Effect of food on the pharmacokinetics, safety and tolerability of budesonide oral suspension in healthy adults: a randomized phase 1 study

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Introduction

- Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease characterized by esophageal dysfunction and eosinophilic inflammation of the esophageal mucosa.[1,2]
- Eohilia™ (budesonide oral suspension [BOS]) 2.0 mg twice daily is a swallowed corticosteroid approved by the US Food and Drug Administration (FDA) for 12-week use in patients aged 11 years and older with EoE.[3]
- Pharmacokinetic (PK) data for BOS (various formulations) have been reported from several studies: a phase 1 study in healthy adults; a phase 2 dose-ranging study in pediatric and adolescent patients with EoE; and a population PK analysis in healthy adults and in pediatric and adult patients with EoE.[4–6]
- Several food effect studies have reported differences in PK parameters for budesonide formulations when administered under fasting or fed conditions in both adult patients with inflammatory bowel disease and in healthy volunteers; however, these differences were not considered to be clinically meaningful.[7–10]
- Until now, the impact of food intake on the bioavailability of budesonide has not been formally investigated for the US FDA-approved BOS formulation.[3]

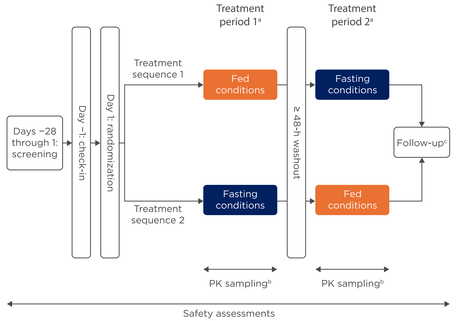
Aim

- To evaluate the relative bioavailability of budesonide following a single oral dose of BOS 2.0 mg administered under fasting and fed conditions in healthy adult volunteers.

Methods

- This was an open-label, randomized, two-period, two-sequence, two-way crossover, phase 1 study in healthy adults aged 19–55 years with a body mass index of 18–32 kg/m² (TAK-721-1003 [NCT06268301]; **Figure 1**).[11]

Figure 1. Study design.



[a]On the first day of each treatment period, participants received a single oral dose of BOS 2.0 mg under fasting or fed conditions, according to the randomization schedule. [b]PK sampling was carried out before dosing and up to 24 hours after dosing in both treatment periods. [c]All participants who received BOS returned to the study site approximately 3 days after the last dose of BOS for follow-up procedures and to determine if any adverse events had occurred since the last study visit.
BOS, budesonide oral suspension; h, hours; PK, pharmacokinetic.

- Participants were randomly assigned to receive a single dose of BOS 2.0 mg under fasting or fed conditions (treatment period 1), with a washout period of at least 48 hours before crossover to the alternative conditions (treatment period 2).
  - Under fasting conditions, participants fasted overnight for at least 10 hours and up to at least 4 hours after dosing.
  - Under fed conditions, participants fasted overnight for at least 10 hours until 30 minutes pre-dose, when they were given a high-fat/high-calorie meal that was consumed within 30 minutes. Participants then fasted for at least 4 hours after dosing.
- Plasma samples for PK analysis were collected before dosing and up to 24 hours after dosing in both treatment periods.
- PK parameters were calculated from plasma budesonide concentration–time profiles by noncompartmental analysis.
- For the primary endpoints, the following parameters were examined: maximum observed concentration (C_{max}); area under the concentration–time curve (AUC) from 0 hours to the time of the last quantifiable concentration (AUC_{last}); and AUC from 0 hours to infinity (AUC_{∞}).
- PK parameters assessed as secondary endpoints were: AUC from 0 to 12 hours (AUC_{0-12}); lag time to the first quantifiable concentration (t_{lag}); time to C_{max} (t_{max}); AUC from the last quantifiable concentration to infinity ($AUC_{extrap\%}$); terminal disposition phase half-life ($t_{1/2z}$); apparent clearance after extravascular administration (CL/F); and apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F).
- Safety endpoints included the incidence, severity and causality of treatment-emergent adverse events (TEAEs).

