Efficacy of deucravacitinib, an oral, selective, tyrosine kinase 2 inhibitor, in patients with moderately to severely active ulcerative colitis and prior exposure to biologic therapy: Subanalysis from the phase 2 LATTICE-UC study

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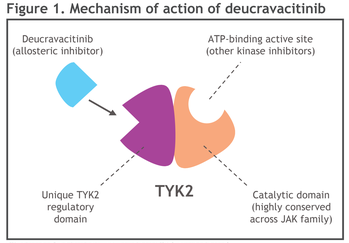
Introduction

- Tyrosine kinase 2 (TYK2) mediates signaling of interleukin (IL)-12, IL-23 and Type 1 interferons (IFNs), key cytokines involved in ulcerative colitis (UC) pathogenesis
- Deucravacitinib, an oral, selective, allosteric TYK2 inhibitor, is approved by the US Food and Drug Administration for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy[1]
  - It selectively binds the TYK2 regulatory domain, thereby locking the enzyme in an inactive state[2] (**Figure 1**)
  - It was efficacious and well tolerated in two phase 3 trials in moderate to severe plaque psoriasis[3,4] and in phase 2 trials in active psoriatic arthritis[5] and systemic lupus erythematosus[6]
- In a phase 2 trial of deucravacitinib in moderately to severely active UC, the primary endpoint, clinical remission at week 12, was not met; however, a treatment effect was observed in patients with prior exposure to ≥ 1 biologic agent[7]

Figure 1. Mechanism of action of deucravacitinib



ATP, adenosine 5′-triphosphate; JAK, Janus kinase; TYK2, tyrosine kinase 2.

Objective

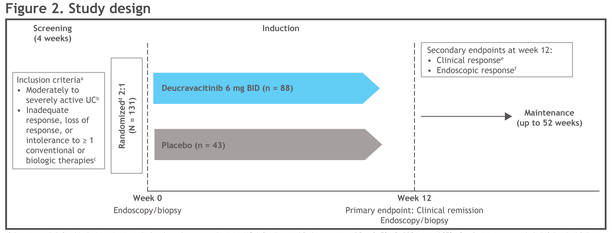
- This post-hoc analysis evaluated the effect of deucravacitinib in biologic-exposed patients with moderately to severely active UC

Methods

Study design

- LATTICE-UC (NCT03934216), a double-blind, placebo-controlled, centrally read, phase 2 trial randomized patients with moderately to severely active UC 2:1 to deucravacitinib 6 mg or placebo twice daily (**Figure 2**)

Figure 2. Study design



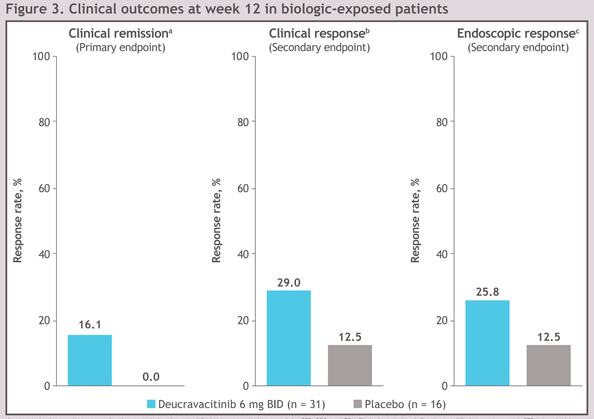
[a]Other protocol-defined inclusion criteria apply. [b]Moderately to severely active UC defined as modified Mayo score of 5 to 9 (ES ≥ 2, RBS ≥ 1, and SFS ≥ 2). [c]Patients were excluded if they had failure or loss of response to JAK inhibitors. [d]Patients were stratified by baseline corticosteroid use and prior exposure to biologics. [e]Clinical response defined as a decrease from baseline in the modified Mayo score of ≥ 2 points and ≥ 30% with decrease in RBS ≥ 1 point or absolute RBS ≤ 1. [f]Endoscopic response defined as Mayo ES ≤ 1.
BID, twice daily; ES, endoscopic subscore; JAK, Janus kinase; RBS, rectal bleeding subscore; SFS, stool frequency subscore; UC, ulcerative colitis.

