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Cobitolimod for Moderate-to-Severe, Left-Sided Ulcerative Colitis (CONDUCT): A Phase 2b, Randomised, Double-Blind, Placebo-Controlled, Dose-Ranging Trial

Raja Atreya*, Laurent Peyrin–Biroulet, Andrii Klymenko, Monica Augustyn, Igor Bakulin, Dusan Slankamenac, Pal Miheller, Antonio Gasbarrini, Xavier Hébuterne, Karin Arnesson, Thomas Knittel, Jan Kowalski, Markus F. Neurath, William J. Sandborn, Walter Reinisch, CONDUCT study group

***Department of Medicine 1, University of Erlangen-Nürnberg, Erlangen, Germany**

Disclosure of Conflicts of Interest

I herewith declare the following paid or unpaid consultancies, business interests or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

Abbvie, Amgen, Biogen, Boehringer Ingelheim GmbH & Co. KG, Celgene, Celltrion Healthcare, Dr Falk Pharma GmbH, Ferring GmbH, GlaxoSmithKlein plc, InDex Pharmaceuticals AB, Janssen-Cilag GmbH, Kliniksa, MSD Sharp & Dome GmbH, Philogen, Pfizer Inc., Roche Pharma, Samsung Bioepsis, Stelic Institute, Sterna Biologicals, Takeda Pharma GmbH & Co. KG, Tillotts Pharma AG

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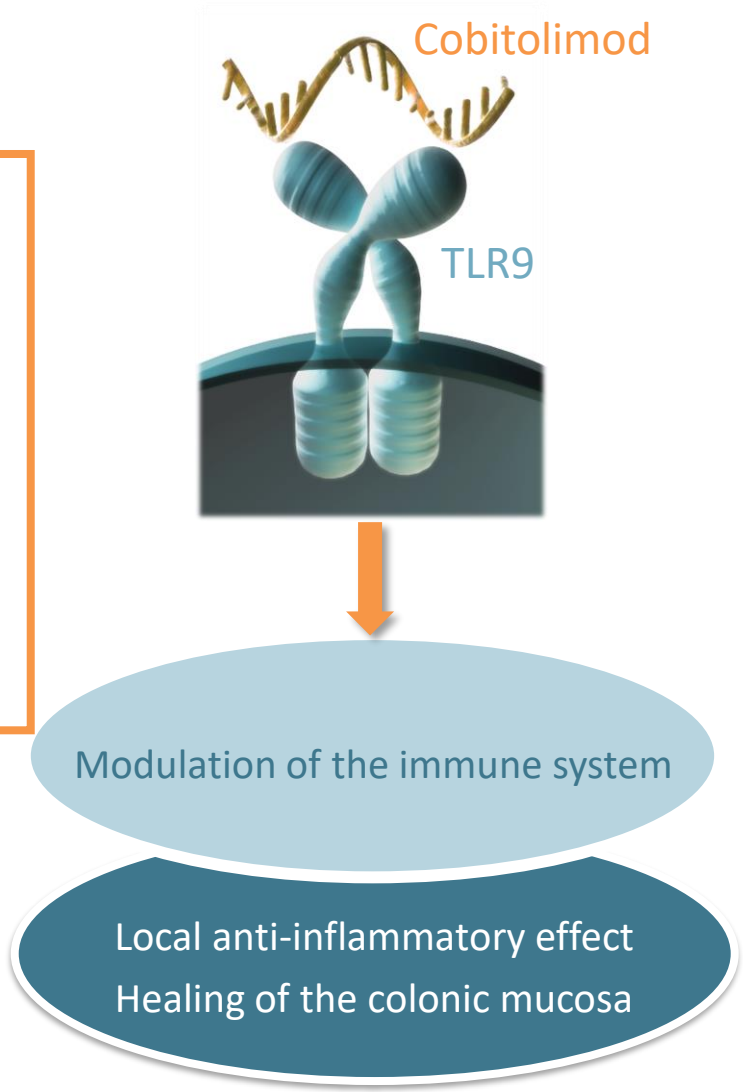
Cobitolimod is a First-in-Class TLR9 Agonist

- Cobitolimod is an oligonucleotide which activates Toll Like Receptor 9 (TLR9) by mimicking microbial DNA
- Cobitolimod modifies the dysregulated mucosal cytokine balance in intestinal inflammation
- Cobitolimod is administered rectally as a 50 ml solution

