ORIGINAL RESEARCH ARTICLE

A Pharmacokinetic Bridging Study to Compare Systemic Exposure to Budesonide between Budesonide Oral Suspension and ENTOCORT EC in Healthy Individuals

Ivy H. Song[1] · Richard D. Finkelman[1] · Lan Lan[1]

Abstract

Background and Objectives Currently, there are no US FDA-approved therapies for eosinophilic esophagitis (EoE). Budesonide oral suspension (BOS; SHP621, TAK-721) is a viscous, muco-adherent, oral formulation of budesonide that is in phase III development for the treatment of EoE. BOS 2 mg twice daily was studied in 12- and 36-week phase III studies for the induction and maintenance of clinical remission in adults and adolescents with EoE (NCT02605837 and NCT02736409). ENTOCORT EC is a gelatin capsule formulation of budesonide that is FDA-approved for the treatment of mild-to-moderate active Crohn's disease (CD) in adults and children. This study compared the systemic exposure to budesonide from BOS with that from ENTOCORT EC, aiming to provide the pharmacokinetic (PK) bridge to the safety data of ENTOCORT EC.

Methods Healthy adult volunteers ($n = 22$) were enrolled in an open-label, single-center, crossover study. Participants received a single oral dose of BOS 2 mg and a single oral dose of ENTOCORT EC 9 mg under fasting conditions in a randomized sequence, with a 48-h washout period between treatments. PK parameters were calculated by non-compartmental analysis and compared between treatments using a mixed-effects model with sequence and treatment as fixed effects and individuals within sequence as a random effect.

Results Plasma budesonide concentrations showed that budesonide was absorbed significantly faster from BOS 2 mg than from ENTOCORT EC 9 mg, with peak concentrations reached at 1.5 and 4 h, respectively ($p < 0.001$). Systemic exposure to budesonide after a single oral dose of BOS 2 mg was lower than that observed after a single oral dose of ENTOCORT EC 9 mg; the least squares geometric mean maximum plasma concentration and the area under the concentration–time curve from the time of dosing to infinity and from the time of dosing to the last measurable concentration of budesonide after BOS 2 mg were 71.1%, 33.5%, and 33.6% of those after ENTOCORT EC 9 mg, respectively. No notable differences in treatment-emergent adverse events were observed between individuals treated with either drug; all events were mild and none resulted in discontinuation from the study.

Conclusions This study demonstrated that systemic exposure to budesonide after a single oral dose of BOS 2 mg was lower than that after a single oral dose of ENTOCORT EC 9 mg. These results provide PK bridging data to compare BOS with therapeutic doses of ENTOCORT EC with respect to safety information.

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Key Summary Points

A pharmacokinetic (PK) bridging study was conducted to compare the systemic exposure to budesonide from budesonide oral suspension (BOS), an oral formulation of budesonide that is in phase III development for the treatment of eosinophilic esophagitis, with that from ENTOCORT EC, a capsule formulation of budesonide indicated for the treatment of Crohn's disease (CD)

Systemic exposure to budesonide from BOS 2 mg twice daily (phase III study dose) was estimated to be lower than that from ENTOCORT EC 9 mg once daily (approved CD induction dose) and similar to that from ENTOCORT EC 6 mg once daily (approved CD maintenance dose)

These results provide PK bridging data to compare BOS 2 mg twice daily with therapeutic doses of ENTOCORT EC with respect to safety information

1 Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease characterized by chronic symptoms of esophageal dysfunction and eosinophilic inflammation [1]. Symptoms in adults include dysphagia, esophageal stricture, and food impaction [2]. These symptoms disrupt and restrict daily activities, affecting the health-related quality of life of patients and their families [3–5]. The estimated prevalence and incidence of EoE in the USA is approximately 0.5–1 per 1000 people and 1 in 10,000 new diagnoses each year, respectively [6].

