I6T-MC-AMAG Statistical Analysis Plan Version 2

A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Subjects with Active Crohn's Disease (SERENITY)

NCT02891226

Approval Date: 16-Mar-2018

1. Statistical Analysis Plan: I6T-MC-AMAG: A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Subjects with Active Crohn's Disease (SERENITY)

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LY3074828 Crohn's Disease

I6T-MC-AMAG is a Phase 2, multicenter study in which subjects with active Crohn's disease are randomized to either LY3074828 or placebo during 3 periods of treatment: Period 1 (Weeks 1 to 12) involves intravenous (IV) administration of LY3074828 versus placebo; Period 2 (Weeks 12 to 52) involves IV and subcutaneous (SC) dosing (uncontrolled); and Period 3 (Weeks 52 to 104) is an extension period that involves SC dosing only.

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Protocol I6T-MC-AMAG
Phase 2

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 28 February 2017
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 16-Mar-2018 GMT

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List of Abbreviations

Term	Definition
ADA	anti-drug antibodies
ADA-	ADA negative
ADA+	ADA positive
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	abdominal pain
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BMC	bowel movement count
BMI	body mass index
BP	blood pressure
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRP	C-reactive protein
CSR	clinical study report
CTMS	Clinical Trial Management System
CTR	Clinical Trial Registry
DSUR	Development Safety Update Report

EC50	half maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EHO	efficacy and health outcomes
Emax	maximum effect
ETV	early termination visit
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy–Fatigue
FCP	fecal calprotectin
GHAS	Global Histologic Disease Activity Score
HLT	high level term
hsCRP	high-sensitivity C-reactive protein
IBDQ	Inflammatory Bowel Disease Questionnaire
ITT	intention to treat/intent-to-treat
IV	intravenous
IWRS	interactive web-response system
LLT	lowest level term
LS	least squares
LY	LY3074828 (Lilly study drug)
LY+FUP	All LY3074828 (Lilly study drug) data for Periods 1-3 plus all Follow-Up combined
mBOCF	modified baseline observation carried forward
CCI [redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
CCI [redacted]	
MMRM	mixed model for repeated measures
NAb	neutralizing antibody
Nab+	NAb positive

CCI	
NRI	non-responder imputation
NRS	numeric rating scale
OI	opportunistic infection
PD	pharmacodynamics
PGRC	Patient's Global Rating of Change
PGRS	Patient's Global Rating of Severity
PK	pharmacokinetics
PT	preferred term
PRO	patient-reported outcomes: a 2-item index comprised of the SF and AP items from the CDAI (unweighted)
PRO2	patient-reported outcomes–2: a 2-item index comprised of the SF and AP items from the CDAI (weighted)
Q4W	every 4 weeks
QIDS-SR16	Quick Inventory of Depressive Symptomatology–Self Report (16 Items)
REML	restricted maximum likelihood
RHI	Robarts Histopathology Index
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
SF-36	36-Item Short Form Health Survey
SI	International System of Units
SMQ	standardized MedDRA query
SOC	system organ class
TE ADA-	treatment-emergent ADA negative

TE ADA+	treatment-emergent ADA positive
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States

3. Revision History

SAP Version 1 was approved prior to the first permanent data transfer.

SAP Version 2 was approved prior to first unblinding. The overall changes and rationale for the changes incorporated in Version 2 are as follows:

- Reflected protocol amendment (a).
- Further defined subject populations, study periods, and baseline/postbaseline for analyses.
- Added exploratory endpoints not specified in protocol based on data from new publications.

4. Study Objectives

Table AMAG.4.1 shows the objectives and endpoints of the study as noted in the protocol. Further details on the endpoints, including derivations, are described in the corresponding section of this SAP.

Table AMAG.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To test the hypothesis that treatment with LY3074828 is superior to placebo in the proportion of subjects with **endoscopic response at Week 12**, defined as 50% reduction from baseline in SES-CD	Proportion of subjects achieving endoscopic response at Week 12
Secondary	
To evaluate the safety and tolerability of treatment with LY3074828	AEs and discontinuation rates; mean change vital signs; laboratory values
To evaluate the effect of LY3074828 on the proportion of subjects with **endoscopic response at Week 52**, defined as 50% reduction from baseline in SES-CD	Proportion of subjects achieving endoscopic response at Week 52
To evaluate the efficacy of treatment with LY3074828 as superior to placebo in **endoscopic remission** (defined as an SES-CD of <4 ileal-colonic or <2 for isolated ileal disease, and no subscore >1) **at Week 12**	Proportion of subjects achieving endoscopic remission at Week 12
To evaluate the effect of LY3074828 on the proportion of subjects with **endoscopic remission** (defined as an SES-CD of <4 ileal-colonic or <2 for isolated ileal disease, and no subscore >1) **at Week 52**	Proportion of subjects achieving endoscopic remission at Week 52
To evaluate the efficacy of treatment with LY3074828 as superior to placebo in **PRO remission** (defined as SF ≤2.5 and AP ≤1) **at Week 12**	Proportion of subjects achieving PRO remission at Week 12
To evaluate the effect of LY3074828 on the proportion of subjects with **PRO remission** (defined as SF ≤2.5 and AP ≤1) **at Week 52**	Proportion of subjects achieving PRO remission at Week 52
To evaluate the effect of LY3074828 on health outcomes/quality-of-life measures (including **PGRS** score, **PGRC** score, **IBDQ** score, **SF-36** score, and **FACIT-Fatigue**) at Weeks 12 and 52	The mean change from baseline for PGRS score, IBDQ score, FACIT-Fatigue, and SF-36, and the mean PGRC at Weeks 12 and 52
To characterize the PK of LY3074828	Clearance and volume of distribution
Tertiary/Exploratory	
To evaluate the efficacy of treatment with LY3074828 as superior to placebo in **PRO2 response** (defined as a PRO2 reduction of ≥5 points) **at Week 12**	Proportion of subjects achieving PRO2 response at Week 12
To evaluate the effect of LY3074828 on the proportion of subjects with **PRO2 response** (defined as a PRO2 reduction of ≥5 points) **at Week 52**	Proportion of subjects achieving PRO2 response at Week 52

Objectives and Endpoints

Objectives	Endpoints
To evaluate the efficacy of treatment with LY3074828 as superior to placebo in **PRO2 remission** (defined as a PRO2 <8) **at Week 12**	Proportion of subjects achieving PRO2 remission at Week 12
To evaluate the effect of LY3074828 on the proportion of subjects with **PRO2 remission** (defined as a PRO2 <8) **at Week 52**	Proportion of subjects achieving PRO2 remission at Week 52
To evaluate the effect of LY3074828 on **durability of endoscopic response at Week 52**	Proportion of subjects achieving endoscopic response at Week 52 who also had endoscopic response at Week 12
To evaluate the effect of LY3074828 on **durability of endoscopic remission at Week 52**	Proportion of subjects achieving endoscopic remission at Week 52 who also had endoscopic remission at Week 12
To evaluate the effect of LY3074828 on **durability of PRO2 response at Week 52**	Proportion of subjects achieving PRO2 response at Week 52 who also had PRO2 response at Week 12
To evaluate the effect of LY3074828 on **durability of PRO2 remission at Week 52**	Proportion of subjects achieving PRO2 remission at Week 52 who also had PRO2 remission at Week 12
To evaluate the efficacy of treatment with LY3074828 as superior to placebo in the **composite of endoscopic and PRO remission at Week 12**	Proportion of subjects achieving both endoscopic and PRO remission at Week 12
To evaluate the effect of LY3074828 on the proportion of subjects with **composite endoscopic and PRO remission at Week 52**	Proportion of subjects achieving both endoscopic and PRO remission at Week 52
To evaluate the effect of LY3074828 on **durability of composite endoscopic and PRO remission at Week 52**	Proportion of subjects achieving both endoscopic and PRO remission at Week 52 who also had both endoscopic and PRO remission at Week 12
[redacted]	
To evaluate the effect of LY3074828 on **BMC** reported using the BMC scale	Change from baseline in reported BMC, at all time points evaluated

Objectives and Endpoints

Objectives	Endpoints
To evaluate the effect of LY3074828 on **QIDS-SR16 at Weeks 12 and 52**	Change from baseline in reported QIDS-SR16 score at Weeks 12 and 52
To explore the development of any anti-LY3074828 antibodies that are formed and their effect on safety, PK, and PD of LY3074828	Proportion of subjects who are ADA+. Proportion of ADA+ subjects who experience certain immunogenicity-specific AEs. CCI [redacted]
To evaluate **changes in CDAI** from baseline	Changes from baseline in CDAI.
To assess the psychometric properties (including reliability, validity, and responsiveness) of the CCI [redacted], BMC, CCI [redacted] CCI [redacted].	CCI [redacted]
To evaluate the elimination of neutrophils from the mucosa by histopathology at Week 52.	Absence of lamina propia and epithelial neutrophils at Week 52 assessed by • GHAS • RHI
Exploratory (not in protocol)	
To evaluate the efficacy of treatment with LY3074828 as superior to placebo in **PRO response** (defined as 30% reduction from baseline in AP or SF with neither worse than baseline) at Week 12	Proportion of subjects achieving PRO response at Week 12.
To evaluate the efficacy of treatment with LY3074828 as superior to placebo in **PRO response** (defined as 30% reduction from baseline in AP or SF with neither worse than baseline) at Week 52	Proportion of subjects achieving PRO response at Week 52.
To evaluate the effect of LY3074828 on **durability of PRO response** at Week 52	Proportion of subjects achieving PRO response at Week 52 who also had PRO response at Week 12.
To evaluate the effect of LY3074828 on **durability of PRO remission** at Week 52	Proportion of subjects achieving PRO remission at Week 52 who also had PRO remission at Week 12.
To evaluate the effect of LY3074828 on **PRO remission at Week 52** among PRO responders **at Week 12**	Proportion of subjects achieving PRO remission at Week 52 out of those patients who had PRO response at Week 12.
To evaluate the efficacy of treatment with LY3074828 as superior to placebo in the **composite of endoscopic response and PRO remission at Week 12**	Proportion of subjects achieving both endoscopic response and PRO remission at Week 12
To evaluate the effect of LY3074828 on the proportion of subjects with the **composite of endoscopic response and PRO remission at Week 52**	Proportion of subjects achieving both endoscopic and PRO remission at Week 52

Objectives and Endpoints

Objectives	Endpoints
To evaluate the effect of LY3074828 on **durability of the composite endoscopic response and PRO remission at Week 52**	Proportion of subjects achieving both endoscopic reponse and PRO remission at Week 52 out of the patients with endoscopic response and PRO remission at Week 12
To evaluate the efficacy of treatment with LY3074828 as superior to placebo in **PRO1 remission** (defined as SF ≤1.5 and AP ≤1 and no worse than baseline) at Week 12	Proportion of subjects achieving PRO1 remission at Week 12.
To evaluate the effect of LY3074828 on the proportion of subjects with **PRO1 remission** at Week 52	Proportion of subjects achieving PRO1 remission at Week 52.
To evaluate the effect of LY3074828 on **CDAI Remission** (defined as CDAI <150)	Proportion of subjects achieving CDAI Remission at Weeks 12 and 52.
To evaluate the effect of LY3074828 on **CDAI Response** (defined as a decrease in CDAI of at least 100 points or CDAI <150)	Proportion of subjects achieving CDAI Response at Weeks 12 and 52.
To evaluate the effect of LY3074828 on **CDAI remission at Week 52 among CDAI Responders** at Week 12	Proportion of subjects achieving CDAI Remission at Week 52 out of those subjects who achieved CDAI response at Week 12.

