

## Principal Investigator

**First Name:** Adam  
**Last Name:** Cheifetz  
**Degree:** MD  
**Primary Affiliation:** Beth Israel Deaconess Medical Center  
**E-mail:** [acheifet@bidmc.harvard.edu](mailto:acheifet@bidmc.harvard.edu)  
**Phone number:** (617) 667-2135  
**Address:** 330 Brookline Ave

**City:** Boston  
**State or Province:** MA  
**Zip or Postal Code:** 02215  
**Country:** United States

## General Information

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

**First Name:** Konstantinos  
**Last name:** Papamichail  
**Degree:** MD, PhD  
**Primary Affiliation:** Beth Israel Deaconess Medical Center

**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?:** Internet Search

## Conflict of Interest

[https://yoda.yale.edu/system/files/yoda\\_project\\_coi\\_form\\_for\\_data\\_requestors\\_2019\\_asc.pdf](https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_asc.pdf)

[https://yoda.yale.edu/system/files/yoda\\_project\\_coi\\_form\\_for\\_data\\_requestors\\_2019\\_kp.pdf](https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_kp.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

### Associated Trial(s):

1. [NCT00771667 - 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 T](#)
2. [NCT01369329 - 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](#)
3. [NCT01369342 - 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 \(UNITI-2\)](#)

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

---

## Research Proposal

### Project Title

Defining a therapeutic drug window following induction ustekinumab therapy in patients with active fistulizing Crohn's disease.

### Narrative Summary:

Two pivotal randomized-controlled trials clearly showed superior clinical response/remission rates after induction ustekinumab treatment compared to placebo in patients with Crohn's disease (CD). Serum ustekinumab concentrations have been related to favorable therapeutic outcomes, such as clinical, biochemical and endoscopic response. Nevertheless, there are limited data on the therapeutic window and role of therapeutic drug monitoring (TDM) in fistula healing. The aim of the study is to investigate the association between serum ustekinumab concentrations and fistula healing in patients with active fistulizing CD.

### Scientific Abstract:

**Background:** Ustekinumab is an effective therapy for Crohn's disease (CD). Recent exposure-response relationship studies have revealed a positive correlation between high serum ustekinumab concentration and favorable therapeutic outcomes, although there are no data regarding fistulizing CD.

**Objective:** To define the therapeutic window for adequate serum ustekinumab concentration associated with fistula healing following induction therapy in patients with active fistulizing CD.

**Study Design:** Post-hoc analysis of the CERTIFI, UNITI-1 and UNITI-2 randomized controlled trials.

**Participants:** Patients with active fistulizing CD who were assessed for a fistula response following ustekinumab induction therapy and had a TDM (n=150).

**Main outcome measure(s):** Association between ustekinumab concentration at week 8 with complete fistula resolution and primary non-response at week 8.

**Statistical Analysis:** Descriptive statistics will be provided with medians and interquartile range for continuous variables and frequency and percentage for categorical variables. A receiver operating characteristic analysis will be performed for infliximab concentrations to trace thresholds associated with outcomes of interest. Ustekinumab concentrations will be compared between groups with the Mann-Whitney U and Kruskal Wallis test, as appropriate. Univariate and multivariate analyses will be performed to identify variables associated with outcomes of interest.

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

Fistulas can develop in up to 50% of patients with Crohn's disease (CD), with perianal fistulas being the most common.<sup>1</sup> The cornerstone of pharmacological treatment for fistulizing CD is anti-tumor necrosis factor (anti-TNF) therapy<sup>2</sup>, although ustekinumab, an interleukin 12/23 p40 inhibitor, may also be a valid treatment option.<sup>3-5</sup> Recent studies have revealed an exposure-response relationship suggesting a positive correlation between high serum ustekinumab concentration and favorable therapeutic outcomes in CD including clinical, biochemical, and endoscopic remission.<sup>6-8</sup> Nevertheless, there are no data on the therapeutic window and role of therapeutic drug monitoring (TDM) of ustekinumab in fistula healing. As pharmacological treatment options in patients with fistulizing CD remain limited, emphasis has to be given to rational decision-making and optimization of therapies utilizing a TDM-based therapeutic approach. This project by defining the adequate drug concentration for better therapeutic outcomes can be the first step for the application of reactive and proactive TDM towards a more personalized ustekinumab therapy in patients with fistulizing CD. This could potentially improve care and reduce the substantial social and economic burden to the community by preventing future CD-related hospitalizations and surgeries.

### Specific Aims of the Project:

#### Specific Aim 1:

To investigate the association between serum ustekinumab concentration at week 8 with complete fistula resolution at week 8.

**Specific Aim 2:**

To investigate the association between serum ustekinumab concentration at week 8 with primary non-response at week 8.