Outcomes

- Clinical outcomes assessed at week 12:
  - Clinical remission (modified Mayo score [MMS] with stool frequency subscore [SFS] ≤ 1 and with ≥ 1-point decrease from baseline, rectal bleeding subscore [RBS] = 0, and endoscopic subscore [ES] ≤ 1)
  - Clinical response (decrease from baseline in MMS ≥ 2 points and ≥ 30% with decrease in RBS ≥ 1 point or absolute RBS ≤ 1)
  - Endoscopic improvement (Mayo ES ≤ 1)
  - Change from baseline in symptomatic Mayo score (RBS + SFS)
- Colonic tissue transcriptomes were assessed via bulk ribonucleic acid sequencing at baseline and week 12 in a subset of biologic-exposed patients
- Differential expression with Limma-Voom and pathway enrichment analysis via Gene Set Enrichment Analysis were performed

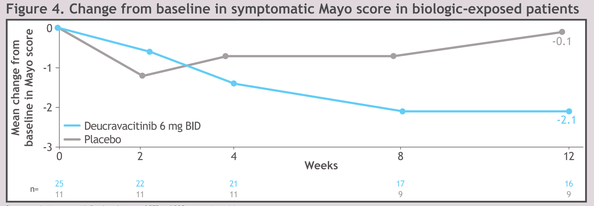
In biologic-exposed patients treated with deucravacitinib, clinical responses were achieved more frequently and Mayo symptomatic scores and fecal calprotectin were decreased compared with placebo

Figure 3. Clinical outcomes at week 12 in biologic-exposed patients



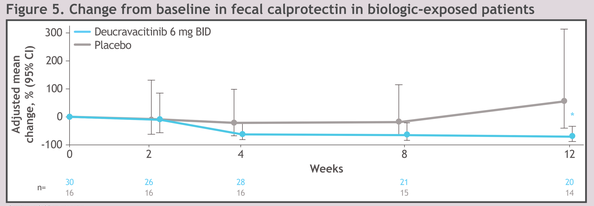
Nonresponder imputation was used to impute missing data. Modified Mayo score is the sum of the SFS, RBS, and ES. [a]Clinical remission defined as modified Mayo score with SFS ≤ 1 and with ≥ 1-point decrease from baseline, RBS = 0, and ES ≤ 1 (modified, excludes friability). [b]Clinical response defined as a decrease from baseline in the modified Mayo score of ≥ 2 points and ≥ 30% with decrease in RBS ≥ 1 point or absolute RBS ≤ 1. [c]Endoscopic response defined as Mayo ES ≤ 1.
BID, twice daily; ES, endoscopic subscore; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

Figure 4. Change from baseline in symptomatic Mayo score in biologic-exposed patients



Symptomatic Mayo score defined as the sum of SFS and RBS at any given visit.
BID, twice daily; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

Figure 5. Change from baseline in fecal calprotectin in biologic-exposed patients



*P value < 0.05 vs placebo.
BID, twice daily; CI, confidence interval.

Results

Baseline demographics and clinical characteristics of biologic-exposed patients

- Of 131 randomized patients, 48 (36.6%) were biologic-exposed
  - Placebo: 16/43 (37.2%)
  - Deucravacitinib 6 mg BID: 32/88 (36.4%)
- The deucravacitinib group had more patients with weight ≥ 90 kg and with an MMS > 7 (**Table 1**)

Table 1. Demographics and baseline clinical characteristics of biologic-exposed patients

	Biologic-exposed subgroup (n = 48)	
	DEUC 6 mg BID (n = 32)	Placebo (n = 16)
Sex, female, n (%)	15 (47)	3 (19)
Age, years, mean (SD)	41 (15)	39 (13)
Race, White, n (%)	28 (88)	11 (69)
Weight, mean, n (%)		
≥ 90 kg	7 (22)	2 (12)
< 90 kg	25 (78)	14 (88)
BMI, kg/m², mean (SD)	25.0 (5.8)	25.0 (5.0)
Duration of disease, years, mean (SD)	9.0 (6.5)	10.0 (5.4)
Concomitant corticosteroid use[a], n (%)	14 (44)	7 (44)
MMS, n (%)		
≤ 7	15 (47)	12 (75)
> 7	16 (50)	3 (19)
ES, mean (SD)	2.8 (0.4)	2.4 (0.5)

[a]Oral corticosteroids (prednisone ≤ 20 mg/day or budesonide MMX ≤ 9 mg/day) were allowed, provided the dose was stable for 2 weeks prior to randomization and stable dose was maintained during the 12-week induction period.
BID, twice daily; BMI, body mass index; DEUC, deucravacitinib; ES, endoscopic subscore; MMS, modified Mayo score; MMX, Multi Matrix System; *n*, number of patients; SD, standard deviation.

