**Narrative Summary:**

Ulcerative colitis (UC) is an inflammatory bowel disease that affects the large intestine and is characterized by diarrhea, rectal bleeding, abdominal pain, urgency, and tenesmus (Tenesmus is the feeling of incomplete evacuation of stool). (1,2) Patients with severe UC and/or corticosteroid-refractory disease are candidates for biologic monoclonal antibody treatments.

Vedolizumab and infliximab are two biologic therapies that have demonstrated efficacy in achieving and maintaining remission through several pivotal placebo-controlled trials, including ACT 1 (NCT00036439), ACT 2 (NCT00096655), and GEMINI 1 (NCT00783718). (3,4) Recently, the VARSITY trial used an active-comparator approach to demonstrate the superiority of vedolizumab to adalimumab among patients with moderate to severe UC.(5) However, network meta-analyses have suggested superiority of infliximab over adalimumab as a first-line biologic treatment in UC patients.(6) There are no head-to-head trials comparing vedolizumab and infliximab.

Given the routine use of vedolizumab and infliximab as a treatment for UC, head-to-head comparisons are needed to better understand the positioning of vedolizumab as a treatment for biologic-naïve UC patients.

The Mayo Score is a tool that is used to determine UC disease activity and is comprised of four patient-reported and endoscopic parameters: stool frequency, rectal bleeding, endoscopic findings, and physician's global assessment. Each parameter is scored from 0 to 3, with higher scores indicating greater disease severity. The total Mayo Score ranges from 0 to 12, while the partial Mayo Score excludes the endoscopic subscore and thus ranges from 0 to 9. (6) While Mayo Scores have been widely used in clinical trials for UC as primary endpoints, mucosal healing (determined by endoscopy) remains an important target of treatment as well.

The primary objective of this study is to compare the efficacy of vedolizumab and infliximab to achieve post-induction (week 6) clinical remission and one year mucosal healing as determined by the Mayo Score. The secondary objectives of this study include clinical remission at one year, mucosal healing at post-induction (week 6). Additionally, clinical response, reduction in markers of disease activity (e.g. fecal calprotectin, C-reactive protein), and reduction in histologic measures of disease activity at post-induction (week 6) and one year will be analyzed.

Data from GEMINI 1 and VARSITY, which is being requested from Vivli, will be pooled to obtain a cohort of biologic-naïve UC patients treated with vedolizumab. Biologic-naïve patients treated with infliximab in ACT 1 and ACT 2 which is being requested from the Yale University Open Data Access (YODA) Project, will be pooled to comprise the infliximab cohort.
Main Outcome Measure and how it will be categorized/defined for your study:

The primary outcome of interest is clinical remission at post-induction (week 6), defined as partial Mayo Score < 2 and rectal bleeding subscore of 0, and mucosal healing at one year, defined as endoscopic subscore ≤ 1 on the Mayo Score.

Secondary outcomes of interest include clinical remission at week 52 (defined as total Mayo Score ≤ 2 and no subscore > 1 on any of the four parameters), clinical response (defined as partial Mayo Score reduction (i.e. stool frequency, rectal bleeding, and physician’s global assessment) of ≥2 and ≥25% from baseline, with a decrease in rectal bleeding subscore of ≥1). Alternative definitions of clinical response may be used in sensitivity analyses, including reduction in total Mayo Score ≥3 and ≥30% from baseline, with a minimum reduction in rectal bleeding subscore of 1 point or absolute rectal bleeding subscore ≤ 1.

Histologic improvement is defined as Robarts Histopathology Index score <5 and/or Geboes score <3.2. Alternative definitions of histologic improvement may be used in sensitivity analyses. Reduction in fecal calprotectin and/or C-reactive protein may be assessed in exploratory analyses and correlated with other objective measures of disease, such as endoscopic or histologic findings. Evaluation of these secondary outcomes will depend on adequate data availability at these time points.