P0694 - Pooled analysis of efficacy and safety of once-daily oral obefazimod in North American patients from the ABTECT Phase 3, double-blind, placebo-controlled induction trials

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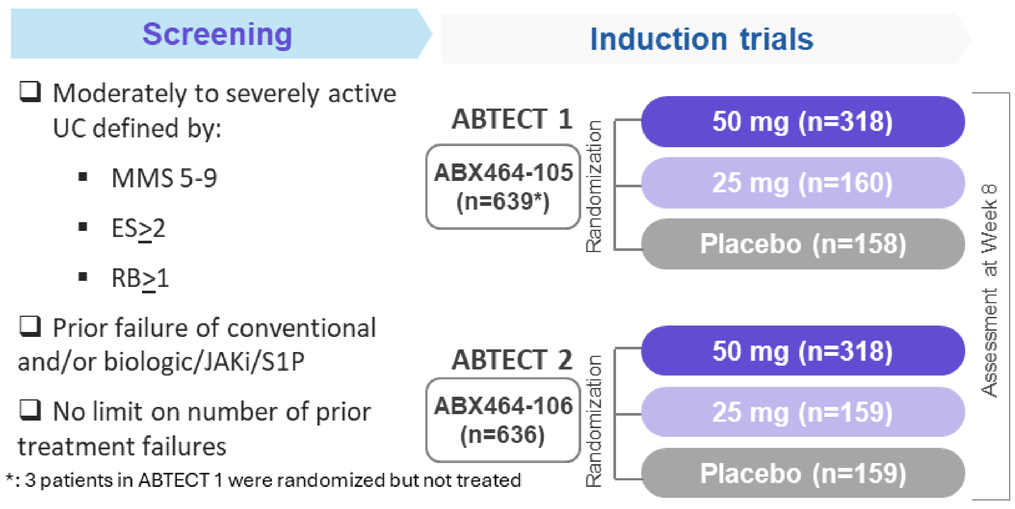
Background

- 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 two 8-week induction ABTECT trials (NCT05507203, NCT05507216), Obe achieved clinically meaningful improvements in clinical, endoscopic and histologic endpoints.
- Here, a pooled analysis evaluates the efficacy and safety of Obe in the North American (NA) subgroup of pts enrolled in the ABTECT induction trials.

Methods

- The multicenter, randomized, double-blind, placebo-controlled ABTECT trials enrolled pts with moderate-to-severe UC (MMS≥ 5, with rectal bleeding sub-score (RBS) ≥ 1 and centrally read endoscopic score (ES) ≥2) who had inadequate response, loss of response, or intolerance to at least one prior therapy (no upper limit), including corticosteroids, immunosuppressants, biologics, S1P receptor modulators and/or JAK inhibitors (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. This post-hoc analysis focuses on pts recruited from study defined NA centers.

