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Alimentary Tract

Clinical efficacy of the Toll-like receptor 9 agonist cobitolimod using patient-reported-outcomes defined clinical endpoints in patients with ulcerative colitis☆

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ABSTRACT

Background: The Toll-like-receptor 9 (TLR-9) agonist cobitolimod (DIMS0150, Kappaproct®) is a promising therapeutic option for ulcerative colitis (UC) patients.
Aims: The objectives of this post-hoc analysis using the COLLECT study data was to investigate the clinical effects of cobitolimod using patient-reported-outcomes (PRO) defined endpoints.
Methods: Dual topical administration of cobitolimod was studied in a randomised, multicentre clinical trial named COLLECT in moderate-to-severe UC patients. Symptomatic remission (SR) was studied in 104 patients based on their e-diary records and was defined as absence of blood in stool and a mean daily stool frequency (SF) < 4.
Results: SR was achieved at week 4 in 17.1% of cobitolimod vs. 5.9% of placebo treated patients ($p = 0.13$), at week 8 in 35.7% vs. 17.6% ($p = 0.07$), and at week 12 in 38.6% vs. 17.6% ($p = 0.04$) of the patients, respectively.
SR rates with cobitolimod and placebo in anti-TNFα experienced patients were smaller but with a broadly similar relative effect-size to anti-TNFα naïve patients. Clinical efficacy was higher in patients with moderate compared to severe disease.
Conclusions: Application of the Toll-like-receptor 9 (TLR-9) agonist cobitolimod is able to induce remission as assessed by PRO measures in UC patients with moderate-to-severe activity as well as in anti-TNFα experienced and naïve patients supporting the overall efficacy of the substance.

1. Introduction

One of the major phenotypes of inflammatory bowel diseases (IBD) is ulcerative colitis (UC), which is characterized by a superficial, continuous mucosal inflammation, which is predominantly limited to the large intestine [1–5]. A large proportion of patients does not respond to available therapies, thereby becoming treatment refractory and often requiring surgical intervention, i.e., proctocolectomy [6,7]. Therefore, therapies with novel modes of actions are needed to augment the therapeutic armamentarium.

The host discerns foreign from self-antigen through pattern recognition receptors (PRR), which detect specific molecular patterns of pathogens [8]. One group of PRRs consists of Toll-like receptors (TLRs) with variable specificities for sensing microbial structures [8]. One of these receptors TLR-9 has over the years received growing interest as a potential point of therapeutic intervention in the treatment of UC. TLR-9 exclusively recognizes bacterial DNA by serving as a ligand for its CG (CpG) motifs [9,10]. These CpG sequence motifs composed of unmethylated CpG dinucleotides have been identified as the immunostimulatory component of bacterial DNA [10]. The ability to modulate the immune system makes the CpG motif an attractive therapeutic target and

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TLR-9 activation has correspondingly been shown to prevent development of mucosal inflammation and promote wound healing in several models of experimental colitis [11–13].

Cobitolimod (formerly known as DIMS0150 or Kappaproct®) is a single strand DNA-based synthetic oligonucleotide (ODN) that contains an unmethylated CpG motif, that activates TLR-9 on target cells such as intestinal T and B lymphocytes and antigen presenting cells (APCs) with potent induction of anti-inflammatory cytokines such as interleukin-10 (IL-10) and type I interferons [14,15]. Although administration of cobitolimod did not meet the pre-specified primary endpoint in the COLLECT study in treatment-refractory UC patients, clinical efficacy could be demonstrated in several secondary endpoints with statistically significant differences in comparison to placebo treatment [16].

The purpose of this post hoc analysis of the COLLECT study data was to investigate the clinical effects of topically administered cobitolimod using patient-reported outcome (PRO) defined endpoints, studying sustained and longer-term effects, and analysing different patient subgroups defined by disease activity or anti-TNFα therapy exposure.

2. Material and methods

2.1. Patients

This retrospective analysis is based on a multicenter, randomized, double-blind, placebo-controlled phase III trial (ClinicalTrials.gov identifier: NCT01493960), which was conducted at 38 centres in 7 countries (Czech Republic, France, Germany, Hungary, Italy, Poland and the United Kingdom) from December 2011 through March 2014. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, was reviewed and approved by regional Independent Ethics Committees (EudraCT nr 2011-003130-14) and by the competent authorities in each country prior to the inclusion of patients (Ethics Committee, University Hospital Hradec Kralove, Czech Republic, November 3, 2011; Comitato Etico, Universita Cattolica Del Sacro Cuore, Italy, March 5, 2012; Ethics Committee for Clinical Pharmacology, Medical Research Council, Budapest, Hungary, September 27, 21011; Decyzja Komisji Etycznej Warszawa, Poland, September 14, 2011; National Research Ethics Service, NRES Committee East Midlands, Leicester, UK, November 21, 2011; Ethics Committee, Hanover Medical School, Germany, December 15, 2011; Comite de Protection des Personnes Ile de France, Aulnay-Sous-Bois Cedex, December 12, 2012). Written informed consent was obtained from all patients prior to any study related procedures.

2.2. Study design

The data presented in this manuscript represents a retrospective analysis of the COLLECT study, which has been described in detail before [17]. Eligible patients were adults with moderate to severely active, UC with a Clinical Activity Index (CAI) [17] of ≥9, and an endoscopic Mayo score ≥2 [18]. Eligible patients were treatment refractory to standard therapy and received concomitant steroid medication before and during the study. The TLR-9 agonist cobitolimod is a fully synthetic 19-mer oligodeoxynucleotide. Patients were randomized in a 2:1 ratio to receive topical administration of cobitolimod (30 mg) via endoscopy using a spray catheter at week 0 and 4 proximal to the site of the heaviest inflammation, or matching placebo diluted in 50 ml of sterile water after adequate bowel cleaning for stool content. In case of pancolitis, the study medication was applied to the transverse colon.

2.3. Endpoints

Endpoints studied in this post hoc analysis include symptomatic remission (SR) defined as absence of blood in stool and a mean daily stool frequency of <4, mucosal healing (MH) defined as a Mayo endoscopic score ≤1 and a combined score for patients who achieved both SR and MH termed clinical remission (CR). As lower GI endoscopy was performed at week 4 and 12, MH could be assessed only at these time-points, while other clinical endpoints were assessed at week 4, 8, and 12.

Sustained SR was defined as SR both at weeks 4 and 12 in a patient, sustained SR in combination with MH was defined as a patient fulfilling SR and MH remission criteria both at weeks 4 and 12. The PRO measures, stool frequency and blood in stool, were analysed using e-diary data with daily assessments from week 0 to 12 entered by the patients [19].