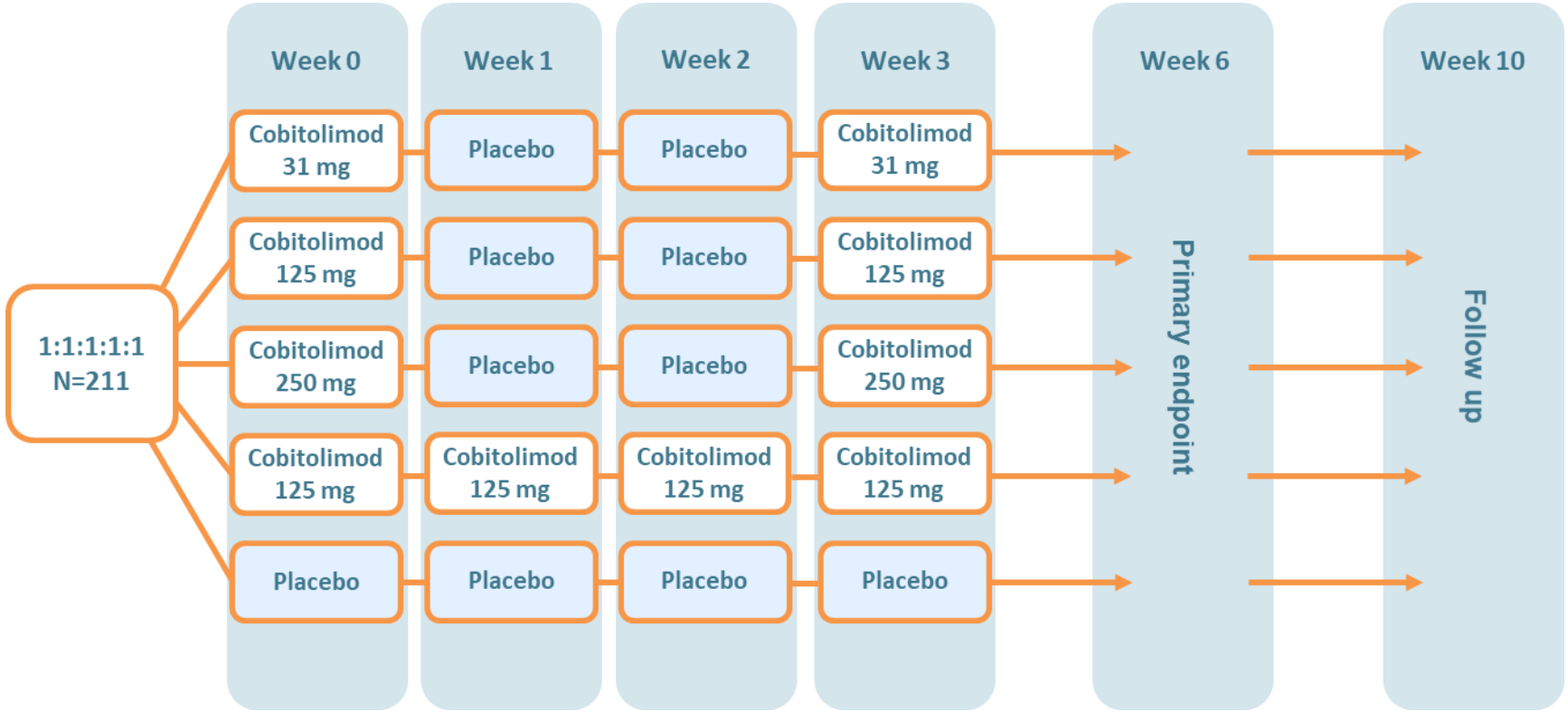


Schmitt et al., J Crohns Colitis. 2020; 14,4: 508-524.

Phase 2b CONDUCT Study Design

Primary objective

To evaluate the efficacy of cobitolimod treatment at different dose levels and frequencies compared to placebo with regard to clinical remission 6 weeks after first treatment, in patients with moderate-to- severe ulcerative colitis



Main inclusion criteria

- Moderate-to-severe, left- sided UC (centrally read)
- Current use, dependency, refractoriness or intolerance to glucocorticosteroids
- Failed immunomodulators and/or biologics
- No concomitant biologics

ClinicalTrials.gov Identifier: NCT03178669

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Cobitolimod is a First-in-Class TLR9 Agonist

Primary endpoint

Clinical Remission at week 6 defined by Modified Mayo sub scores:

i) Rectal bleeding of 0
ii) Stool frequency of 0 or 1
(with at least one point decrease from Baseline), and
iii) Endoscopy score of 0 or 1 (excluding friability), centrally read

Statistical design

One-sided test of the null hypothesis, that there is no difference in the primary endpoint between each active treatment arm and placebo, with a type I error rate of 0.10. Appropriate to provide high statistical power to detect a clinically meaningful effect while maintaining an acceptable sample size.