Fig. 1: Design of ABTECT induction trials

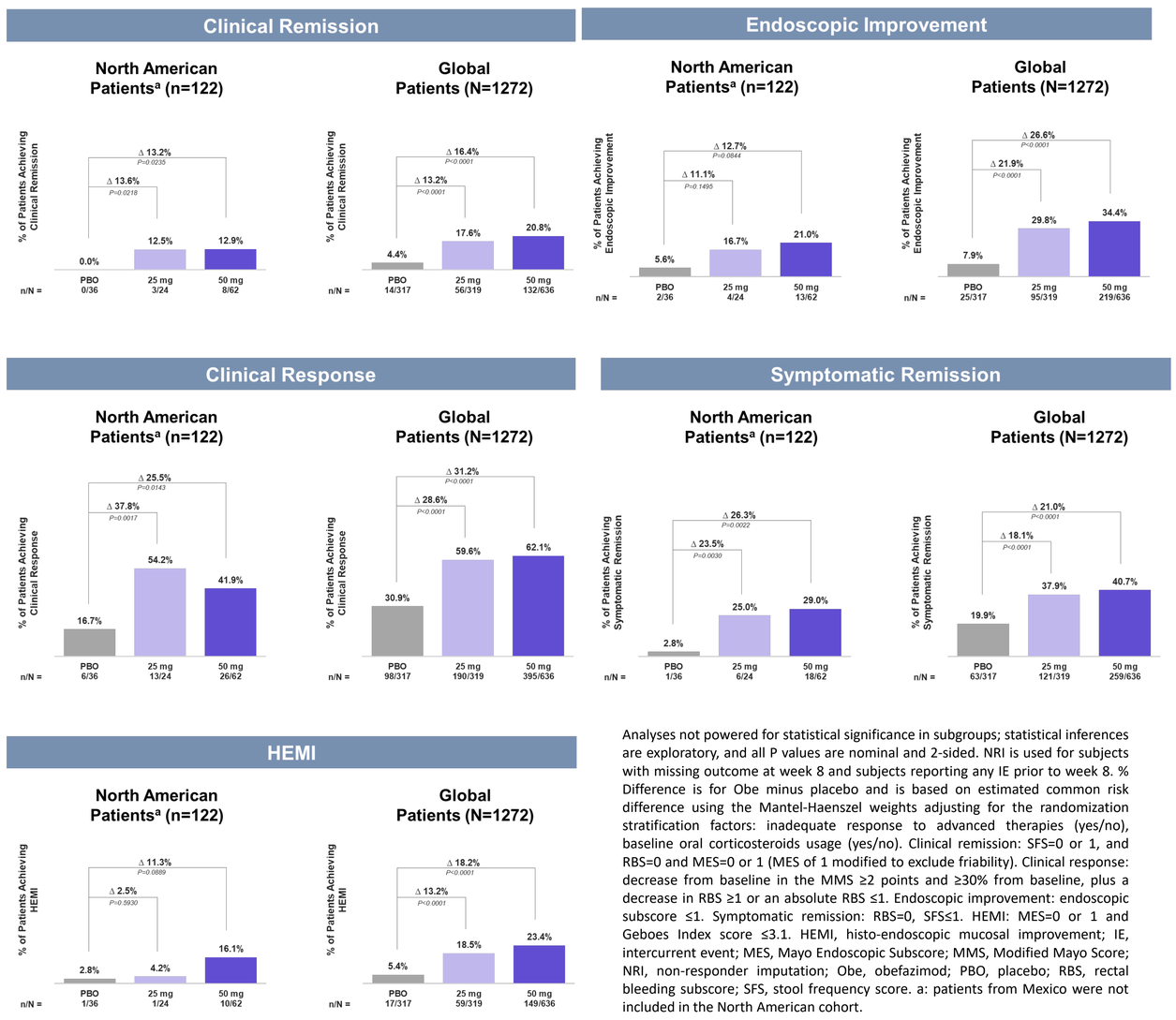


- Efficacy endpoints included clinical remission (per MMS), clinical response, endoscopic improvement, symptomatic remission, and histo-endoscopic mucosal improvement (HEMI).
- Treatment emergent adverse events (TEAEs), serious TEAEs and dropout rates were evaluated.

Results

- Among the 1272 pts randomized and treated in the ABTECT trials, 122 were NA pts (116 from USA and 6 from Canada).
- Baseline demographics were balanced across treatment groups, but NA pts on Obe-50 were more refractory and had more extensive disease vs. overall population on Obe-50.
- A higher proportion of NA pts receiving Obe-25 or Obe-50 vs. PBO achieved all efficacy endpoints including clinical remission, endoscopic improvement, clinical response, symptomatic remission and HEMI (Fig.2).
- Headache was the most common TEAE (Obe-25: 29.2%; Obe-50: 24.2%; PBO: 5.6%) (Table 1).
- No serious TEAEs occurred with Obe-25, and the rate with Obe-50 was similar to PBO.
- TEAE leading to study discontinuations were less frequent with Obe-25 (4.2%) and Obe-50 (6.5%) vs PBO (13.9%).
- No opportunistic infections or malignancies were reported.

Fig. 2: Eight-week efficacy of Obe in North American vs global population: pooled ABTECT trials



Analyses not powered for statistical significance in 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. Symptomatic remission: RBS=0, SFS≤1. HEMI: MES=0 or 1 and Geboes Index score ≤3.1. HEMI, histo-endoscopic mucosal improvement; IE, intercurrent event; MES, Mayo Endoscopic Subscore; MMS, Modified Mayo Score; NRI, non-responder imputation; Obe, obefazimod; PBO, placebo; RBS, rectal bleeding subscore; SFS, stool frequency score. a: patients from Mexico were not included in the North American cohort.

Table 1: Summary of adverse events of Obe in the subgroup of NA patients

	Obe-50 (n=62)	Obe-25 (n=24)	PBO (n=36)
Any TEAEs, n (%)	41 (66.1)	16 (66.7)	21 (58.3)
TEAE leading to study discontinuation, n (%)	4 (6.5)	1 (4.2)	5 (13.9)
Serious TEAE, n (%)	2 (3.2)	0	3 (8.3)
TEAE leading to death, n (%)	0	0	0
Malignancies	0	1 (4.2)[a]	0
Serious/severe/opportunistic infections	0	0	0
TEAEs occurring in patients (≥3% in Obe groups and greater than PBO), n (%)			
Headache	15 (24.2)	7 (29.2)	2 (5.6)
Arthralgia	6 (9.7)	0	1 (2.8)
Nausea	6 (9.7)	5 (20.8)	0
Vomiting	5 (8.1)	2 (8.3)	0
Abdominal pain	2 (3.2)	0	0
Blood cholesterol increased	2 (3.2)	0	1 (2.8)
Cataract	2 (3.2)	0	0
Haemoglobin decreased	2 (3.2)	0	1 (2.8)
Hypertriglyceridaemia	2 (3.2)	0	0
Lipase increased[b]	2 (3.2)	1 (4.2)	1 (2.8)
Muscle spasms	2 (3.2)	0	0
SARS-CoV-2 test positive	2 (3.2)	0	0
Blood fibrinogen increased	1 (1.6)	1 (4.2)	0
Abdominal tenderness	0	1 (4.2)	1 (2.8)
Amnesia	0	1 (4.2)	0
Amylase increased	0	2 (8.3)	1 (2.8)
Aphasia	0	1 (4.2)	0
Heart rate increased	0	1 (4.2)	0
Parosmia	0	1 (4.2)	0
Peripheral swelling	0	1 (4.2)	0
Pyoderma gangrenosum	0	1 (4.2)	0
Rash	0	1 (4.2)	1 (2.8)
Rash papular	0	1 (4.2)	0
Respiratory tract congestion	0	1 (4.2)	0
Tension headache	0	1 (4.2)	0
Weight increased	0	1 (4.2)	0

[a]Pyoderma gangrenosum, [b]to date, no safety signals have been observed related to either elevations in lipase or more specifically to pancreatitis

Conclusions

- In the ABTECT induction trials, clinically meaningful improvements in all efficacy measures were observed in NA pts with moderately to severely active UC.
- Obe treatment demonstrated a favorable safety profile in this subgroup, consistent with the overall study population.

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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