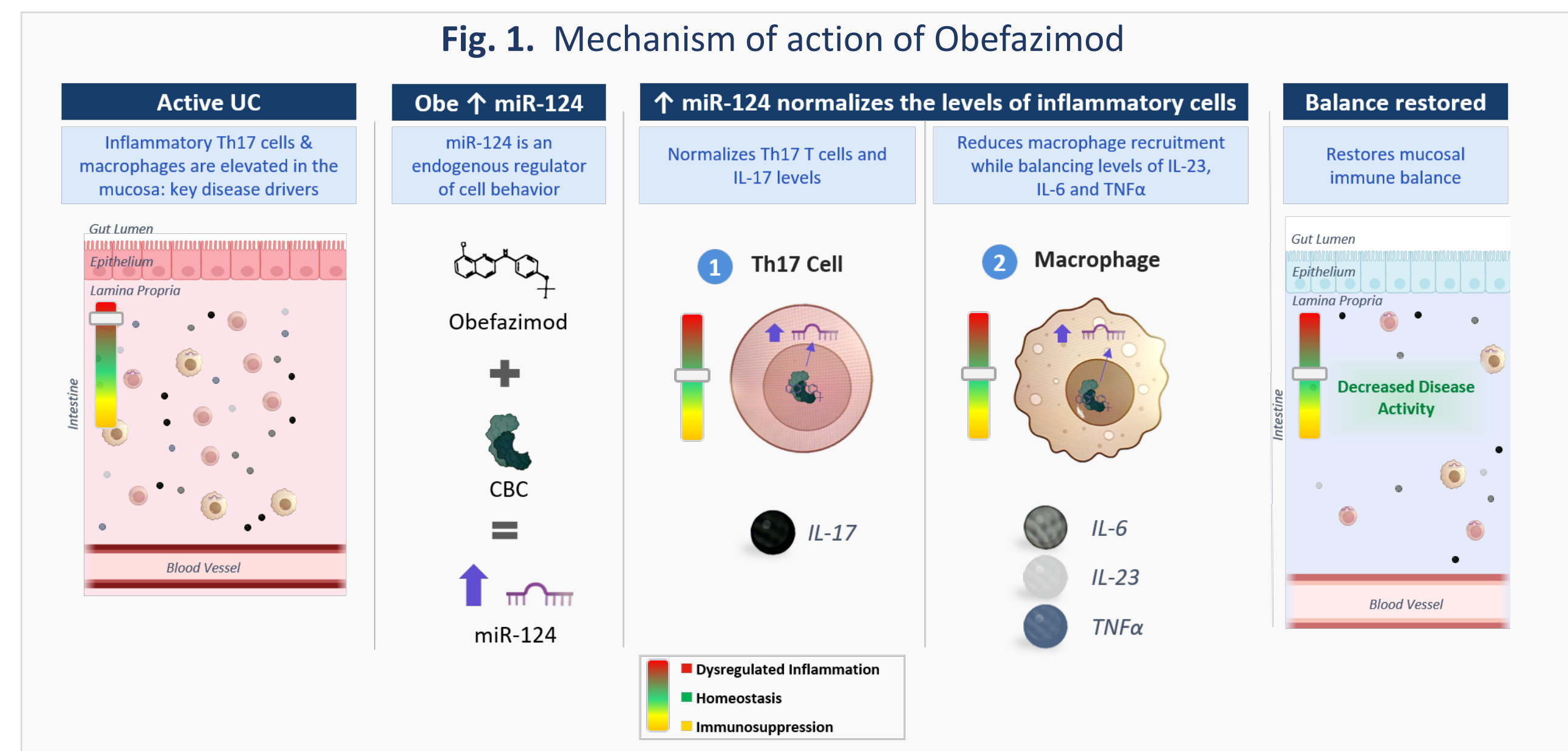


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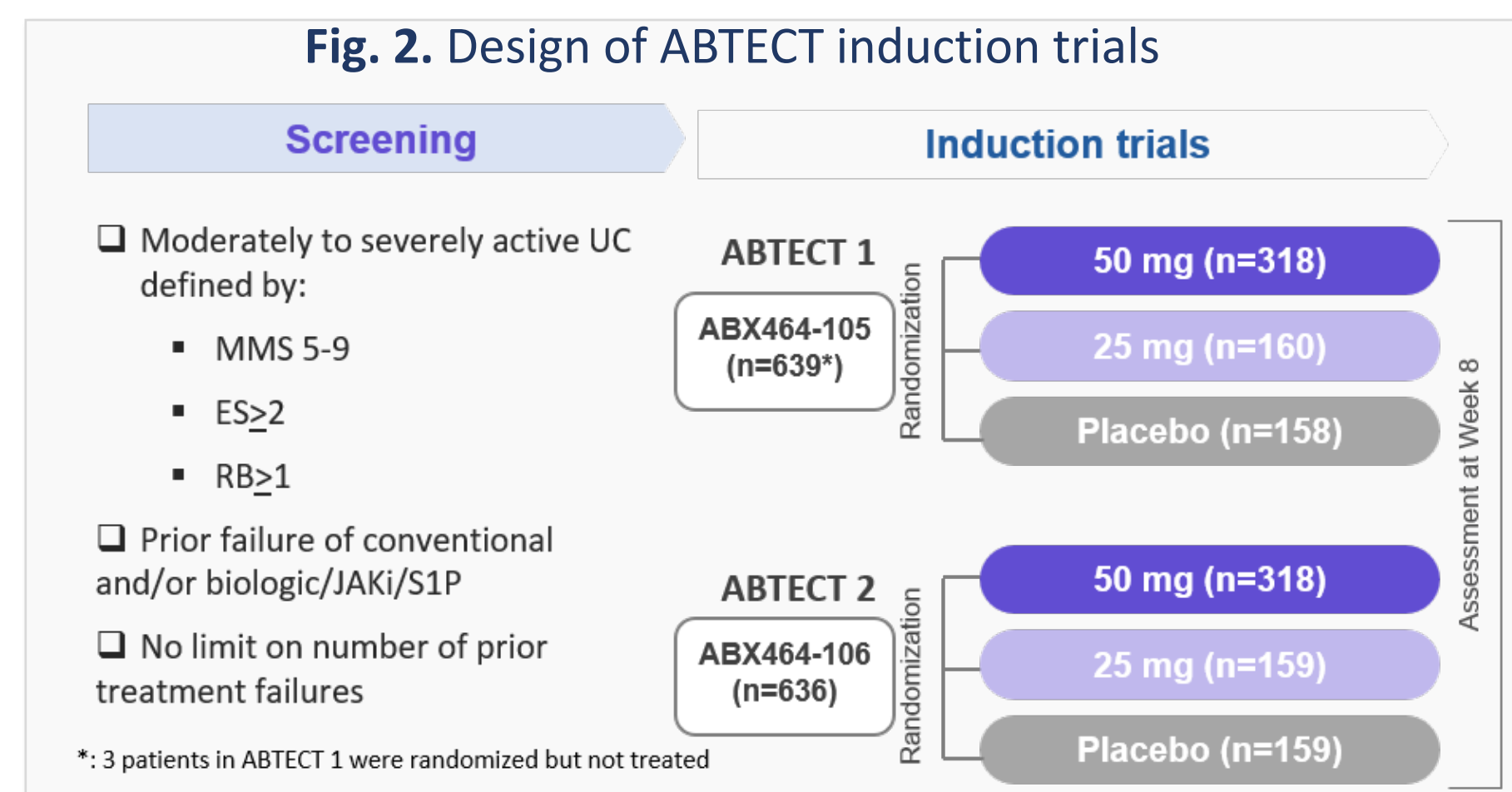
Background

- Obefazimod (Obe) is an oral, once-daily (QD), small molecule that enhances the expression of microRNA-124, thereby restoring intestinal immune balance through regulation of Th17 cells and macrophage activity (Fig. 1).
- Obe has shown efficacy in patients (pts) with moderately to severely active ulcerative colitis (UC) in the Phase 3 ABTECT induction trials (NCT05507203, NCT05507216) [1]. Here we report an integrated safety analysis of Obe in the ABTECT trials with a specific focus on immunosuppression-related treatment-emergent adverse events (TEAEs).



