A PHASE 1/2 RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF THE INDUCTION OF CLINICAL RESPONSE AND REMISSION USING A NOVEL IMMUNOTHERAPY (QBECO) IN SUBJECTS WITH MODERATE TO SEVERE CROHN'S DISEASE

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Introduction

The lack of clear understanding of the etiology of Crohn's disease (CD) has contributed to suboptimal treatment approaches that leave a significant portion of patients experiencing progression and worsening disease[1]. In addition, the aggressive immune suppression currently used to manage CD comes with increased risk of infections, malignancy, and other adverse effects[2]. There is a need for new treatment approaches that achieve deep remission, have a good safety profile, and are cost effective for patients and the healthcare system in the long-term. **QBECO, an investigational biologic derived from inactivated *E. coli*, provides a novel immunotherapy strategy for CD that aims to restore innate immune function and clear dysbiosis, leading to the reestablishment of barrier function and immune homeostasis in the GI tract.**

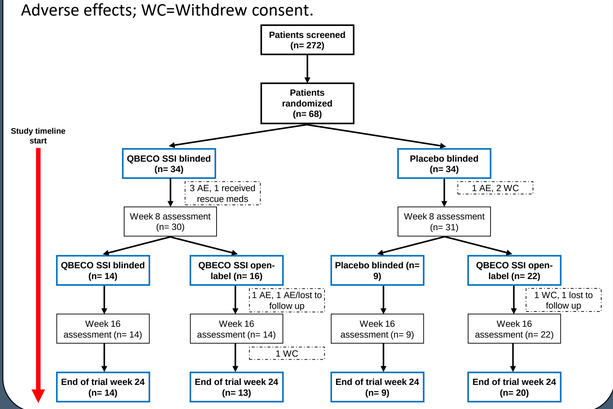
Objective

The aim of this proof-of-concept study was to assess safety, efficacy, and compliance of QBECO treatment, designed to restore innate immune function in subjects with moderate-to-severe CD.

Methods

68 patients with moderate-to-severe CD (Crohn's Disease Activity Index [CDAI] score of 220-450) were randomized 1:1 to receive blinded QBECO or placebo (PBO) by subcutaneous injection every other day for 8 weeks. Treatment from weeks 9-16 is described in **Figure 1**. Primary endpoints were safety and clinical improvement at Week 8. Secondary endpoints included clinical response and remission rates at Week 8.

Figure 1 Study design, patient randomization and flow-through. The study was divided into three phases: Phase 1 treatment (weeks 1 to 8), Phase 2 treatment (weeks 9-16) and Post-treatment follow-up (weeks 17-24). Dashed boxes contain study withdrawal information. SSI=Site Specific Immunomodulator. AE= Adverse effects; WC=Withdrew consent.



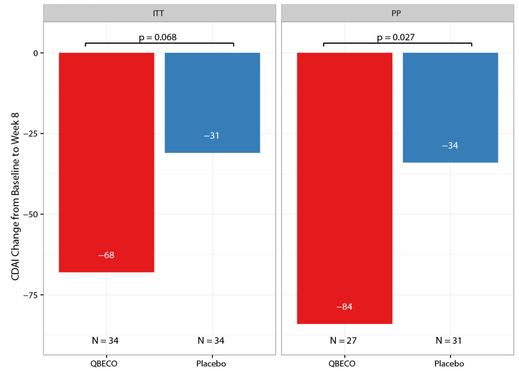
Results

Baseline characteristics of participants in the randomized groups are presented in **Table 1**. Unequal distribution of subjects with prior exposure to anti-TNFα treatment occurred, resulting in 59% of the QBECO group comprising these more difficult to treat patients vs 21% in the PBO group (p=0.003). Mean reduction in CDAI from baseline to Week 8 was greater in patients treated with QBECO vs PBO in both the Intention-to-Treat (ITT) and Per Protocol (PP) analyses (**Figure 2**).

Table 1 Summary of baseline characteristics and demographic variables. IQR = Interquartile Range

Variable	QBECO (n=34)	Placebo (n=34)	p-value
Years since initial Crohn's diagnosis,			
Median (IQR)	9.2 (3.8, 13.2)	6.0 (3.7, 10.9)	0.429
Age at initial Crohn's diagnosis			
Median (IQR)	30.0 (20.2, 39.2)	24.7 (20.3, 31.4)	0.315
CDAI			
Median (IQR)	268.0 (241.0, 331.0)	260.0 (233.0,	0.303
CDAI ≥ 250			
n (%)	24 (70.6)	19 (55.9)	0.315
Fecal calprotectin (µg/g)			
Median (IQR)	450.0 (260.3, 641.2)	518.9 (242.3, 782.5)	0.581
C-reactive protein (mg/L)			
Median (IQR)	8.5 (4.0, 21.4)	11.5 (5.4, 24.0)	0.251
Prior anti-TNFα use			
n (%)	20 (58.8)	7 (20.6)	0.003
Concomitant therapy for CD			
n (%)	27 (79.4)	25 (73.5)	0.567

Figure 2 Mean change in CDAI score from baseline to study Week 8 by treatment group



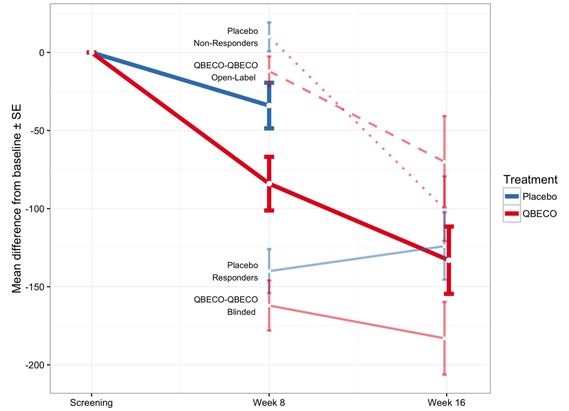
Clinical response, improvement and remission rates at Week 8 with QBECO (n=34) were 41.2%, 32.4%, 29.4% vs 25.8%, 23.5%, 23.5% for PBO (n=34); p>0.05 (ITT analysis). Patients treated with QBECO continued to improve through Week 16 (**Table 2**), experiencing a further mean reduction in CDAI score of 50 points after Week 8, reaching a 130 point reduction in CDAI by Week 16 (**Figure 3**, PP analysis), indicating a longer induction timepoint may be more optimal.