Abbreviations: ADA+ = positive for anti-drug antibodies; AE = adverse event; AP = abdominal pain; BMC = bowel movement count; CDAI = Crohn's Disease Activity Index; CCI [redacted]; CRP = C-reactive protein; EC50 = half maximal effective concentration; Emax = maximum effect; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; FCP = fecal calprotectin; GHAS = Global Histologic Disease Activity Score; IBDQ = Inflammatory Bowel Disease Questionnaire; NRS = numeric rating scale; PD = pharmacodynamics; PGRC = Patient's Global Rating of Change; PGRS = Patient's Global Rating of Severity; PK = pharmacokinetics; PRO = patient-reported outcomes; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self Report (16 Items); RHI = Robarts Histologic Index; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency; SF-36 = 36-Item Short Form Health Survey.

5. Study Design

Study AMAG is a multicenter, randomized, parallel-arm, placebo-controlled trial in which approximately 180 subjects will be randomized. Subjects will be stratified to the following categories, and the exact number enrolled in either group will be dependent upon the enrollment rate of each subject population:

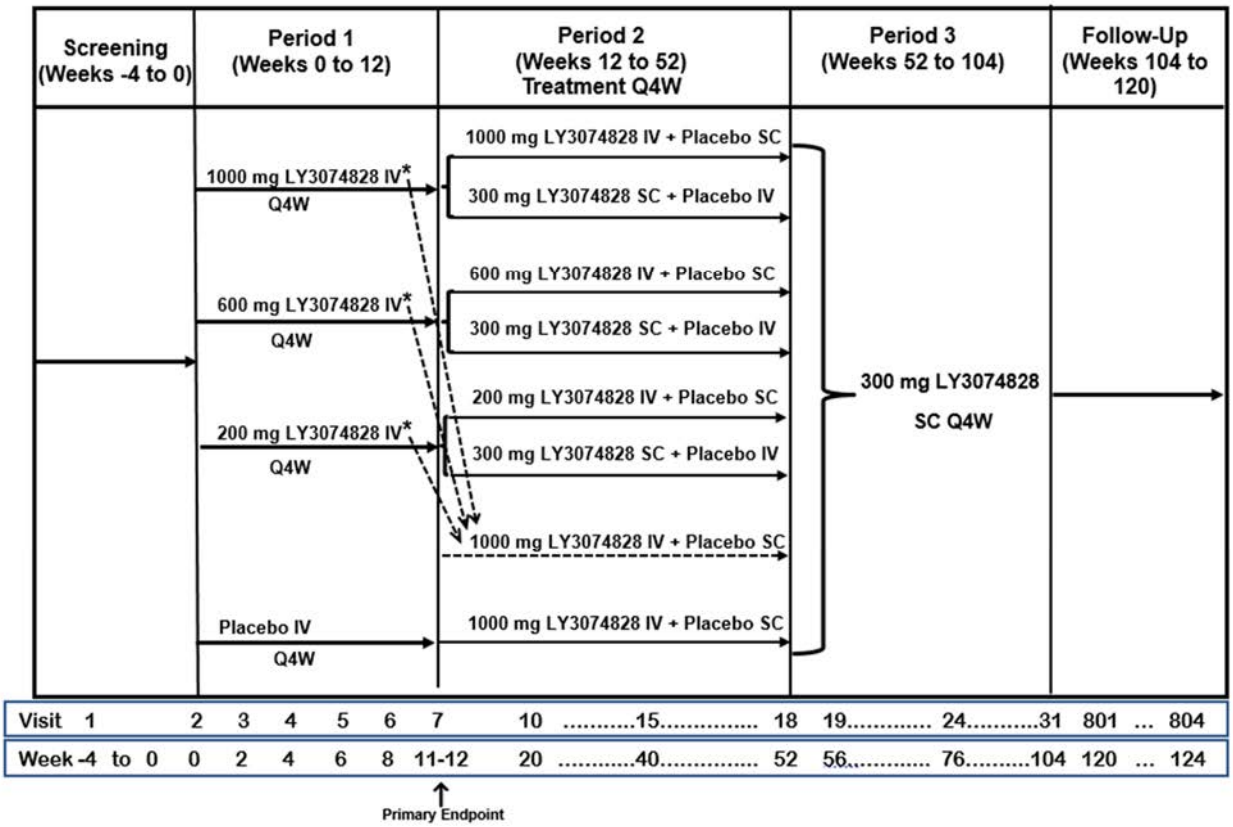
- A minimum of approximately 30% of subjects will be naive to biologic Crohn's disease (CD) therapy (including experimental biologic CD therapy).
- At least 50% of the subjects will be prior biologic CD therapy-experienced (including experience with experimental biologic CD therapy).

Study Periods:

- Screening (approximately 4 weeks): Subjects will be evaluated for study eligibility ≤28 days before the baseline visit.
  Period 1 (Weeks 0 to 12): A 12-week dosing period is designed to evaluate the efficacy and safety of LY3074828 administered intravenously at Weeks 0, 4, and 8. At baseline, subjects will be randomized with a 2:1:1:2 allocation across the 4 treatment arms (1000, 600, and 200 mg LY3074828, and placebo) and stratified on the basis of previous exposure to biologic therapy for treatment of CD.
- Period 2 (Weeks 12 to 52): Subjects will receive both IV and SC dosing to maintain blinding from Weeks 12 through 48.
  - All subjects who received LY3074828 treatment in Period 1 and who achieved an improvement in their Simple Endoscopic Score for Crohn's Disease (SES-CD) score from baseline at Week 12 (determined by the central reader) will be re-randomized evenly to either:
    1) continue Period 1 treatment assignment (IV LY3074828 1000 mg, 600 mg, or 200 mg every 4 weeks [Q4W]) with placebo administered subcutaneously.
    2) IV placebo Q4W with SC LY3074828 300 mg Q4W.
  - All subjects who received LY3074828 treatment in Period 1 and who did not achieve an improvement from baseline SES-CD score at Week 12 will receive IV LY3074828 1000 mg and SC placebo Q4W.
  - All subjects who received placebo in Period 1 will receive IV LY3074828 1000 mg and SC placebo Q4W.

  Re-randomization will be stratified based on endoscopic response (i.e., achieving a 50% reduction in SES-CD score from baseline).
- Period 3 (Weeks 52 to 104): All subjects with clinical benefit and continuing on study treatment may proceed to Period 3 and receive SC 300 mg LY3074828 Q4W open label starting at Week 52 through Week 104. Clinical benefit is defined as having an endoscopic response (50% reduction from baseline in SES CD score), or a 25% reduction from baseline in SES CD score, combined with a 40% reduction from baseline in stool frequency (SF) or abdominal pain (AP) score. Subjects not receiving clinical benefit at Week 52 will discontinue treatment and will enter the Follow-Up period.

- Follow-Up Period (Weeks 104 to 120): At Week 104, subjects will stop treatment and be followed for safety for an additional 16 weeks. Figure AMAG.5.1 illustrates the study design.



Abbreviations: ETV = early termination visit; IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease.
*Subjects who have not had any improvement in SES-CD score from baseline at Week 12, as determined by the central reader, will receive IV LY3074828 1000 mg + SC placebo.

NOTE:

Period 1:

- Subjects who discontinue treatment may continue in the study according to the visit schedule into Period 2.
- In IWRS these subject will be randomized as "No treatment for Period 2.".
- Subjects who ETV will continue to Visit 804/ET.

Period 2:

- Subjects who discontinue treatment may continue in the study according to the visit schedule during Period 2.
- At Week 52/Visit 18, subjects who have previously discontinued treatment or do not have clinical benefit will continue to Visit 801 of the Follow-up Period.
- Subjects who ETV will continue to Visit 804/ET.

Period 3:

- Subjects who discontinue treatment in Period 3 may continue in Period 3 and then proceed to Week 104/Visit 801 of the Follow-up Period.

Figure AMAG.5.1. Study design.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or its designee.

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), minimum, median, and maximum. Categorical data will be summarized in terms of the number of subjects in the analysis population, the number of subjects providing data at the relevant time point, frequency counts, and the percentages corresponding to the appropriate method. All confidence intervals (CIs) and statistical tests will be 2-sided unless otherwise specified.

All tests of the primary and secondary treatment effects, including health outcomes measurements will be conducted at a 2-sided alpha level of 0.10, unless otherwise stated.

The Schedule of Activities outlined in the protocol specifies the allowable windows for assessments. Assessments performed outside these windows are not expected to affect the primary outcomes and, as such, no subject /assessment will be excluded from any analysis due to this reason.

Data collected at early termination (ETV) visits will be entered under the visit in which it occurs. For by-visit summaries, only visits in which a measure was scheduled to be collected will be summarized.

Data summaries, analyses of results, and listings will be generated using SAS® Version 9.2 or later. Pharmacokinetic/pharmacodynamic (PK/PD) analyses will be carried out using other appropriate software. Not all displays described in this SAP will necessarily be included in the clinical study reports (CSRs). Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of or in addition to a static display. Any display described in this statistical analysis plan (SAP) and not provided will be available upon request.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

6.1.1. Subject Population for Analyses

Efficacy and safety analyses will be conducted on the populations defined in Table AMAG.6.1.