No blood in stool was defined as a patient having reported 7 consecutive days without blood in stool, stool frequency <4 was defined as a mean daily reported stool occurrence below 4 over 7 consecutive days.

The clinical endpoints were studied in different patient subgroups defined either by disease activity at baseline and in regard to pre-treatment with an anti-TNFα agent. Disease activity was measured using the CAI score, which ranges from 0 to 23 and differentiates between patient populations with moderate (CAI index = 9), moderate to severe (CAI index = 10–11) and severe (CAI index ≥ 12) disease activity, and using the C-reactive protein (CRP) levels to separate patients with normal (<5 mg/ml) or elevated (>5 mg/ml) CRP.

2.4. Patient disposition

A total of 162 UC patients were screened for inclusion in the study, of which 131 were randomized with 87 in the cobitolimod and 44 patients in the placebo treatment group. Overall 119 subjects were initiated in the e-diary system from which 15 patients had no valid baseline data and were therefore excluded. Thereby the observed cases population with available e-diary data at baseline consisted of 104 patients, which were used for data analysis in this report. Within these 104 patients of the observed cases population complete data were available from 99 patients at week 4 and 87 patients at week 12. There was overall e-diary compliance to all protocolled daily assessments of 86.3% from baseline to week 12. Demographics of the observed cases population are summarized in Table 1.

2.5. Statistical analysis

All data were presented using descriptive statistics, with frequency and relative frequency for categorical variables and mean, standard deviation, minimum and maximum for continuous variables. For the e-diary assessment, 70 plus 34 patients in the cobitolimod and placebo group respectively were reporting data. Therefore, analyses were based on these 104 subjects. All tests were two-sided and $p < 0.05$ was regarded as statistically significant. Due to the small number of subjects a meaningful statistical analysis of the various subgroups (disease activity, TNF exposure) was not possible.

Missing data for the analysis population with eligible e-diary data (n = 104) was replaced using the last-observation-carried-forward (LOCF) method, which practically means that they were imputed with a non-responder value for missing data, i.e. no remission. This was a conservative approach. Categorical endpoints were analysed using the Cochran Mantel-Haenszel method controlling for categories of CAI scores at baseline. The statistical hypothesis tested was, Odds Ratio (OR) = 1, i.e. no difference between treat-

Table 1
Summary of demographic and baseline characteristics of patients in the observed cases population. Percentage calculated for the number of subjects by treatment group.

Parameter		Placebo (N = 34)	Cobitolimod (N = 70)	Overall (N = 104)
Age (years)	Mean (SD)	41.6 (12.24)	41.9 (14.2)	41.8 (13.5)
	Median	41.5	38.5	39.5
	Range	22, 67	19, 72	19, 72
Gender, n (%)	Male	23 (67.6)	41 (58.6)	64 (61.5)
	Female	11 (32.4)	29 (41.4)	40 (38.5)
Race, n (%)	White	43 (100.0)	69 (98.6)	103 (99.0)
	Asian	0 (0.0)	1 (1.4)	1 (1.0)
	Black	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)	Mean (SD)	75.6 (19.06)	72.9 (13.49)	73.8 (15.48)
	Median	74.5	73.3	73.8
	Range	45, 130	45, 103	45, 130
UC duration (years)[a]	Mean (SD)	7.7 (6.3)	9.7 (8.2)	9.1 (7.7)
	Median	5.3	7.5	6.5
	Range	1.6, 29.6	0.5, 42.8	0.5, 42.8
CAI score[b]				
CAI 9	n	9	20	29
	%	27.3	29.4	28.7
CAI 10–11	n	17	31	48
	%	51.5	45.6	47.5
CAI ≥ 12	n	7	17	24
	%	21.2	25.0	23.8
Endoscopic Mayo score[c]				
Score 0	n	0.0	0.0	0.0
	%	0.0	0.0	0.0
Score 1	n	0.0	0.0	0.0
	%	0.0	0.0	0.0
Score 2	n	14	31	45
	%	41.2	44.3	43.3
Score 3	n	20	39	59
	%	58.8	55.7	56.7
Extent of inflammation				
Left-sided	n	19	51	70
	%	55.9	72.9	67.3
Extensive	n	15	19	34
	%	44.1	27.1	32.7
CRP				
CRP ≤ 5 mg/ml	n	17	40	57
	%	50.0	57.1	54.8
CRP > 5 mg/ml	n	17	30	47
	%	50.0	42.8	45.2
Prior anti-TNFα therapy, n (%)				
Yes		17 (50.0)	30 (42.9)	47 (45.2)
No		17 (50.0)	40 (57.1)	57 (54.8)

SD = standard deviation.
UC = ulcerative colitis.
CAI = clinical activity index.
[a] Duration is calculated from the date of UC onset to the date of Visit 1.
[b] Last observation carried forward approach was used for missing data.
[c] Endoscopic Mayo score 0 = normal or inactive (mild granularity, oedema); score 1 = mild friability, erythema, decreased vascular pattern; score 2 = moderate friability, erosions, marked erythema, absent vascular pattern; score 3 = spontaneous bleeding, ulceration.

ment groups with regard to the endpoints defined in this study. Data derivation and statistical analyses were done using IBMSPSS version 22.

Multivariate analyses were performed using the logistic regression analysis for the endpoints of SR and CR respectively. The regression models were built in three steps. The first model (model 1) was based on the univariate analysis calculating the OR for the comparison of the two treatment arms with no adjustment for other factors. The second model (model 2) was including an adjustment for disease severity at baseline using the baseline categories of CAI scores: moderate (CAI index = 9), moderate to severe (CAI index = 10–11) and severe disease (CAI index ≥ 12). The third model (model 3) included an adjustment for three factors, disease severity at baseline, prior use of anti-TNFα treatment (naïve versus non-naïve) and CRP levels (CRP < 5 versus CRP > 5). All these were included as fixed factors together with the treatment factor (cobitolimod versus placebo). Results are presented using Odds Ratio, OR, together with the p-value. An OR > 1 indicates a beneficial efficacy in favour of cobitolimod compared to placebo with regard to SR and CR, respectively.

