CLINICAL STUDY PROTOCOL

RCT01374

Placebo Rates in Inflammatory Bowel Disease: An Individual Patient Data Meta-analysis of Randomized Controlled Trials

Protocol Version 01
September 29, 2020

Sponsor: Alimentiv Inc.
100 Dundas Street, Suite 200
London, ON
Canada N6A 5B6

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PROTOCOL APPROVAL PAGE

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Dr. Vipul Jairath, MD PhD
Vice President, Medical Research & Development, Alimentiv Inc.

GY Zou, PhD
Biostatistician Director, Alimentiv Inc.

Sigrid Nelson, MSc
Manager, Scientific Writing, Alimentiv Inc.

Date

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<td>6-mercaptopurine</td>
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<td>AE</td>
<td>adverse event</td>
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<td>AP</td>
<td>abdominal pain</td>
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<td>AZA</td>
<td>azathioprine</td>
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<td>CD</td>
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<td>CI</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>Global Histologic Disease Activity Score</td>
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<td>HRQOL</td>
<td>health-related quality of life</td>
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<td>IBD</td>
<td>inflammatory bowel disease</td>
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<td>IBDQ</td>
<td>Inflammatory Bowel Disease Questionnaire</td>
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<td>ICH</td>
<td>International Council for Harmonisation</td>
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<td>IEC</td>
<td>independent ethics committee</td>
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<td>IQR</td>
<td>interquartile range</td>
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<tr>
<td>IPD</td>
<td>individual participant (or patient) data</td>
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<td>IRB</td>
<td>institutional review board</td>
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<td>JAK</td>
<td>Janus kinase</td>
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<td>Mayo Clinic Score</td>
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<td>methotrexate</td>
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<td>PRO2</td>
<td>2-item patient-reported outcome</td>
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<td>RB</td>
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<td>S1PR</td>
<td>sphingosine 1-phosphate receptor</td>
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<td>SAE</td>
<td>serious adverse event</td>
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<td>SAP</td>
<td>statistical analysis plan</td>
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<td>SD</td>
<td>standard deviation</td>
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<td>SES-CD</td>
<td>Simple Endoscopic Score for Crohn’s Disease</td>
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<tr>
<td>SF</td>
<td>stool frequency</td>
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<tr>
<td>STAT</td>
<td>signal transducers and activators of transcription</td>
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<td>TNF</td>
<td>tumor necrosis factor</td>
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<td>-------</td>
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<tr>
<td>UC</td>
<td>ulcerative colitis</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
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1 INTRODUCTION

The placebo response in clinical trials is a complex phenomenon that is influenced by multiple factors including the type of intervention, the method and frequency of treatment, response expectancy, patient-provider interactions, behavioral conditioning, and the clinical context.\(^1\text{-}^3\) Understanding the factors associated with the placebo response in inflammatory bowel disease (IBD) trials is crucial for designing efficient clinical trials and interpretation of trial results.

Factors affecting the placebo response include natural variation in underlying disease, regression toward the mean, and the “true” placebo effect which is likely attributable to interrelated environmental and psychosocial factors.\(^3\) In clinical trials, these factors include patient expectations of treatment benefits, the response to observation and assessment (Hawthorne effect), the response to administration of a therapeutic ritual, the patient-physician relationship, and intrinsic features of trial design. In addition to clinical characteristics, evaluation of the baseline molecular profile (e.g. through ribonucleic acid (RNA) and/or protein levels) may help further our understanding of factors influencing placebo response.

We have published systematic reviews and meta-analyses for Crohn’s disease (CD) and ulcerative colitis (UC) randomized controlled trials (RCTs) and determined the pooled placebo clinical remission and response rates, as well as the factors influencing them. In 67 CD induction trials, the pooled placebo remission and response rates were 18% (95% confidence interval [CI]: 16-21%) and 28% (95% CI: 24-32%), respectively.\(^4\) The corresponding rates for 40 maintenance trials were 32% (95% CI: 25-39%) and 26% (95% CI: 19-35%), respectively. In UC, the pooled placebo remission and response rates for 58 induction trials were 12% (95% CI: 9-15%) and 33% (95% CI: 30-36%), respectively and 17% (95% CI: 10-27%) and 23% (95% CI: 19-28%) for 12 maintenance trials, respectively.\(^3\) More recently, we reported the pooled endoscopic placebo rates based on patient-level data from 5 CD induction trials using central endoscopy reading and found the pooled response rate to be 16.2% (95% CI, 10.5-22.0) and the rate of remission to be 5.2% (95% CI, 1.7-8.8%).\(^5\) Prior exposure to tumor necrosis factor (TNF) antagonists (odds ratio, 0.31; 95% CI, 0.10–0.93; \(P = .036\)) was independently associated with lower placebo response rates.

In these aforementioned meta-analyses, we also assessed disease- and trial-related covariates influencing placebo clinical remission and response rates. In CD, maintenance studies enrolling subjects with lower Crohn’s Disease Activity Index (CDAI) scores were associated with higher placebo remission rates, but lower response rates.\(^4\) Induction studies with more follow-up visits and of longer duration were associated with higher placebo remission rates, whereas trials enrolling patients with less severe disease activity and longer study duration were associated with lower placebo response rates. In UC induction trials, less stringent endoscopic disease activity criterion for trial eligibility was associated with higher placebo remission and response rates.\(^3\) Trials with a minimum rectal bleeding (RB) subscore and subjects with a disease duration ≤ 5 years were associated with higher placebo response rates. For trial-related covariates, only the time-point of primary endpoint assessment for the induction period was found to be associated with placebo remission rates.

Although the systematic reviews and meta-analyses identified some key trial- and disease-related characteristics associated with placebo clinical response and remission rates which may help inform clinical trial design, the major limitation to these analyses is the lack of individual subject-level data. Access to subject-level data from the placebo arms of multiple UC and CD trials would allow a rigorous assessment of placebo rates and subject-level factors associated with the placebo response.
response. In addition, placebo rates in important groups of patients relevant to modern day clinical trials can be assessed, such as rates in patients without exposure to biologics versus those with prior exposure, those receiving concomitant steroids at baseline or not, within different trial periods, from different geographical locations, by baseline disease severity, and by levels of specific proteins and/or RNA. We believe a centralized data repository of individual participant or patient data (IPD) of thousands of subjects within placebo arms will be a major initiative to the field of drug development for IBD.

1.1 RATIONALE FOR STUDY

Determining the subject- and trial-level factors that influence placebo response, non-response, and hyper-response in IBD clinical trials may help to inform the design and efficiency of future clinical trials in UC and CD. This will be accomplished by collecting anonymized IPD from placebo arms of RCTs published within the past 10 years, as these trials were most likely designed to meet recent contemporary regulatory guidelines (e.g. use of centralized endoscopy), performed more extensive outcome analyses (e.g., patient-reported, histological, and biochemical analyses), and enrolled subjects more closely resembling the current IBD population (e.g., subjects with previous exposure to biologics).

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to estimate the placebo clinical response and remission rates in induction and maintenance periods of CD and UC trials and identify factors influencing these rates.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to:

1. Estimate the response and remission rates (including endoscopic, histologic, and clinical-based definitions) in induction and maintenance periods of CD and UC trials and identify factors influencing these rates

2. Assess the primary objective and secondary objective 1 in TNF antagonist-naïve and TNF antagonist-exposed subjects

3. Assess the primary objective and secondary objective 1 according to the number of biologics previously exposed to, and class of biologic

4. Determine factors associated with placebo hyper-response in induction and maintenance periods of CD and UC trials

5. Estimate the adverse event (AE) and serious adverse event (SAE) rates in induction and maintenance periods of CD and UC trials and identify factors influencing the rates and severity

2.3 EXPLORATORY OBJECTIVES

Exploratory objectives of this study are to determine:

1. The molecular profile (protein and/or RNA levels) predicting placebo response in subjects with available molecular data.
2. The impact of central reading and adjudication models on placebo rates, if these data are available.