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Patient Demographics at Baseline

	COBITOLIMOD				PLACEBO (n=44)	OVERALL (n=211)
	30 mg x 2 (n=40)	125 mg x 2 (n=43)	125 mg x 4 (n=42)	250 mg x 2 (n=42)		
Age Mean year (SD)	47.4 (16.4)	47.0 (16.9)	47.2 (14.9)	46.2 (14.0)	45.5 (15.2)	46.6 (15.4)
Gender female %	35.0	53.5	42.9	38.1	25.0	38.9
UC duration Mean year (SD)	7.88 (6.48)	8.46 (7.43)	8.14 (6.77)	7.89 (6.83)	7.36 (7.28)	7.94 (6.92)
Mayo score Mean (SD)	8.5 (1.2)	8.0 (1.8)	8.3 (1.7)	8.5 (1.3)	8.3 (1.6)	8.3 (1.5)
Rectosigmoid colon disease extent descending colon endoscopic score = 0, %	57.5	51.2	54.8	45.2	47.7	51.2
Descending colon disease extent descending colon endoscopic score ≥1, %	42.5	48.8	45.2	54.8	52.3	48.8

Full analysis set

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Concomitant and Prior Medication

	COBITOLIMOD				PLACEBO (n=44)	OVERALL (n=211)
	30 mg x 2 (n=40)	125 mg x 2 (n=43)	125 mg x 4 (n=42)	250 mg x 2 (n=42)		
Concomitant glucocorticosteroids %	45.0	30.2	33.3	40.5	38.6	37.4
Concomitant 5-ASA %	87.5	88.4	78.6	78.6	88.6	84.4
Dose prednisolone, mg/day Mean (SD)	15.7 (5.3)	15.0 (4.6)	15.0 (6.2)	12.5 (4.5)	14.8 (5.6)	14.6 (5.2)
Concomitant AZA/6-MP %	22.5	13.9	23.8	21.4	15.9	19.4
Prior use of TNF-α inhibitor %	22.5	23.3	28.6	21.4	18.2	22.7
Prior use of vedolizumab %	10.0	7.0	7.1	11.9	0	7.1

Full analysis set

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Primary Endpoint

Clinical Remission at Week 6*	COBITOLIMOD				PLACEBO (n=44)
	30 mg x 2 (n=40)	125 mg x 2 (n=43)	125 mg x 4 (n=42)	**250 mg x 2 (n=42)**	
% of patients	12.5 %	4.7 %	9.5 %	**21.4 %**	6.8 %
Δ to placebo	5.7 %	-2.1 %	2.7 %	**14.6 %**	
Odds Ratio	2.0	0.7	1.4	**3.8**	
P-value one-sided test (pre-specified)	0.1806	0.6649	0.3279	**0.0247**	
P-value two-sided test	0.3612	0.6701	0.6559	**0.0495**	

*Full analysis set, NRI *Primary Endpoint = Clinical Remission at Week 6 defined as Modified Mayo sub scores: i) rectal bleeding of 0, ii) stool frequency of 0 or 1 and iii) endoscopy score of 0 or 1 (excluding friability)*