There are currently no US FDA-approved therapies for EoE. Clinical guidelines recommend proton pump inhibitors, dietary therapies, swallowed topical corticosteroids (STCs), and esophageal dilation [7, 8]. Consistent and effective delivery is key to the efficacy of STCs [9]; consequently, their off-label use in the treatment of EoE can be problematic. Administration of STCs using metered-dose inhalers can result in suboptimal drug delivery, and budesonide slurries mixed by patients produce variable drug concentrations and mucosal contact times, which may limit their effectiveness in treating EoE symptoms [10]. Given the clinical outcomes associated with EoE and the absence of approved treatments indicated for the disease, there is an unmet need for novel therapies.

Budesonide oral suspension (BOS) is a muco-adherent formulation of budesonide with standardized viscosity and concentration, designed to increase the residence time of the drug on the esophageal surface [11]. BOS is in development for the treatment of EoE in adults and adolescents as a swallowed suspension. In a phase II clinical trial (ClinicalTrials.gov identifier: NCT01642212), BOS 2 mg twice daily significantly improved dysphagia symptoms, histological response, and eosinophil counts in adolescents and adults (11–40 years of age) with EoE [11]. Given the unmet medical need for an approved treatment for EoE, BOS was granted breakthrough designation by the FDA in 2016. Phase III trials in patients with EoE who were 11–55 years of age were initiated and have since been completed (ClinicalTrials.gov identifiers: NCT02605837 and NCT02736409).

Following oral administration and absorption, budesonide undergoes high (80–90%) first-pass hepatic metabolism via cytochrome P450 (CYP) 3A4 and has a high plasma clearance of approximately 0.9–1.8 L/min in healthy individuals [12–14]. Budesonide is also a substrate of P-glycoprotein, which is highly expressed in the colon and small intestine [15–17]. Consequently, orally administered budesonide has high topical glucocorticoid activity with minimal systemic exposure [13, 18]. The systemic effects mediated by corticosteroids are minimized for budesonide, which may be attributed to its relatively low bioavailability [18]. The major metabolites of budesonide, 6β-hydroxy budesonide, and 16α-hydroxy prednisolone have negligible glucocorticoid activity (< 1%) and are predominantly excreted renally [14]. Several budesonide products are approved for different indications in the USA and other countries, including RHINOCORT (McNeil Products Ltd, Berkshire, UK), a nasal spray indicated for the treatment of seasonal allergic rhinitis (64 mg once daily), and ENTOCORT EC (AstraZeneca, Södertälje, Sweden), an oral formulation indicated for the induction (9 mg once daily) and maintenance (6 mg once daily) treatment of mild-to-moderate active Crohn's disease (CD) [14, 19]. Thus, the safety of budesonide has been evaluated extensively. This analysis compared systemic exposure to budesonide from the BOS formulation used in phase III trials with that from ENTOCORT EC, and aimed to provide a pharmacokinetic (PK) bridge to the safety data of ENTOCORT EC.

2 Methods

2.1 Study Design and Population

This phase I crossover study aimed to compare the PK of budesonide from a single oral dose of BOS 2 mg (0.2 mg/mL in a volume of 10 mL) with a single oral dose of ENTOCORT EC 9 mg (three 3 mg gelatin capsules) in healthy individuals.

BOS 2 mg twice daily is the dose used in ongoing phase III studies in patients with EoE; therefore, BOS 2 mg was selected for this single-dose, blinded study [20, 21]. In adults, the recommended dose of ENTOCORT EC is 9 mg once daily and 6 mg once daily for the treatment and maintenance of clinical remission of mild-to-moderate active CD, respectively [14]. ENTOCORT EC 9 mg once daily was selected as the comparative clinical dose because the PK of budesonide from this formulation are dose proportional following repeated oral administration of 3–15 mg [14].