Additional exploratory analyses may be established during the review of study results.

3 STUDY DESIGN

This study is an IPD meta-analysis to investigate factors affecting placebo rates in IBD RCTs while minimizing bias arising from the heterogeneity of analyzing protocols between trials. IPD will be obtained for subjects randomized to the placebo group in published phase 2 and 3 induction and maintenance RCTs evaluating the safety and efficacy of biologics and small molecule drugs in moderately to severely active CD and UC. Studies were identified by systematic review of all phase 2 and phase 3 trials from the last 10 years (2010-present). IPD (e.g., baseline demographic, disease, and clinical characteristics, concomitant medications, previous exposure to biologics, molecular profile) will be obtained and subject, disease, clinical, and trial characteristics that may be associated with a placebo response in clinical and endoscopic disease activity will be identified for induction and maintenance trials. After this repository is established, the repository will be continually updated on an intermittent basis as eligible trials are published.

3.1 SEARCH CRITERIA

A search of MEDLINE (1948-January 2020), EMBASE (1947-January 2020), the Cochrane Central Register of Controlled Trials (2020), and the Cochrane IBD/Functional Bowel Disorders review group specialized trials register was performed without language restriction from inception to January 2020 for all published induction and maintenance RCTs in CD and UC. Published trials were reviewed to identify all RCTs published since 2010, evaluating the safety and efficacy of biologics or small molecule drugs for moderately to severely active CD and UC.

3.2 TRIAL DATASETS TO BE USED IN THIS ANALYSIS

Data will be extracted from the RCTs identified by our search. See Appendix A for a list of identified RCTs. All sponsors will first be sent an introductory letter about the study and to ascertain their interest in providing data for this study. Sponsors who express an interest in participating will be approached with a data sharing agreement to seek use of anonymized data, with a request for a core set of trial-level and subject-level data (Section 4.1). Some data may be extracted from the study protocol.

4 STUDY PROCEDURES

Data and units of measure (where applicable) will be extracted from the trial databases described in Appendix A. No personally identifiable information will be extracted. All study data will have already been deidentified and coded by unique patient identifier numbers during the conduct of the original trial. Deidentified data obtained from sponsors will be pooled for analysis. In addition, the original study protocol (Version 1), annotated case report form, and data dictionary will be obtained for each trial, if possible, to aid in interpreting the data.

Data will ONLY be extracted from UC trials that used the modified definition of “no friability” for the Mayo Clinic Score (MCS) endoscopic subscore (MES) = 1 as recommended by the United States Food and Drug Administration (US FDA).
4.1 DATA COLLECTION

Information to be extracted from the trial databases include:

4.1.1 TRIAL-RELATED INFORMATION

1. Trial start date (date first subject enrolled)
2. Design (induction only, induction and maintenance [2-arm parallel group, multi-arm parallel group, crossover, factorial, cluster, other])
3. Stratification factors and their definition, if stratified randomization was used
4. Number of treatment arms (including placebo)
5. Trial phase
6. Location (single centre, multicentre [single country], multicentre [international])
7. Number of centres in trial
8. Route of administration
9. Total number of randomized subjects
10. Randomization ratio
11. Total number of subjects randomized to placebo arm
12. Number of subjects randomized (total and per intervention group)
13. Blinding (single, double, unblinded)
14. Number of screening visits
15. Minimum disease activity score for study inclusion
16. Minimum endoscopic disease activity for study inclusion? (yes/no) If yes, what was the minimum score?
17. Centrally read endoscopy at baseline? (yes/no)
18. Reading paradigm employed at baseline (1 central reader, 1 local + 1 central reader, 2 central readers, other) and strategy to resolve scoring disagreements (second independent central reader, forced adjudication, average score, other), if available
19. Minimum RB subscore for trial inclusion? (yes/no) If yes, what was the minimum score? (UC trials)
20. Minimum abdominal pain (AP) subscore for trial inclusion? (yes/no) If yes, what was the minimum score? (CD trials)
21. Minimum stool frequency (SF) subscore for trial inclusion? (yes/no) If yes, what was the minimum score? (CD trials)
22. Histologic confirmation of disease for trial entry? (yes/no)
23. Other essential eligibility criteria? (explain)
24. Time point of primary outcome evaluation (for induction and maintenance treatment, if applicable) (weeks)
25. Total number of follow-up visits (from baseline to end of induction treatment and maintenance treatment, if applicable)
26. Frequency of follow-up visits (e.g., every 4 weeks, etc)
27. Endoscopic findings included in primary outcome? (yes/no)
28. Centrally read endoscopic disease activity at endpoint? (yes/no)
29. Reading paradigm employed at endpoint (1 central reader, 1 local + 1 central reader, 2 central readers, other) and strategy to resolve scoring disagreements (second independent central reader, forced adjudication, average score, other), if available
30. Histology included as outcome measure? (yes/no)
31. Central reading of histologic disease activity? (yes/no)
32. Trial end date (date of last study visit for last subject)

4.1.1.1 Permitted Medications at Baseline
1. 5-aminosalicylic acid (5-ASA) drugs permitted at trial entry? (yes/no)
2. Calcineurin inhibitor treatment (e.g., cyclosporine, tacrolimus) permitted at trial entry? (yes/no)
3. 6-mercaptopurine (6-MP) permitted at trial entry? (yes/no)
4. Azathioprine (AZA) permitted at trial entry? (yes/no)
5. Methotrexate (MTX) permitted at trial entry? (yes/no)
6. Oral corticosteroids permitted at trial entry? (yes/no)
   • Maximum permitted dose (describe dosing regimen, if applicable)
7. Required tapering of corticosteroids during the trial? (yes/no) If yes,
   • When was tapering started (week)
   • Recommended tapering regimen? (yes/no) If yes, describe regimen
   • When was tapering to be completed (week)
   • Re-escalation of corticosteroids permitted during the trial? (yes/no) If yes, to what dose?
   • Corticosteroid cessation required for primary endpoint (i.e., corticosteroid-free disease remission)

4.1.2 SITE-RELATED INFORMATION
1. Location (country)
2. Investigative site type (private practice, hospital, academic centre, etc)
4.1.3 Subject Characteristics (CD and UC)

The following individual subject data will be extracted from the trial database for subjects with CD and UC, if available:

1. Age at enrollment
2. Gender
3. Body mass index (BMI)
4. Ethnicity
5. Date of birth (month/year)
6. Age at diagnosis/year of diagnosis
7. Disease duration at baseline (months)
8. Prior surgery for IBD? (yes/no)
9. Smoking (previous, current)
10. Endoscopy score/subscore at enrolment
11. Molecular profile
   - RNA and protein data from colonic biopsies (including location of biopsy and disease activity score for biopsy location [i.e., MES, Global Histologic Disease Activity Score [GHAS], etc])
   - RNA and protein data from blood

4.1.4 Subject Characteristics (CD Only)

The following individual subject data will be extracted from the trial database for subjects with CD, if available:

1. Disease location based on Montreal criteria\(^{12}\) at diagnosis (e.g., ileal, colonic, ileocolonic, or isolated upper disease)
2. Disease behavior based on Montreal criteria\(^{12}\) at diagnosis (e.g., non-stricturing/penetrating, stricturing, or penetrating)
3. Perianal fistula/abscess
   - Prior history of perianal fistula/abscess? (yes/no)
   - Perianal fistula/abscess at baseline? (yes/no)

4.1.5 Subject Characteristics (UC Only)

The following individual subject data will be extracted from the trial database for subjects with UC, if available:

1. Disease extent based on Montreal criteria\(^{12}\) at diagnosis (e.g., proctitis, left-sided UC, or extensive UC)
4.1.6 **CONCOMITANT TREATMENTS (CD AND UC)**

The following data will be extracted from the trial database for subjects with CD and UC, if available:

1. Concomitant 5-ASA drugs at baseline? (yes/no)
2. Concomitant calcineurin inhibitor (e.g., cyclosporine, tacrolimus) at baseline? (yes/no)
3. Concomitant 6-MP at baseline? (yes/no)
4. Concomitant AZA at baseline? (yes/no)
5. Concomitant MTX at baseline? (yes/no)
6. Concomitant oral corticosteroid at baseline? (yes/no) If yes, dose?

