

## Principal Investigator

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## General Information

### Key Personnel (in addition to PI):

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**Are external grants or funds being used to support this research?:** No external grants or funds are being used to support this research.

**How did you learn about the YODA Project?:** Colleague

## Conflict of Interest

[https://yoda.yale.edu/system/files/yoda\\_coi\\_2021-4779-\\_narula.pdf](https://yoda.yale.edu/system/files/yoda_coi_2021-4779-_narula.pdf)

[https://yoda.yale.edu/system/files/yoda\\_coi\\_2021-4779-\\_wong.pdf](https://yoda.yale.edu/system/files/yoda_coi_2021-4779-_wong.pdf)

## Certification

**Certification:** All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

**Data Use Agreement Training:** As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. [NCT00036439 - C0168T37 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis](#)
2. [NCT00096655 - C0168T46 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis](#)
3. [NCT01369329 - CNTO1275CRD3001 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist](#)

[Therapy \(UNITI-1\)](#)

4. [NCT01369342 - CNTO1275CRD3002 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease \(UNITI-2\)](#)
5. [NCT00488631 - C0524T18 - A Phase 3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Maintenance Therapy, Administered Subcutaneously, in Subjects With Moderately to Severely Active Ulcerative Colitis](#)
6. [NCT01369355 - CNTO1275CRD3003 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease](#)

**What type of data are you looking for?:** Individual Participant-Level Data, which includes Full CSR and all supporting documentation

## Research Proposal

### Project Title

Predictors of Placebo Response and Remission in Ulcerative Colitis and Crohn's Disease

### Narrative Summary:

Treatments for ulcerative colitis (UC) and Crohn's disease (CD) must demonstrate efficacy and safety to obtain regulatory approval. Clinical trials for UC and CD are designed to assess the effect of a treatment and are often placebo-controlled when assessing novel biologic drugs. Despite receiving placebo, patients may still experience an improvement in their condition. The primary objective of this study is to evaluate predictors of clinical response among patients who received placebo treatment.

### Scientific Abstract:

#### Background

It is unclear what factors influence clinical response among patients who received placebo treatment in clinical trials of UC and CD.

#### Objectives

This study aims to evaluate predictors of clinical response at week 6 among patients who received placebo treatment in six clinical trials of UC and at week 4 or 6 among patients who received placebo in four clinical trials of CD.

#### Study Design

The proposed study will be a post-hoc analysis of GEMINI 1, ACT 1, and ACT 2, which were all multicentre, randomized, placebo-controlled and double-blind trials for UC. Data from the UNITI studies, GEMINI-2, GEMINI-3, and CLASSIC-1 will be analyzed for CD.

#### Study Population

Participants who received placebo treatment throughout the entire duration of the trials will be included in this analysis.

#### Outcomes

Clinical response at the end of induction was assessed at week 6 in all trials included in this analysis. For the UC population, the secondary outcomes which require data from the total Mayo score, week 6 will be used for the GEMINI 1 study and week 8 for the ACT 1, ACT 2, PURSUIT, ULTRA, and OCTAVE studies. For the CD population, clinical response was assessed at week 4 for the CLASSIC-1 study and at week 6 for the UNITI and GEMINI studies.

#### Statistical Analysis

Univariate analyses will be conducted to assess potential baseline predictors of clinical response at week 6.

Multivariable logistic regression models will include predictors with a p-value < 0.05 on univariate analysis.