Table 2 Summary of the proportion of individuals with Crohn's disease who had a response (CDAI≥70-point decrease), improvement (CDAI≥100-point decrease), or went into remission (CDAI ≤ 150) with QBECO SSI

ITT	Weeks on SSI	Response % (n)	Improvement % (n)	Remission % (n)
QBECO-QBECO n=34	8	41 (14)	32 (11)	29 (10)
	16	50 (17)	44 (15)	35 (12)
QBECO-QBECO (anti-TNFα naïve) n=14	8	64 (9)	50 (7)	50 (7)
	16	71 (10)	64 (9)	50 (7)
Open-label QBECO* (anti-TNFα naïve) n=17	8	71 (12)	47 (8)	47 (8)

* Placebo non-responders at Week 8, switched to QBECO.

Figure 3 Change in CDAI score in study groups Week 8 and 16 (Per Protocol)



Patients naïve to prior anti-TNFα treatment achieved higher response and remission rates at Week 8 with QBECO (n= 14) compared with PBO (n= 27) (**Table 3**).

Table 3 Clinical response at Week 8 by past exposure to anti-TNFα treatment

Week 8 endpoint	QBECO % (n)	Placebo % (n)	p-value	Difference (%)
Anti-TNFα-naive	64.3 (9) 95% CI [35.1,87.2]	26.9 (7) 95% CI [11.6,47.8]	0.041	+37.4
Prior anti-TNFα-exposed	25 (5) 95% CI [8.7,49.1]	28.6 (2) 95% CI [3.7,71]	1.00	-3.6

QBECO treatment was well tolerated; **Table 4** lists the adverse events experienced in 5% or more of the study participants while blinded. Most adverse events were Grade 1 (58.8% on PBO; 73.5% on QBECO). Grade 3 reactions were uncommon (2.9% on PBO; 8.8% on QBECO).

No significant differences in adverse events between PBO and QBECO groups were identified, except for increased frequency of transient flu-like symptoms in the QBECO group, which may be related to QBECO's mechanism of action of bacterial clearance.

Table 4 Common adverse effects

Preferred term	Number (%) of patients All (n=68)	QBECO (n=34)	Placebo (n=34)
Any Adverse Event	*45 (66.2)*	*25 (73.5)*	*20 (58.8)*
Abdominal tenderness	3 (4.4)	1 (2.9)	2 (5.9)
Mouth ulceration	2 (2.9)	2 (5.9)	0 (0.0)
Nausea	8 (11.8)	6 (17.6)	2 (5.9)
Fatigue	8 (11.8)	4 (11.8)	4 (11.8)
Influenza like illness	14 (20.6)	10 (29.4)	4 (11.8)
Injection site bruising	2 (2.9)	0 (0.0)	2 (5.9)
Injection site pain	2 (2.9)	2 (5.9)	0 (0.0)
Injection site pruritus	5 (7.4)	5 (14.7)	0 (0.0)
Pyrexia	11 (16.2)	8 (23.5)	3 (8.8)
Dizziness	2 (2.9)	2 (5.9)	0 (0.0)
Headache	6 (8.8)	2 (5.9)	4 (11.8)
Cough	2 (2.9)	2 (5.9)	0 (0.0)
Oropharyngeal pain	2 (2.9)	2 (5.9)	0 (0.0)

Genotype analysis, which was conducted in consenting patients (n=30), identified three IBD-related single-nucleotide polymorphisms (SNPs) of high relevance to QBECO mechanism of action (MOA) that segregated with QBECO response. In addition, composite model comprised of baseline serum cytokine biomarkers highly relevant to QBECO MOA and baseline clinical/demographic data could predict, after optimism-adjustment to correct for over-estimation of model fit (AUROC ≥ 7), a patient's likelihood to respond to QBECO treatment by Week 8.

Discussion and Conclusions

Patients treated with QBECO experienced greater benefit over PBO in reducing disease activity by Week 8. Symptom improvement continued to Week 16, suggesting a longer time-frame to assess QBECO induction may be more optimal. Statistically significant improved response was achieved at Week 8 in anti-TNFα naïve subjects (64.3% vs. 26.9%; p = 0.041). The genetic and biomarker analyses provide early indications that the elusive personalized approach to CD treatment may be feasible with QBECO therapy. A planned follow-on study will evaluate mucosal healing, optimal time-frames to response and remission in patients with and without past anti-TNFα exposure, as well as genetic and cytokine correlations with QBECO response, to optimize patient selection and study design for moving QBECO to Phase 3 trials.

References

1. Magro F, Dias CC, Coelho R, et al. Impact of Early Surgery and Immunosuppression on Crohn's Disease Disabling Outcomes. Inflamm Bowel Dis 2017;23:289-97.
2. McLean MH, Neurath MF, Durum SK. Targeting interleukins for the treatment of inflammatory bowel disease-what lies beyond anti-TNF therapy? Inflamm Bowel Dis 2014;20:389-97.