P1048 - Impact of age of subjects on the efficacy and safety of once-daily oral obefazimod in moderately to severely active ulcerative colitis: week 8 results from the ABTECT-1 and ABTECT-2 Phase 3, double-blind, placebo-controlled induction trials

European Crohn's and Colitis Organisation
This poster was presented at the annual ECCO Congress.
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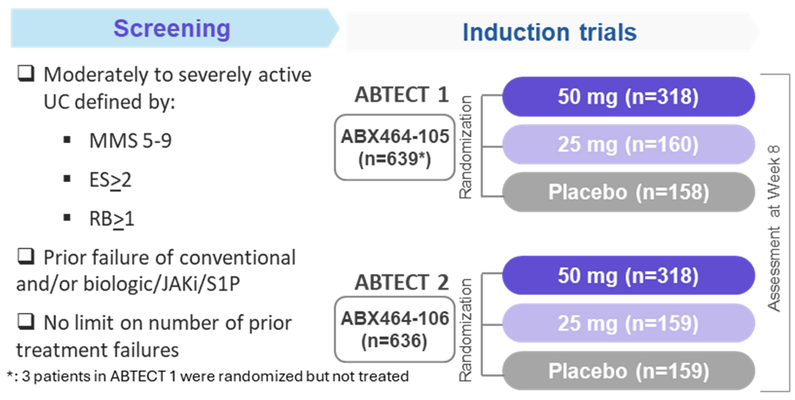
Background

- 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.
- Considering that UC is more commonly seen in the older population and studies are needed in this pt group, we evaluated the impact of age on efficacy and safety of Obe in pts with UC 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 (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.

Fig. 1: Design of ABTECT induction trials



- In this post-hoc analysis, pts were categorized by age: <65 years old (yo), ≥65 yo, >median of 41 yo or ≤median of 41 yo. Efficacy endpoints included 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

- Among the 1272 randomized and treated pts in ABTECT trials, 1183 were <65 yo and 89 were ≥65 yo; by median age, 606 pts were >41 yo and 666 pts were ≤41 yo. In both trials, baseline demographics and disease characteristics were generally similar between treatment groups, regardless of age group.
- In a pooled analysis, a higher proportion of pts receiving Obe-25 or Obe-50 vs PBO achieved clinical remission across age subgroups and met most clinical and endoscopic endpoints across age subgroups with nominal significance (Fig.2, Table 1).