3. Results

3.1. Symptomatic and clinical remission rates as assessed by patient reported outcomes according to e-diary data

SR was achieved in 17.1% of cobitolimod treated vs. 5.9% of placebo-treated patients (p = 0.13) at week 4 (Fig. 1A). At week 8,

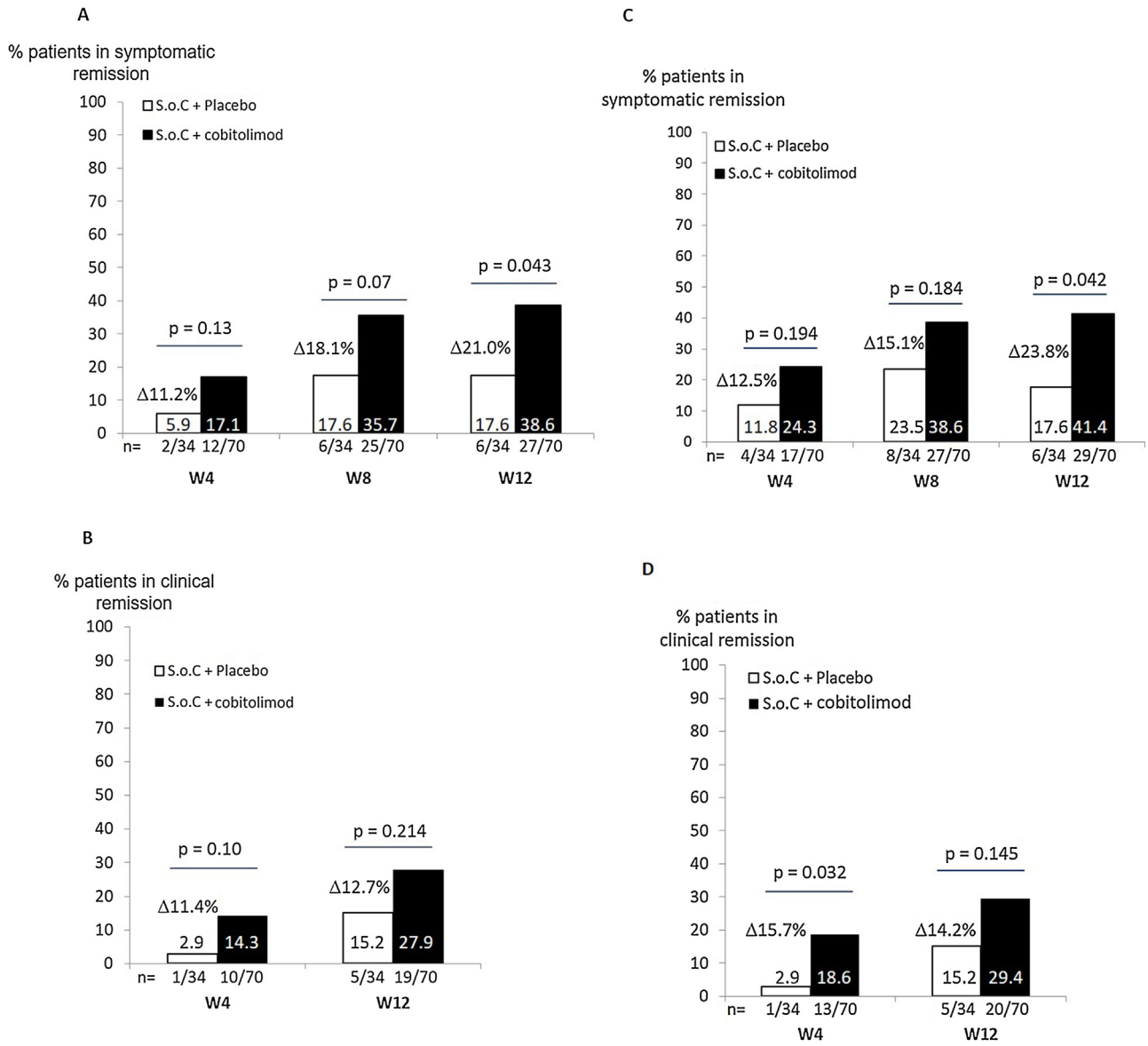


Fig. 1. Symptomatic and clinical remission.
(A) SR rates of placebo or cobitolimod treated patients at week 4 (W4), 8 (W8) or week 12 (W12) defined as a blood in stool score of 0 and a stool frequency of less than 4 stools per day.
(B) CR rates of placebo or cobitolimod treated patients at week 4 (W4) or week 12 (W12) defined as a blood in stool score of 0 a, a stool frequency of less than 4 stools per day and an endoscopy Mayo score of ≤ 1.
(C) SR rates of placebo or cobitolimod treated patients at week 4 (W4), 8 (W8) or week 12 (W12) defined as a blood in stool score of 0 and a stool frequency of less than 5 stools per day.
(D) CR rates of placebo or cobitolimod treated patients at week 4 (W4) or week 12 (W12) defined as a blood in stool score of 0 a, a stool frequency of less than 5 stools per day and an endoscopy Mayo score of ≤ 1.
S.o.C. = standard of care, observed cases set (cobitolimod n = 70, placebo n = 34) was used for the analysis.

the corresponding SR rates were 35.7% vs. 17.6% (p = 0.07) (Fig. 1A) and at week 12 they were 38.6% vs. 17.6% (p = 0.043), respectively (Fig. 1A). CR was achieved in 14.3% of patients in the cobitolimod group vs. 2.9% of patients in the placebo group (p = 0.10) at week 4, respectively (Fig. 1B). At week 12, the corresponding figures were 27.9% vs. 15.2% (p = 0.214), respectively (Fig. 1B).

Using a less stringent stool frequency endpoint definition, i.e. a mean daily stool frequency (SF) < 5, SR was achieved in a higher percentage of cobitolimod and placebo-treated patients at all time points studied. However, the relative differences between the two groups were similar to the values observed for a SF < 4 (Fig. 1C).

Using the mean daily SF < 5 cut off, CR was achieved in the cobitolimod group and the placebo group at very similar levels as observed for a SF < 4 (Fig. 1D).

In all subsequent analysis (Figs. 2–5) the more stringent endpoint definition using a mean daily SF < 4 was used.

3.2. Sustained remission after dual topical administration of cobitolimod

Sustained SR at both weeks 4 and 12 was achieved in 12.9% of the cobitolimod vs. 2.9% of the placebo-treated patients (p = 0.14) (Fig. 2A).