4.1.7 **PREVIOUS MEDICAL TREATMENTS (CD AND UC)**

The following data will be extracted from the trial database for subjects with CD and UC, if available:

1. Previous exposure to a biologic? (yes/no) If yes,
   - How many different biologics (approved or experimental monoclonal antibody, antisense oligonucleotide, or other therapy)? List the class and name of each biologic (e.g., anti-TNF, anti-interleukin, anti-cell adhesion molecule, etc)
2. Previous failure/intolerance to a biologic? (yes/no) If yes,
   - How many different biologics (approved or experimental monoclonal antibody, antisense oligonucleotide, or other therapy)? List the class and name of each biologic (e.g., anti-TNF, anti-interleukin, anti-cell adhesion molecule, etc)
3. Previous exposure to a oral small molecule drug? (yes/no) If yes,
   - How many different oral small molecule drugs? List the class and name of each small molecule drug (e.g., Janus kinase/signal transducers and activators of transcription [JAK/STAT] inhibitors, phosphodiesterase 4 [PDE4] inhibitors, sphingosine 1-phosphate receptor [S1PR] modulators, etc)
4. Previous failure/intolerance to a oral small molecule drug? (yes/no) If yes,
   - How many different small molecule drugs? List the class and name of each small molecule drug (e.g., JAK/STAT inhibitors, PDE4 inhibitors, S1PR modulators, etc)
5. 5-ASA drug treatment? (yes/no)
6. Calcineurin inhibitor treatment (e.g., cyclosporine, tacrolimus)? (yes/no)
7. 6-MP treatment? (yes/no)
8. AZA treatment? (yes/no)
9. MTX treatment? (yes/no)
10. Oral corticosteroid treatment? (yes/no)
4.1.8 **DISEASE ACTIVITY AT BASELINE (CD AND UC)**

The following data will be extracted from the trial database for subjects with CD and UC, if available:

1. Albumin level (including units of measure)
2. C-reactive protein (CRP) level (including units of measure)
3. Fecal calprotectin (FCP) level (including units of measure)
4. Fecal lactoferrin level (including units of measure)
5. Health-related quality of life score (HRQOL) (e.g., Inflammatory Bowel Disease Questionnaire [IBDQ], 32-item Crohn’s and Ulcerative Colitis Questionnaire [CUCQ-32], other [describe index used])

4.1.9 **DISEASE ACTIVITY AT BASELINE (CD ONLY)**

The following individual CD subject data will be extracted from the baseline visit, if available:

1. Clinical disease activity as assessed by the CDAI score (with individual diary components to allow calculation of 2-item patient-reported outcome [PRO2] score, if possible)
2. Endoscopic disease activity as assessed by the Simple Endoscopic Score for CD (SES-CD) or Crohn’s Disease Endoscopic Index of Severity (CDEIS) (both local and central reader scores will be extracted where applicable). Overall score and full breakdown per component and segment.
3. Histologic disease activity as assessed by the GHAS (ileal, colonic, and total GHAS, if available) (both local and central reader scores will be extracted where applicable)

4.1.10 **DISEASE ACTIVITY AT BASELINE (UC ONLY)**

The following individual UC subject data will be extracted from the baseline visit, if available:

1. Disease activity as assessed by the MCS, with scores for each of the individual subscores. MCS scores will ONLY be extracted from trials that used the modified definition of “no friability” for the MES = 1 as recommended by the US FDA (both local and central reader scores will be extracted where applicable)
2. Histologic disease activity as assessed by the Geboes Score, with subscores for individual histological items, if available (both local and central reader scores will be extracted if applicable)

4.1.11 **DISEASE ACTIVITY AT END OF TREATMENT (CD AND UC)**

Raw data for end of treatment visits will be collected, as opposed to scores derived by imputation methods (e.g., last observation carried forward, etc). If an imputation method was used to determine the end of treatment score for a subject, the subject should be flagged in the database.

The following data will be extracted from the trial database (separately for induction and maintenance periods) for subjects with CD and UC, if available:

1. Timepoint of primary endpoint (weeks)
2. Date of visit
3. Albumin level (including units of measure)
4. CRP level (including units of measure)
5. FCP level (including units of measure)
6. Fecal lactoferrin level (including units of measure)
7. HRQOL score (e.g., IBDQ, CUCQ-32, other [describe index used])
8. Frequency and severity of AEs and SAEs, by preferred term
9. Molecular profile
   • RNA and protein data from colonic biopsies (including location and disease activity score for the biopsy location [i.e., MES, GHAS, etc])
   • RNA and protein data from blood

4.1.12 DISEASE ACTIVITY AT END OF TREATMENT (CD ONLY)
The following individual CD subject data will be extracted from the primary endpoint visit (separately for induction and maintenance periods), if available:
   1. Clinical disease activity as assessed by the CDAI (with individual diary components to allow calculation of the PRO2 score, if possible)
   2. Endoscopic disease activity as assessed by the SES-CD or CDEIS (both local and central reader scores will be extracted where applicable). Overall score and full breakdown per component and segment.
   3. Histologic disease activity as assessed by the GHAS (ileal, colonic and total GHAS, if available) (both local and central reader scores will be extracted if applicable)

4.1.13 DISEASE ACTIVITY AT END OF TREATMENT (UC ONLY)
The following individual UC subject data will be extracted from the primary endpoint visit (induction and maintenance periods), if available:
   1. Disease activity as assessed by the MCS with scores for each of the individual subscores (both local and central reader scores will be extracted where applicable)
   2. Histologic disease activity as assessed by the Geboes Score, with subscores for the individual histological items, if available (both local and central reader scores will be extracted if applicable)

5 ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING
As this is a retrospective study based on existing data, safety reporting is not applicable for this study.

6 STATISTICAL METHODS
A full statistical analysis plan (SAP) will be developed for this study that will provide an in-depth overview of the planned statistical analyses described in the following sections.
Minor changes to the analysis plan will be provided in the SAP and not in the protocol.
6.1 BASELINE DEMOGRAPHIC INFORMATION

An overview of the data that will be extracted from the clinical trial databases for trial subjects who had both baseline and primary endpoint visit clinical disease activity assessments (induction and maintenance) and received placebo treatment is provided in Section 3.2.