Results

Participant demographics and clinical characteristics

- In total, 20 participants entered and completed the study, the majority of whom were female (60%), White (55%) and not Hispanic or Latino (85%).
- Participants had a mean (standard deviation [SD]) age of 35.7 (10.0) years and a mean (SD) body mass index of 27.6 (2.7) kg/m².

PK parameters

- Plasma budesonide concentration–time profiles following a single dose of BOS 2.0 mg under fasting and fed conditions are shown in **Figure 2**; key plasma budesonide PK parameters are shown in **Table 1**.
- When compared with participants who received BOS 2.0 mg under fasting conditions, those who received BOS 2.0 mg under fed conditions had:
  - ~13% lower geometric mean C_{max} (604.1 pg/mL vs 692.9 pg/mL)
  - ~26% and ~27% higher geometric mean AUC_{last} and AUC_{∞} (3529 pg·h/mL vs 2811 pg·h/mL and 3892 pg·h/mL vs 3075 pg·h/mL, respectively)
  - ~1 hour longer median t_{max} (2.52 h vs 1.29 h; $p < 0.001$).
- Geometric mean AUC_{0-12} was higher under fed conditions than under fasting conditions (3208 pg·h/mL vs 2728 pg·h/mL); however, arithmetic mean CL/F and V_z/F were lower (565.8 L/h vs 744.2 L/h and 3686 L vs 4358 L, respectively).

Safety and tolerability

- All TEAEs were mild or moderate in severity; there were no deaths, serious TEAEs or TEAEs leading to study discontinuation or withdrawal.

Pre-dose food does not have a clinically meaningful effect on systemic exposure to budesonide oral suspension (BOS) 2.0 mg in healthy adults. However, patients should not eat or drink for 30 minutes after taking BOS.

Conclusions

- **The results suggest that despite slight differences in budesonide PK parameters between fasting and fed conditions, a clinically meaningful effect of pre-dose food on systemic exposure to budesonide (US FDA-approved BOS formulation)[3] is not expected.**
- **This study provides key information for patients with EoE, demonstrating that a single dose of BOS 2.0 mg can be taken without dietary restrictions before dosing. As per the prescribing information, patients should wait at least 30 minutes before eating or drinking after taking BOS.[3]**

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Table 1. Key PK parameters for plasma budesonide after a single oral dose of BOS 2.0 mg under fasting and fed conditions in healthy adults.

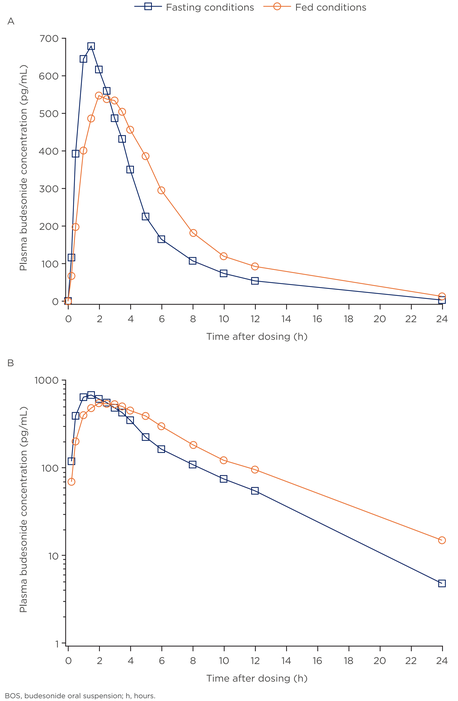
PK parameter	Fasting conditions (n = 20)[a]	Fed conditions (n = 20)[b]
C_{max}, pg/mL		
Geometric mean (geometric CV%)	692.9 (54.4)	604.1 (46.6)
Geometric LS mean ratio, % (90% CI)[c]	87.18 (74.80, 101.61)	
AUC_{last}, pg·h/mL		
Geometric mean (geometric CV%)	2811 (57.5)	3529 (52.1)
Geometric LS mean ratio, % (90% CI)[c]	125.54 (113.85, 138.41)	
AUC_{∞}, pg·h/mL		
Geometric mean (geometric CV%)	3075 (57.0)	3892 (47.1)
Geometric LS mean ratio, % (90% CI)[c]	126.56 (116.60, 137.36)	
AUC_{0-12}, pg·h/mL		
Geometric mean (geometric CV%)	2728 (53.0)	3208 (42.2)
t_{lag}, h		
Median (min, max)	0.33 (0.26, 0.56)	0.31 (0.25, 0.53)
Median difference (90% CI)[d]	0.003 (−0.041, 0.049)	
t_{max}, h		
Median (min, max)	1.29 (0.55, 2.57)	2.52 (1.01, 6.03)
Median difference (90% CI)[d]	0.884 (0.472, 1.285)	
$AUC_{extrap\%}$, %		
Arithmetic mean (SD)	8.455 (4.734)	9.006 (7.272)
$t_{1/2z}$, h		
Arithmetic mean (SD)	4.457 (1.435)	4.933 (1.388)
CL/F, L/h		
Arithmetic mean (SD)	744.2 (406.0)	565.8 (262.0)
V_z/F, L		
Arithmetic mean (SD)	4358 (2155)	3686 (1175)