Table AMAG.6.1. Subject Populations for Analyses

Population	Description
Efficacy and Health Outcomes (EHO)	
Intent-to-treat (ITT)	All randomized subjects at Period 1, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Subjects will be analyzed according to the treatment to which they were randomized. Note: Subjects who are screen failures and inadvertently randomized that did not receive study treatment will be excluded from the ITT population.
Modified Intent-to-Treat (mITT)	All randomized subjects at Period 1 who receive at least 1 dose of study treatment (regardless if the subject does not receive the correct treatment, or otherwise does not follow the protocol). Subjects will be analyzed according to the treatment to which they were randomized. Note: If deemed necessary, select endpoints (Endoscopic Response at Week 12, Endoscopic Remission at Week 12, PRO Remission at Week 12, and CDAI Total Score through Week 12) will be analyzed based on this population.
EHO Group 2	All subjects (including non-improvers and placebo subjects) entering Period 2. Subjects will be analyzed according to the treatment to which they were randomized in Period 2. Note: Subjects who discontinue treatment in Period 1 may continue in the study according to the visit schedule into Period 2. These subjects will be excluded from this population. If deemed necessary, the data for these subjects will be reviewed.
EHO Group 3	All subjects with clinical benefit at the end of Period 2 and continuing to Period 3.
Safety	
Safety Population Period 1	All randomized subjects at Period 1 who received at least 1 dose of study treatment during Period 1. Subjects will be analyzed according to the treatment to which they were randomized. This population is identical to the mITT population described above.
Safety Population Period 2	All subjects (including non-improvers and placebo subjects) entering Period 2 who received at least 1 dose of study treatment during Period 2. Subjects will be analyzed according to the treatment to which they were randomized in Period 2. Note: Subjects who discontinue treatment may continue in the study according to the visit schedule into Period 2. These subjects will not be dosed and therefore will not be part of this population.
Safety population All SC LY	All subjects who received at least 1 dose of LY3074828 SC treatment.
Safety Population All LY	All subjects who received at least 1 dose of LY3074828 treatment.

6.1.2. Study Period

Table AMAG.6.2 defines the study periods.

Table AMAG.6.2. Study Periods

Period	Start Date	End Date
Study Baseline	Informed Consent date	Prior to Visit 2 dose date/time. If dose date is missing, the last date at Visit 2 will be used.
Period 1 (Weeks 0-12)	After Study Baseline end date.	Prior to Visit 8 dose date/time or the date of the ETV (if it occurs between Visits 2 and 8). If dose date is missing, the last date at Visit 8 will be used.
Period 2 (Weeks 12-52)	After Period 1 end date.	Prior to Visit 18 dose date/time or the date of the ETV (if it occurs between Visits 8 and 18). If dose date is missing, the last date at Visit 18 will be used.
Period 3 (Weeks 52-104)	Only for subjects with Clinical Benefit: After Period 2 end date.	Visit 31 dose date or the date of the ETV (if it occurs between Visits 18 and 31). If dose date is missing, the last date at Visit 31 will be used.
Follow-up (Weeks 104-120)	• Subjects completed treatment and Period 3: After Period 3 end date. • Subjects discontinued treatment in Period 2 but completed Period 2: After Period 2 end date. • Subjects with no Clinical Benefit and did not enter Period 3: After Period 2 end date. • Subjects discontinued treatment in Period 3 but completed Period 3: After Period 3 end date.	Visit 804 dose date or the date of the ETV (if it occurs between Visits 801 and 804), whichever is earliest.

Abbreviation: ETV = early termination visit.

6.1.3. Baseline and Postbaseline for Efficacy and Health Outcomes Analyses

Table AMAG.6.3 describes the baseline and postbaseline definitions for efficacy and health outcomes analyses.

Table AMAG.6.3. Baseline and Postbaseline Definitions for Efficacy and Health Outcomes Analyses

Efficacy Analysis Population	Analysis Type	Baseline (Periods as defined in Table AMAG.6.2)	Postbaseline (Periods as defined in Table AMAG.6.2)
ITT, mITT, EHO Group 2, EHO Group 3.	All efficacy and health outcomes analysis.	Baseline is the last non-missing (scheduled or unscheduled) assessment during the Study Baseline period. If time is not collected for a measurement taken on Visit 2 dose date, it will be assumed that it occurred prior to first dose.	Postbaseline: starts at Period 1 start date and ends at the Period end date for the analysis period(s) of interest.

Abbreviations: EHO = efficacy and health outcomes; ITT = intent to treat;

6.1.4. Baseline and Postbaseline for Safety Analyses

Table AMAG.6.4 describes the baseline and postbaseline definitions for safety analyses. Note that an alternative baseline definition may be considered after the IA #1 DBL (example, for Safety Population Period 2, the screening period will be used as the baseline for subjects receiving LY in Period 1; for subjects first receiving LY in Period 2 [i.e., PBO subjects in Period 1], the baseline period will be the time interval [equal in length to screening] leading up to LY administration).

Table AMAG.6.4. Baseline and Postbaseline Definitions for Safety Analyses

Safety Group	Analysis Type	Baseline (Periods as defined in Table AMAG.6.2)	Postbaseline (Periods as defined in Table AMAG.6.2)
Safety Population Period 1 *[Weeks 0-12 (Placebo-Controlled)]*	1.1) Treatment-Emergent Adverse Events	The baseline period is defined as the Study Baseline period. If time is not collected for an event starting on Visit 2 dose date, it will be assumed that it occurred after first dose.	Period 1 (Weeks 0-12): starts at Period 1 start date and ends at Period 1 end date or the day of the study treatment disposition visit (whichever is earliest) unless otherwise noted.
	1.2) Treatment-Emergent Abnormal Labs and Vital Signs	All scheduled and unscheduled measurements recorded during the baseline period as defined above (1.1). If time is not collected for a measurement taken on Visit 2 dose date, it will be assumed that it occurred prior to first dose.	Period 1 will be defined as above (1.1). All scheduled and unscheduled measurements will be included.
	1.3) Change from Last Baseline to Week *xx* and to Last Postbaseline for Labs and Vital Signs	The last scheduled non-missing assessment recorded during the baseline period defined above (1.1). If time is not collected for a measurement taken on Visit 2 dose date, it will be assumed that it occurred prior to first dose.	Period 1 as defined above (1.1). Only scheduled visits will be included. The ETVs are considered scheduled visits.

Baseline and Postbaseline Definitions for Safety Analyses

Safety Group	Analysis Type	Baseline (Periods as defined in Table AMAG.6.2)	Postbaseline (Periods as defined in Table AMAG.6.2)
Safety Population Period 2 *[Weeks 12-52]*	2.1) Treatment-Emergent Adverse Events	An event ongoing at the time of the first dose of Period 2 study treatment. If time is not collected for an event starting on Visit 8 dose date, it will be assumed that it occurred after first dose.	Period 2 (Weeks 12-52): starts at Period 2 Start Date and ends at Period 2 End Date or the day of the study treatment disposition visit (whichever is earliest) unless otherwise noted.
	2.2) Treatment-Emergent Abnormal Labs and Vital Signs	The last non-missing assessment (scheduled or unscheduled) recorded prior to the first dose of Period 2 study treatment. If time is not collected for a measurement taken on Visit 8 dose date, it will be assumed that it occurred prior to first dose.	Period 2 will be defined as above (2.1). All scheduled and unscheduled measurements will be included.
	2.3) Change from Last Baseline to Week *xx* and to Last Postbaseline for Labs and Vital Signs	The last non-missing scheduled assessment recorded prior to the first dose of Period 2 study treatment. If time is not collected for a measurement taken on Visit 8 dose date, it will be assumed that it occurred prior to first dose.	Period 2 will be defined as above (2.1). Only scheduled visits will be included. The ETVs are considered scheduled visits.
Safety population All SC LY *[All treatment periods where LY SC is administered]*	3.1) Treatment-Emergent Adverse Events	An ongoing event at the time of the first dose of LY SC treatment. If time is not collected for an event starting on the first dose date, it will be assumed that it occurred after first dose.	LY SC Treatment Period: starts at the administration of the first dose of LY SC treatment and ends at the study treatment disposition visit (ie, the last visit at which the LY SC treatment was administered).
	3.2) Treatment-Emergent Abnormal Labs and Vital Signs	The last non-missing assessment (scheduled or unscheduled) recorded prior to the first dose of LY SC treatment. If time is not collected for a measurement taken on first dose date, it will be assumed that it occurred prior to first dose.	LY SC Treatment Period will be defined as above (3.1). All scheduled and unscheduled measurements will be included.
	3.3) Change from Last Baseline to Week *xx* and to Last Postbaseline for Labs and Vital Signs	The last non-missing scheduled assessment recorded prior to the first dose of LY SC. If time is not collected for a measurement taken on first dose date, it will be assumed that it occurred prior to first dose.	LY SC Treatment Period will be defined as above (3.1). Only scheduled visits will be included. The ETVs are considered scheduled visits.

Baseline and Postbaseline Definitions for Safety Analyses

Safety Group	Analysis Type	Baseline (Periods as defined in Table AMAG.6.2)	Postbaseline (Periods as defined in Table AMAG.6.2)
Safety Population All LY (a) *[All treatment periods where LY (IV or SC) is administered]*	4a.1) Treatment-Emergent Adverse Events	Randomized to LY at Period 1: The baseline period is defined as the Study Baseline period. If time is not collected for an event starting on Visit 2 dose date, it will be assumed that it occurred after first dose. Randomized to Placebo at Period 1: An ongoing event at the time of the first dose of Period 2 study treatment of LY. If time is not collected for an event starting on Visit 8 dose date, it will be assumed that it occurred after first dose.	Randomized to LY at Period 1: LY Treatment Period: starts at Period 1 Start Date and ends at the study treatment disposition visit (ie, the last visit at which the LY treatment was administered). Randomized to Placebo at Period 1: LY Treatment Period: starts at the administration of the first dose of Period 2 study treatment of LY and ends at the study treatment disposition visit (ie, the last visit at which the LY treatment was administered).
	4a.2) Treatment-Emergent Abnormal Labs and Vital Signs	Randomized to LY at Period 1: Baseline will be all scheduled and unscheduled measurements recorded during the baseline period as defined above (4a.1). If time is not collected for a measurement taken on Visit 2 dose date, it will be assumed that it occurred prior to first dose. Randomized to Placebo at Period 1: The last non-missing assessment (scheduled or unscheduled) recorded prior to the first dose of Period 2 LY study treatment. If time is not collected for a measurement taken on Visit 8 dose date, it will be assumed that it occurred prior to first dose.	Randomized to LY at Period 1: LY Treatment Period will be defined as above (4a.1). All scheduled and unscheduled measurements will be included. Randomized to Placebo at Period 1: LY Treatment Period will be defined as above (4a.1). All scheduled and unscheduled measurements will be included.