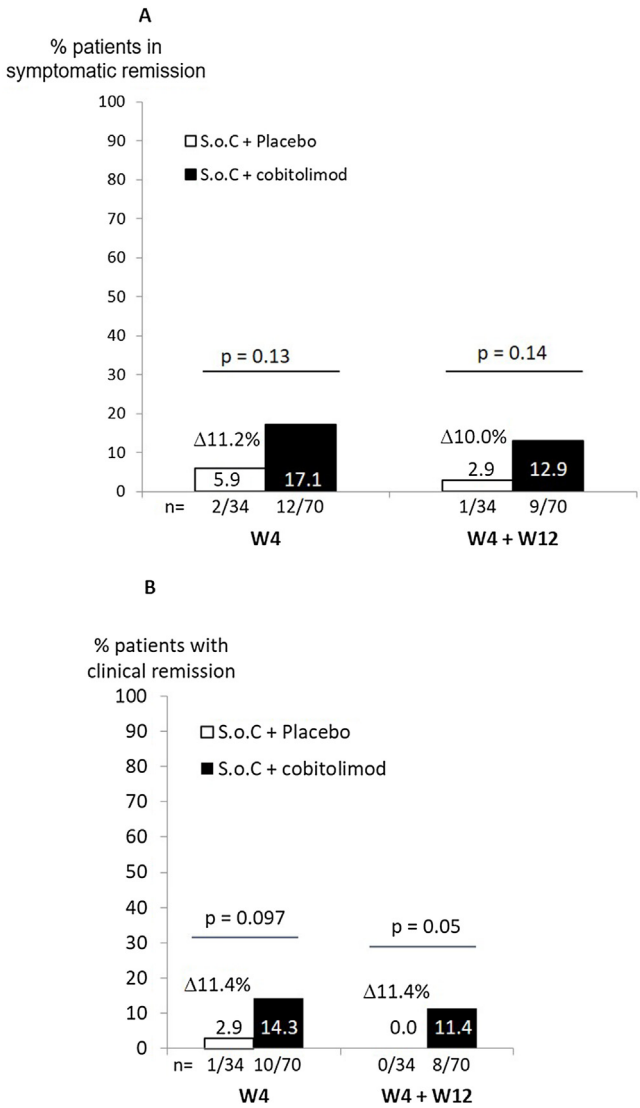


Fig. 2. Sustained remission.
(A) Proportion of placebo or cobitolimod treated patients with SR at week 4, weeks 4 and 8 and weeks 4, 8 and 12 weeks.
(B) Proportion of patients with CR at week 4 and weeks 4 and 12.
S.o.C. = standard of care.

MH was evident in 32.9% of the cobitolimod vs. 20.6% and of the placebo treated patients (p = 0.25) at 4 weeks. Sustained MH for weeks 4 and 12, i.e. MH both at week 4 and week 12, was present in 25.7% vs. 17.6% of cases (p = 0.46), respectively.

CR at week 4, which was sustained/maintained at week 12, was achieved in 11.4% in the cobitolimod vs. 0% in the placebo treated patients (p = 0.05) (Fig. 2B).

3.3. Remission rates according to disease severity

In the observed cases population (n = 104) at baseline 28.7% of the patients had a moderate disease (CAI = 9), 47.5% of the patients were in a moderate to severe disease setting (CAI = 10–11), while a severe disease with a CAI score of 12 or more was evident in 23.8% of the patients.

In the moderate patient population (CAI = 9) SR was achieved in 20%/45%/35% of the cobitolimod vs. 20%/10%/10% of placebo treated patients at week 4/8/12, respectively (Fig. 3A). These differences could not be statistically assessed due to the low number of subjects among the subgroups, which was also true for the other disease severity categories tested and described in the following.

In the moderate to severe patient population (CAI = 10–11) SR was evident in a range of 23%–48% in the cobitolimod and 0%–18% respectively in the placebo treated patients with relative effect sizes (deltas between cobitolimod and placebo) ranging from 17.9% to 30.8% (Fig. 3A). There was some variation observed among groups of disease severity at baseline (CAI) with regard to SR, but there were no statistical evidences for these differences and there were only 25 patients in the most severe group. At week 4 the SR rate of placebo patients was 0% (0/17 pts.) in the moderate to severe patient population and 20% (2/10 pts.) in the moderate patient population. The variation observed in those results is explained by only two subjects and therefore no conclusion can be made and it should be interpreted as a random variation.

In the severe patient population (CAI ≥ 12) SR rates ranged from 0% to 29% among weeks 4–12 and were similar between cobitolimod and placebo treated patients (Fig. 3A).

In the moderate patient population MH was reported in 50% and 50% of the cobitolimod vs. 23% and 39% of the placebo treated patients at weeks 4 and 12, respectively. In the moderate to severe patient population MH was present in 40% and 46% of the cobitolimod vs. 20% and 55% in the placebo-treated patients at week 4/12, respectively and in the severe patient population 9% and 27% of the cobitolimod vs. 20% and 50% of the placebo-treated patients showed MH at weeks 4 and 12, respectively.

Cobitolimod treated patients with moderate disease showed CR rates of around 20% at weeks 4 and 12 with relative effect sizes of about 10% (Fig. 3B). In patients with moderate to severe disease CR was achieved in 16% and 35% of cobitolimod treated patients at week 4 and 12 with relative effect sizes of 16% and 23%. In contrast, CR in patients with severe disease was overall lower (0%–29%) and similar between cobitolimod and placebo treated patients (Fig. 3B).

3.4. Relationship between remission rates and CRP levels

At baseline 55% of the patients had normal CRP levels (CRP ≤ 5 mg/ml), whereas elevated levels (CRP > 5 mg/ml) were evident in 45% of the patients.

In the patient subgroup with normal CRP levels (CRP ≤ 5 mg/ml) at baseline SR was achieved in the range of 20% (week 4)–50% (week 12) of the cobitolimod treated patients with relative effect sizes of 8% (week 4)–21% (week 12) (Fig. 4A). In the patients with elevated CRP levels SR rates were lower ranging from 13% (week 4)–23% (week 12) in the cobitolimod treated patients but relative effect-sizes were similar (Fig. 4A).

In patients with normal CRP values at baseline MH was reported in 46% and 54% for cobitolimod vs. 17% and 39% for placebo treated patients at week 4 and 12, respectively. In the patient population with CRP > 5 mg/ml MH rates were again lower with 22% and 25% of the cobitolimod vs. 20% and 45% in placebo treated patients at week 4 and 12, respectively.

In the patients with normal CRP levels CR was achieved in 17.5% (week 4) and 34.2% (week 12) for cobitolimod treated patients. In the patient population with elevated CRP values CR rates were lower, 10% (week 4) and 20% (week 12) both in the cobitolimod treated patients (Fig. 4B). Relative effect size in favour of cobitolimod was similar and around 10% for all time points and subgroups by CRP levels.