Design

- The multicenter, randomized, double-blind, placebo-controlled ABTECT induction trials enrolled pts with moderate-to-severe UC who had inadequate response, loss of response, or intolerance to ≥ 1 prior therapy (no limit). 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. 2).



- TEAEs, serious TEAEs, discontinuation rates and primary reasons were assessed in the pooled population from the ABTECT trials among pts who received Obe-50, Obe-25, or PBO for 8 weeks.
- To further characterize the safety profile of Obe, opportunistic infections, malignancies, and other immunosuppression-related events were specifically assessed.

Results

- 1272 pts were randomized and treated in ABTECT induction trials, 636 pts received Obe-50, 319 received Obe-25, and 317 received PBO. Baseline demographics and disease characteristics were comparable across treatment groups with median exposures of 60-61 days (Table 1).
- Proportions of pts who reported at least one TEAE were 60.2%, 48.9%, and 50.8% for Obe-50, Obe-25, and PBO, respectively.
- Overall rates of serious TEAEs were comparable across groups, ranging from 2.2% to 3.1% with Obe vs 3.2% with PBO.

Table 1: Integrated summary of safety of obefazimod in Phase 3 ABTECT induction trials
safety set - pooled ABTECT trials

	Obe-50 (n=636)	Obe-25 (n=319)	PBO (n=317)
Duration of exposure, days Mean (SD)	58.8 (12.62)	59.5 (11.14)	58.7 (11.14)
Median [Min, Max]	60.0 [1, 106]	61.0 [4, 96]	61.0 [5, 102]
Any TEAEs, n (%) *	383 (60.2)	156 (48.9)	161 (50.8)
TEAE related to study drug, n (%)	226 (35.5)	86 (27)	55 (17.4)
TEAE leading to study discontinuation, n (%)	30 (4.7)	6 (1.9)	13 (4.1)
Related TEAE leading to study discontinuation, n (%)	20 (3.1)	4 (1.3)	6 (1.9)
Serious TEAE, n (%)	20 (3.1)	7 (2.2)	10 (3.2)
Related, serious TEAE, n (%)	3 (0.5)	2 (0.6)	2 (0.6)
TEAE leading to death, n (%)	0	0	0
Malignancies, n (%)	1 (0.2)**	0	0
Serious/severe/opportunistic infections [‡] , n (%)	4 (0.6)	1 (0.3)	1 (0.3)
TEAEs occurring in pts (≥ 3% in obe groups and greater than PBO), n (%)			
Headache	148 (23.3)	48 (15.0)	18 (5.7)
Nausea	46 (7.2)	16 (5.0)	4 (1.3)
Abdominal pain	24 (3.8)	2 (0.6)	2 (0.6)
Lipase increased [‡]	27 (4.2)	9 (2.8)	7 (2.2)
Headaches occurring in pts			
Time to onset of first TE headache per subject (days), median	1.0	1.0	7.0
Duration of headache for all TE headaches, days, median	2.0	3.0	2.0

Obe: obefazimod; TEAE: treatment emergent adverse event. *: n (%): number (and percentage) of pts with TEAEs. **: Prostate cancer stage I in a patient who received obefazimod for two weeks. †: the only opportunistic infection was aspergillosis in a placebo patient. ‡: Unrelated to clinical pancreatitis. To date, no safety signals have been observed related to either elevations in lipase or more specifically to pancreatitis.