Baseline and Postbaseline Definitions for Safety Analyses

Safety Group	Analysis Type	Baseline (Periods as defined in Table AMAG.6.2)	Postbaseline (Periods as defined in Table AMAG.6.2)
	4a.3) Change from Last Baseline to Week *xx* and to Last Postbaseline for Labs and Vital Signs	Randomized to LY at Period 1: The last scheduled non-missing assessment recorded prior to the date of first dose of study treatment during the baseline period defined above (4a.1). If time is not collected for a measurement taken on Visit 2 dose date, it will be assumed that it occurred prior to first dose. Randomized to Placebo at Period 1: The last non-missing scheduled assessment recorded prior to the first dose of Period 2 study treatment. If time is not collected for a measurement taken on Visit 8 dose date, it will be assumed that it occurred prior to first dose.	Randomized to LY at Period 1: LY Treatment Period will be defined as above (4a.1). Only scheduled measurements will be included. The ETVs are considered scheduled visits. Randomized to Placebo at Period 1: LY Treatment Period will be defined as above (4a.1). Only scheduled measurements will be included. The ETVs are considered scheduled visits.
Safety Population All LY (b) *[All treatment periods where LY (IV or SC) is administered and Follow-Up]*	4b.1) Treatment-Emergent Adverse Events	Randomized to LY at Period 1: The baseline period is defined as the Study Baseline period. If time is not collected for an event starting on Visit 2 dose date, it will be assumed that it occurred after first dose. Randomized to Placebo at Period 1: An ongoing event at the time of the first dose of Period 2 study treatment of LY. If time is not collected for an event starting on Visit 8 dose date, it will be assumed that it occurred after first dose.	Randomized to LY at Period 1: LY Treatment Period: starts at Period 1 Start Date and ends at Week 120 (Visit 804). Note that this will include the period after discontinuing treatment. Randomized to Placebo at Period 1: LY Treatment Period: starts at the administration of the first dose of Period 2 study treatment of LY and ends at Week 120 (Visit 804). Note that this will include the period after discontinuing treatment.

Baseline and Postbaseline Definitions for Safety Analyses

Safety Group	Analysis Type	Baseline (Periods as defined in Table AMAG.6.2)	Postbaseline (Periods as defined in Table AMAG.6.2)
	4b.2) Treatment-Emergent Abnormal Labs and Vital Signs	Randomized to LY at Period 1: Baseline will be all scheduled and unscheduled measurements recorded during the baseline period as defined above (4b.1). If time is not collected for a measurement taken on Visit 2 dose date, it will be assumed that it occurred prior to first dose. Randomized to Placebo at Period 1: The last non-missing assessment (scheduled or unscheduled) recorded prior to the first dose of Period 2 LY study treatment. If time is not collected for a measurement taken on Visit 8 dose date, it will be assumed that it occurred prior to first dose.	Randomized to LY at Period 1: LY Treatment Period will be defined as above (4b.1). All scheduled and unscheduled measurements will be included. Randomized to Placebo at Period 1: LY Treatment Period will be defined as above (4b.1). All scheduled and unscheduled measurements will be included.
	4b.3) Change from Last Baseline to Week *xx* and to Last Postbaseline for Labs and Vital Signs	Randomized to LY at Period 1: The last scheduled non-missing assessment recorded prior to the date of first dose of study treatment during the baseline period defined above (4b.1). If time is not collected for a measurement taken on Visit 2 dose date, it will be assumed that it occurred prior to first dose. Randomized to Placebo at Period 1: The last non-missing scheduled assessment recorded prior to the first dose of Period 2 study treatment. If time is not collected for a measurement taken on Visit 8 dose date, it will be assumed that it occurred prior to first dose.	Randomized to LY at Period 1: LY Treatment Period will be defined as above (4b.1). Only scheduled measurements will be included. The ETVs are considered scheduled visits. Randomized to Placebo at Period 1: LY Treatment Period will be defined as above (4b.1). Only scheduled measurements will be included. The ETVs are considered scheduled visits.

6.1.5. Treatment Groups by Analysis Population and Analysis Period

Table AMAG.6.5 provides the treatment groups to be displayed for each analysis population and analysis period.

Table AMAG.6.5. Treatment Groups by Analysis Population and Analysis Period

Analysis Population	Analysis Period	Treatment Groups	Treatment-Group Comparison, When Applicable
ITT, mITT, Safety Population Period 1	Period 1	• PBO • 200 mg IV • 600 mg IV • 1000 mg IV • All LY • Total	For ITT and mITT: • 200 mg IV vs PBO • 600 mg IV vs PBO • 1000 mg IV vs PBO For Safety Population Period 1: • All LY vs PBO
EHO Group 2, EHO Group 3	Periods 1, 2, 3 and f/u (where applicable)	• 200 mg IV/200 mg IV • 600 mg IV/600 mg IV • 1000 mg IV/1000 mg IV • LY IV/300 mg SC • 1000 mg IV for subjects showing no improvement[#] in SES-CD from baseline at Week 12 • Placebo/1000 mg IV • Total	N/A
Safety Population Period 2	Period 2	• 200 mg IV/200 mg IV • 600 mg IV/600 mg IV • 1000 mg IV/1000 mg IV • LY IV/300 mg SC • 1000 mg IV for subjects showing no improvement# in SES-CD from baseline at Week 12 • Placebo/1000 mg IV • All LY IV • Total	N/A
Safety population All SC LY	All treatment periods where LY SC is administered (time during either Periods 2-3)	• 300 mg SC *	N/A
Safety Population All LY	All treatment periods where LY (IV or SC) is administered	• LY Treatment *	N/A

Treatment Groups by Analysis Population and Analysis Period

Analysis Population	Analysis Period	Treatment Groups	Treatment-Group Comparison, When Applicable
Safety Population All LY	All treatment periods where LY (IV or SC) is administered and Follow-Up Period	• LY Treatment and after *	N/A

Abbreviations: EHO = efficacy and health outcomes; f/u = follow-up; ITT = intent to treat; IV = intravenous; mITT = modified intent to treat; N/A = not applicable; PBO = placebo; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease.

6.1.6. Statistical Methodology

The following general statistical models will be used in the analysis of efficacy, health outcomes, and selected safety measures for Periods 1, 2, 3, and/or the Follow-Up Period. In the detailed descriptions of each measure in the following sections of this plan, these models will be referred to and any exceptions or additions to the model will be stated as appropriate.

6.1.6.1. Logistic Regression Model

The primary analysis of categorical efficacy and health outcomes variables will use a logistic regression analysis with treatment, geographic region, and prior biologic CD therapy (prior biologic experience versus prior biologic naive) in the model. The proportions and 90% CIs will be reported. For each treatment comparison, an estimate of the odds ratio, corresponding Wald 90% CI, and p-value will be presented.

6.1.6.2. Cochran-Mantel-Haenszel (CMH)

Secondary analysis of select categorical efficacy and health outcomes variables will be conducted using a Cochran-Mantel-Haenszel (CMH) test that stratifies by (that is, controls for) prior biologic CD therapy use. A Fisher's exact test may be utilized when deemed appropriate.

6.1.6.3. Mixed Model for Repeated Measures (MMRM)

The primary analyses for all continuous efficacy and health outcomes variables will be based on the mixed model for repeated measures (MMRM) analysis method. The MMRM analyses will be conducted using a restricted maximum likelihood (REML)-based repeated measures approach. When MMRM is used, the model includes treatment, geographic region, prior biologic CD therapy use (prior biologic experience versus prior biologic naive), baseline score, visit, and the interaction of treatment-by-visit and baseline-by-visit as fixed factors.

The covariance structure to model the within-subject errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, will be used. The first structure to yield convergence will be used for inference. The Newton-Raphson with ridging optimization technique will be used to aid with convergence. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Type III sums of

squares for the least squares (LS) means will be used for the statistical comparison; the 90% CI will also be reported. Treatment group comparisons with placebo at Week 12 (Visit 8) will be tested.

6.1.6.4. Analysis of Covariance (ANCOVA)

A sensitivity analysis of treatment comparisons of continuous efficacy variables may be conducted using analysis of covariance (ANCOVA) with treatment, geographic region, baseline value, and prior biologic CD therapy use (prior biologic experience versus prior biologic naive) in the model. Type III sums of squares for the LS means will be used for the statistical comparison; the 90% CI will also be reported.

6.2. Adjustments for Covariates

The randomization at the beginning of Period 1 is stratified by previous biologic CD therapy: previous exposure to biologic therapy for treatment of CD, and naive to biologic therapy for treatment of CD. Unless otherwise specified, all efficacy and health outcomes analyses will include the stratification factor in the models. Geographic region will also be included as a covariate in the models.

Unless otherwise specified, analyses will be performed utilizing the methodology and covariates described in Section 6.1.6.

6.3. Handling of Dropouts or Missing Data

6.3.1. Non-Responder Imputation (NRI)

The primary outcome is the proportion of subjects with endoscopic response at 12 weeks. For this and other categorical efficacy endpoints, non-responder imputation (NRI) will be used for missing clinical assessment values. Specifically, all subjects who discontinue from the study treatment at any time prior to Week 12 for any reason or fail to have an adequate Week 12 efficacy assessment, will be considered a non-responder at Week 12. Randomized subjects without at least 1 postbaseline observation will also be defined as non-responders for the NRI analysis.

Similarly, subjects who discontinue from the study treatment for any reason at any time prior to Week 52 for any reason or fail to have an adequate Week 52 efficacy assessment, will be considered a non-responder at Week 52. Subjects (including non-improvers and placebo subjects) without at least 1 Period 2 observation will also be defined as non-responders for the NRI analysis at Week 52.

The NRI may be applied at any time point specified for analysis. In general, a subject will be defined as a non-responder from the time of treatment discontinuation and onward. If a measurement is taken at the time point of treatment discontinuation, this measurement will be used to define if a subject is a responder or not for the particular time point; measurements taken at subsequent time points will be defined as non-responder.

6.3.2. Modified Baseline Observation Carried Forward (mBOCF)

A modified baseline observation carried forward (mBOCF) analysis will be performed on key continuous efficacy endpoints.