3.5. Remission rates according to previous anti-TNFα therapy

In the observed cases population, over 40% of the patients (50% in the placebo group and 43% in the cobitolimod group) had received prior anti-TNFα agent treatments of which infliximab with 81.3% of cases was the most commonly used. Three quarters of the patients

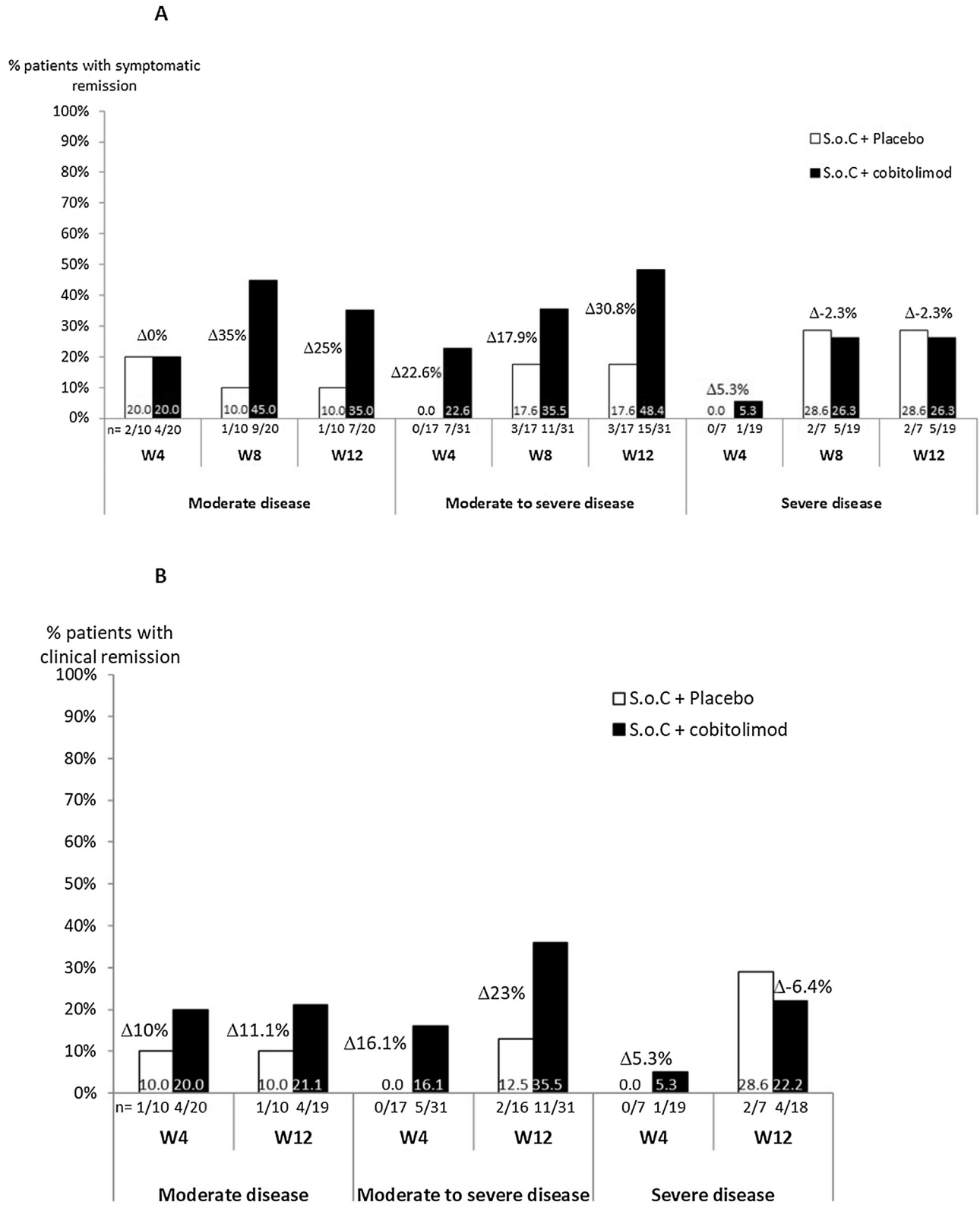
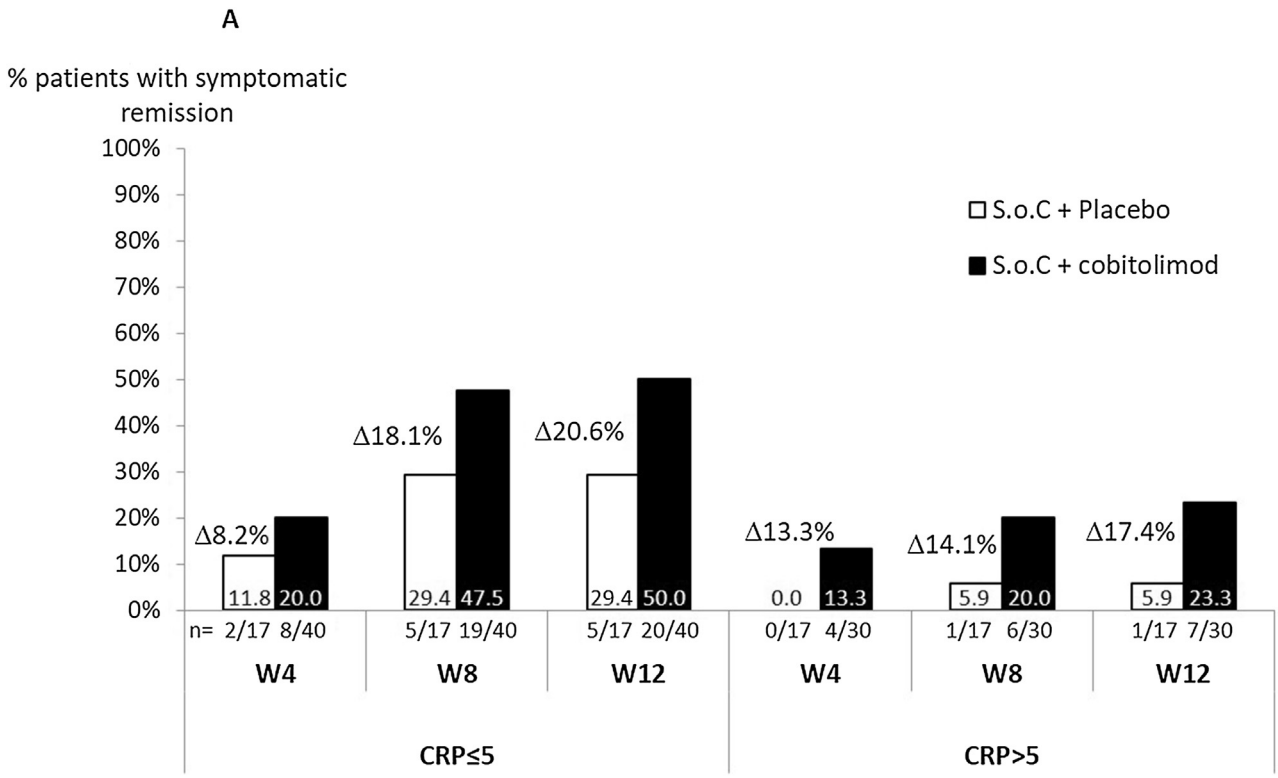


Fig. 3. Symptomatic and clinical remission in patients with moderate, moderate to severe and severe disease.
At study start patients had active UC with either moderate (CAI index = 9), moderate to severe (CAI index = 10–11) or severe (CAI index ≥ 12) disease activity and were treated with placebo or cobitolimod. (A) Proportion of patients with SR at 4, 8 or 12 weeks. (B) Proportion of patients with CR at 4 or 12 weeks.
S.o.C. = standard of care.

who had received prior anti-TNFα therapy were classified as treatment refractory.

