P0690 - Impact of concomitant use of corticosteroids on efficacy and safety of obefazimod at week 8 of induction trials in patients with moderately to severely active ulcerative colitis: results from the ABTECT-1 and ABTECT-2 Phase 3, double-blind, placebo-controlled induction trials

European Crohn's and Colitis Organisation
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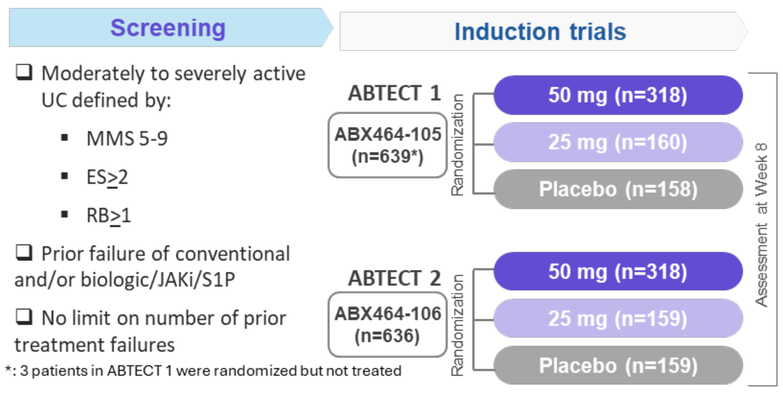
Background

- Obefazimod (Obe) is an oral, once-daily (QD), small molecule that enhances expression of microRNA-124, which restores mucosal immune balance through regulation of Th17 cells and macrophages. Obe has shown efficacy in patients (pts) with moderately to severely active ulcerative colitis (UC) [1-3].
- In Phase 3 ABTECT-1 [NCT05507203] and ABTECT-2 [NCT05507216] 8-week induction trials, Obe achieved clinically meaningful improvements in clinical, endoscopic and histologic endpoints.
- We evaluated the effect of concomitant corticosteroid (CS) use on the efficacy and safety of Obe in pts enrolled in ABTECT trials.

Methods

- The two multicenter, randomized, double-blind, placebo-controlled ABTECT trials enrolled pts with moderate-to-severe UC who had inadequate response, loss of response, or intolerance to at least one prior therapy, including corticosteroids, immunosuppressants, biologics, S1P receptor modulators and/or JAK inhibitors (with no upper limit) (Fig. 1).
- Pts were randomized 2:1:1 to Obe 50 mg QD (Obe-50), Obe 25 mg QD (Obe-25) or placebo (PBO) for 8 weeks.

Fig. 1: Design of ABTECT induction trials

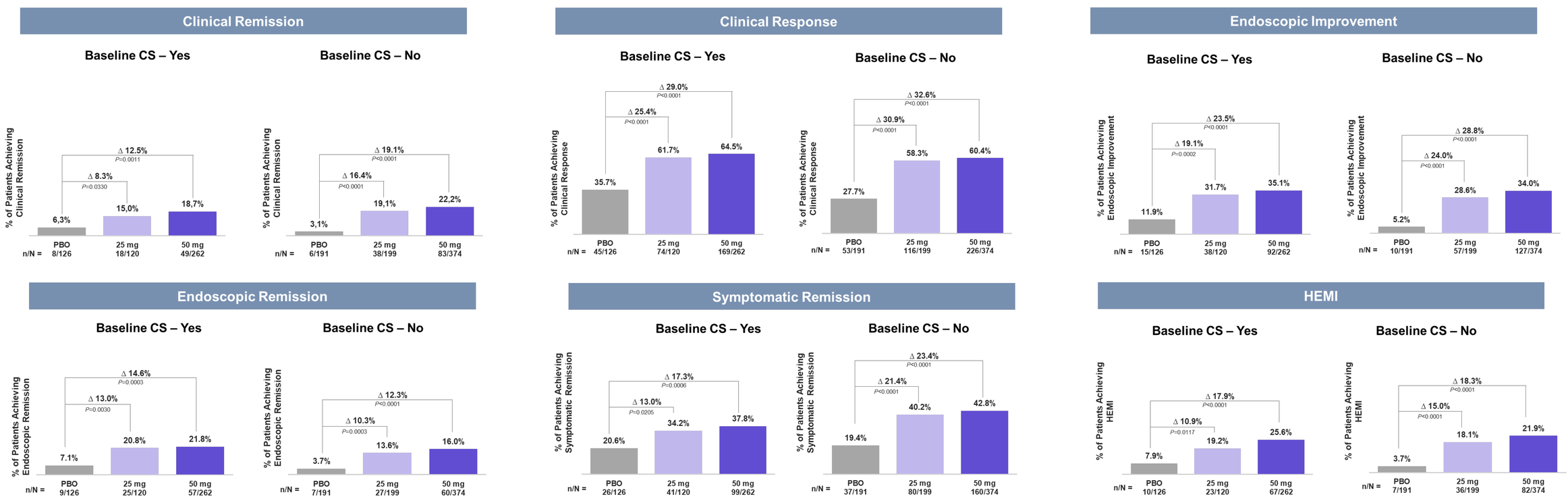


- Pts were categorized based on concomitant CS use at baseline (CS-Yes/CS-No); CS were to be stable ≥2 weeks before screening (max 15 mg prednisone, 9 mg budesonide, 5 mg beclomethasone); CS dose was held constant through week 8.
- Efficacy endpoints were clinical remission/response, endoscopic improvement/remission, symptomatic remission, and histo-endoscopic mucosal improvement (HEMI). All p-values are nominal. Treatment emergent adverse events (TEAEs), serious TEAEs and study discontinuation rates were examined.