### **Brief Project Background and Statement of Project Significance:**

Ulcerative colitis (UC) and Crohn's disease (CD) are types of inflammatory bowel disease. UC affects the large intestine and is characterized by diarrhea, rectal bleeding, abdominal pain, urgency, and tenesmus (1,2). CD can affect any area along the gastrointestinal tract, although many patients present with disease in the ileum and colon and experience symptoms including abdominal pain, weight loss, and diarrhea (3). Treatments for UC and CD must demonstrate efficacy and safety to obtain regulatory approval. Clinical trials for UC and CD are designed to assess the effect of a treatment and are often placebo-controlled when assessing novel biologic drugs. Placebo treatments do not contain any ingredients of therapeutic value and are often considered 'sugar pills'. Despite receiving placebo, patients may still experience an improvement in their condition. Although high placebo response rates in clinical trials have been previously reported, it is unclear what factors may influence the response rate. Previous meta-analyses for UC have suggested factors such as disease duration, endoscopic disease severity, rectal bleeding score at baseline, and class of treatment may play a role in placebo response and remission rates (3). The primary objective of this study is to evaluate predictors of clinical response among patients who received placebo treatment. Data from GEMINI 1 (NCT00783718), ACT 1 (NCT00036439), and ACT 2 (NCT00096655) will be pooled to obtain a cohort of UC patients who were treated with placebo for the entire duration of the trial. Data from UNITI-1 (NCT01369329), UNITI-2 (NCT01369342), IM-UNITI (NCT01369355), GEMINI-2 (NCT00783692), GEMINI-3 (NCT01224171), and CLASSIC-1 (NCT00055523) will be assessed for CD.

### **Specific Aims of the Project:**

The proposed study aims to evaluate potential factors that may influence clinical response at the end of induction therapy (week 6 for UC and week 4 or 6 for CD). Secondary outcomes include clinical remission (week 6 or 8) and mucosal healing (week 6 or 8) as determined by the Mayo Score for UC and Simple Endoscopic Score for CD (SES-CD) for CD. Outcomes at other time points, including week 14, 30, and one year, may be evaluated as part of exploratory analyses. While these analyses are intended to be hypotheses generating, we hypothesize that concomitant corticosteroid use and established biomarkers for UC and CD, including C-reactive protein and fecal calprotectin, are independent predictors for clinical response at the end of induction.

### **What is the purpose of the analysis being proposed? Please select all that apply.**

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

## **Research Methods**

### **Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

#### **Study Design**

The proposed study will be a post-hoc analysis of GEMINI 1, ACT 1, ACT 2, PURSUIT, ULTRA, and OCTAVE, which were all multicentre, randomized, placebo-controlled and double-blind trials for UC. Data from the UNITI studies, GEMINI-2, GEMINI-3, and CLASSIC-1 will be analyzed for CD.

#### **Study Population**

Participants who received placebo treatment throughout the entire duration of the trials will be included in this analysis.

### **Main Outcome Measure and how it will be categorized/defined for your study:**

#### **Ulcerative Colitis**

The primary outcome of interest is clinical response at post-induction (week 6), defined as a reduction in the Mayo score  $\geq 3$  points and a decrease  $\geq 30\%$  from baseline, with a decrease  $\geq 1$  point for the rectal bleeding subscore (RBS) or an absolute RBS  $\geq 1$ . Secondary outcomes of interest include clinical remission at week 6 or 8 (defined as total Mayo Score  $\leq 2$  and no subscore  $> 1$  on any of the four parameters) and mucosal healing at week 6 or 8 (defined as Mayo endoscopic subscore  $\leq 1$ ). For these secondary outcomes, week 6 will be used as the timepoint for the GEMINI trial and week 8 for ACT 1 and ACT 2 as total Mayo scores were available during these timepoints. Alternative definitions of clinical response, CR, and MH may be used in sensitivity analyses. Evaluation of these

exploratory outcomes will depend on adequate data availability at these time points.

#### Crohn's Disease

The primary outcome of clinical response at post-induction (week 4 or 6) will be defined as CDAI  $\geq$  100 point reduction from baseline.

#### **Main Predictor/Independent Variable and how it will be categorized/defined for your study:**

The independent variables are potential baseline predictors of clinical response, including age, concomitant immunomodulator use, concomitant corticosteroid use (and dose), disease extent, prior surgical history, current smoking, sex, C-reactive protein, fecal calprotectin, albumin, race, extraintestinal manifestations, disease duration and severe Mayo endoscopic score. Where possible, predictors will be dichotomized.

#### **Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:**

Univariate analyses will also be conducted to evaluate associations that may exist between covariates (e.g. sex, age, disease duration, disease location) and the outcome of interest. Variables found to have an association ( $p < 0.10$ ) will be included in the multivariate model.