- The most frequent TEAEs ($\geq 3\%$ in Obe-treated pts and greater than PBO) included headache, nausea, abdominal pain, and an increase in serum lipase unrelated to clinical pancreatitis. Headache TEAEs were mild, transient, short in duration (median: 2-3 days).
- Rates of infection-related TEAEs among pts were very low, generally below 1% (Table 2). There was no signal for serious, severe, or opportunistic infections or malignancies in the ABTECT induction trials (Table 3).

Conclusions

- This integrated safety analysis of obefazimod in the two completed Phase 3 ABTECT induction trials showed a favorable safety and tolerability profile, consistent with what was observed in the Phase 2 trials.
 - Obe fazimod demonstrates low rates of serious and/or infection-related TEAEs, consistent with its proposed mechanisms of targeted immune modulation and restoration of mucosal immune balance.
- 

- TEAEs leading to study discontinuation occurred at similar rates across treatment groups, ranging from 1.9% to 4.7% with Obe vs 4.1% with PBO (Table 1).
- Headache TEAEs rarely led to discontinuation (0-1.1%).

Table 2: Treatment Discontinuations in Phase 3 ABTECT induction trials - safety set-pooled ABTECT trials

	Obe-50 (n=636)	Obe-25 (n=319)	PBO (n=317)
Subjects who discontinued the study, n (%)***	54 (8.5)	23 (7.2)	31 (9.7)
<i>Reason for study discontinuation, n (%)†:</i>			
Adverse event	31 (57.4)	8 (34.8)	14 (45.2)
Withdrawal by subject	13 (24.1)	10 (43.5)	10 (32.3)
Lack of efficacy	2 (3.7)	2 (8.7)	1 (3.2)
Lost to follow-up	4 (7.4)	1 (4.3)	1 (3.2)
Non-compliance with study drug	2 (3.7)	0	0
Protocol deviation	1 (1.9)	1 (4.3)	3 (9.7)
Physician decision	1 (1.9)	0	1 (3.2)
Never dosed	0	1 (4.3)	1 (3.2)
<i>TEAEs (>1 in obe groups) leading to study drug discontinuation</i>			
Ulcerative colitis	7 (1.1)	2 (0.6)	7 (2.2)
Headache	7 (1.1)	1 (0.3)	0
Vomiting	4 (0.6)	1 (0.3)	0
Abdominal pain upper	3 (0.5)	0	0
Nausea	3 (0.5)	1 (0.3)	0
Pancreatitis acute	2 (0.3)	1 (0.3)	1 (0.3)

Obe: obefazimod; TEAE: treatment emergent adverse event. ***: Percentages are calculated relative to the number of randomized pts (ie, N=636, 320, 319 for Obe-50, Obe-25, PBO, respectively). †: Percentages are calculated relative to the number of pts who discontinued the study

Table 3: Infection-related TEAEs in Phase 3 ABTECT induction trials - safety set-pooled ABTECT trials

Infection related TEAEs $\geq 0.5\%$ in Obe groups Preferred Term, n (%)*	Obe-50 (n=636)	Obe-25 (n=319)	PBO (n=317)
Nasopharyngitis	14 (2.2)	9 (2.8)	10 (3.2)
Upper respiratory tract infection	7 (1.1)	3 (0.9)	6 (1.9)
COVID-19	6 (0.9)	4 (1.3)	1 (0.3)
Influenza	6 (0.9)	3 (0.9)	1 (0.3)
Urinary tract infection	5 (0.8)	2 (0.6)	0
Pneumonia	4 (0.6)	0	1 (0.3)
Rhinitis	4 (0.6)	2 (0.6)	0
Respiratory tract infection viral	3 (0.5)	0	1 (0.3)
Sinusitis	3 (0.5)	0	0
Appendicitis	0	2 (0.6)	0
Gastrointestinal infection	0	2 (0.6)	0
Viral upper respiratory tract infection	0	2 (0.6)	1 (0.3)

*: n (%): number (and percentage) of pts with TEAEs