Healthy adults who were 18–50 years of age, inclusive, with a body mass index (BMI) of 18–30 kg/m^2, inclusive, a body weight ≥ 50 kg, and hemoglobin levels ≥ 12 g/dL were included in this randomized, open-label, single-center, crossover study. Individuals with a current or recent (within the past year) history of any gastrointestinal (GI) disorder, such as esophagitis, gastroesophageal reflux disease or gastritis, or of any medical condition requiring corticosteroid treatment, or who might have required corticosteroid treatment during the study (e.g. eczema, asthma or allergic rhinitis) were excluded from the study. Those who had used any medication (including over-the-counter, herbal or homeopathic preparations), with the exception of hormone replacement therapy or hormonal contraceptives and occasional use of ibuprofen or acetaminophen, within the 14 days prior to the first dose of either study drug were also excluded, as were individuals who had ingested known CYP3A4 inhibitors within the 7 days prior to the first dose of study treatment. Any individuals who had received BOS 2 mg, ENTOCORT EC 9 mg, or any other corticosteroid within 30 days of the first dose of study medication were also excluded.

Participants were randomly assigned to one of two treatment sequences. In treatment sequence 1, participants received a single oral dose of BOS 2 mg, followed by a single oral dose of ENTOCORT EC 9 mg with a 48-h washout period between each treatment. Participants in treatment sequence 2 received ENTOCORT EC 9 mg first, followed by BOS 2 mg, with a 48-h washout period between each treatment (Fig. 1). Participants were required to fast for approximately 10 h before dose administration and to continue fasting through to 4 h after administration of each study drug. In addition, water intake was restricted (except for water to administer ENTOCORT EC), starting 4 h before and continuing up to 2 h after administration of each drug. After study treatment, patients received a follow-up telephone call, during which any serious adverse events (SAEs), adverse events (AEs), and use of concomitant medications were recorded.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. Approval from an Institutional Review Board was obtained, and informed consent was obtained from all individual participants included in the study.

2.2 PK Assessments

Serial blood draws for PK assessments were performed up to 24 h after dosing: every 15 min up to 1 h postdose; at 1.5 h postdose; every 2 h up to 16 h postdose; and at 24 h postdose. Blood samples were immediately chilled and centrifuged (at 4 °C) at 1500 g for 15 min. The separated plasma samples were stored at −70 °C and shipped to the bioanalytical laboratory for analysis. Plasma concentrations of budesonide were determined using a validated bioanalytical method [22]. Budesonide was obtained from Sigma-Aldrich (St Louis, MO, USA) and was subsequently used to prepare standard and quality control solutions, which were determined based on the nominal concentrations of budesonide.
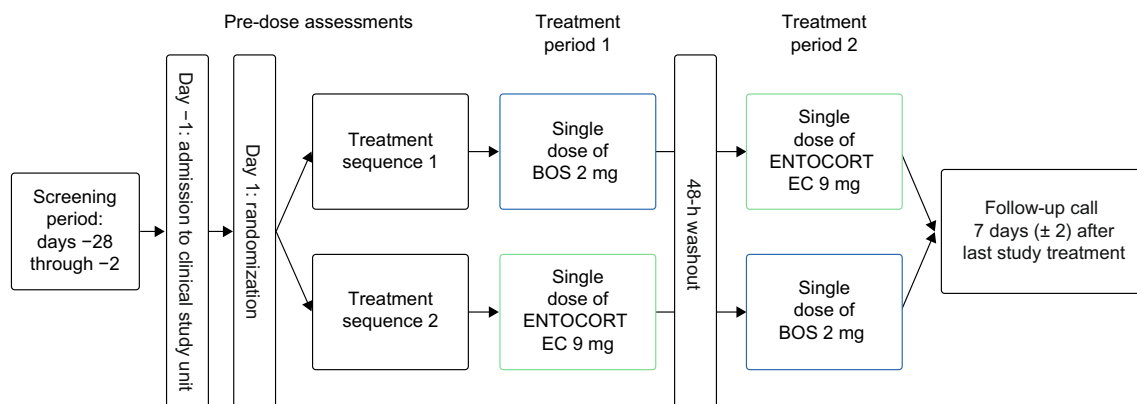