#### **Statistical Analysis Plan:**

##### Ulcerative Colitis

In GEMINI 1, 135 patients were randomized to continuous placebo. In ACT 1 and ACT 2, 121 and 123 patients were randomized to placebo, respectively. In ULTRA there were 246 patients randomized to receive placebo, while in PURSUIT, there were a total of 129 patients were placebo-induction responders and 230 placebo-induction nonresponders. In OCTAVE-1 and OCTAVE-2, 122 and 112 patients were randomized to placebo, respectively. The maintenance studies are being requested as one year may be evaluated as part of secondary endpoints. Therefore, the eligible study population includes 839 patients. Data from these trials are being requested as common time points were used and included a placebo-controlled arm. Mayo Scores were captured at two common time points of interest (week 6 or 8 and one year) in GEMINI 1, ACT 1, ACT 2, PURSUIT, OCTAVE, and ULTRA.

##### Crohn's Disease

In UNITI, a total of 133 patients were randomized to placebo throughout the induction and maintenance phases. In GEMINI-2 and GEMINI-3, a total of 148 participants received continuous placebo. In CLASSIC-1, a total of 74 patients were randomized to placebo. Patients who crossed over between treatments at any point during any of the trials will be excluded from the analysis. Therefore, the eligible study population includes a maximum of 355 participants.

Patients with missing outcome data will be excluded from the primary analysis. However, if deemed infeasible based on power considerations, analyses will be conducted on an intention-to-treat basis where patients with missing data will be assumed to not have achieved the outcomes of interest.

Logistic regression will be used to assess the treatment effect on the outcome of interest. Univariate analyses will be conducted to identify associations between covariates and the outcome of interest, and any variables with a p-value  $< 0.05$  will be included in the multivariate model, if more than one predictor is found to be significant on univariate analysis.

Continuous variables will be presented as means (and standard deviations [SD] or as medians and interquartile ranges [IQR]), if the data is skewed. Binary variables will be presented as proportions or percentages. Descriptive statistics will be used to summarize baseline demographics, disease characteristics and outcome parameters of included patients. Differences between groups will be compared using the Mann-Whitney U test or chi-squared test. Data will be analyzed using Stata, which is available on the Vivli and YODA Project secure platform.

Software Used:

STATA

#### **Project Timeline:**

Date to start project: November 2021

Date to complete analysis: December 2021

Date to complete manuscript: January 2021

### **Dissemination Plan:**

Anticipated products include abstracts and posters, which may be presented at scientific meetings such as Canadian Digestive Diseases Week, Digestive Disease Week, and European Crohn's and Colitis Organization. A manuscript is expected to result from this study and will be submitted to peer-reviewed journals such as Gastroenterology, American Journal of Gastroenterology, and Clinical Gastroenterology and Hepatology. All products resulting from this research project, which may include abstracts, manuscripts, posters, and slide decks will be shared with Vivli and the YODA Project at least 30 days prior to the time of submission or public disclosure. Target audiences include clinicians and researchers with an interest in inflammatory bowel disease.

### **Bibliography:**

1. Danese S, Fiocchi C. Ulcerative colitis. *N Engl J Med* 2011;365:1713–1725.
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3. Feuerstein JD, Cheifetz AS. Crohn disease: epidemiology, diagnosis, and management. In *Mayo Clinic Proceedings* 2017 Jul 1 (Vol. 92, No. 7, pp. 1088-1103). Elsevier.
4. Jairath V, Zou GY, Parker CE, MacDonald JK, AlAmeel T, Al Beshir M, Almadi MA, AlTaweel T, Atkinson NS, Biswas S, Chapman T. Placebo response and remission rates in randomised trials of induction and maintenance therapy for ulcerative colitis. *Cochrane Database of Systematic Reviews*. 2017(9).

### **Supplementary Material:**

[https://yoda.yale.edu/sites/default/files/extended\\_research\\_protocol\\_for\\_yoda\\_1.docx](https://yoda.yale.edu/sites/default/files/extended_research_protocol_for_yoda_1.docx)