Descriptive statistics will be used to report demographic information for CD and UC trials, including age and endoscopy score at enrollment (mean, standard deviation [SD], median, interquartile range [IQR]), gender, BMI, ethnicity, smoking status, disease duration (median, IQR), prior surgery for IBD (% of subjects), prior exposure to biologics (% of subjects), prior exposure to anti-TNFs (% of subjects), prior exposure to small molecule drugs (% of subjects), prior failure/intolerance to biologics (% of subjects), prior failure/intolerance to anti-TNFs (% of subjects), prior failure/intolerance to small molecule drugs (% of subjects), concomitant 5-ASA drugs (% of subjects), concomitant calcineurin inhibitors (% of subjects), concomitant immunomodulators (% of subjects), and concomitant corticosteroids (% of subjects). The disease location (% of subjects with ileal, colonic, or ileocolonic) and behavior (% of subjects with inflammatory, stricturing, or fistulizing disease), and active fistula (% of subjects) for CD trials and disease extent (ulcerative proctitis, left-sided UC, or extensive UC) for UC trials, based upon the Montreal classification, will also be reported.

6.2 DISEASE ACTIVITY MEASURES

The following will be reported for the baseline (Week 0) and primary endpoint assessment visits for both induction and maintenance periods:

6.2.1 CD TRIALS

1. CDAI (mean, SD, median, IQR)
2. Each subcomponent of the CDAI, if available
3. Change in the total CDAI from baseline and change in each component of the CDAI
4. PRO2, if SF and AP subscores of the CDAI are available (median, IQR)
5. Change in PRO2 scores
6. Albumin levels (median, IQR)
7. Change in albumin levels
8. CRP levels (median, IQR)
9. Change in CRP levels
10. FCP levels (median, IQR)
11. Change in FCP levels
12. Fecal lactoferrin levels (median, IQR)
13. Change in fecal lactoferrin levels
14. SES-CD/CDEIS (median, IQR)
15. Each subcomponent of the SES-CD/CDEIS, per segment
16. Change in total SES-CD/CDEIS score and change in each component of the SES-CD/CDEIS, per segment
17. Total, colonic, and ileal GHAS (median, IQR), if available
18. Change in total, colonic, and ileal GHAS, if available
19. HRQOL index score (median, IQR)
20. Change in HRQOL index score

A statistical comparison will be made for the change in the CDAI, PRO2 (if CDAI component scores are available), albumin, CRP, FCP, fecal lactoferrin, overall SES-CD/CDEIS, each subcomponent of the SES-CD/CDEIS, total, colonic, and ileal GHAS, and HRQOL index score from baseline to primary endpoint assessment visits. A graph will be plotted of baseline entry CDAI against the change in CDAI (from baseline to primary assessment visits).

6.2.2 UC TRIALS
1. MCS (median, IQR)
2. Each subcomponent of the MCS (median, IQR)
3. Change in the total MCS score and change in each subcomponent of the MCS
4. Albumin levels (median, IQR)
5. Change in albumin levels
6. CRP levels (median, IQR)
7. Change in CRP levels
8. FCP levels (median, IQR)
9. Change in FCP levels
10. Fecal lactoferrin levels (median, IQR)
11. Change in fecal lactoferrin levels
12. Geboes Score (median, IQR)
13. Change in Geboes Score
14. Robarts Histopathology Index (RHI) score (to be calculated from Geboes subscores, if available) (median, IQR)
15. Change in RHI score
16. HRQOL index score (median, IQR)
17. Change in HRQOL index score

A statistical comparison will be made for the change in the MCS, each subcomponent of the MCS, albumin, CRP, FCP, fecal lactoferrin, Geboes Score, RHI score, and HRQOL index score from baseline to primary endpoint assessment visits. A graph will be plotted of baseline entry MCS against the change in MCS (from baseline to primary assessment visits).
6.3 IMPROVEMENT IN DISEASE ACTIVITY INDICES

6.3.1 CD TRIALS

6.3.1.1 Clinical Response

Clinical response (as defined in the trial) of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no). As different definitions for clinical response have been used in CD trials, we will also assess the placebo response rates based upon these definitions of clinical response, if data is available:

1. A decrease from baseline in the total CDAI of ≥ 70 points
2. A decrease from baseline in the total CDAI of ≥ 100 points
3. A decrease from baseline in the PRO2 of 5 points
4. A decrease from baseline in the PRO2 of 8 points

A definition of hyper-response will be provided in the SAP. Alternative definitions of clinical response may be explored and will be described in the SAP.

6.3.1.2 Clinical Remission

Clinical remission at the primary endpoint visit (as defined in the trial) of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no).

As different definitions for clinical remission have been used in CD trials, we will also assess the placebo remission rates based on these definitions of clinical remission, if data is available:

1. CDAI < 150 points
2. PRO2 ≤ 8 points
3. SF ≤ 1.5 and AP ≤ 1.0, with neither worse than baseline score

Alternative definitions of clinical remission may be explored and will be described in the SAP.

6.3.1.3 Sustained Clinical Remission

Sustained clinical remission, will be defined as a subject who is in clinical remission based upon the above definitions (i.e., as defined in the trial, CDAI < 150 points, PRO2 ≤ 2 points, SF ≤ 1.5, and AP ≤ 1.0, with neither worse than baseline score) at both the end of induction and maintenance periods.

Alternative definitions of sustained clinical remission may be explored and will be described in the SAP.

6.3.1.4 Corticosteroid-free Clinical Remission

Corticosteroid-free clinical remission at the primary endpoint visit (as defined in the trial) of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no).

As different definitions for clinical remission have been used in CD trials, we will also assess the placebo remission rates based on these definitions of corticosteroid-free clinical remission, if data is available:

1. CDAI < 150 and not receiving oral corticosteroids
2. PRO2 ≤ 8 points and not receiving oral corticosteroids
3. SF ≤ 1.5 and AP ≤ 1.0 (with neither being worse than baseline score) and not receiving oral corticosteroids

Alternative definitions of corticosteroid-free clinical remission may be explored and will be described in the SAP.

6.3.1.5 Sustained Corticosteroid-free Clinical Remission

Sustained corticosteroid-free clinical remission, will be defined as a subject who is in clinical remission based upon the above definitions (i.e., as defined in the trial, CDAI < 150 points, PRO2 ≤ 2 points, SF ≤ 1.5, and AP ≤ 1.0, with neither worse than baseline score) at both the end of induction and maintenance periods.

Alternative definitions of sustained corticosteroid-free clinical remission may be explored and will be described in the SAP.

6.3.1.6 Endoscopic Response

Endoscopic response (as defined in the trial) of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no).

As different definitions for endoscopic response have been used in CD trials, we will also assess the placebo response rates based on these definitions of endoscopic response.

1. A ≥ 25% reduction from baseline in the SES-CD/CDEIS
2. A ≥ 50% reduction from baseline in the SES-CD/CDEIS

Alternative definitions of endoscopic response may be explored and will be described in the SAP.

6.3.1.7 Endoscopic Remission

Endoscopic remission at the primary endpoint visit (as defined in the trial) of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no).

As different definitions for endoscopic remission have been used in CD trials, we will also assess the placebo remission rates based on these definitions of endoscopic remission:

1. SES-CD/CDEIS ≤ 4, or ≤ 2 for isolated ileitis
2. SES-CD/CDEIS ≤ 2

Alternative definitions of endoscopic remission may be explored and will be described in the SAP.

6.3.1.8 Histologic Response

A ≥ 50% decrease in the total GHAS from baseline to the primary endpoint visit of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no).

6.3.1.9 Histologic Remission

A widely accepted definition of histologic remission in CD does not currently exist. Exploratory definitions of histologic remission may be assessed and described in the SAP.
6.3.2 UC TRIALS

6.3.2.1 Clinical Response

Clinical response (as defined in the trial) of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no).