Fig. 1 Phase I crossover study design. Participants were randomly assigned to one of two treatment sequences, with a 48-h washout period between each treatment: BOS 2 mg (0.2 mg/mL in a volume of 10 mL) or ENTOCORT EC 9 mg (three 3-mg gelatin capsules) after a 10-h fasting period. Serial blood samples for determining plasma budesonide concentrations were collected in both treatment periods at predose and through 24 h postdose. *BOS* budesonide oral suspension

2.3 PK Data Analysis

Analyses of PK data were performed for all participants who had taken at least one dose of BOS 2 mg or ENTOCORT EC 9 mg and who had at least one measurable postdose plasma concentration of budesonide that was reportable for either treatment. PK parameters were calculated from the plasma concentration–time data using non-compartmental methods, and all calculations were based on actual sampling times. PK parameters measured were area under the concentration–time curve from the time of dosing to infinity (AUC_∞); area under the concentration–time curve from the time of dosing to the last measurable concentration (AUC_t); maximum observed plasma concentration (C_{max}); apparent clearance (CL/F); terminal half-life ($t_{1/2}$); time to first quantifiable plasma concentration after dosing (t_{lag}); time of C_{max} (t_{max}); and apparent volume of distribution associated with the terminal slope (V_z/F).

2.4 Safety Assessments

Safety was evaluated by daily recording of AEs throughout the study period and by the assessment of vital signs (every day), clinical laboratory parameters (day − 1 and final day of treatment), and 12-lead electrocardiograms (ECGs; days 1, 2, 4, and 5). An AE was defined as any untoward medical event that occurred after the individual provided informed consent to participate in the study, irrespective of whether or not it was associated with BOS 2 mg or ENTOCORT EC 9 mg, and irrespective of whether or not it was deemed by the investigator to be treatment-related. Treatment-emergent AEs (TEAEs) were defined as any AE that started, deteriorated in severity, or increased in severity on or after the date of the first dose of study drug through to 3 days after the last dose administered in each of the respective study periods.

2.5 Statistical Analyses

Log-transformed PK parameters (AUC_∞, AUC_t, and C_{max}) were compared between treatments using a mixed-effect model for a crossover design with fixed factors for sequence and treatment, and a random factor for individuals within sequence. Point estimates and associated 90% confidence intervals (CIs) were constructed for the differences in log-transformed PK parameters. These values were back-transformed to provide point estimates for the ratio of geometric least squares means and associated 90% CIs on the original scale. The geometric mean t_{max} of budesonide was compared with BOS 2 mg and ENTOCORT EC 9 mg treatments using the Wilcoxon signed-rank test.

3 Results

3.1 Baseline Demographics and Clinical Characteristics

In total, 22 individuals with a mean (standard deviation [SD]) age of 39.2 years (10.2) and a mean (SD) BMI of 27.8 kg/m^2 (2.3) were enrolled in this study; 50% were women. Eleven participants were assigned to treatment sequence 1 and 11 were assigned to treatment sequence 2; all participants completed the study (Table 1). Baseline demographics were generally similar between the two treatment sequence groups, with some differences noted for ethnicity (Table 1). In treatment sequence group 1, six participants (54.5%) were Hispanic or Latino and five participants (45.5%) were non-Hispanic or non-Latino. In treatment sequence group 2, nine participants (81.8%) were Hispanic or Latino and two participants (18.2%) were non-Hispanic or non-Latino.

Table 1 Baseline demographics and characteristics

Demographic/characteristic	Treatment sequence 1	Treatment sequence 2	Overall
N	11	11	22
Age, years	37.5 (11.5)	40.9 (9.0)	39.2 (10.2)
Men [n (%)]	4 (36.4)	7 (63.6)	11 (50.0)
Race [n (%)]			
White	10 (90.9)	9 (81.8)	19 (86.4)
Black	1 (9.1)	2 (18.2)	3 (13.6)
Ethnicity [n (%)]			
Hispanic or Latino	6 (54.5)	9 (81.8)	15 (68.2)
Non-Hispanic or non-Latino	5 (45.5)	2 (18.2)	7 (31.8)
Weight, kg	75.6 (10.1)	80.8 (12.4)	78.2 (11.3)
Height, cm	164.2 (9.5)	170.5 (9.8)	167.4 (10.0)
BMI, kg/m^2	28.0 (2.0)	27.7 (2.7)	27.8 (2.3)