Fig. 2: Efficacy in the pooled ABTECT 1 and ABTECT 2 population by age subgroups

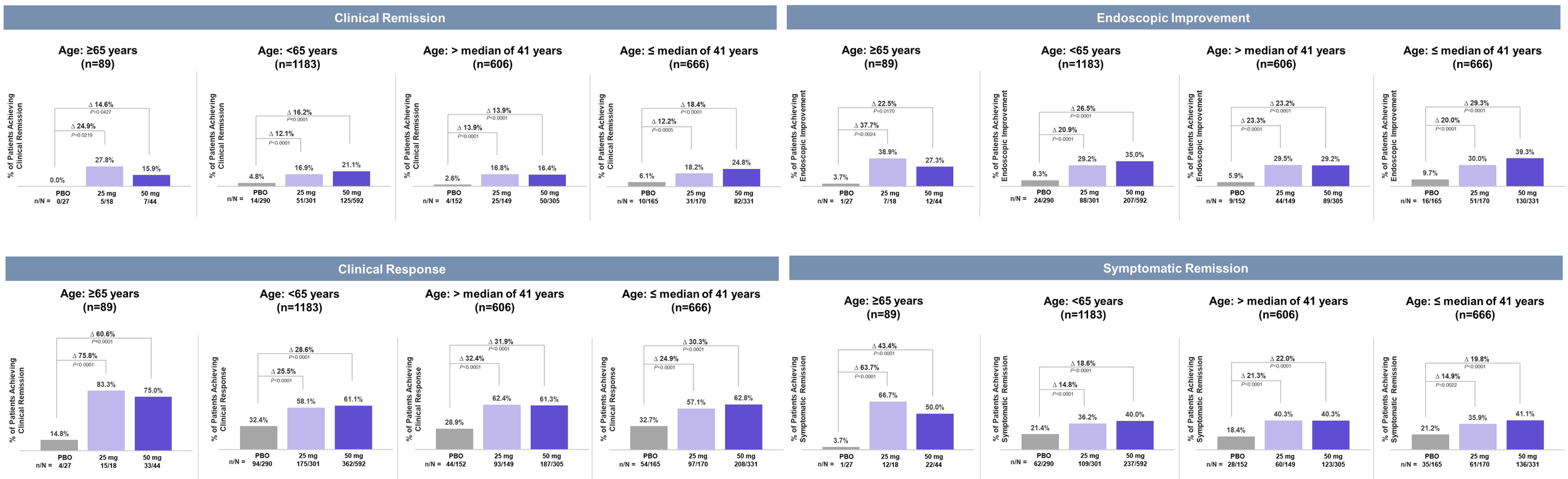


Table 1: Endoscopic remission and HEMI by age subgroups - pooled ABTECT studies

		Age ≥ 65 years (N=89)			Age < 65 years (N=1183)			Age > median of 41 years (N=606)			Age ≤ median of 41 years (N=666)		
		PBO (N= 27)	Obe 25 (N= 18)	Obe 50 (N=44)	PBO (N= 290)	Obe 25 (N= 301)	Obe 50 (N=592)	PBO (N= 152)	Obe 25 (N= 149)	Obe 50 (N=305)	PBO (N= 165)	Obe 25 (N= 170)	Obe 50 (N=331)
Endoscopic remission	% (n)	0	16.7 (3)	9.1 (4)	5.5 (16)	16.3 (49)	19.1 (113)	3.9 (6)	16.8 (25)	15.1 (46)	6.1 (10)	15.9 (27)	21.5 (71)
	Placebo adjusted Δ %		16.3	11.4		10.6	13.4		12.4	11.1		10.1	15.4
	p-value		p=0.0422	p=0.0542		p<0.0001	p<0.0001		p=0.0003	p=0.0004		p=0.0029	p<0.0001
HEMI	% (n)	3.7 (1)	22.2 (4)	9.1 (4)	5.5 (16)	18.3 (55)	24.5 (145)	4.6 (7)	19.5 (29)	17.7 (54)	6.1 (10)	17.6 (30)	28.7 (95)
	Placebo adjusted Δ %		22.3	2.9		12.8	18.8		14.9	13.4		11.7	22.5
	p-value		p=0.0242	p=0.5954		p<0.0001	p<0.0001		p<0.0001	p<0.0001		p=0.0007	p<0.0001

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 sub-score ≤1. Endoscopic remission: endoscopic subscore=0. Symptomatic remission: RBS=0, SFS ≤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.

- Among pts <65 yo, TEAEs occurred in 59.8%, 49.5%, and 50.3% of those receiving Obe-50, Obe-25, and PBO, respectively. For patients ≥65 yo, rates were 65.9%, 38.9%, and 55.6%.
- Headache was the most frequent TEAE when treated with Obe across all age groups.
- Rates of serious TEAEs and TEAEs leading to study drug discontinuation were similar between Obe and PBO.
- No signal was observed for serious, severe, or opportunistic infections or malignancies.

Conclusions

- In both ABTECT induction trials in pts with moderately to severely active UC, obefazimod demonstrated consistent efficacy and safety across age subgroups with no new or unexpected safety findings.

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

Disclosures : *FM (consultant or speaker's fees) AbbVie, Amgen, Biogen, Celgene, Celltrion, Dr Falk Pharma, Ferring Pharmaceuticals, Hospira, Janssen, Laboratórios Vitória, MSD, Pfizer, Sandoz, Takeda, UCB, Vifor (Grant) GEDII and National Science Foundation; HT (consultant or speaker's fees) Abbvie, Abivax, Dr Falk Pharma, ferring, Galapagos, Microbiotica, MSD, Pfizer, Takeda; SN (consultant or speaker's fees) Abbvie, Takeda, Celltrion Healthcare, Pfizer, Galapagos, J&J, Lilly, Fresenius, Amgen, Medac, MSD; SM (speaker's fees) Abivax; RR (consultant or speaker's fees) AbbVie, Abivax, Janssen (Grant) AbbVie, Abivax, Alexion, AstraZeneca, Eli Lilly, Janssen, Mirador, Spytherapeutics, Ventix, Xelcor; LH (consultant or speaker's fees) J&J, AbbVie, Takeda, Ventyx, Abivax, BMS, Lilly, MSD, Sanofi; AY (consultant or speaker's fees) Takeda, Pfizer, Roche, Merck, Abbvie, Eli Lilly. Bristol Myers Squibb, Celltrion, J&J.*

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