As different definitions for clinical response have been used in UC trials, we will also assess the placebo response rates based on these definitions of clinical response:

1. Decrease in the MCS of $\geq 3$ points and $\geq 30\%$ reduction from baseline AND a $\geq 1$-point decrease in RB or an absolute RB subscore $\leq 1$

2. Decrease in the Adapted MCS (MCS with physician global assessment excluded) of $\geq 2$ points and a $\geq 35\%$ reduction from baseline AND a $\geq 1$-point decrease in RB or an absolute RB subscore $\leq 1$

A definition of hyper-response will be provided in the SAP. Alternative definitions of clinical response may be explored and will be described in the SAP.

6.3.2.2 Clinical Remission

Clinical remission at the primary endpoint visit (as defined in the trial) of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no).

As different definitions for clinical remission have been used in the UC trials, we will also assess the placebo remission rates based on these definitions of clinical remission:

1. MCS $\leq 2$ with no subscore $> 1$

2. MES $\leq 1$, a $\geq 1$-point decrease in SF from baseline to achieve a SF $\leq 1$, and RB = 0

Alternative definitions of clinical remission may be explored and will be described in the SAP.

6.3.2.3 Sustained Clinical Remission

Sustained clinical remission, will be defined as, clinical remission based upon the above definitions at both the end of induction and maintenance periods.

Alternative definitions of sustained clinical remission may be explored and will be described in the SAP.

6.3.2.4 Corticosteroid-free Clinical Remission

Corticosteroid-free clinical remission at the primary endpoint visit (as defined in the trial) of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no).

As different definitions for clinical remission have been used in UC trials, we will also assess the placebo remission rates based on these definitions of corticosteroid-free clinical remission:

1. MCS $\leq 2$ with no subscore $> 1$ and not receiving oral corticosteroids

2. MES $\leq 1$, SF $\leq 1$, and RB = 0 and not receiving oral corticosteroids

Alternative definitions of corticosteroid-free clinical remission may be explored and will be described in the SAP.
6.3.2.5 Sustained Corticosteroid-free Clinical Remission
Sustained clinical remission, will be defined as a subject who is in clinical remission based upon the above definitions at the end of both induction and maintenance periods.
Alternative definitions of sustained corticosteroid-free clinical remission may be explored and will be described in the SAP.

6.3.2.6 Endoscopic Response
An endoscopic response (defined as a MES ≤ 1) at the primary endpoint visit of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no).
Alternative definitions of endoscopic response may be explored and will be described in the SAP.

6.3.2.7 Endoscopic Remission
Endoscopic remission (defined as a MES = 0) at the primary endpoint visit of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no).
Alternative definitions of endoscopic remission may be explored and will be described in the SAP.

6.3.2.8 Histologic Response
Histologic response at the primary endpoint visit (as defined in the trial) of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no).
Where possible, we will also assess the placebo response rates based on these definitions of histologic response for trials with histologic data:

1. Geboes Score < 3.1
2. A 7-point decrease from baseline in the RHI score
Alternative definitions of histologic response may be explored and will be described in the SAP.

6.3.2.9 Histologic Remission
Histologic remission at the primary endpoint visit (as defined in the trial) of the induction period and the maintenance period (if applicable) will be dichotomized into a binary response (yes/no).
Where possible, we will assess the placebo remission rates based on these definitions of histologic remission for trials with histologic data:

1. Geboes Score < 2.0
2. Geboes subscores of 0 for neutrophils in lamina propria, neutrophils in epithelium, and erosions or ulcerations
3. RHI ≤ 3 with subscores of 0 for lamina propria neutrophils and neutrophils in epithelium
Alternative definitions of histologic remission may be explored and will be described in the SAP.

6.4 ANALYSIS OF PLACEBO RESPONSE EVENTS
Summary statistics will be used to describe study and individual participant characteristics for data obtained from the CD and UC trials listed in Appendix A. The means (medians), SD, and ranges will be analyzed for continuous variables, while categorical variables will be presented as
frequencies and percentages, such as for binary outcomes (e.g., subject exhibits a clinical response [yes, no]) and AEs and SAEs (by preferred term and severity).

Both two-stage and one-stage meta-analyses will be conducted for outcome data. In the two-stage analysis, proportions from all studies will be pooled using conventional meta-analysis methods.\textsuperscript{14} This data will also be used to investigate how characteristics of studies may affect study-aggregate proportions using metaregression and/or study-subgroup analyses (i.e., based on previous TNF experience and number and class of biologics). For metaregression analyses, continuous factors will be centered and unadjusted estimates (95\% 2-sided CIs) for outcome proportions obtained, as well as, estimates adjusted by important factors. Factors with a P < .1 will be selected in metaregression. Adjusted proportions will be obtained using the estimated intercept. Data analysis will be performed using the metafor package in R.\textsuperscript{15}

In the one-stage analysis, the generalized linear mixed-effects approach will be used.\textsuperscript{16} The final model for each outcome will be based on Bayesian information criterion. Adjusted proportions will be obtained from the final model with independent variables centered. Data analysis will be performed using the lmer function in the lme4 package in R.\textsuperscript{17}

6.5 EXPLORATORY ANALYSES

Exploratory analyses, such as the effect of central reading and adjudication models on placebo response rates will be described in the SAP.

Additional exploratory analyses may be defined in the SAP, during analysis, or in response to peer review.

6.5.1 IDENTIFYING MOLECULAR PROFILE FACTORS PREDICTING PLACEBO RESPONSE

The levels of RNA (gene expression) and proteins from intestinal biopsy or blood will be selected and included as factors in the final models, either alone or in combination with the factors identified in Section 6.4. Selected factors may be individual genes or proteins or profiles (combinations of genes and/or proteins) identified in metaregression (P < .1). Profiles may include aggregated expression levels of genes in biological pathways and processes or principle component scores as described by Morgan et al.\textsuperscript{18} Details will be provided in the SAP.

6.6 HANDLING OF MISSING DATA

Statistical analyses will be performed on the data received, using a complete-case analysis basis. Depending on the severity of missing data, we will attempt to use multiple imputation as a sensitivity analysis. Further details on the handling of missing data will be provided in the SAP.

7 ETHICAL CONSIDERATIONS

The current study will be conducted in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

7.1 INSTITUTIONAL REVIEW BOARD

All relevant documents for this study will be submitted to an appropriate institutional review board (IRB) or independent ethics committee (IEC) for review. A signed and dated letter documenting IRB/IEC approval must be obtained prior to study initiation. The IRB/IEC must be notified of all subsequent protocol amendments.
7.2 INFORMED CONSENT

The data to be analyzed in this study was obtained during the execution of separate clinical trial protocols. The informed consents obtained during the clinical trials complied with ICH GCP, all applicable regulatory requirement(s), and permitted secondary research use of the data collected. Additional subject consent will not be obtained.

7.3 CONFIDENTIALITY OF SUBJECT RECORDS

All data to be collected for this study has previously been de-identified, and thus will not include any personally identifying information. Subject information used will comply with the requirements for the protection of privacy of individually identifiable health information. The analyses performed in this study will not affect the subject’s treatment and/or well-being.

7.4 RISK-BENEFIT ASSESSMENT

7.4.1 POTENTIAL SUBJECT RISKS

As this is a retrospective data analysis study, the primary risk is breach of confidentiality and privacy. However, subject data used in this study will be deidentified to minimize this risk.

7.4.2 POTENTIAL SUBJECT BENEFITS

Subjects will receive no direct benefits of being included in this retrospective study.

7.4.3 OVERALL RISK-BENEFIT ASSESSMENT

This study involves no more than minimal risk to subjects.

8 ADMINISTRATIVE REQUIREMENTS

8.1 DATA SHARING AGREEMENT

This study will develop a repository of trial- and subject-related data. Data sharing agreements will be developed between Alimentiv Inc. and sponsors detailing the terms of access and use of all data received from sponsors.