BMI body mass index, *SD* standard deviation

Data are expressed as mean (SD) unless otherwise stated

3.2 PK Results

PK parameters (AUC_∞, $t_{1/2}$, CL/F and V_z/F) could not be reliably calculated for one individual who received ENTOCORT EC 9 mg. Following oral administration of BOS 2 mg, mean plasma concentrations of budesonide increased steadily and peaked approximately 1.5 h after dosing (Fig. 2). In contrast, ENTOCORT EC 9 mg showed significantly slower absorption than BOS 2 mg, with the peak plasma concentration at approximately 4 h ($p < 0.001$) [Table 2]. Systemic exposure to budesonide after a single oral dose of BOS 2 mg was lower than after a single dose of ENTOCORT EC 9 mg; the geometric least squares mean AUC_t, AUC_∞, and C_{max} values for BOS 2 mg were 33.6%, 33.5%, and 71.1%, respectively, of those observed for ENTOCORT EC 9 mg (Table 2).

3.3 Safety Results

In total, six participants (27.3%) experienced TEAEs. Four individuals (18.2%) treated with BOS 2 mg reported four TEAEs, and two individuals (9.1%) treated with ENTOCORT EC 9 mg reported two TEAEs. All TEAEs were reported as mild in severity. No TEAEs resulted in treatment discontinuation (Table 3). There were no notable differences in TEAEs between the two treatments. No clinically relevant changes in vital signs, clinical laboratory parameters, or ECG parameters were observed after treatment with BOS or ENTOCORT EC.

4 Discussion

This study provides PK bridging data to compare the safety of BOS with that of ENTOCORT EC. The rate of absorption of budesonide from BOS 2 mg was faster than that from ENTOCORT EC 9 mg, with the mean peak plasma concentration occurring 2.5 h earlier. This observation is consistent with the differences in the formulations and anticipated locations of action of each drug. Although both drugs are administered orally, ENTOCORT EC is formulated for release in
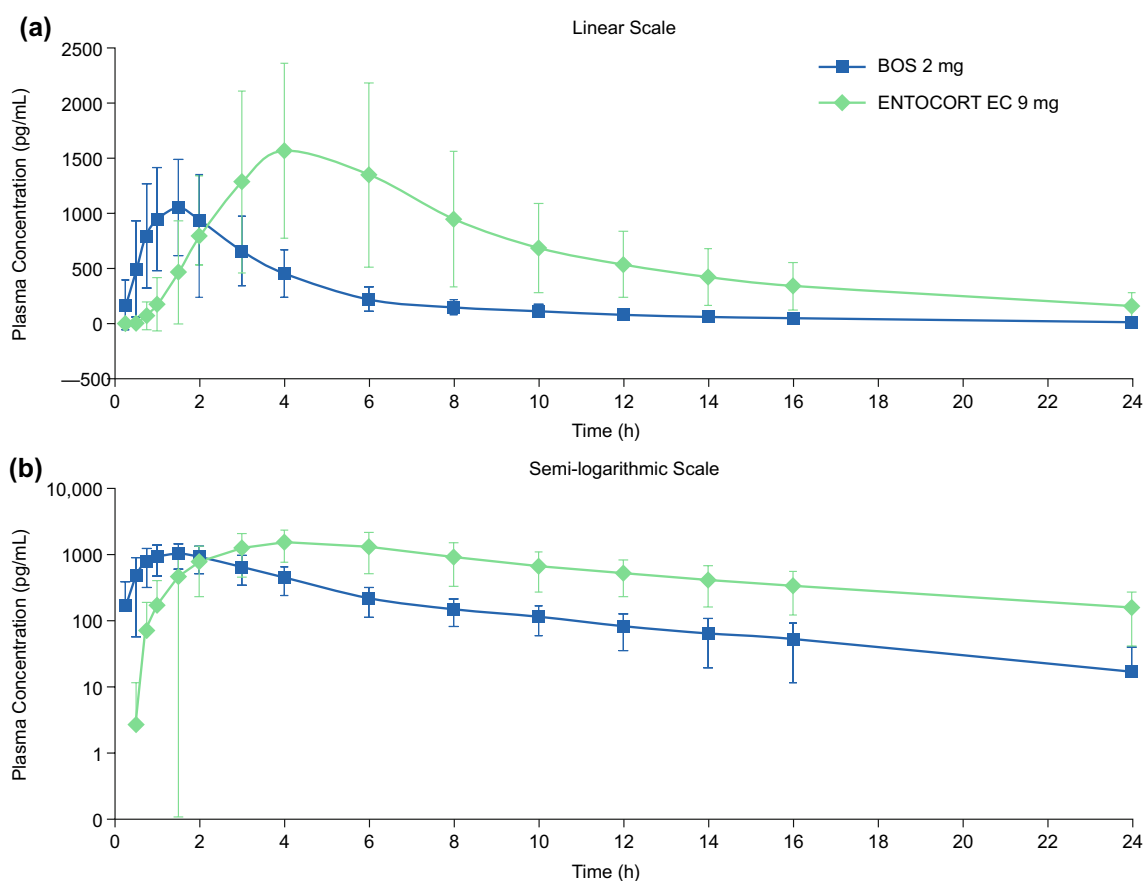