This is both a sensitivity analysis and an analysis for regulatory agencies that prefer an alternative to MMRM. For subjects discontinuing investigational product due to an adverse event (AE), the baseline observation will be carried forward to the corresponding primary endpoint for evaluation. For subjects discontinuing investigational product for any other reason, the last non-missing postbaseline observation before discontinuation will be carried forward to the corresponding endpoint for evaluation. Randomized subjects without at least 1 postbaseline observation will not be included for evaluation with the exception of subjects discontinuing study treatment due to an AE.

6.4. Multicenter Studies

This study will be conducted by multiple investigators at multiple sites internationally. Randomization to treatment groups will not be stratified by country. However, the countries will be categorized into geographic regions for use as a covariate during applicable analyses.

Unless otherwise specified, the statistical analysis models will adjust for geographic region (United States [US] versus non-US).

6.5. Multiple Comparisons/Multiplicity

No multiplicity adjustment will be done for testing primary or secondary hypotheses for this Phase 2 study.

6.6. Subject Disposition

All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

Disposition data will be summarized by treatment group for Periods 1, 2, 3, and Follow-Up using the ITT Population. Period 1 will use the treatment groups defined for the ITT population. Periods 2, 3, and Follow-Up will use the treatment groups for EHO Group 2.

The number and percentage of subjects randomized and completing the study or discontinuing the study drug/study early will be presented. Reasons for discontinuing the study drug and reasons for discontinuing study will be summarized.

6.7. Subject Characteristics

Demographic and baseline disease characteristics, including medical history and detailed CD history, will be summarized by treatment group and overall for the ITT population. Demographic characteristics will include sex, weight, height, smoking habits, race and ethnicity. Age and body mass index (BMI) will be calculated and summarized. Baseline disease

characteristics, such as age at diagnosis, location and duration of disease, prior biologic CD therapy, will be summarized.

No inferential analysis for the comparability of demographic and baseline disease characteristics across treatment groups will be performed.

6.8. Treatment Compliance

Subjects who are noncompliant according to the definition in Section 7.6 of the protocol will be listed by treatment and will also be counted as protocol deviations. A subject will be considered noncompliant if he or she fails to attend for administration of study medication within the required treatment window as defined in the Schedule of Activities (Section 2) in the protocol, or if the prescribed dosage was not administered.

Study treatment administration data at all treatment visits will be listed for the ITT population.

6.9. Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary.

Prior medications are those medications that start and stop prior to the date of first dose of study treatment in Period 1.

Concomitant medications are those medications:

- that start before the administration of first dose of study treatment in Period 1 and continue into the treatment period. This will be considered as **current** medication.
- that start on or after the first dose of study treatment in Period 1. Note that the medication will be assigned to the treatment period in which they are taken. For example, if a subject is receiving medication during Period 1 and has a stop date during Period 2, the same medication will be counted in Period 1 and Period 2 summaries.

Prior medications will be presented by ATC class and preferred term (PT) by treatment group for the ITT Population. Reasons for discontinuing previous CD therapy will be reviewed.

Concomitant medications considered current will be presented similarly by ATC class and PT.

Concomitant medications not considered current will be summarized separately for the following:

1. CD medication (including corticosteroids)
2. remaining medications (excluding CD medications)

The summaries will present the number and percentage of subjects taking concomitant medication by ATC class and PT for Period 1 (ITT population), Period 2 (EHO Group 2), Period 3 (EHO Group 3), and Follow-Up (ITT population).

Visual techniques will be used to examine subjects' use of corticosteroid in the context of treatment group, treatment start and stop dates, medication start and stop dates, and dose.

6.10. Efficacy Analyses

The efficacy endpoints are defined by time point and outcome measure in Table AMAG.6.6. In addition, changes in Crohn's Disease Activity Index (CDAI) from baseline will be evaluated as exploratory analyses.

Table AMAG.6.6. Efficacy Endpoints

	Response	Remission	Durability
SES-CD	**Weeks 12 [a], 52 [b]**	Weeks 12 [b], 52 [b]	Week 52 [b] (Response, Remission)
PRO	Weeks 12 [c], 52 [c]	Weeks 12 [b], 52 [b]	Week 52 [c] (Response, Remission)
PRO2	Weeks 12 [c], 52 [c]	Weeks 12 [c], 52 [c]	Week 52 [c] (Response, Remission)
PRO1		Weeks 12 [c], 52 [c]	
Composite[d]		Weeks 12 [c], 52 [c]	Week 52 [c]
Composite[e]		Weeks 12 [c], 52 [c]	Week 52 [c]

Abbreviations: PRO = patient-reported outcomes; SES-CD = Simple Endoscopic Score for Crohn's Disease.

[a] Primary Endpoint
[b] Secondary Endpoints
[c] Exploratory Endpoints
[d] Endoscopic Remission and PRO Remission
[e] Endoscopic Response and PRO Remission

6.10.1. Primary Outcome and Methodology

The primary outcome is stated in Table AMAG.6.6 and its derivations/analyses are described in Table AMAG.6.7 and Table AMAG.6.8.

6.10.2. Secondary Efficacy Analyses

The secondary outcomes are stated in Table AMAG.6.6 and their derivations/analyses are described in Table AMAG.6.7 and Table AMAG.6.8.

6.10.3. Exploratory Efficacy Analyses

The exploratory outcomes are stated in Table AMAG.6.6 and their derivations/analyses are described in Table AMAG.6.7 and Table AMAG.6.8.

Table AMAG.6.7. Description and Derivation of Efficacy Endpoints

Measure	Description / Timing	Variable	Derivation / Comment
SES-CD	SES-CD is based on 4 endoscopic variables (presence and size of ulcers, proportion of surface covered by ulcers, proportion of surface affected by disease, and presence and severity of stenosis). The 4 endoscopic variables are scored from 0 to 3 in each of 5 bowel segments (ileum; right, transverse, and left colon; and rectum): presence and size of ulcers (none = score 0; diameter 0.1–0.5 cm = score 1; 0.5–2 cm = score 2; >2 cm = score 3); extent of ulcerated surface (none = 0; <10% = 1; 10–30% = 2; >30% = 3); extent of affected surface (none = 0; <50% = 1; 50–75% = 2; >75% = 3); and presence and type of narrowings (none=0; single, can be passed=1; multiple, can be passed=2; cannot be passed=3). Complete details of the calculation of the SES-CD are given in Appendix 2. Higher SES-CD scores indicate more severe disease. SES-CD scores are obtained at Weeks 0, 12, and 52.	Endoscopic Response	Endoscopic response at Week *x* is defined as a 50% reduction in SES-CD at Week X when compared with baseline. Endpoints: • Proportion of subjects with endoscopic responses at Week 12 • Proportion of subjects with endoscopic responses at Week 52
		Endoscopic Remission	Endoscopic remission at Week *x* is defined as an SES-CD of <4 ileal-colonic or <2 for isolated ileal disease, and no subscore >1 at Week *x*. Endpoints: • Proportion of subjects with endoscopic remission at Week 12 • Proportion of subjects with endoscopic remission at Week 52
		Durability of Endoscopic Response	Endpoint: Proportion of subjects with endoscopic response at both Weeks 12 and 52 (ie, of those subjects who achieved an endoscopic response at Week 12, the proportion who maintained an endoscopic response at Week 52).
		Durability of Endoscopic Remission	Endpoint: Proportion of subjects with endoscopic remission at both Weeks 12 and 52 (ie, of those subjects who achieved an endoscopic remission at Week 12, the proportion who maintained an endoscopic remission at Week 52).

Description and Derivation of Efficacy Endpoints

Measure	Description / Timing	Variable	Derivation / Comment
CDAI	The CDAI is an 8-item disease activity measure comprised of 3 patient-reported and 5 physician-reported/laboratory items. Subject responses are summed over a 7-day period and subsequently weighted, yielding a total score range of 0-600 points. For all endpoints derived using CDAI in this table, 7 days of subject-reported data within a 12-day period prior to a visit will be utilized to calculate scores. Data will be excluded from score calculations when collected on day(s) of colonoscopy prep, day of colonoscopy procedure, and 2 days after colonoscopy procedure. If after excluding these values 4 days of data are not available, the value will be set to missing. CDAI data is collected at every visit during the Screening through Follow-Up Periods visits.	PRO Remission	PRO remission is defined as SF ≤2.5 and AP ≤1 and no worse than baseline at Week *x*. PRO remission = (7 day average of SF) ≤2.5 and no worse than baseline and (7 day average of AP score) ≤1 and no worse than baseline SF captures the number of liquid or very soft stools. AP score is classified as 0=none, 1=mild, 2=moderate, 3=severe. Endpoints: • Proportion of subjects with PRO remission at Week 12 • Proportion of subjects with PRO remission at Week 52
		PRO Response	PRO response is defined as a decrease of at least 30% in either SF or AP and neither of them worse than baseline Endpoints: • Proportion of subjects with PRO response at Week 12 • Proportion of subjects with PRO response at Week 52
		Durability of PRO Remission	• Endpoint: Proportion of subjects with PRO remission at both Weeks 12 and 52 (ie, of those subjects who achieved a PRO remission at Week 12, the proportion who maintained a PRO remission at Week 52).
		Durability of PRO Response	• Endpoint: Proportion of subjects with PRO response at both Weeks 12 and 52 (ie, of those subjects who achieved a PRO response at Week 12, the proportion who maintained a PRO response at Week 52).
		PRO Remission in PRO Responders	Endpoint: Proportion of subjects with PRO remission at Week 52 and PRO response at Week 12 (ie, of those subjects who achieved a PRO response at Week 12, the proportion who achieved a PRO remission at Week 52).