8.2 DATA TRANSFER

All datasets will be requested in a Clinical Data Interchange Standards Consortium (CDISC)-compliant format, specifically Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets, or if the data does not exist in this format then in an alternate format to be agreed upon in advance. The data structure, file format, and how the data will be transferred will be detailed in the data sharing agreement. Sponsors will also be asked to share the relevant metadata for these datasets (e.g. Define.XML). All data will be transferred in an encrypted format from each sponsor using a secure file repository.

8.3 DATA QUALITY ASSURANCE

The quality of all data received will have been reviewed during the conduct of the original clinical trial and will not be reviewed by Alimentiv staff.

For all data involving a unit of measure (e.g., serum biomarker levels), the unit of measure used in the trial will also be extracted and received data converted to the International System of Units, if required.
8.4 PUBLICATION POLICY

The findings from this study may be published in a scientific journal or presented at a scientific meeting. Authorship of publications will be determined based upon International Committee of Medical Journal Editors criteria.
9 REFERENCES


## 10 APPENDICES

### Appendix A Overview of Trial Datasets to be Used in this Study

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Trial ID (clinicaltrials.gov identifier)</th>
<th>Study Drug</th>
<th>Disease</th>
<th>Trial Phase</th>
<th>Clinical Disease Activity Index</th>
<th>Definition of Clinical Response</th>
<th>Publication Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbvie</td>
<td>M04-729; M06-837 (NCT00445939 &amp; NCT00445432)</td>
<td>Adalimumab</td>
<td>CD - Japan</td>
<td>2/3</td>
<td>CDAI</td>
<td>1. A ≥ 70-point decrease in the total CDAI 2. A ≥ 100-point decrease in the total CDAI</td>
<td>2012; 2014</td>
<td>19, 20</td>
</tr>
<tr>
<td>Abbvie</td>
<td>M14-233 (NCT02499783)</td>
<td>Adalimumab</td>
<td>CD - China</td>
<td>3</td>
<td>CDAI (Week 4)</td>
<td>A ≥ 70-point decrease in the total CDAI</td>
<td>In Press</td>
<td>21</td>
</tr>
<tr>
<td>Abbvie</td>
<td>ULTRA 1 (NCT00385736)</td>
<td>Adalimumab</td>
<td>UC</td>
<td>3</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and a ≥ 30% decrease from baseline, and a ≥ 1-point decrease in the RB score or a RB score ≤ 1</td>
<td>2011</td>
<td>22</td>
</tr>
<tr>
<td>Abbvie</td>
<td>ULTRA 2 (NCT00408629)</td>
<td>Adalimumab</td>
<td>UC</td>
<td>3</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and a ≥ 30% decrease from baseline, and a ≥ 1-point decrease in the RB score or a RB score ≤ 1</td>
<td>2012</td>
<td>23</td>
</tr>
<tr>
<td>Abbvie</td>
<td>M10-447 (NCT00853099)</td>
<td>Adalimumab</td>
<td>UC - Japan</td>
<td>2/3</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and a ≥ 30% decrease from baseline, and a ≥ 1-point decrease in the RB score or a RB score ≤ 1</td>
<td>2014</td>
<td>24</td>
</tr>
<tr>
<td>Abbvie</td>
<td>M10-222 (NCT00562887)</td>
<td>Briakinumab (ABT-874)</td>
<td>CD</td>
<td>2b</td>
<td>CDAI</td>
<td>A ≥ 70-point decrease in the total CDAI</td>
<td>2015</td>
<td>25</td>
</tr>
<tr>
<td>Abbvie</td>
<td>1311.6 (NCT02031276)</td>
<td>Risankizumab</td>
<td>CD</td>
<td>2</td>
<td>CDAI</td>
<td>Total CDAI &lt; 150 OR a ≥ 100-point decrease in the CDAI from baseline</td>
<td>2017</td>
<td>26</td>
</tr>
<tr>
<td>Abbvie</td>
<td>CELEST; M13-740 (NCT02365649)</td>
<td>Upadacitinib (ABT-494)</td>
<td>CD</td>
<td>2</td>
<td>CDAI</td>
<td>Total CDAI &lt; 150 AND a ≥ 70-point decrease in the CDAI from baseline</td>
<td>In Press</td>
<td>27</td>
</tr>
<tr>
<td>Abbvie</td>
<td>U-ACHIEVE; M14-234 (NCT02819635)</td>
<td>Upadacitinib (ABT-494)</td>
<td>UC</td>
<td>3</td>
<td>Adapted 9-point MCS</td>
<td>A ≥ 2-point decrease in the Adapted 9-point MCS and a ≥ 30% from baseline, and a 1-point decrease in the RB score or a RB score ≤ 1</td>
<td>2020</td>
<td>28</td>
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<td>Abbvie</td>
<td>ABX464-101 (NCT03093259)</td>
<td>ABX464</td>
<td>UC</td>
<td>2a</td>
<td>MCS</td>
<td>Not defined</td>
<td>2019</td>
<td>29</td>
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<tr>
<td>Sponsor</td>
<td>Trial ID (clinicaltrials.gov identifier)</td>
<td>Study Drug</td>
<td>Disease</td>
<td>Trial Phase</td>
<td>Clinical Disease Activity Index</td>
<td>Definition of Clinical Response</td>
<td>Publication Year</td>
<td>Reference</td>
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<tr>
<td>Allergan</td>
<td>D5170C00001 (NCT01714726)</td>
<td>MEDI2070</td>
<td>CD</td>
<td>2a</td>
<td>CDAI</td>
<td>Total CDAI &lt; 150 AND a ≥ 100-point decrease in the CDAI from baseline</td>
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<td>30</td>
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<tr>
<td>Amgen</td>
<td>20110232 (NCT01696396)</td>
<td>Abrilumab (AMG181; MEDI7183)</td>
<td>CD</td>
<td>2b</td>
<td>CDAI</td>
<td>A ≥ 100-point decrease in the total CDAI</td>
<td>2017</td>
<td>31</td>
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<tr>
<td></td>
<td>20110166 (NCT01694485)</td>
<td>Abrilumab (AMG181; MEDI7183)</td>
<td>UC</td>
<td>2b</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2019</td>
<td>32</td>
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<td></td>
<td>20090072 (NCT01150890)</td>
<td>Brodalumab (AMG 827)</td>
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<td>2</td>
<td>CDAI</td>
<td>A ≥ 100-point decrease in the total CDAI</td>
<td>2016</td>
<td>33</td>
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<tr>
<td>Arena Pharmaceuticals</td>
<td>APD334-003 (NCT02447302)</td>
<td>Etrasimod (APD334)</td>
<td>UC</td>
<td>2</td>
<td>MCS</td>
<td>A ≥ 2-point decrease in the modified MCS and a ≥ 30% decrease from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2020</td>
<td>34</td>
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<tr>
<td>AstraZeneca</td>
<td>D8830C00002 (Eudra-CT Number: 2005-002319-26)</td>
<td>AZD9056</td>
<td>CD</td>
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<td>CDAI</td>
<td>A ≥ 70-point decrease in the total CDAI</td>
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<td>D2211C00001 (NCT01482884)</td>
<td>Tralokinumab</td>
<td>UC</td>
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<td>MCS</td>
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<td>AstraZeneca/Aagen</td>
<td>D5172C00001 (NCT01959165)</td>
<td>Abrilumab (MEDI7183)</td>
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<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2019</td>
<td>37</td>
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<td>Bausch Healthcare</td>
<td>MT-1303-E13 (NCT02378688)</td>
<td>Amiselimod (MT-1303)</td>
<td>CD</td>
<td>2</td>
<td>CDAI</td>
<td>1. A ≥ 100-point decrease in the total CDAI 2. A ≥ 70-point decrease in the total CDAI</td>
<td>2019</td>
<td>38</td>
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<td>Bristol-Myers Squibb</td>
<td>IM101-084 (NCT00406653)</td>
<td>Abatacept (BMS-1888667)</td>
<td>CD</td>
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<td>CDAI</td>
<td>A ≥ 100-point decrease in the total CDAI or absolute CDAI &lt; 150 points</td>
<td>2012</td>