Fig. 2 Mean ± SD plasma concentrations of budesonide over time after a single dose of BOS 2 mg or ENTOCORT EC 9 mg on linear and semi-logarithmic scales. Plasma concentrations of budesonide peaked at approximately 1.5 h for BOS 2 mg and showed significantly faster absorption than ENTOCORT EC 9 mg, which peaked at approximately 4 h after dosing. *BOS* budesonide oral suspension, *SD* standard deviation

Table 2 Summary of budesonide pharmacokinetic parameters

PK parameter	Treatment	
	BOS 2 mg [$n=22$]	ENTOCORT EC 9 mg [$n=22$]
AUC_∞, h × ng/mL		
n	22	21
Geometric mean (95% CI)	4.524 (3.612–5.666)	13.745[a] (10.446–18.085)
Ratio of geometric LS means (90% CI) relative to ENTOCORT EC 9 mg	0.335 (0.302–0.373)[a]	0.335 (0.302–0.373)[a]
AUC_t, h × ng/mL		
n	22	22
Geometric mean (95% CI)	4.257 (3.394–5.339)	12.682 (9.807–16.402)
Ratio of geometric LS means (90% CI) relative to ENTOCORT EC 9 mg	0.336 (0.301, 0.374)	0.336 (0.301, 0.374)
C_{max}, ng/mL		
Geometric mean (95% CI)	1.063 (0.863–1.310)	1.496 (1.165–1.921)
Ratio of geometric LS means (90% CI) relative to ENTOCORT EC 9 mg	0.711 (0.638–0.792)	0.711 (0.638–0.792)
$t_{1/2}$, h		
Geometric mean (95% CI)	5.05 (4.40–5.79)	6.02[a] (5.55–6.53)
CL/F, L/h		
Geometric mean (95% CI)	442.1 (353.0–553.6)	654.8[a] (497.6–861.6)
V_z/F, L		
Geometric mean (95% CI)	3218.5 (2804.3–3693.9)	5688.1[a] (4496.0–7196.2)
t_{max}, h		
Median (min, max)	1.5 (0.5, 2.0)	4.0 (2.0, 6.0)
t_{lag}, h		
Median (min, max)	0 (0, 0.25)	0.5 (0.25, 1.02)

AUC_∞ area under the concentration–time curve from the time of dosing to infinity, *AUC_t* area under the concentration–time curve from the time of dosing to the last measurable concentration, *BOS* budesonide oral suspension, *CI* confidence interval, *CL/F* apparent clearance, *C_{max}* maximum observed concentration, *LS* least squares, *PK* pharmacokinetic, *$t_{1/2}$* terminal half-life, *t_{lag}* time to first quantifiable plasma concentration after dosing, *t_{max}* time to C_{max}, *V_z/F* apparent volume of distribution associated with the terminal slope

[a]For these calculations, the number of participants was 21 because PK parameters could not be calculated for one individual who received ENTOCORT EC 9 mg

the small intestine, whereas BOS is a viscous suspension, designed to increase the residence time of budesonide on the esophageal surface [11, 15].