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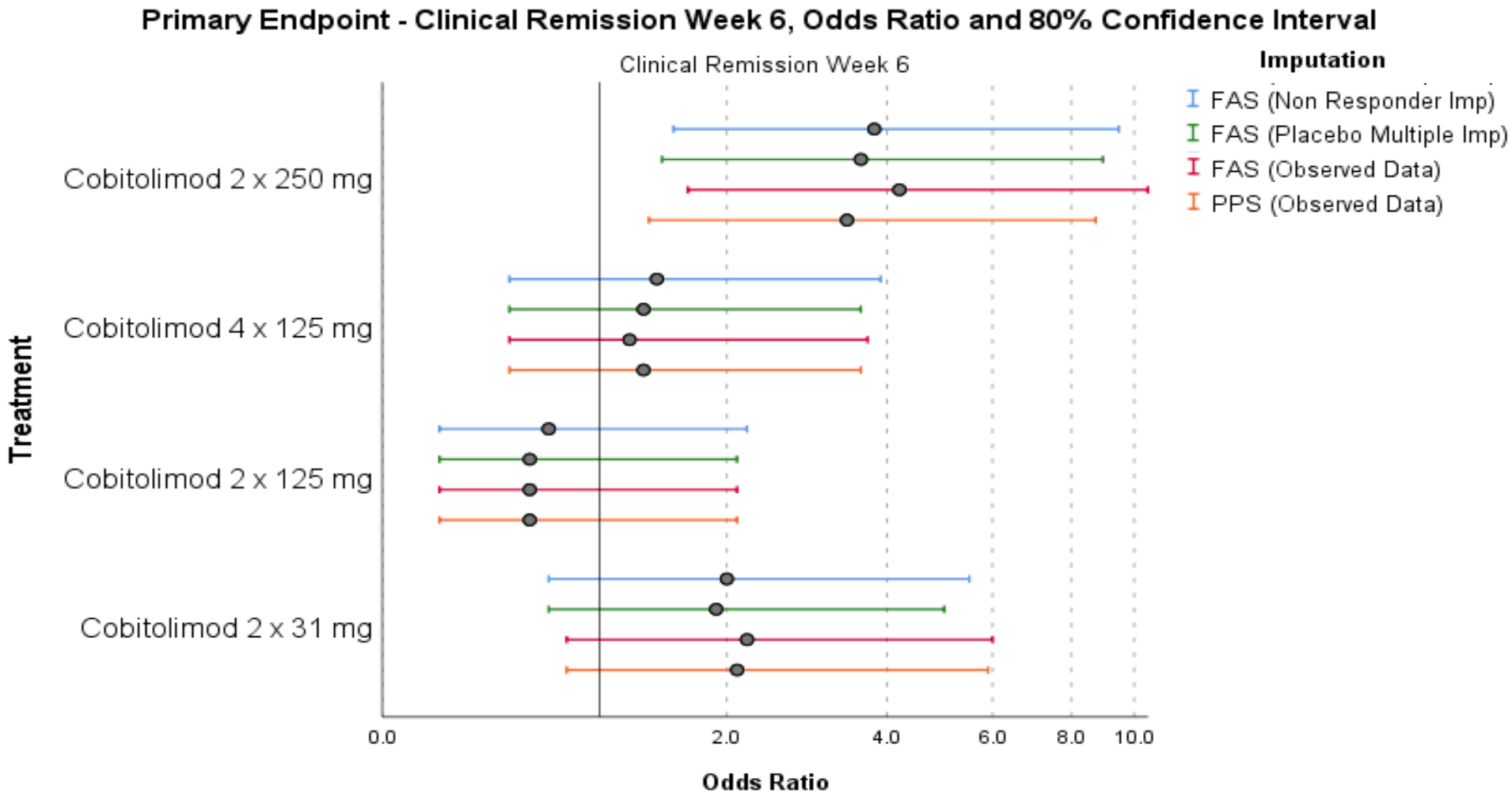
Sensitivity Analyses of the Primary Endpoint



Selection of Secondary Exploratory Endpoints

Week 6	COBITOLIMOD				PLACEBO (n=44)
	30 mg x 2 (n=40)	125 mg x 2 (n=43)	125 mg x 4 (n=42)	**250 mg x 2 (n=42)**	
Clinical remission, full Mayo Score %	15.2	2.4	7.7	**20.0***	7.7
Symptomatic remission %	27.0	26.2	25.0	**35.1***	20.9
Endoscopic remission %	20.6	12.2	25.6	**40.5**	30.0
Clinical response %	51.5	43.9	38.5	**57.1**	51.3
Normalization (<250 mg/kg)# of faecal calprotectin %	21.4	23.5	20.6	**15.2**	6.7

*One-sided p-value (pre-specified with cut-off <0.10), *p<0.1.*
Clinical remission, full Mayo score: i) rectal bleeding subscore of 0, ii) stool frequency subscore of 0 or 1 (with at least one point decrease from baseline), iii) centrally read endoscopy score of 0 or 1 and iiii) PGA score of 0 or 1. Symptomatic remission: Mayo subscores i) rectal bleeding of 0, ii) stool frequency of 0 or 1 (with at least one point decrease from baseline). Endoscopic improvement: Mayo endoscopic subscore of 0 or 1. Clinical response: three point and ≥30% decrease from baseline in the sum of the full Mayo score.
#Normalization of faecal calprotectin to <250 mg/kg in patients with faecal calprotectin >250 mg/kg at baseline

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Safety

Treatment Emergent Adverse Events No of patients (%)	COBITOLIMOD				PLACEBO (n=44)
	30 mg x 2 (n=40)	125 mg x 2 (n=43)	125 mg x 4 (n=42)	250 mg x 2 (n=42)	
Patients with AEs	10 (25.0%)	17 (39.5%)	15 (35.7%)	18 (42.9%)	21 (47.7%)
Patients with Serious AEs	2 (5.0%)	0	2 (4.8%)	4 (9.5%)	2 (4.5%)
Deaths	0	0	0	0	1 (2.3%)

Safety analysis set, some patients have reported several adverse events

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Summary

- First clinical trial that has been conducted specifically in patients with left-sided ulcerative colitis using centrally read endoscopy
- Topical administration of 2x250mg of the TLR9 agonist cobitolimod is effective to induce clinical remission
- Cobitolimod was well tolerated and no safety signals were detected
- TLR9 activation is a promising novel therapeutic option in UC patients and is planned to be confirmed in an upcoming phase III program

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