Description and Derivation of Efficacy Endpoints

Measure	Description / Timing	Variable	Derivation / Comment
		PRO2 Response	PRO2 is a 2-item index comprised of the SF and AP items from the CDAI (weighted). The total PRO2 is comprised of the average daily scores over 7 days, weighted using the CDAI multiplication factors for SF and AP items. (See Appendix 6 for complete details on the CDAI form.) PRO2 = (7 day average of SF)*2 + (7 day average of AP score)*5 Proportion of subjects with PRO2 reduction of at least 5 points at Week *x* compared with baseline. Endpoints: • Proportion of subjects with PRO2 response at Week 12 • Proportion of subjects with PRO2 response at Week 52
		PRO2 Remission	See PRO2 calculations above. Proportion of subjects with PRO2 <8 at Week *x*. Endpoints: • Proportion of subjects with PRO2 remission at Week 12 • Proportion of subjects with PRO2 remission at Week 52
		Durability of PRO2 Response	Endpoint: Proportion of subjects with PRO2 response at both Weeks 12 and 52 (ie, of those subjects who achieved a PRO2 response at Week 12, the proportion who maintained a PRO2 response at Week 52).
		Durability of PRO2 Remission	Endpoint: Proportion of subjects with PRO2 remission at both Weeks 12 and 52 (ie, of those subjects who achieved a PRO2 remission at Week 12, the proportion who maintained a PRO2 remission at Week 52).
		PRO1 Remission	PRO1 remission is defined as SF ≤1.5 and AP ≤1 and no worse than baseline for both SF and AP at Week *x*. PRO remission = (7 day average of SF) ≤2.5 and no worse than baseline and (7 day average of AP score) ≤1 and no worse than baseline. Endpoints: • Proportion of subjects with PRO1 remission at Week 12 • Proportion of subjects with PRO1 remission at Week 52

Description and Derivation of Efficacy Endpoints

Measure	Description / Timing	Variable	Derivation / Comment
		CDAI Total Score	The derivation is based on the CDAI questionnaire in Appendix 6. It also utilizes the standard weights table in that section. Endpoint: Changes from baseline.
		CDAI Remission	See CDAI Total Score calculations above. Proportion of subjects with CDAI Total Score <150 at Week x. Endpoints: • Proportion of subjects with CDAI remission at Week 12 • Proportion of subjects with CDAI remission at Week 52
		CDAI Response	See CDAI Total Score calculations above. Proportion of subjects achieving a CDAI reduction of ≥100 from baseline or CDAI <150 at Week x. Endpoints: • Proportion of subjects with CDAI response at Week 12 • Proportion of subjects with CDAI response at Week 52
		CDAI Remission in CDAI Responders	Endpoints: • Among CDAI responders at Week 12, the proportion of subjects with CDAI remission at Week 52.
Composite Endoscopic and PRO Remissions	Endoscopic remission: See SES-CD section above. PRO remission: See CDAI section above.	Composite of Endoscopic and PRO Remissions	Proportion of subjects achieving both endoscopic and PRO remissions at Week *x*. Endpoints: • Proportion of subjects achieving both endoscopic and PRO remissions at Week 12 • Proportion of subjects achieving both endoscopic and PRO remissions at Week 52
		Durability of Composite Endoscopic and PRO Remissions	Endpoint: Proportion of subjects achieving both endoscopic and PRO remissions at Week 52 who also had both endoscopic and PRO remissions at Week 12 (that is, of those subjects who achieved both endoscopic and PRO remissions at Week 12, the proportion who maintained both endoscopic and PRO remissions at Week 52).

Description and Derivation of Efficacy Endpoints

Measure	Description / Timing	Variable	Derivation / Comment
Composite Endoscopic Response and PRO Remission	Endoscopic response: See SES-CD section above. PRO remission: See CDAI section above.	Composite of Endoscopic Response and PRO Remission	Proportion of subjects achieving both endoscopic reponse and PRO remission at Week *x*. Endpoints: • Proportion of subjects achieving both endoscopic response and PRO remission at Week 12 • Proportion of subjects achieving both endoscopic and PRO remissions at Week 52
		Durability of Composite Endoscopic Response and PRO Remission	Endpoint: Proportion of subjects achieving both endoscopic response and PRO remission at Week 52 who also had both endoscopic response and PRO remission at Week 12 (that is, of those subjects who achieved both endoscopic response and PRO remission at Week 12, the proportion who maintained both endoscopic response and PRO remission at Week 52).

Abbreviations: AP = abdominal pain; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; PRO = patient-reported outcomes; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

Table AMAG.6.8 describes the analysis methods, population, and time points/associated study periods for each analysis.

Table AMAG.6.8. Description of Efficacy Analyses

Measure	Variable	Analysis Method (Section 6.1.6)	Population (Table AMAG.6.1)	Time Point
SES-CD	Endoscopic Response	Primary Analysis: Logistic regression analysis with NRI	ITT Population	Week 12
		Secondary Analysis: CMH with NRI	ITT Population	Week 12
		Descriptive Statistics with NRI	EHO Group 2	All scheduled visits through Week 52
	Endoscopic Remission	Primary Analysis: Logistic regression analysis with NRI	ITT Population	Week 12
		Secondary Analysis: CMH with NRI	ITT Population	Week 12
		Descriptive Statistics with NRI	EHO Group 2	All scheduled visits through Week 52
	Durability of Endoscopic Response	Descriptive Statistics with NRI	EHO Group 2	Week 52
	Durability of Endoscopic Remission	Descriptive Statistics with NRI	EHO Group 2	Week 52
CDAI	PRO Remission	Primary Analysis: Logistic regression analysis with NRI	ITT Population	Week 12
		Secondary Analysis: CMH with NRI	ITT Population	Week 12
		Descriptive Statistics with NRI	EHO Group 2, EHO Group 3	All scheduled visits through Week 120 (where applicable)
	PRO Response	Primary Analysis: Logistic regression analysis with NRI	ITT Population	Week 12
		Secondary Analysis: CMH with NRI	ITT Population	Week 12
		Descriptive Statistics with NRI	EHO Group 2, EHO Group 3	All scheduled visits through Week 120 (where applicable)
	Durability of PRO Remission	Descriptive Statistics with NRI	EHO Group 2	Week 52
	Durability of PRO Response	Descriptive Statistics with NRI	EHO Group 2	Week 52
	PRO Remission in PRO Responders	Descriptive Statistics with NRI	EHO Group 2	Week 52
	PRO2 Response	Primary Analysis: Logistic regression analysis with NRI	ITT Population	Week 12

Description of Efficacy Analyses

Measure	Variable	Analysis Method (Section 6.1.6)	Population (Table AMAG.6.1)	Time Point
		Secondary Analysis: CMH with NRI	ITT Population	Week 12
		Descriptive Statistics with NRI	EHO Group 2, EHO Group 3	All scheduled visits through Week 120 (where applicable)
	PRO2 Remission	Primary Analysis: Logistic regression analysis with NRI	ITT Population	Week 12
		Secondary Analysis: CMH with NRI	ITT Population	Week 12
		Descriptive Statistics with NRI	EHO Group 2, EHO Group 3	All scheduled visits through Week 120 (where applicable)
	Durability of PRO2 Response	Descriptive Statistics with NRI	EHO Group 2	Week 52
	Durability of PRO2 Remission	Descriptive Statistics with NRI	EHO Group 2	Week 52
	PRO1 Remission	Primary Analysis: Logistic regression analysis with NRI	ITT Population	Week 12
		Secondary Analysis: CMH with NRI	ITT Population	Week 12
		Descriptive Statistics with NRI	EHO Group 2, EHO Group 3	All scheduled visits through Week 120 (where applicable)
	CDAI Total Score - change from baseline	Primary Analysis: MMRM	ITT Population	Week 12
		Sensitivity Analysis: ANCOVA (mBOCF)	ITT Population	Week 12
		Descriptive Statistics	EHO Group 2, EHO Group 3	All scheduled visits through Week 120 (where applicable)
	CDAI Remission	Primary Analysis: Logistic regression analysis with NRI	ITT Population	Week 12
		Descriptive Statistics with NRI	EHO Group 2, EHO Group 3	All scheduled visits through Week 120 (where applicable)
	CDAI Response	Primary Analysis: Logistic regression analysis with NRI	ITT Population	Week 12
		Descriptive Statistics with NRI	EHO Group 2, EHO Group 3	All scheduled visits through Week 120 (where applicable)
	CDAI Remission in CDAI Responders	Descriptive Statistics with NRI	EHO Group 2	Week 52

Description of Efficacy Analyses

Measure	Variable	Analysis Method (Section 6.1.6)	Population (Table AMAG.6.1)	Time Point
Composite endoscopic and PRO remissions	Composite of endoscopic and PRO remissions	Primary Analysis: Logistic regression analysis with NRI	ITT Population	Week 12
		Secondary Analysis: CMH with NRI	ITT Population	Week 12
		Descriptive Statistics with NRI	EHO Group 2	All scheduled visits through Week 52
	Durability of composite endoscopic and PRO remissions	Descriptive Statistics with NRI	EHO Group 2	Week 52
Composite endoscopic response and PRO remission	Composite of endoscopic response and PRO remission	Primary Analysis: Logistic regression analysis with NRI	ITT Population	Week 12
		Secondary Analysis: CMH with NRI	ITT Population	Week 12
		Descriptive Statistics with NRI	EHO Group 2	All scheduled visits through Week 52
	Durability of composite endoscopic response and PRO remission	Descriptive Statistics with NRI	EHO Group 2	Week 52

Abbreviations: CDAI = Crohn's Disease Activity Index; CMH = Cochran-Mantel-Haenszel; EHO = efficacy and health outcomes; ITT = intent-to-treat; NRI = non-responder imputation; PRO = patient-reported outcomes; SES-CD = Simple Endoscopic Score for Crohn's Disease.

6.11. Health Outcomes/Quality-of-Life Analyses

There are 9 self-administered questionnaires used for measuring health outcomes in this trial. CDAI is not included in Table AMAG.6.9, as it is described in the previous section. The health outcomes derivations/analyses are described in Table AMAG.6.10 and Table AMAG.6.11.