[a]Fasting participants were those who received BOS 2.0 mg under fasting conditions in either treatment period 1 or 2 of the study. [b]Fed participants were those who received BOS 2.0 mg under fed conditions in either treatment period 1 or 2 of the study. [c]Geometric LS means were calculated by exponentiating the LS means derived from the linear mixed-effects model. Geometric LS mean ratios were calculated as: 100*LS mean for fed conditions/LS mean for fasting conditions. [d]Median differences (fasting vs fed conditions) and 90% CIs were estimated using the Hodges–Lehmann method and Walsh averages.
AUC, area under the concentration–time curve; AUC_{∞}, AUC from 0 hours to infinity; AUC_{0-12}, AUC from 0 to 12 hours; $AUC_{extrap\%}$, AUC from the last quantifiable concentration to infinity; AUC_{last}, AUC from 0 hours to time of the last quantifiable concentration; BOS, budesonide oral suspension; CI, confidence interval; CL/F, apparent clearance after extravascular administration; C_{max}, maximum observed concentration; CV%, percentage coefficient of variation; h, hours; LS, least-squares; PK, pharmacokinetic; SD, standard deviation; $t_{1/2z}$, terminal disposition phase half-life; t_{lag}, lag time to the first quantifiable concentration; t_{max}, time to C_{max}; V_z/F, apparent volume of distribution during the terminal disposition phase after extravascular administration.

References

1. Dellon ES *et al. Gastroenterology* 2018;155:1022–33.e10.
2. Collins MH *et al. Am J Surg Pathol* 2019;43:1501–9.
3. Takeda Pharmaceuticals America, Inc. Prescribing information, Eohilia, US Food and Drug Administration, 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213976s000lbl.pdf (Accessed August 9, 2024).
4. Song IH *et al. Drugs R D* 2020;20:359–67.
5. Gupta SK *et al. J Pediatr Gastroenterol Nutr* 2022;75:186–91.
6. Song IH *et al. Am J Gastroenterol* 2020;115:S0440.
7. Lundin P *et al. Aliment Pharmacol Ther* 2001;15:45–51.
8. Edsbäcker S *et al. Aliment Pharmacol Ther* 2003;17:525–36.
9. Salix Pharmaceuticals, Inc., a division of Bausch Health US, LLC. Prescribing information, Uceris (budesonide) extended-release tablets. US Food and Drug Administration, 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203634s007lbl.pdf (Accessed August 9, 2024).
10. AstraZeneca. Prescribing information, Entocort EC (budesonide) delayed-release capsules. US Food and Drug Administration, 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021324s023lbl.pdf (Accessed August 9, 2024).
11. ClinicalTrials.gov. NCT06268301. Available from: https://clinicaltrials.gov/study/NCT06268301 (Accessed August 9, 2024).

Figure 2. Arithmetic mean plasma budesonide concentrations over time after a single oral dose of BOS 2.0 mg under fasting and fed conditions in healthy adults on linear (A) and semi-logarithmic (B) scales.



BOS, budesonide oral suspension; h, hours.

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Disclosures

AJP, **JW**, **NKD**, **CAR** and **AS** are employees of Takeda Development Center Americas, Inc. **VY** is an employee of Takeda Pharmaceuticals USA, Inc. All authors are stockholders of Takeda Pharmaceutical Company Limited.