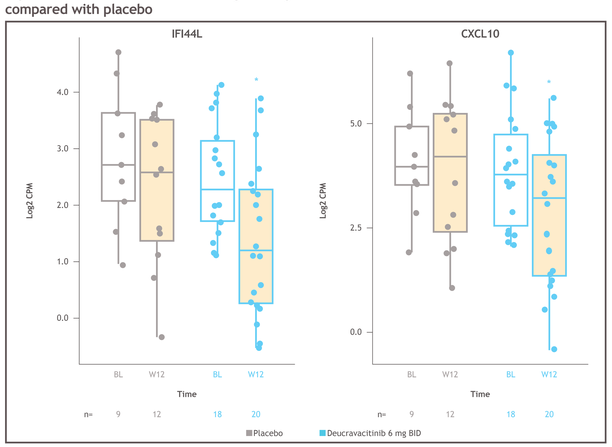
Clinical outcomes at week 12 in biologic-exposed patients

- At week 12, clinical remission, clinical response, and endoscopic improvement rates were higher in the deucravacitinib group compared with placebo (**Figure 3**)
- Greater mean changes from baseline in symptomatic Mayo score were observed at week 12 with deucravacitinib (-2.1) vs placebo (-0.1) (**Figure 4**)

Biomarkers at week 12 in biologic-exposed patients

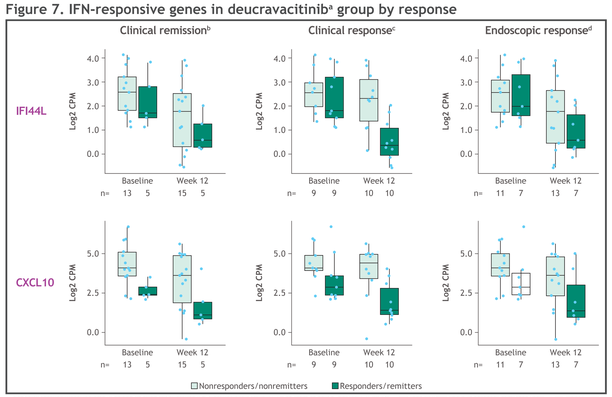
- A greater reduction in fecal calprotectin was observed with deucravacitinib than placebo ($P < 0.05$ at week 12) (**Figure 5**)
- IFN-responsive genes, such as IFI44L and chemokine ligand 10, were significantly reduced in colonic tissues at week 12 compared to baseline with deucravacitinib treatment (false discovery rate < 0.1) but not with placebo (**Figure 6**)

Figure 6. Greater decrease in IFN-regulated genes in colonic tissue in deucravacitinib compared with placebo



- In patients treated with deucravacitinib, greater decreases in IFN-responsive genes were observed in responders/remitters compared with nonresponders/nonremitters (**Figure 7**)

Figure 7. IFN-responsive genes in deucravacitinib[a] group by response



[a]Placebo subgroups were too small for analysis; only deucravacitinib groups are shown. [b]Clinical remission defined as MMS with SFS ≤ 1 and with ≥ 1-point decrease from baseline, RBS = 0, and ES ≤ 1 (modified, excludes friability). [c]Clinical response defined as a decrease from baseline in the MMS of ≥ 2 points and ≥ 30% with decrease in RBS ≥ 1 point or absolute RBS ≤ 1. [d]Endoscopic response defined as Mayo ES ≤ 1.
BID, twice daily; CPM, counts per million; CXCL10, chemokine ligand 10; ES, endoscopic subscore; MMS, modified Mayo score; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

Conclusions

- The analysis of the biologic-exposed subset of patients with moderate to severe active ulcerative colitis demonstrated target engagement by deucravacitinib, and the level of target engagement was paralleled by clinical success
- Biologic-exposed patients treated with deucravacitinib had:
  - Greater improvements in clinical outcomes compared with placebo
  - Greater decreases in fecal calprotectin and colonic IFN-responsive genes compared with placebo
- The decreases in IFN-responsive gene biomarkers were associated with clinical response or remission, suggesting that inhibition of TYK2 pathways may be beneficial for ulcerative colitis
- These results provide evidence of inhibition of the TYK2 pathway and suggest that a higher dose of deucravacitinib needs to be examined for clinical efficacy

References

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Acknowledgments

- This study was sponsored by Bristol Myers Squibb. Professional medical writing assistance was provided by Gorica Malisanovic, MD, PhD, at Peloton Advantage, LLC, an OPEN Health company, and funded by Bristol Myers Squibb
- All authors contributed to and approved the presentation
- The authors acknowledge all participants and investigators involved in the trial. The authors would also like to acknowledge Walid Elsharkawi (employed by Bristol Myers Squibb at the time the study was conducted) for study oversight and data management

Disclosures

- **SS:** Consulting and speaker fees: Amgen, AbbVie, BMS, Falk, Galapagos/Gilead, Genentech/Roche, Janssen, MSD, Pfizer, and Takeda
- **NP:** Speaker, advisory, consultant and/or research grants: AbbVie, Allergan, AstraZeneca, Bristol Myers Squibb, Celgene, Celltrion, Dr Falk Pharma UK Ltd, Ferring, Galapagos, Janssen, Pfizer, Roche, Sobi, Takeda, Tillotts, and Vifor
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