<td>39</td>
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<td>Sponsor</td>
<td>Trial ID (clinicaltrials.gov identifier)</td>
<td>Study Drug</td>
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<tr>
<td>Bristol-Myers Squibb (cont’)</td>
<td>IM101-108 (NCT00410410)</td>
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<td>UC</td>
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<td>MCS</td>
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<td>2012</td>
<td>39</td>
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<td>MDX-1100-06; IM129-004 (NCT00656890)</td>
<td>Eldelumab BMS-936557 MDX-1100</td>
<td>UC</td>
<td>2</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2014, 2016</td>
<td>40, 41</td>
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<td>IM129-008 (NCT01466374)</td>
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<td>CD</td>
<td>2a</td>
<td>CDAI</td>
<td>A ≥ 100-point decrease in the total CDAI or absolute CDAI &lt; 150 points</td>
<td>2017</td>
<td>42</td>
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<td>Celgene</td>
<td>TOUCHSTONE, RPC01-3101 (NCT02435992)</td>
<td>Ozanimod (RPC1063)</td>
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<td>2a</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2016</td>
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<td>GED-0301-CD-001 (NCT02367183)</td>
<td>Mongersen (GED-0301)</td>
<td>CD</td>
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<td>CDAI</td>
<td>A ≥ 100-point decrease in the total CDAI</td>
<td>2020</td>
<td>44</td>
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<td></td>
<td>CC-10004-UC-001 (NCT02289417)</td>
<td>Apremilast (CC-10004)</td>
<td>UC</td>
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<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>In Press</td>
<td>45</td>
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<tr>
<td>EA Pharma</td>
<td>AJM300/CT3 (JapicCTI-132293)</td>
<td>AJM300</td>
<td>UC</td>
<td>2a</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2015</td>
<td>46</td>
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<tr>
<td>Eli Lilly</td>
<td>I6T-MC-AMAC (NCT02589665)</td>
<td>Mirikizumab (LY3074828)</td>
<td>UC</td>
<td>2</td>
<td>Adapted 9-point MCS</td>
<td>A ≥ 2-point decrease in adapted 9-point MCS and a ≥ 35% from baseline with either a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2020</td>
<td>47</td>
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<tr>
<td>Facet Biotech / PDL Biopharma</td>
<td>707 (NCT00072943)</td>
<td>Fontolizumab (HuZAF)</td>
<td>CD</td>
<td>2</td>
<td>CDAI</td>
<td>A ≥ 100-point decrease in the total CDAI</td>
<td>2010</td>
<td>48</td>
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<td>Trial ID (clinicaltrials.gov identifier)</td>
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<td>Disease</td>
<td>Trial Phase</td>
<td>Clinical Disease Activity Index</td>
<td>Definition of Clinical Response</td>
<td>Publication Year</td>
<td>Reference</td>
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<td>Ferring Pharmaceuticals / Cytokine Pharmasciences Inc.</td>
<td>CNI-1493-CD04 (NCT00739986)</td>
<td>Semapimod HCl</td>
<td>CD</td>
<td>2</td>
<td>CDAI</td>
<td>A ≥ 70-point decrease in the total CDAI</td>
<td>2010</td>
<td>49</td>
</tr>
<tr>
<td>Galapagos NV</td>
<td>FITZROY (NCT02048618)</td>
<td>Filgotinib (GLPG0634; GS-6034)</td>
<td>CD</td>
<td>2</td>
<td>CDAI</td>
<td>A ≥ 100-point decrease in the total CDAI</td>
<td>2017</td>
<td>50</td>
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<tr>
<td></td>
<td>GLPG1205-CL-211 (NCT02337608)</td>
<td>GLPG1205</td>
<td>UC</td>
<td>2</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2017</td>
<td>51</td>
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<tr>
<td>Gilead Sciences</td>
<td>GS-US-395-1663 (NCT02405442)</td>
<td>Andecaliximab (GS-5745)</td>
<td>CD</td>
<td>2</td>
<td>PRO2</td>
<td>A PRO2 score ≤ 8</td>
<td>2018</td>
<td>52</td>
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<tr>
<td></td>
<td>GS-US-326-1100 (NCT02520284)</td>
<td>Andecaliximab (GS-5745)</td>
<td>UC</td>
<td>2/3</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2018</td>
<td>53</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>PROTECT-1, CL004 282 (NCT00306215)</td>
<td>Vercirnon (GSK1605786A, CCX282-B)</td>
<td>CD</td>
<td>2</td>
<td>CDAI</td>
<td>A ≥ 70-point decrease in the total CDAI</td>
<td>2013</td>
<td>54</td>
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<td></td>
<td>SHIELD-1, CCX114151 (NCT01277666)</td>
<td>Vercirnon (GSK1605786A, CCX282-B)</td>
<td>CD</td>
<td>3</td>
<td>CDAI</td>
<td>1. A ≥ 100-point decrease in the total CDAI</td>
<td>2015</td>
<td>55</td>
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<tr>
<td>Hoffman-La Roche</td>
<td>BERGAMOT, GA29144 (NCT02394028)</td>
<td>Etrolizumab (rhuMAb β7)</td>
<td>CD</td>
<td>3</td>
<td>CDAI</td>
<td>1. A ≥ 70-point decrease in the total CDAI 2. A ≥ 100-point decrease in the total CDAI</td>
<td>2018, 2020</td>
<td>56, 57</td>
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<td></td>
<td>ABS4986g, LAUREL, HICKORY (NCT01336465; NCT02165215; NCT02100696)</td>
<td>Etrolizumab (rhuMAb β7)</td>
<td>UC</td>
<td>2/3</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2014, 2020</td>
<td>57, 58</td>
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<td>Hoffman-La Roche (cont’d)</td>
<td>RLBHUHT R&amp;D 2709 (NCT00261118)</td>
<td>Rituimab</td>
<td>UC</td>
<td>2/3</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS</td>
<td>2011</td>
<td>59</td>
</tr>
<tr>
<td>Janssen-Ortho</td>
<td>PURSUIT-SC, PURSUIT-M CR014176, C0524T17 (NCT00487539; NCT00488631)</td>
<td>Golimumab-SC (CNTO 149)</td>
<td>UC</td>
<td>2/3</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2014</td>
<td>60, 61</td>
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<td>PURSUIT-J, CR100937, CNTO148UCO3001 (NCT01863771)</td>
<td>Golimumab-SC</td>
<td>UC - Japan</td>
<td>3</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2017</td>
<td>62</td>
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<tr>
<td></td>
<td>PURSUIT-IV, CR014188, C0524T16, 2006-003397-94 (NCT00488774)</td>
<td>Golimumab-IV (CNTO 148)</td>
<td>UC</td>
<td>2/3</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2015</td>
<td>63</td>
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<tr>
<td>Study performed at Jinan Military General Hospital</td>
<td>Infliximab</td>
<td>UC - China</td>
<td>3</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2015</td>
<td>64</td>
<td></td>
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<tr>
<td>CERTIFI, CR015238 C0743T26 (NCT00771667)</td>
<td>Ustekinumab</td>
<td>CD</td>
<td>2b</td>
<td>CDAI</td>
<td>A ≥ 100-point decrease in the total CDAI</td>
<td>2012</td>
<td>65</td>
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<tr>
<td>UNITI-1 and 2. CR018415 CNTO1275CRD3001 (NCT01369329 &amp; NCT01369342)</td>
<td>Ustekinumab</td>
<td>CD</td>
<td>3</td>
<td>CDAI</td>
<td>A ≥ 100-point decrease in the total CDAI or a total score &lt; 150</td>
<td>2016</td>
<td>66</td>
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<td>IM-UNITI (NCT01369355)</td>
<td>Ustekinumab</td>
<td>CD</td>
<td>3</td>
<td>CDAI</td>