Table AMAG.6.9. Health Outcomes Endpoints

Health Outcomes Endpoint	Response
PGRS (Patient's Global Rating of Severity) (Daily) [a]	Weeks 12, 52
PGRC (Patient's Global Rating of Change) [a]	
IBDQ (Inflammatory Bowel Disease Questionnaire score) [a]	
FACIT-Fatigue (Functional Assessment of Chronic Illness Therapy–Fatigue) [a]	
SF-36 (Medical Outcomes 36-Item Short Form Health Survey score) Version 2 [a]	
[redacted]	
BMC (Bowel Movement Count) (Daily) [b]	
QIDS-SR16 (Quick Inventory of Depressive Symptomatology–Self Report [16 Items]) [b]	
[redacted]	Week 12

[a] Secondary Endpoints
[b] Exploratory Endpoints

Table AMAG.6.10. Description and Derivation of Health Outcomes Endpoints Except CDAI

Measure	Description / Timing	Variable	Derivation / Comment
PGRS	The PGRS is a 1-item patient-rated questionnaire designed to assess the subjects' rating of their disease symptom severity over the past 24 hours. Responses are graded on a 6-point scale in which a score of 1 indicates the subject has no symptoms (that is, "none") and a score of 6 indicates that the subject's symptom are "very severe." PGRS is collected daily during Screening, Periods 1, 2, and 3, but only the last 12 days prior to each visit in the Schedule of Activities of the protocol will be considered for analysis.	Mean PGRS score	7 days of subject-reported data within a 12-day period prior to a visit will be utilized to calculate the average PGRS scores. Data will be excluded from score calculation when collected on day(s) of colonoscopy prep, day of colonoscopy procedure, and two days after colonoscopy procedure. If after excluding these values 4 days of data are not available, the value will be set to missing.
PGRC	The PGRC scale is a patient-rated instrument designed to assess the subjects' rating of change in their symptom(s). Responses are graded on a 7-point Likert scale in which a score of 1 indicates that the subject's symptom is "very much better," a score of 4 indicates that the subject's symptom has experienced "no change," and a score of 7 indicates that the subject's symptom is "very much worse." PGRC is assessed at Weeks 4, 11-12, 16, 24, 32, 44, 52, 56, 72, 88, and 104 during Periods 1, 2, and 3 per the Schedule of Activities in the protocol.	PGRC score	PGRC is a single score collected at each study visit. No derivation is required for analysis.
IBDQ	The IBDQ is a 32-item self-administered questionnaire. The IBDQ has 4 dimensions: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items) (Feagan et al. 2011). Responses are graded on a 7-point Likert scale in which 7 denotes "not a problem at all" and 1 denotes "a very severe problem." Scores range from 32 to 224; a higher score indicates a better quality of life. IBDQ is assessed at Screening, Baseline, and Weeks 4, 11-12, 16, 24, 32, 44, 52, 56, 72, 88, and 104 during Periods 1, 2, and 3 per the Schedule of Activities in the protocol.	IBDQ score	The scores from each of the 32 questions will be summed to find the total IBDQ score. Instructions for handling missing values are described in Appendix 3.
		IBDQ Responder	Proportion of subjects achieving the IBDQ MCID where MCID is defined as an improvement (increase from baseline) ≥ 16 points in the IBDQ score.

Description and Derivation of Health Outcomes Endpoints Except CDAI

Measure	Description / Timing	Variable	Derivation / Comment
FACIT-Fatigue	The FACIT-Fatigue is a 13-item instrument developed to measure fatigue in chronic illness subjects. It has been validated for use in IBD subjects. Total score ranges from 0 to 52 based on a rating of 4-point Likert scale. Higher scores are better. FACIT-Fatigue is assessed at Screening, Baseline, and Weeks 4, 11-12, 16, 24, 32, 44, 52, 56, 72, 88, 104, and 120 during Periods 1, 2, 3, and Follow-Up per the Schedule of Activities in the protocol.	FACIT-Fatigue total score	The algorithm for scoring the FACIT-Fatigue is found in Appendix 4, following the questionnaire. All responses are added with equal weight to obtain the total score. In cases where some answers may be missing, a total score is prorated from the score of the answered items, so long as more than 50% of the items (ie, at least 7 of 13) were answered.
		FACIT-Fatigue Responder	Proportion of subjects achieving the FACIT-Fatigue MCID where MCID is defined as an improvement (increase from baseline) ≥ 3.56 points in the FACIT-Fatigue score.

Description and Derivation of Health Outcomes Endpoints Except CDAI

Measure	Description / Timing	Variable	Derivation / Comment
SF-36 Version 2	The SF-36 Version 2 is a 36-item patient-administered measure designed to be a short, multi-purpose assessment of health in the areas of physical functioning, role-physical, role-emotional, bodily pain, vitality, social functioning, mental health, and general health. The 2 over-arching domains of mental well-being and physical well-being are captured by the MCS and PCS scores. The summary scores range from 0 to 100, with higher scores indicating better levels of function and/or better health. Items are answered on Likert scales of varying lengths. SF-36 is assessed at Screening, Baseline, and Weeks 4, 11-12, 16, 24, 32, 44, 52, 56, 72, 88, 104, and 120 during Periods 1, 2, 3, and Follow-Up per the Schedule of Activities in the protocol.	SF-36 Domain Scores: • physical functioning • role-physical • role-emotional • bodily pain • vitality • social functioning • mental health • general health SF-36 PCS SF-36 MCS	Health Outcomes Scoring Software 5.0 will be used to calculate the scores.
		SF-36 PCS Responder SF-36 MCS Responder	Proportion of subjects achieving the SF-36 PCS MCID where MCID is defined as an improvement (increase from baseline) ≥ 2.5 points in PCS. Proportion of subjects achieving the SF-36 MCS MCID where MCID is defined as an improvement (increase from baseline) ≥ 2.5 points in MCS

CCI

Description and Derivation of Health Outcomes Endpoints Except CDAI

Measure	Description / Timing	Variable	Derivation / Comment
BMC	Due to the significant impact of SF on subjects' lives, the BMC will be used to measure "stool frequency in the past 24 hours" using an electronic daily diary. In order to encourage consistent diary recording, subjects should enter daily diary data continuously throughout the study. BMC is collected daily during Screening, Periods 1, 2, 3, and Follow-Up, but only the last 12 days prior to each visit in the Schedule of Activities of the protocol will be considered for analysis.	Mean BMC score	7 days of subject-reported data within a 12-day period prior to a visit will be utilized to calculate the average BMC scores. Data will be excluded from score calculation when collected on day(s) of colonoscopy prep, day of colonoscopy procedure, and two days after colonoscopy procedure. If after excluding these values 4 days of data are not available, the value will be set to missing.
QIDS-SR16	The QIDS-SR16 is a self-administered 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (APA 1994). A patient is asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores demoting greater symptom severity. The domains assessed by the instrument include: 1) sad mood, 2) concentration, 3) self-criticism, 4) suicidal ideation, 5) interest, 6) energy/fatigue, 7) sleep disturbance (initial, middle, and late insomnia or hypersomnia), 8) decrease/increase in appetite/weight, and 9) psychomotor agitation/retardation. Additional information and the QIDS-SR16 questions may be found at the University of Pittsburgh IDS/QIDS internet page [www.http://www.ids-qids.org/]. QIDS-SR16 is assessed Weeks -4, 0, 11-12, 52, 104, and 120 during Screening, Periods 1, 2, 3, and Follow-Up.	QIDS-SR16 total score	The algorithm for scoring the QIDS-SR16 is found in Appendix 5.

Description and Derivation of Health Outcomes Endpoints Except CDAI

Measure	Description / Timing	Variable	Derivation / Comment
CCI			

Therapy–Fatigue; IBD = inflammatory bowel disease; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = mental component summary; CCI PCS = physical component summary; PGRC = Patient's Global Rating of Change; PGRS = Patient's Global Rating of Severity; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self Report (16 Items); SF-36 = 36-Item Short Form Health Survey.

Table AMAG.6.11. Description of Health Outcomes Analyses

Measure	Variable	Analysis Method (Section 6.1.6)	Population (Table AMAG.6.1)	
PGRS	Mean PGRS score	Primary Analysis: MMRM – change from baseline	ITT Population	
		Sensitivity Analysis: ANCOVA (mBOCF) – change from baseline	ITT Population	
		Descriptive statistics – observed values	EHO Group 2	
PGRC	PGRC score	Descriptive statistics – observed values	ITT Population, EHO Group 2	
IBDQ	IBDQ score	Primary Analysis: MMRM – change from baseline	ITT Population	
		Sensitivity Analysis: ANCOVA (mBOCF) – change from baseline	ITT Population	
		Descriptive statistics – observed values	EHO Group 2	
	IBDQ Responder	Primary Analysis: Logistic regression analysis with NRI	ITT Population	
		Descriptive statistics with NRI	EHO Group 2	
FACIT-Fatigue	FACIT-Fatigue Total score	MMRM – change from baseline	ITT Population	
		Descriptive statistics – observed values	EHO Group 2	
	FACIT-Fatigue Responder	Primary Analysis: Logistic regression analysis with NRI	ITT Population	
		Descriptive statistics with NRI	EHO Group 2	
SF-36 Version 2	SF-36 Domain Scores: • physical functioning • role-physical • role-emotional • bodily pain • vitality • social functioning • mental health • general health SF-36 physical component score SF-36 mental component score	MMRM – change from baseline	ITT Population	
		Descriptive statistics – observed values	EHO Group 2	

Measure	Variable	Analysis Method (Section 6.1.6)	Population (Table AMAG.6.1)	
	SF-36 PCS Responder SF-36 MCS Responder	Primary Analysis: Logistic regression analysis with NRI	ITT Population	
		Descriptive statistics with NRI	EHO Group 2	
CCI				
BMC	Mean BMC score	Primary Analysis: MMRM – change from baseline	ITT Population	
		Sensitivity Analysis: ANCOVA (mBOCF) – change from baseline	ITT Population	
		Descriptive statistics – observed values	EHO Group 2	
		Additional exploratory/psychometric analyses will be described in a separate health outcomes SAP; these analyses will be conducted by Lilly GPORWE.		
QIDS-SR16	QIDS-SR16 total score	MMRM – change from baseline	ITT Population	
		Descriptive statistics – observed values	EHO Group 2	
CCI				

Abbreviations: ANCOVA = analysis of covariance; BMC = bowel movement count; CCI EHO = efficacy and health outcomes; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy–Fatigue; GPORWE = Global Patient Outcomes and Real World Evidence; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT = intent-to-treat; mBOCF = modified baseline observation carried forward; MMRM = mixed model for repeated measures; CCI ; PGRC = Patient's Global Rating of Change; PGRS = Patient's Global Rating of Severity; QIDS-SR16 = Quick Inventory of Depressive Symptomatology–Self Report (16 Items); SAP = statistical analysis plan; SF-36 = 36-Item Short Form Health Survey.

CCI

6.13. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Details of PK/PD analyses can be found in a separate PK/PD analysis plan.

6.14. Safety Analyses

All safety evaluations will be based upon the Safety Population as defined in Table AMAG.6.1.

Safety and tolerability will be evaluated in terms of AEs, clinical laboratory evaluations, vital signs and physical characteristics, safety in special groups and circumstances, including adverse events of special interest (AESI).

Unless otherwise specified, the primary presentations of safety for each of the safety groups will be as follows:

Safety Population Period 1:
Treatment comparisons between all Period 1 LY dose regimens (200 mg IV, 600 mg IV, 1000 mg IV) combined and placebo will be conducted using a Fisher's exact test for select categorical safety outcomes. The p-values are shown to facilitate the review of important safety data and subsequent prioritization and summarization of the data in CSRs. Odds ratios will be created with combined LY as the numerator and placebo as the denominator.