In the anti-TNFα experienced patient subgroup SR was ranging from 7% (week 4) to 27% (week 12) for cobitolimod vs. 6% at weeks 4, 8 and 12 of the placebo treated patients (Fig. 5A). In the anti-TNFα naïve patient population SR rates were higher with 25%–48% in the cobitolimod treated patients with relative effect sizes of around 18% (Fig. 5A).



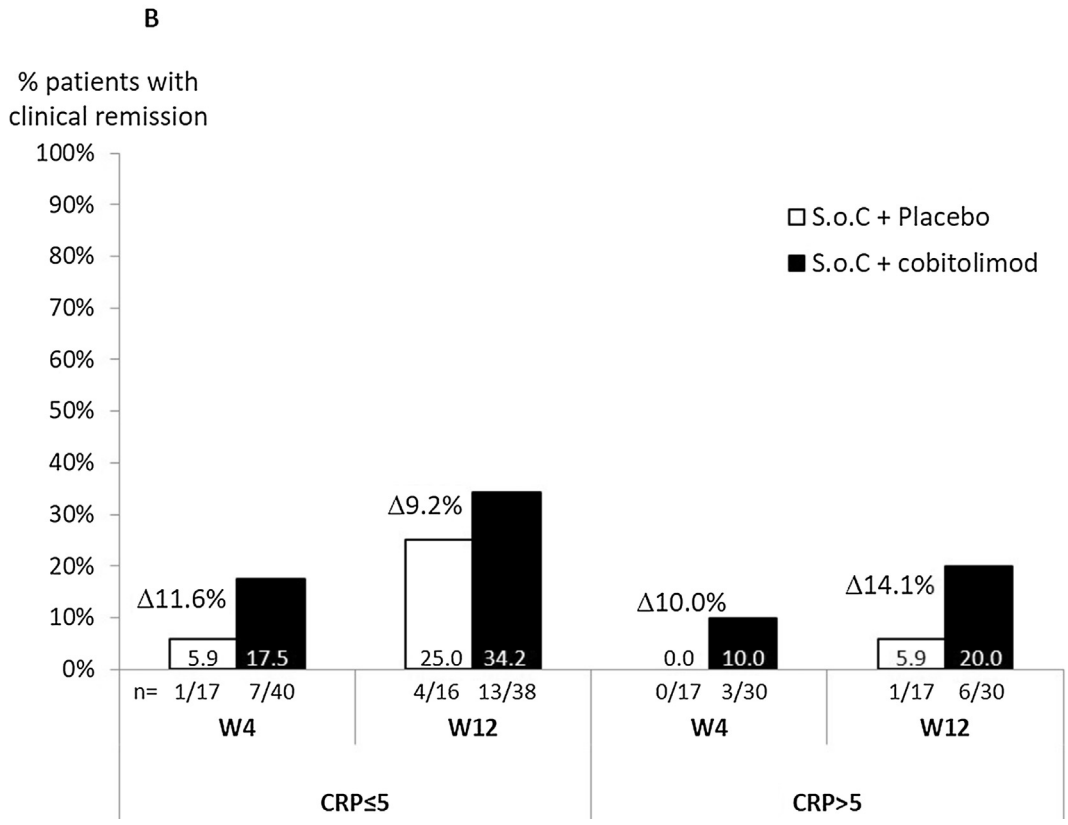
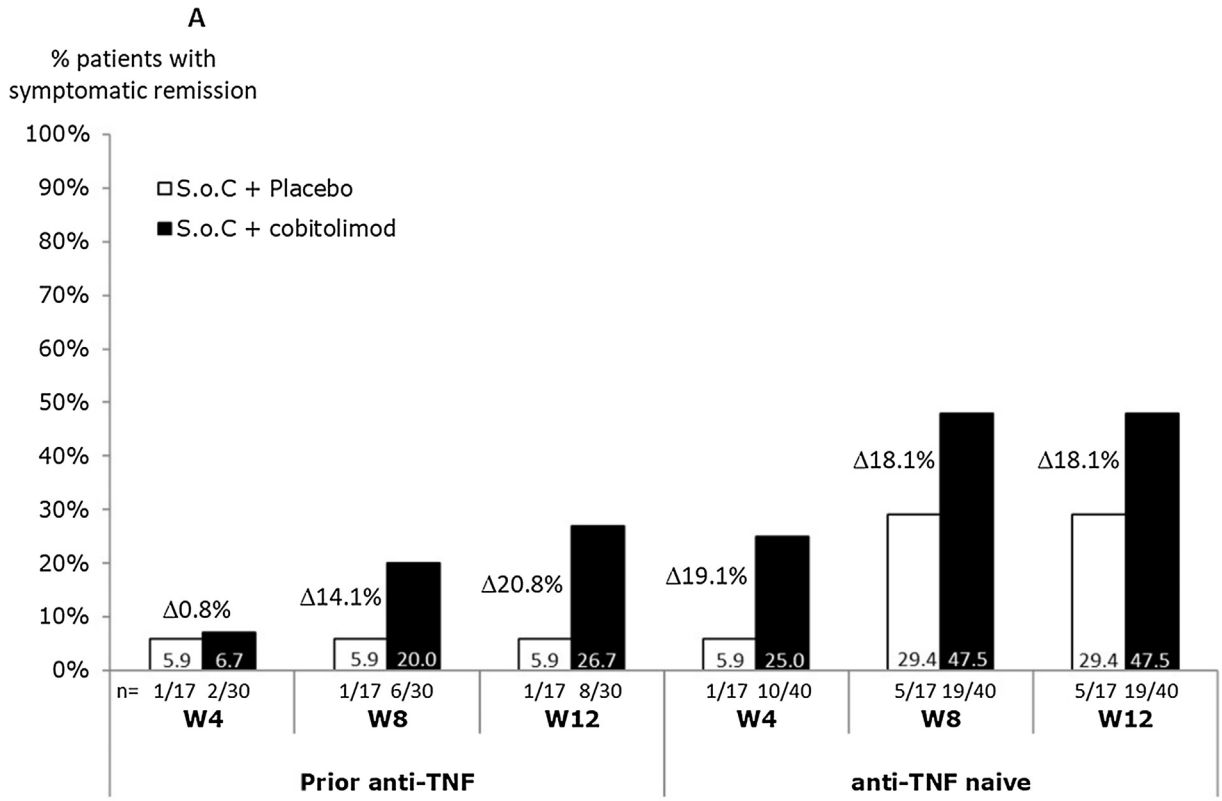


