

## Principal Investigator

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## General Information

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**Are external grants or funds being used to support this research?:** External grants or funds are being used to support this research.

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**How did you learn about the YODA Project?:** Scientific Publication

## Conflict of Interest

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## 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. [NCT00487539 - C0524T17 - A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Subcutaneously, in Subjects with Moderately to Severely Active Ulcerative Colitis](#)
2. [NCT00771667 - C0743T26 - A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Ustekinumab Therapy in Subjects With Moderately to Severely Active Crohn's Disease Previously Treated With TNF Antagonist Therapy](#)
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](#)
7. [NCT00488774 - C0524T16 - A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Intravenously, in Subjects With Moderately to Severely Active Ulcerative Colitis](#)
8. [NCT02407236 - CNTO1275UCO3001 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis](#)

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

## Research Proposal

### Project Title

The Relationship between The Time to Achieve Clinical or Biomarker Remission and Long-term Outcomes in Inflammatory Bowel Disease

### Narrative Summary:

Inflammatory bowel disease (IBD), consist of Crohn's disease and ulcerative colitis, is a chronic inflammatory disease involved gastrointestinal tract. In IBD patients, achieving clinical or biomarker remission is associated with good prognosis and set as a short-term treatment target. However, some question still puzzles clinicians: When is the best time to assess this treatment target? Dose the time to achieve clinical or biomarker remission relate with long-term outcomes? To answer this question, we will perform a post hoc analysis and investigate the prognostic values of achieving clinical or biomarker remission in different time.

### **Scientific Abstract:**

**Background:** Inflammatory bowel disease (IBD), is a chronic inflammatory disease involved gastrointestinal tract. In IBD patients, achieving clinical and biomarker remission is associated with good prognosis and set as a short-term treatment target in the latest consensus.

**Objective:** This study aims at investigating the relationship between time to achieve clinical or biomarker remission and long-term outcome in IBD patients.

**Study Design:** This is a post hoc analysis including three clinical trials (UNITI, UNIFI and PURSUIT). Clinical remission was assessed by CDAI for CD or partial mayo score for UC. C-reactive protein and faecal calprotectin were used to assess biomarker remission. This study will analyse the predictive ability of clinical or biomarker remission at different time for long term outcome.

**Participants:** Patients who completed an induction study and participate in the maintenance study will be included.

**Main Outcome Measure(s):** The primary outcome is endoscopic remission at week 52. Secondary outcomes include endoscopic improvement, histological remission and clinical remission at week 52.

**Statistical Analysis:** Multivariate logistic regression will be used to assess the relationship between clinical or biomarker remission at different time and the likelihood of achieving endoscopic remission, endoscopic improvement or histological remission at week 52, after adjusting for confounders. Subgroup analyses by disease type (CD or UC), treatment allocation, disease activity at baseline and disease phenotype

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

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is a chronic and disable inflammatory disease involved gastrointestinal tract. (1) IBD patients have a remitting-relapsing disease course and will obtain a poor prognosis if they failure to achieve specific treatment targets, like mucosal healing, clinical remission and biomarker remission. (2) (3) Studies showed that achieving clinical or biomarker remission at week 6-22 after treatment is associated with good prognosis (4-8) . Furthermore, clinical and biomarker remission are recommended to be set as short-term treatment target in the latest consensus. (2) However, whether the time to achieving clinical or biomarker remission impact the long-term outcome is still unknow.

Therefore, it is still lacking evidence to determine the best time to assess clinical or biomarker remission for predicting long-term prognosis. To solve this problem, we will preform a post hoc analysis based on the data from UNITI trail(UNITI-1, UNITI-2 and IM-UNITI), UNIFI trail and PURSUIT (PURSUIT-SC, PURSUIT-IV and PURSUIT-M) trail. The primary objective of this study is to investigate the relationship between time to achieve clinical or biomarker remission and long-term outcome, such as endoscopic remission, histological remission and clinical remission, in IBD patients. Multivariate logistic regression will be used to assess the relationship between clinical or biomarker remission at different time and the likelihood of achieving endoscopic remission, endoscopic improvement or histological remission at week 52, after adjusting for confounders. Subgroup analyses by disease type (CD or UC), treatment allocation, disease activity at baseline and disease phenotype will be performed.

