/EEA demonstrated a statistically significant improvement in the primary endpoint, defined as histological remission at Week 12, for both active treatment groups compared with placebo. The magnitude of the treatment effect was consistent across histological and endoscopic parameters.

With regard to clinical symptoms, improvements were observed in all study arms, including placebo. The difference between active treatment and placebo in patient-reported symptom outcomes was limited. symptoms improvement did not consistently correlate with histological remission, and the placebo group showed a comparatively high rate of clinical remission at Week 12.
Therefore, while a clear histological treatment effect was demonstrated, the evidence for a distinct and clinically meaningful symptomatic benefit over placebo is less robust, considering the high placebo effect. The relationship between histological remission and patient-relevant long-term clinical outcomes remains uncertain and will be further characterised in the post approval setting.

The safety data from study BUU-5/EEA are generally consistent with the known safety profile of topical budesonide. Reported adverse reactions included local candidiasis and effects on the HPA axis (e.g. decreased cortisol, adrenal insufficiency/suppression) across phases of the study. One case of adrenal insufficiency identified during the open-label extension led to treatment discontinuation and resolved.

Corticosteroids, including topical formulations, may negatively affect growth, which is of particular relevance in the paediatric population. The placebo-controlled treatment period was of limited duration and was not designed to robustly assess growth. Sensitive longitudinal growth assessments were not systematically implemented. Therefore, an effect on growth cannot be excluded based on the available data. However, suppression of the HPA axis is a well-recognised class effect of corticosteroids and is addressed in the SmPC (sections 4.4 and 4.8).

9.6.2. Balance of benefits and risks

The study demonstrated clear effects on histological endpoints, including histological healing, which are expected to translate into long-term clinical benefits such as a reduced risk of complications and decreased need for invasive procedures. When combined with a safety profile consistent with both the adult data and the known profile of topical budesonide, these findings support a favourable benefit-risk assessment.

9.7. Benefit-risk conclusions

The benefit-risk balance is considered positive.