Fig. 4. Symptomatic and clinical remission in patients with normal and elevated CRP levels.
At study start patients had normal CRP (CRP < 5 mg/ml) or elevated CRP levels (CRP > 5 mg/ml) and were treated with placebo or cobitolimod. (A) Proportion of patients with SR at 4, 8 or 12 weeks. (B) Proportion of patients with CR at 4 or 12 weeks.
S.o.C. = standard of care.



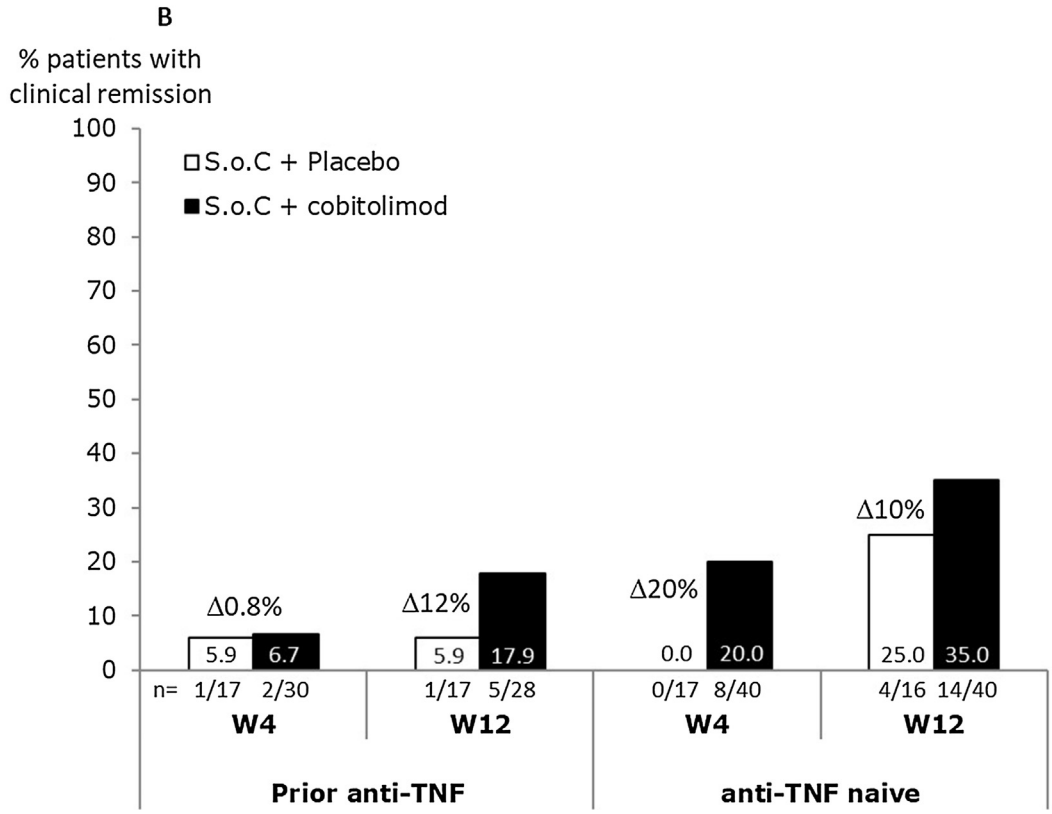


Fig. 5. Symptomatic and clinical remission in anti-TNFα-antibody pre-treated and naïve patients.
Patients have received prior anti-TNFα therapy (prior anti-TNFα) or were anti-TNFα-antibody naïve (anti-TNFα naïve) and were treated with placebo or cobitolimod. (A) Proportion of patients with SR at 4, 8 or 12 weeks. (B) Proportion of patients with CR at 4 or 12 weeks.
S.o.C. = standard of care.

Table 2
Multivariate logistic regression analysis of the endpoints symptomatic and clinical remission.

Endpoint	Model 1[a]		Model 2[b]		Model 3[c]		Correlation to baseline characteristics (from model 3)			
	Cobitolimod vs placebo		Cobitolimod vs placebo		Cobitolimod vs placebo		Anti-TNF-alpha naïve (vs experienced)		CRP < 5 (vs CRP ≥ 5)	
	OR[d]	p-Value	OR	p-Value	OR	p-Value	OR[e]	p-Value	OR[f]	p-Value
Symptomatic remission[g]										
Week 4	3.31	0.132	3.65	0.107	3.23	0.149	3.16	0.159	1.83	0.361
Week 8	2.59	0.064	2.64	0.061	2.58	0.088	4.74	0.08	4.31	0.06
Week 12	2.93	0.036	3.08	0.03	2.94	0.050	2.95	0.042	4.68	0.003
Clinical remission[h]										
Week 4	5.50	0.110	5.98	0.097	5.45	0.117	2.23	0.341	1.87	0.399
Week 12	2.16	0.163	2.19	0.162	1.88	0.281	3.80	0.033	2.90	0.049

[a] Unadjusted.
[b] Adjusted for disease severity at baseline.
[c] Adjusted for i) severity ii) anti-TNF and iii) CRP.
[d] Odd ratios (OR) > 1.0 is in favour of cobitolimod.
[e] OR > 1.0 is in favour of anti-TNF-alpha naïve patients.
[f] OR > 1.0 is in favour of CRP < 5.
[g] No blood in stool and stool frequency <4.
[h] No blood in stool and stool frequency <4 and endoscopic Mayo score ≤ 1.

Mucosal healing was achieved in the anti-TNFα experienced patient subgroup in 18.5% and 28.6% for cobitolimod vs. 23.5% and 50% for placebo treated patients at weeks 4 and 12. In the anti-TNFα naïve patients mucosal healing rates were 25% and 61% in the cobitolimod vs. 6% and 54% in placebo treated patients at weeks 4 and 12, respectively.

For CR the anti-TNFα experienced patients showed CR rates of up to 18% for cobitolimod vs. 6% for placebo treated patients (Fig. 5B). In the anti-TNFα naïve patient population CR rates were higher, up to 35%, for cobitolimod treated patients with relative effect sizes ranging from 10% to 20% (Fig. 5B).