**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:**

Post-hoc analysis of the randomized controlled trials CERTIFI (A Study of Safety and Effectiveness of Ustekinumab in Patients With Moderate to Severe Active Crohn's Disease Who Have Been Previously Treated With Anti-TNF Therapy) (RCT) and UNITI (A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Patients with Moderately to-Severely Active Crohn's Disease) composed of two identical induction studies (UNITI-1, including patients with primary nonresponse, secondary loss of response, or unacceptable adverse events to previous anti-TNF therapy, and UNITI-2, including patients who had failure or unacceptable adverse events to conventional therapy with immunomodulators or corticosteroids) regarding only the patients who received induction ustekinumab (active drug) therapy and had active fistulizing CD and both TDM and an evaluation of fistulas at week 8 (n=150).<sup>5</sup> These patients had their fistulas assessed by physical exam (including gentle compression).

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

• Main outcome measures of interest include:

1. Complete fistula resolution, defined as 100% reduction in draining fistulas at week 8.
2. Primary non-response, defined as lack of at least 50% reduction from baseline in the number of draining fistulas at week 8.

• Secondary outcome measures of interest include:

1. Clinical remission, defined as a CD Activity Index (CDAI) score of  $\leq 150$ , at week 8.
2. C-reactive protein (CRP) normalization at week 8 in patients with an elevated CRP ( $>5$  mg/L) at week 0.
3. Composite remission, defined as both complete fistula resolution and clinical remission at week 8.

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

Main predictor/independent variables associated with outcomes of interest include:

- Serum ustekinumab concentrations at week 8 associated with outcomes of interest.

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

Other variables associated with outcomes of interest include:

- gender
- age
- disease duration
- CDAI at baseline
- CRP at baseline
- concomitant immunomodulators (thiopurines / methotrexate) at baseline
- previous anti-TNF therapy

**Statistical Analysis Plan:**

Descriptive statistics will be provided with medians and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables. A receiver operating characteristic (ROC) analysis will be performed for ustekinumab concentrations to trace thresholds associated with outcomes of interest. Optimal thresholds will be chosen by using the Youden index, which maximizes the sum of the specificity (SP) and sensitivity (SN) of the ROC curve. SN, SP, positive predictive value, and negative predictive value will be also calculated. Ustekinumab concentrations at week 8 will be compared between groups with the Mann-Whitney U test.

Serum ustekinumab concentrations will be categorized also into quartiles. Rates of complete fistula resolution and primary non-response and as well as other (secondary) outcome measures of interest at week 8 will be compared across ustekinumab serum concentration quartiles with the chi-square test (linear-by-linear association). The Kruskal-Wallis and the chi-square test will be used to compare continuous or discrete variables, respectively, across quartile groups. Univariate and multivariate logistic regression analyses will be performed to identify variables independently associated with outcomes of interest. The results will be expressed as odds ratio (OR) with 95% confidence intervals, followed by the corresponding P-value. Results will be considered statistically significant when  $P < 0.05$ .

### **Project Timeline:**

It is estimated that it will take 5-6 months to review the appropriate data. Statistical analyses will take another 2-3 months, while manuscript preparation will take approximately another 2-3 months. Consequently, the whole project will be completed in 9-12 months.

### **Dissemination Plan:**

Presentation of the results to national and international medical congresses including Digestive Disease Week (DDW), Advances in IBD (AIBD), American College of Gastroenterology (ACG), European Crohn's and Colitis Organization (ECCO) and publication of the data in a high impact medical journal such as the American Journal of Gastroenterology, Clinical Gastroenterology and Hepatology, or the Journal of Crohn's and Colitis.

### **Bibliography:**

1. Gecse KB, Sebastian S, Hertogh G, et al. Results of the Fifth Scientific Workshop of the ECCO [II]: Clinical Aspects of Perianal Fistulising Crohn's Disease-the Unmet Needs. *J Crohns Colitis* 2016;10(7):758-65.
2. Yassin NA, Askari A, Warusavitarne J, et al. Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease. *Aliment Pharmacol Ther* 2014;40(7):741-9
3. Sandborn WJ, Gasink C, Gao LL et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012;367:1519–28.
4. Feagan BG, Sandborn WJ, Gasink C et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2016;375:1946–60.
5. Sands BE, Gasink C, Jacobstein D, et al. Fistula healing in pivotal studies of ustekinumab in Crohn's disease. 2017;152(5, Supplement 10):S185.
6. Adedokun OJ, Xu Z, Gasink C, et al. Pharmacokinetics and exposure response relationships of ustekinumab in patients with Crohn's disease. *Gastroenterology*.;154:1660-71.
7. Battat R, Kopylov U, Bessissow T, et al. Association between ustekinumab trough concentrations and clinical, biomarker, and endoscopic outcomes in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2017;15:1427-1434.
8. Verstockt B, Dreesen E, Noman M, et al. Ustekinumab exposure-outcome analysis in Crohn's disease only in part explains limited endoscopic remission rates. *J Crohns Colitis*. 2019 Jan 30. doi: 10.1093/ecco-jcc/jjz008. [Epub ahead of print]