Based on the geometric mean half-life of budesonide (5.1 h) observed in this study, there is no expected accumulation with once-daily dosing, and minimal (< 15%) expected accumulation of BOS with twice-daily dosing (used in phase III studies). Systemic exposure to budesonide from ENTOCORT EC 9 mg in this study was similar to a previous investigation of PK in healthy adults in which the mean C_{max} and the steady state AUC for budesonide were 1.50 ± 0.79 ng/mL and 14.13 ± 7.33 h × ng/mL, respectively, following oral administration of ENTOCORT EC 9 mg once daily [14].

Systemic exposure to budesonide observed after a single dose of BOS 2 mg was lower than that after a single dose of ENTOCORT EC 9 mg, as shown by the lower geometric mean AUC_∞, AUC_t, and C_{max}. ENTOCORT EC 9 mg once daily is approved for the treatment of mild-to-moderate

active CD involving the ileum and/or the ascending colon, and ENTOCORT EC 6 mg once daily is approved for the maintenance of clinical remission of mild-to-moderate CD [14]. The clinical dosing regimen for both the induction and maintenance of clinical remission of EoE studied in the phase III pivotal trial program for BOS is 2 mg twice daily [20, 21]. Within therapeutic doses, budesonide exhibits linear PK properties; following repeated oral administration of 3–15 mg, the PK of budesonide from ENTOCORT EC is dose proportional [15]. Therefore, PK parameters for BOS 2 mg twice daily and ENTOCORT EC 9 mg once daily and 6 mg once daily were estimated by superposition using the PK data from a single oral dose of BOS 2 mg and a single oral dose of ENTOCORT EC 9 mg determined in this study, under the assumption of linear and time-independent PK. When accounting for the different dosing frequencies of BOS and ENTOCORT EC, the daily AUC and the C_{max} of budesonide from BOS 2 mg twice daily at steady state are

Table 3 Treatment-emergent adverse events by system organ class and treatment at onset

	BOS 2 mg [$n=22$]		ENTOCORT EC 9 mg [$n=22$]	
	n (%)	m	n (%)	m
TEAEs				
All	4 (18.2)	4	2 (9.1)	2
Serious	0	0	0	0
Severe	0	0	0	0
Related to study drug	4 (18.2)	4	2 (9.1)	2
TEAEs by system organ class				
Gastrointestinal disorders	2 (9.1)	2	1 (4.5)	1
Dry mouth	1 (4.5)	1	1 (4.5)	1
Flatulence	1 (4.5)	1	0	0
Nervous system disorders	2 (9.1)	2	1 (4.5)	1
Dizziness	0	0	1 (4.5)	1
Headache	2 (9.1)	2	0	0

BOS budesonide oral suspension, *n* number of participants, *m* number of events, *TEAEs* treatment-emergent adverse events

estimated to be approximately 67% and 71%, respectively, of these parameters from ENTOCORT EC 9 mg once daily, and similar to those from ENTOCORT EC 6 mg once daily.