<td>A ≥ 100-point decrease in the total CDAI or a total score &lt; 150</td>
<td>2016</td>
<td>66</td>
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<td>Study Drug</td>
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<td>Trial Phase</td>
<td>Clinical Disease Activity Index</td>
<td>Definition of Clinical Response</td>
<td>Publication Year</td>
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<tr>
<td>Janssen-Ortho (cont’d)</td>
<td>UNIFI (NCT02407236)</td>
<td>Ustekinumab</td>
<td>UC</td>
<td>3</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2019</td>
<td>67</td>
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<tr>
<td></td>
<td>CR102640 (NCT01959282)</td>
<td>Peficitinib (JNJ-54781532; ASP015K)</td>
<td>UC</td>
<td>2b</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2018</td>
<td>68</td>
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<tr>
<td>Novartis Pharmaceuticals</td>
<td>CAIN457A2202E1 (NCT01009281)</td>
<td>Secukinumab (AIN457)</td>
<td>CD</td>
<td>2a</td>
<td>CDAI</td>
<td>A ≥ 100-point decrease in the total CDAI</td>
<td>2012</td>
<td>69</td>
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<td>Pfizer</td>
<td>B2421003 (NCT01284062)</td>
<td>Anrukinzumab (IMA-638)</td>
<td>UC</td>
<td>2a</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2015</td>
<td>70</td>
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<td>A3921083 (NCT00615199; NCT01393626;</td>
<td>Tofacitinib (CP-690-550)</td>
<td>CD</td>
<td>2</td>
<td>CDAI</td>
<td>1. A ≥ 70-point decrease in the total CDAI 2. A ≥ 100-point decrease in the total CDAI</td>
<td>2014; 2017</td>
<td>71, 72</td>
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<td></td>
<td>NCT01393899)</td>
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<td>A3921063 (NCT00787202)</td>
<td>Tofacitinib (CP-690,550)</td>
<td>UC</td>
<td>2</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline</td>
<td>2012</td>
<td>73</td>
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<td>OCTAVE 1, 2 &amp; Sustain (NCT01465763,</td>
<td>Tofacitinib (CP-690,550)</td>
<td>UC</td>
<td>3</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2017</td>
<td>74</td>
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<td></td>
<td>NCT01458951, NCT01458574)</td>
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<td></td>
<td>TURANDOT (NCT01620255)</td>
<td>PF-00547659</td>
<td>UC</td>
<td>2</td>
<td>MCS</td>
<td>A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1</td>
<td>2011, 2017</td>
<td>75, 76</td>
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<tr>
<td></td>
<td>OPERA (NCT01276509)</td>
<td>PF-00547659</td>
<td>CD</td>
<td>2</td>
<td>CDAI</td>
<td>A ≥ 70-point decrease in the total CDAI</td>
<td>2018</td>
<td>77</td>
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<tr>
<td></td>
<td>ANDANTE I &amp; II (NCT01287897)</td>
<td>PF-04236921</td>
<td>CD</td>
<td>2</td>
<td>CDAI</td>
<td>A ≥ 70-point decrease in the total CDAI</td>
<td>2019</td>
<td>78</td>
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<tr>
<td>Protagonist Therapeutics Inc.</td>
<td>PTG-100-02 (NCT02895100)</td>
<td>PTG-100</td>
<td>UC</td>
<td>2</td>
<td>MCS</td>
<td>Not reported</td>
<td>2018</td>
<td>79</td>
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<td>Sponsor</td>
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</table>
| Qu Biologicals            | QBECO-01 (NCT01809275)                  | QBECO                               | CD      | 1/2         | CDAI                            | 1. A ≥ 70-point decrease in the total CDAI  
2. A ≥ 100-point decrease in the total CDAI                                                                 | 2019            | 80        |
| Sterna Biologicals       | SECURE (NCT02129439)                    | SB012 (Gata 3-specific DNAzyme)     | UC      | 2a          | UC                             | Not defined                                                                                   | 2018            | 81        |
| Synta Pharmaceuticals Corporation | 5326-07 (NCT00138840)                   | Apilimod mesylate (STA-5326 mesylate) | CD      | 2           | CDAI                            | A ≥ 100-point decrease in the total CDAI                                                                 | 2010            | 82        |
| Takeda                   | Gemini I (NCT00783718)                  | Vedolizumab (MLN0002)               | UC      | 3           | MCS                            | A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1 | 2013            | 83        |
|                          | VISIBLE 1, MLN0002SC-3027 (NCT02611830) | Vedolizumab (MLN0002)               | UC      | 3           | MCS                            | A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1 | 2020            | 84        |
| Gemini II, C13007 (NCT00783692) | Vedolizumab (MLN0002)                  | CD                                  | 3       | CDAI        | A ≥ 100-point decrease in the total CDAI                                      | 2013            | 85        |
| Gemini III, C13011 (NCT01224171) | Vedolizumab (MLN0002)                  | CD                                  | 3       | CDAI        | A ≥ 100-point decrease in the total CDAI                                      | 2014            | 86        |
| MLN0002/CCT-101 (NCT02039505) | Vedolizumab (MLN0002)                  | UC - Japan                          | 3       | MCS         | A ≥ 3-point decrease in the MCS and ≥ 30% from baseline, and a ≥ 1-point decrease in the RB subscore or a RB subscore ≤ 1 | 2019            | 87        |
| MLN0002/CCT-001 (NCT02038920) | Vedolizumab (MLN0002)                  | CD - Japan                          | 3       | CDAI        | A ≥ 100-point decrease in the total CDAI                                      | 2020            | 88        |
| Teva Pharmaceuticals      | CD-LAQ-201 (NCT00737932)               | Laquinimod (TV-5600; ABR-215062)    | CD      | 2a          | CDAI                            | 1. A ≥ 70-point decrease in the total CDAI  
2. A ≥ 100-point decrease in the total CDAI                                                                 | 2015            | 89        |
<table>
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<tr>
<th>Sponsor</th>
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<tbody>
<tr>
<td>Theravance Biopharma</td>
<td>0157, RHEA (NCT03758443)</td>
<td>TD-1473</td>
<td>UC</td>
<td>2b/3</td>
<td>MCS</td>
<td>A ≥ 2-point decrease and ≥ 30% reduction in the Adapted MCS, with a ≥ 1-point decrease in the RB subscore or a RB subscore ≤1</td>
<td>2019</td>
<td>90</td>
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<tr>
<td>UCB Pharma</td>
<td>Certolizumab-pegol (CZP) in TNF antagonist-naïve patients</td>
<td>Certolizumab-pegol (CDP870)</td>
<td>CD</td>
<td>3</td>
<td>CDAI</td>
<td>A ≥ 100-point decrease in the total CDAI</td>
<td>2011</td>
<td>91</td>
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</table>

Abbreviations: AP, abdominal pain; CD, Crohn’s disease; CDAI, Crohn’s Disease Activity Index; cont’d, continued; MCS, Mayo Clinic Score; PMCS, partial Mayo Clinic Score; PRO2, 2-item patient-reported outcome; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.