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

This study aims at investigating the relationship between time to achieve clinical or biomarker remission and long-term outcome, such as endoscopic remission, histological remission and clinical remission, in IBD patients. Moreover, we will also evaluate the prognostic value of time to achieve clinical or biomarker response for long-term outcome in IBD. The scientific hypothesis of this study is that achieving clinical or biomarker remission more early predicts a better long-term outcome.

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

Research on clinical prediction or risk prediction

## **Research Methods**

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

The source of the data will be from UNITI (UNITI-1, UNITI-2 and IM-UNITI), UNIFI and PURSUIT (PURSUIT-SC, PURSUIT-IV and PURSUIT-M). Patients who completed an induction study and participate in the maintenance study will be included.

**Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:**

The primary outcome is endoscopic remission at week 52. Endoscopic remission is a dichotomized variable and defined as Simple Endoscopic Score for Crohn's disease (SES-CD)  $\geq 2$  for CD or mayo endoscopic score  $< 2$  for UC. Secondary outcomes include endoscopic improvement, histological remission and clinical remission at week 52. All the secondary outcomes are dichotomized variables. Endoscopic improvement is defined as SES-CD or mayo endoscopic score reduce more than 50% from baseline. Histological remission will be assessed by available histologic scores, such as Geboes, Naini/Cortina, GHAS. Clinical remission is defined as CDAI less than 150 for CD or partial mayo score  $\geq 2$  and no subscore  $> 1$  on any of the four parameters for UC.

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

The main predictors of this study include clinical remission and biomarker remission at different time, including week 2, 4, 6, 8, 12, 14. Clinical remission is defined as CDAI less than 150 for CD or partial mayo score  $\geq 2$  and no subscore  $> 1$  on any of the four parameters for UC. Biomarker remission is assessed by CRP or faecal calprotectin (if available).

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

Other variables of interest include clinical response, biomarker response, improvement of clinical manifestation (evaluated by subscore of CDAI for CD or mayo score for UC), improvement of endoscopic activity or histological activity, disease activity at baseline, age, gender, treatment allocation, concomitant therapy, disease duration, disease location, disease behaviour, prior biologic exposure. Continuous variables and categorized variables will be described as median (interquartile range) and proportion (percentage), respectively.

**Statistical Analysis Plan:**

Continuous and categorical variables are described as median (interquartile range, IQR) and proportion (percentage), respectively. The Mann-Whitney test and  $\chi^2$  test were performed to evaluate the difference for continuous and categorical variables, respectively. A p-value less than 0.05 was considered as statistical significance. Univariate logistic analysis will be conducted to analyse the association of candidate predictors and outcomes. Multivariate logistic analysis will be performed on predictors with statistical significance in univariate analysis and potential confounders (like disease duration, treatment allocation). Furthermore, we will perform subgroup analyses by disease type (CD or UC), treatment allocation, disease activity at baseline disease phenotype. Missing value for major outcome will be excluded from statistical analysis. Missing values for other variables will be imputed by simple imputation, using the mice package in R.

Software Used:

RStudio

**Project Timeline:**

Start date - October 2022

Analysis completion date - January 2023

Manuscript draft - March 2023

Submitted for publication - May 2023

**Dissemination Plan:**

The products of this project will be submitted to scientific conference, such as Digestive Disease Week, European Crohn's and Colitis Organization and Asian Crohn's and Colitis Organization. A manuscript will also be submitted for publication in peer-reviewed journals. The acknowledgement for YODA Project will be presented in all products of this study.

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