Results

- In both ABTECT trials, 508 pts (39.9%) used concomitant CS at baseline through week 8 (CS-Yes) and 764 pts (60.1%) did not (CS-No). Baseline demographics and disease characteristics were similar between treatment groups, regardless of baseline CS status.
- In the pooled analysis, a higher proportion of pts receiving Obe-25 or Obe-50 vs. PBO achieved clinical remission across CS-Yes and CS-No subgroups and met all other endpoints across CS-Yes and CS-No subgroups with nominal significance (Fig.2).
- Comparable efficacy across all endpoints was observed in both CS-Yes and CS-No subgroups.

Fig. 2: Efficacy in the pooled ABTECT 1 and ABTECT 2 population by baseline CS use



Pooled analyses were not powered for statistical comparisons between subgroups; statistical inferences are exploratory, and all P values are nominal and 2-sided. NRI is used for subjects with missing outcome at week 8 and subjects reporting any IE prior to week 8; % Difference is for Obe minus placebo and is based on estimated common risk difference using the Mantel-Haenszel weights adjusting for the randomization stratification factors: inadequate response to advanced therapies (yes/no), baseline oral corticosteroids usage (yes/no). Clinical remission: SFS=0 or 1, and RBS=0 and MES=0 or 1 (MES of 1 modified to exclude friability). Clinical response: decrease from baseline in the MMS ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1. Endoscopic improvement: endoscopic subscore ≤1. Endoscopic remission: endoscopic subscore=0. Symptomatic remission: RBS=0, SFS ≤1. Symptomatic response: a reduction from baseline in pMMS of ≥1 point and a relative reduction from baseline in pMMS of ≥30%, and a reduction from baseline in RBS of ≥1 point and/or RBS ≤1.HEMI: histo-endoscopic mucosal improvement is defined as MES=0 or 1 and Geboes Index score ≤3.1. Endoscopic improvement/symptomatic remission were co-primary endpoints for the EMA and were met by both doses in both trials. Symptomatic remission was an "other secondary" endpoint, not multiplicity controlled, for the FDA and health authorities other than the EMA. HEMI, histo-endoscopic mucosal improvement; PBO, placebo.

- Among CS-Yes pts, TEAE rates ranged from 45.0% to 56.5% across treatment groups; among CS-no pts, rates ranged from 51.3% to 62.8% (Table 1).
- Headache was the most frequent TEAE across subgroups.
- Among CS-Yes and CS-No pts, rates of serious TEAEs and TEAE leading to study discontinuation were comparable between treatments.
- No signal was observed for serious, severe, or opportunistic infections or malignancies.

Table 1: Summary of adverse events

	Pts with baseline CS-Yes (N=508)			Pts with baseline CS-No (N=764)		
	Obe-50 (n=262)	Obe-25 (n=120)	PBO (n=126)	Obe-50 (n=374)	Obe-25 (n=199)	PBO (n=191)
Any TEAEs, n (%)						
TEAE related to study drug, n (%)	148 (56.5)	54 (45.0)	62 (49.2)	235 (62.8)	102 (51.3)	99 (51.8)
TEAE leading to study discontinuation, n (%)	12 (4.6)	1 (0.8)	7 (5.6)	18 (4.8)	5 (2.5)	6 (3.1)
Serious TEAE, n (%)	8 (3.1)	3 (2.5)	6 (4.8)	12 (3.2)	4 (2.0)	4 (2.1)
TEAE leading to death, n (%)	0	0	0	0	0	0
Malignancies	0	1 (0.8)[a]	1 (0.8)[b]	1 (0.3)[c]	0	0
Serious/severe/opportunistic infections	2 (0.8)	1 (0.8)	0	2 (0.5)	0	0
TEAEs ≥3% in Obe groups and greater than PBO), n (%)						
Headache	52 (19.8)	18 (15.0)	7 (5.6)	96 (25.7)	30 (15.1)	11 (5.8)
Nausea	13 (5.0)	3 (2.5)	1 (0.8)	34 (9.1)	13 (6.5)	3 (1.6)
Anaemia	12 (4.6)	1 (0.8)	13 (10.3)	10 (2.7)	11 (5.5)	7 (3.7)
Nasopharyngitis	7 (2.7)	4 (3.3)	3 (2.4)	7 (1.9)	5 (2.5)	7 (3.7)
Lipase increased[d]	6 (2.3)	4 (3.3)	1 (0.8)	21 (5.6)	5 (2.5)	6 (3.1)
Abdominal pain	6 (2.3)	1 (0.8)	0	18 (4.8)	1 (0.5)	2 (1.0)
Abdominal pain upper	2 (0.8)	2 (1.7)	1 (0.8)	16 (4.3)	3 (1.5)	1 (0.5)
Vomiting	6 (2.3)	2 (1.7)	0	12 (3.2)	5 (2.5)	1 (0.5)

[a]Pyoderma gangrenosum, [b]Human chorionic gonadotropin increased, [c]Prostate cancer stage I, [d]To date, no safety signals have been observed related to either elevations in lipase or more specifically to pancreatitis. Obe, obefazimod; PBO, placebo; TEAE, treatment-emergent adverse event.

Conclusions

In both ABTECT induction trials in patients with moderately to severely active UC, obefazimod demonstrated consistent efficacy and safety irrespective of baseline CS status.

References 1: Vermeire S et al. *J Crohns Colitis*. 17: 1689-97, 2023 - 2: Vermeire S et al. *Gastroenterology*. 160: 2595-98, 2021 - 3: Vermeire S et al. *The Lancet Gastroenterology & Hepatology*. 7: 1024-35, 2022

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