3.6. Multivariate logistic regression analysis

Results from the model 1 with unadjusted estimation of the odds ratio, OR (cobitolimod/placebo) for SR revealed that there was a three-fold odds for SR in cobitolimod compared to placebo patients, which was slightly lower at week 12 compared to week 4 after treatment but statistically significant ($p = 0.036$) (Table 2). Less significant results at week 4 were explained by the difference (delta) between the treatment arms at week 4 (11.2%) compared to week 12 (21%), but in terms of OR they were similar.

In model 2, where results were adjusted for baseline disease severity defined by the CAI scores, OR for SR was around 3 at weeks 4, 8 and 12 and statistical significant at week 12 (Table 2).

In model 3, where results were adjusted for the three factors disease severity at baseline, prior anti-TNFα experience and CRP levels at baseline, the estimated efficacy of SR was very similar to the unadjusted estimates and statistical significant at week 12 ($p = 0.05$) (Table 2).

In addition, findings from model 3 showed that there were significant differences among subgroups of patients defined by the factors of anti-TNFα experience and CRP levels, independently from the treatment effect size. Results reveal that anti-TNFα naïve patients (compared to experienced) were having a three-fold or greater OR for SR at week 4 to week 12, where week 12 results were statistical significant. The subgroup of patients, who had normal CRP levels at baseline, was more likely to reach SR (Table 2), with statistically significant results at week 12.

4. Discussion

According to the FDA and STRIDE recommendations, PRO should be applied in combination with endoscopy, to define the primary and main secondary endpoints in clinical trials for UC [20–24]. Accordingly, we performed a post-hoc analysis using the PROs rectal bleeding and stool frequency as reported by e-diary data entry of the patients in order to re-assess the therapeutic efficacy of the Toll-like receptor-9 agonist cobitolimod in the randomised, placebo-controlled COLLECT study. Our exploratory post-hoc results provide supportive evidence of a considerable clinically relevant effect size in favour of cobitolimod versus placebo in endpoints based on patient-reported outcomes in addition to the results of the primary analysis based on endpoints determined by the CAI criteria to define clinical disease activity. Findings are similar in both the entire patient population and in subgroups also after adjusting for important factors such as disease severity or prior anti-TNFα-antibody use. The factors of prior use of anti-TNF-α antibodies and CRP levels were statistically significant and were prognostic factors for the endpoints analysed.

Twenty patients from the FAS population consisting of 124 patients have not reported any data in the e-diary and were excluded from this post hoc analysis. This might have created a potential bias in the estimated difference in efficacy. However, since the decision of these patients for not reporting any e-diary data was made before they were introduced to any study treatment, they are all unrelated to any experience of treatment effect, Therefore, this is to be considered of minor impact on the estimated results. Other weaknesses of this report include the relative small sample size of the observed cases population limiting the statistical power, the post hoc approach used for the data analysis as well as the lack of a central reading of endoscopy results. Despite these potential weaknesses the approach to use patient-reported outcomes defined endpoints, resulted in clinically meaningful findings with implications for clinical studies in the UC field. It also showed that future studies should emphasize in increasing the patient e-diary compliance.

Interestingly, the COLLECT study showed clinically meaningful and positive effects at week 12 using the endpoint measure SR, while no difference between cobitolimod or placebo treated patients was demonstrated in the primary endpoint at week 12 defined by the applied disease activity measure CAI [16]. This illustrates that the patient reported outcomes consisting of rectal bleeding and stool frequency, combined with endoscopy as a co-primary endpoint represent an appropriate outcome measure for UC trials.

Furthermore, our post-hoc analysis of sustained clinical outcomes provide evidence of longer-lasting effects of a dual exposure

to cobitolimod in patients with moderate to severe ulcerative colitis. Patients being in SR or CR at week 4 could largely maintain that benefit until week 12. This suggests on the one hand a fast onset of the drug action and on the other hand remarkable effects over time. It is tempting to speculate that these fast and prolonged effects might be due to a basic modulatory effect of cobitolimod on the gut immune system.

Overall, patients with moderate or moderate to severe disease seem to have better absolute and relative remission rates compared to patients with severe disease as assessed by the CAI score at study entry. Therefore, dual administration of cobitolimod seems to be particularly effective in patients with moderately-active UC. Better treatment outcome in moderate patients compared to severely active UC patients is in line with results of a number of other clinical trials evaluating the effect of TNFα inhibitors [25], integrin inhibitors such as vedolizumab [6,26,27], etrolizumab [28] and the anti-MAdCAM antibody (PF-00547659) [29] or the sphingosine-1-phosphate (S1P) subtype 1 (S1P1) receptor agonist ozanimod [30].

In addition, our post-hoc results suggest that cobitolimod is potent to induce SR and CR both in subgroups of anti-TNFα experienced and naïve patients. Remission rates of SR and CR in the subgroup of anti-TNFα experienced patients were smaller compared to naïve patients at all time points assessed. Again, the observation of a better absolute treatment outcome in anti-TNFα naïve patients compared to anti-TNFα pre-treated patients is in line with other clinical studies studying compounds already approved or in clinical development [6,23–25]. As demonstrated by the model 3 in the multivariate logistic regression analyses, the significant but effect-size independent impact of prior use of anti-TNFα agents and also CRP levels on the two outcomes of SR and CR is an important finding. Therefore, it is important to consider at least anti-TNFα use for stratification for treatment allocation in the design stage of the next clinical trials with cobitolimod in patients with UC.

In summary, this report underscores that patient-reported endpoints assessed by e-diary are responsive to treatment and highly useful tools to measure clinical efficacy of novel drugs in UC patients. Using these endpoints the presented post hoc analysis suggests that dual topical administration of cobitolimod is able to induce remission in clinically relevant subgroups of UC patients. The therapeutic potential of dose-optimized cobitolimod will be explored in placebo-controlled prospective clinical trials.

Conflict of interest

Raja Atreya has served as speaker, consultant and an advisory board member for IndexPharmaceuticals and has received research funding from Index Phramaceuticals.

Walter Reinisch has served as consultant and an advisory board member for IndexPharmaceuticals.

Laurent Peyrin–Biroulet has served as consultant and an advisory board member for IndexPharmaceuticals.

Charlotte Admyre is an employee of InDex Pharmaceuticals.

Thomas Knittel owns stocks and shares in Index Phrmaceuticals and works as consultant of InDex Pharmaceuticals.

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Markus Neurath has served as consultant and an advisory board member for IndexPharmaceuticals.

Christopher Hawkey has served as consultant and an advisory board member for IndexPharmaceuticals

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