Although this study was not designed to evaluate the oral bioavailability of budesonide, the bioavailability for BOS 2 mg is estimated to be 50.8% higher than that of ENTOCORT EC 9 mg, based on the dose-normalized AUC. As the oral bioavailability of budesonide from ENTOCORT EC 9 mg is reported to be 9% in healthy adults in a fasted state [14], the oral bioavailability of budesonide from BOS 2 mg is calculated to be 13.6% in healthy adults. Complete absorption of budesonide was observed following oral administration of ENTOCORT EC and other capsule formulations [12, 23]; therefore, complete absorption of budesonide following BOS administration is also expected. Given the differences in the formulations of BOS and ENTOCORT EC, budesonide is anticipated to be absorbed completely and mostly metabolized in the esophagus and upper GI tract following treatment with BOS, whereas budesonide from ENTOCORT EC is released and subsequently absorbed and metabolized in the lower GI tract. The higher oral bioavailability of budesonide from BOS compared with ENTOCORT EC observed in this study may be attributed to the lower first-pass metabolism of budesonide in the esophagus compared with the small intestine and colon as a consequence of the partition of esophageal drainage between the systemic (avoiding first-pass metabolism in the liver) and portal veins [24], the lower presence of CYP3A4 in the esophageal mucosa [25], and the higher presence of P-glycoprotein (of which budesonide is a substrate) in the small intestine [15–17].

4.1 Study Limitations

This study evaluated the PK of BOS in healthy individuals rather than patients with EoE; however, we expect the PK of BOS to be similar in these two populations based on findings from a population PK analysis that identified no significant differences in the PK of budesonide from BOS between healthy individuals and patients with EoE (internal data on file, 2019). In support, similar budesonide PK were reported in both healthy individuals and patients with CD who received ENTOCORT EC 9 mg [26]. We also note that FDA guidelines recommend PK bridging studies in healthy individuals or patients to assess drug safety [27]. An additional limitation of this study is the difference in dosing frequencies between BOS (2 mg twice daily) and ENTOCORT EC (9 mg once daily). Although PK data obtained after repeated doses may be the most relevant, we propose that an analysis of single-dose PK is appropriate because budesonide PK were shown to be linear and time-independent [14]. Although the ENTOCORT EC 6 mg once-daily dose was not directly assessed in this study, systemic exposure to budesonide from ENTOCORT EC is linear between 3 and 15 mg. Therefore, budesonide PK from ENTOCORT EC 6 mg once daily can be estimated via extrapolation of ENTOCORT EC 9 mg once-daily PK data by direct dose adjustment. Thus, we propose that only including the ENTOCORT EC 9 mg once-daily regimen in this study was appropriate and sufficient to compare ENTOCORT EC with BOS.

To address the limitations of this study, we provide a direct comparison of systemic exposure of budesonide between BOS 2 mg twice daily observed in patients with EoE in the phase III study of BOS and ENTOCORT EC in patients with CD. In the phase III study of BOS, the systemic exposure to budesonide after BOS 2 mg twice daily (mean daily AUC 10.1 h × ng/mL; C_{max} 0.92 ng/mL) in patients with EoE was lower than after ENTOCORT EC 9 mg once daily (mean daily AUC 15.1 h × ng/mL; C_{max} 1.7 ng/mL) and similar to ENTOCORT EC 6 mg once daily (mean daily AUC 10.1 h × ng/mL; C_{max} 1.13 ng/mL) in patients with CD, based on dose proportional PK [14, 28].

5 Conclusion

This study demonstrated that systemic exposure to budesonide after a single oral dose of BOS 2 mg was lower than that after a single oral dose of ENTOCORT EC 9 mg. Systemic exposure to budesonide from BOS 2 mg twice daily was estimated to be lower than that from ENTOCORT EC 9 mg once daily. Both drugs were well tolerated. These results provide PK bridging data to compare BOS 2 mg twice daily with therapeutic doses of ENTOCORT EC with respect to safety information.

Declarations

Conflicts of Interest Ivy H. Song, Richard D. Finkelman, and Lan Lan are full-time employees of Shire, a member of the Takeda group of companies, and stockholders of Takeda.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the IntegReview Independent Review Board (dated 5 October 2017).

Consent to participate Consent to participate was obtained from all individuals included in this study.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Informed consent Informed consent was obtained from all individual participants included in this study.

Authors' contributions All authors contributed to the study design and analysis, and critically reviewed the manuscript.

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