Safety Population Period 2, Safety Population All SC LY, and Safety Population All LY:
Descriptive statistics will be used to identify potential safety signals.

For Safety Population All LY, the following periods (where applicable) will be considered:

- All treatment periods where LY (IV or SC) is administered
- All treatment periods where LY (IV or SC) is administered and Follow-Up

Visualization tools will be used to facilitate the review and understanding of the study-level safety data.

In the event differential dropout rates are seen or to further investigate events of interest, summary tables comparing exposure-adjusted incidence rate (that is, person-time-adjusted incidence rates) may be generated for applicable safety evaluations of interest.

6.14.1. Extent of Exposure

Duration of exposure to study treatment will be summarized by treatment group for Safety Population Period 1, Safety Population Period 2, Safety Population All SC LY, and Safety Population All LY. For each of the Safety Populations, exposure will be calculated as the period defined in Table AMAG.6.4 plus 1 day.

Total patient-years of exposure will be reported for each of the Safety Populations by treatment (where applicable). Descriptive statistics (n, mean, SD, minimum, first quartile, median, third quartile, and maximum) will be provided for patient-days of exposure and the frequency of subjects falling into the following different exposure ranges, as appropriate, will be summarized:

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, ≥120 days, ≥183 days, ≥365 days, ≥548 days, and ≥730 days.
- >0 to < 7 days, ≥7 to <14 days, ≥14 to <30 days, ≥30 to < 60 days, ≥60 to <90 days, ≥90 to <120 days, ≥120 to <183 days, ≥183 to <365 days, ≥365 days to <548 days, ≥548 days to <730 days, and ≥730 days.

Overall exposure will be summarized in total patient-years, derived in the following manner:

- Exposure in patient-years = Sum of duration of exposure in days (for all subjects in treatment group) / 365.25.

Additional exposure ranges may be considered if necessary.

No p-values will be reported in these tables as they are intended to describe the characteristics of the Safety Populations.

Reasons for not taking planned treatment and reasons for IV interruptions will be reviewed.

6.14.2. Adverse Events

6.14.2.1. Analysis of Adverse Events (AEs)

A TEAE is defined as an event that first occurred or worsened in severity after baseline. Both the date/time of the event and the date/time of the dose are considered when determining TEAEs. TEAEs will be assigned to the study period(s) (see Table AMAG.6.4) to which they are considered treatment-emergent:

- For each Medical Dictionary for Regulatory Activities (MedDRA) PT, treatment-emergence will be determined based on whether the PT first occurred during the treatment period or whether any lowest level term (LLT) associated with the PT increased in severity relative to baseline.

- The maximum severity recorded for each LLT prior to the first dose date/time in the period will be used as the pre-treatment severity for that LLT. If an event during the baseline period has missing severity, and the event persists during the treatment period, then it will be considered as treatment-emergent, regardless of the postbaseline level of severity. Events with a missing severity during the treatment period will be considered treatment-emergent.
- Adverse events with a particular LLT will be classified as treatment-emergent if they first start on or after the first dose date/time in the treatment period (that is, a subject has no preexisting conditions with that LLT), or if the severity is greater than the pre-treatment severity for that LLT. If a partial AE start date/time is present, the date/time will be compared as far as possible to the treatment start date/time in order to determine whether the event is treatment-emergent or not. If there is any doubt, the event will be flagged as treatment-emergent.

In an overview table, the number and percentage of subjects who experienced a TEAE, serious adverse event (SAE), died due to an AE, or discontinued from study treatment due to an AE will be summarized by treatment. These summaries will be presented for Safety Population Period 1, Safety Population Period 2, Safety Population All SC LY, and Safety Population All LY. Note that for events that are gender-specific, the denominator and computation of the percentage will include only subjects from the given gender.

The percentages of subjects with TEAEs will be summarized by treatment using MedDRA PT nested within system organ class (SOC). Statistical comparisons as noted in Section 6.14 will be applied at both the SOC and PT levels. Events will be ordered by decreasing frequency in the total LY treatment group within SOC. These summaries will be presented for Safety Population Period 1, Safety Population Period 2, Safety Population All SC LY, and Safety Population All LY. As an additional table or figure, for Safety Population Period 1, the percentages of subjects with TEAEs will be summarized by treatment using MedDRA PT (without regard to SOC). Events will be ordered by decreasing frequency in the total LY treatment group.

The percentages of subjects with TEAEs by maximum severity will be summarized by treatment using MedDRA PT. For each subject and TEAE, the maximum severity for the MedDRA PT is the maximum postbaseline severity observed from all associated LLTs mapping to the MedDRA PT. Only counts and percentages will be included for the TEAEs by maximum severity. This summary will be presented for Safety Population Period 1, Safety Population Period 2, Safety Population All SC LY, and Safety Population All LY.

6.14.2.2. Common Adverse Events

The percentage of subjects with TEAEs will be summarized by treatment using MedDRA PT for the common TEAEs (occurred in ≥5% of subjects [before rounding] of any treatment group). Events will be ordered by decreasing frequency in the total LY treatment group. The summary will be presented for Safety Population Period 1.

6.14.2.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

A listing of all deaths will be provided.

The number and percentage of subjects who experienced an SAE (including deaths) during the treatment period will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency in the total LY treatment group within SOC. The summaries will be presented for Safety Population Period 1, Safety Population Period 2, Safety Population All SC LY, and Safety Population All LY.

The number and percentage of subjects who permanently discontinued from study treatment due to an AE (including AEs that led to death) during the treatment period will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency in the total LY treatment group within SOC. The summaries will be presented for Safety Population Period 1, Safety Population Period 2, Safety Population All SC LY, and Safety Population All LY.

6.14.3. Clinical Laboratory Evaluation

Summaries will be provided in both International System of Units (SI) and US conventional units (when different). Normal limits from the performing lab will be used to define low and high.

Some of the analyses below may be incorporated into interactive display tools instead of or in addition to a static display. As such, the box plots for changes from baseline and the shifts to low/high summaries will be presented in a static display; the box plots for observed values, scatter plots and shift tables will be reviewed, if necessary, as an interactive display.

The following will be conducted for laboratory analyte measurements collected quantitatively:

- Box plots for observed values: Values at each visit (starting at randomization) will be displayed in box plots for subjects who have both a baseline and a result for the specified visit. Unplanned measurements will be excluded. Baseline will be the last non-missing observation in the baseline period. Original-scale data will be used for the display. These box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.
- Box plots for change values: Change from baseline to each visit will be displayed in box plots for subjects who have both a baseline and a result for the specified visit. Change from baseline to last observation will also be summarized and analyzed for subjects who have both baseline and at least 1 postbaseline result. Baseline will be the last non-missing observation in the baseline period. The last non-missing observation in the treatment period will be used as the last observation. Unplanned measurements will be excluded. The change from baseline to last observation will be summarized within the box plot of changes (rightmost column), and descriptive summary statistics will be included in a table below the box plot.

- Outlier/shift displays focusing on low values: A scatter plot, a shift table, and a shift to low table will be created. Unplanned measurements will be included. The scatter plot will plot the minimum value during the baseline period versus the minimum value during the treatment period. The shift table will include the number and percentage of subjects within each baseline category (minimum value is low, normal, high, or missing) versus each postbaseline category (minimum value is low, normal, high, or missing) by treatment. Subjects in the Safety Population will be included in the shift table. The shift from normal/high to low table will include the number and percentage of subjects by treatment whose minimum baseline result is normal or high and whose minimum treatment result is low. Subjects whose minimum baseline result is normal or high and have at least one result during the treatment period are included. The Fisher's exact test will be used to compare percentages of subjects who shift from normal/high to low between all Period 1 LY dose regimens (200 mg IV, 600 mg IV, 1000 mg IV) combined and placebo for Safety Population Period 1.
- Outlier/shift displays focusing on high values: The same approach described for low values will be used, except maximum values will replace minimum values.

Box plots will be displayed for Safety Population Period 1. Spaghetti plots will be explored to evaluate individual subject trends over time across the whole study. The summary of treatment-emergent abnormal, high, or low laboratory results at any time will be provided for Safety Population Period 1, Safety Population Period 2, Safety Population All SC LY, and Safety Population All LY.

For laboratory analyte measurements, a listing of abnormal findings will be created. The listing will include subject ID, treatment group, laboratory collection date, analyte name, and analyte finding.

6.14.4. Vital Signs and Physical Characteristics

As described in Section 6.14.3, some of the analyses below may be incorporated into interactive display tools instead of or in addition to a static display. As such, the box plots for changes from baseline and the shifts to low/high summaries will be presented in a static display; the box plots for observed values, scatter plots and shift tables will be reviewed, if necessary, as an interactive display.

The following will be conducted for vital signs and physical characteristics (systolic blood pressure [BP], diastolic BP, pulse, weight, BMI):

- Box plots for observed values: To be created as described in Section 6.14.3 for laboratory analyte measurements.
- Box plots for change values: To be created as described in Section 6.14.3 for laboratory analyte measurements.
- Outlier/shift displays focusing on low values: To be created as described in Section 6.14.3 for laboratory analyte measurements, except the definition of treatment-emergent includes a threshold for change in addition to a limit as described in Table AMAG.6.12. A treatment-emergent low result is defined as a change from a value

greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time that meets the specified change criteria during the treatment period. The denominator will be subjects whose values are greater than or equal to the low limit at all baseline visits. To assess decreases, change from the minimum value during the baseline period to the minimum value during the treatment period will be used.

- Outlier/shift displays focusing on high values: The same approach described for low values will be used, except to assess increases, maximum values will replace minimum values. High limits will replace low limits.

Box plots will be displayed for Safety Population Period 1. Spaghetti plots will be explored to evaluate individual subject trends over time across the whole study. The summary of treatment-emergent high or low vital signs results at any time will be provided for Safety Population Period 1, Safety Population Period 2, Safety Population All SC LY, and Safety Population All LY.

Table AMAG.6.12. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight and Changes for Adults

Parameter	Low	High
Systolic BP (mm Hg)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Weight (kg)	(Loss) decrease ≥7%	(Gain) increase ≥7%

Abbreviation: BP = blood pressure.

6.14.5. Electrocardiograms

Complete electrocardiogram (ECG) data will not be part of the clinical database for this study. Per protocol, any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the investigational treatment will be reported to Lilly or its designee as an AE via electronic case report form (eCRF).

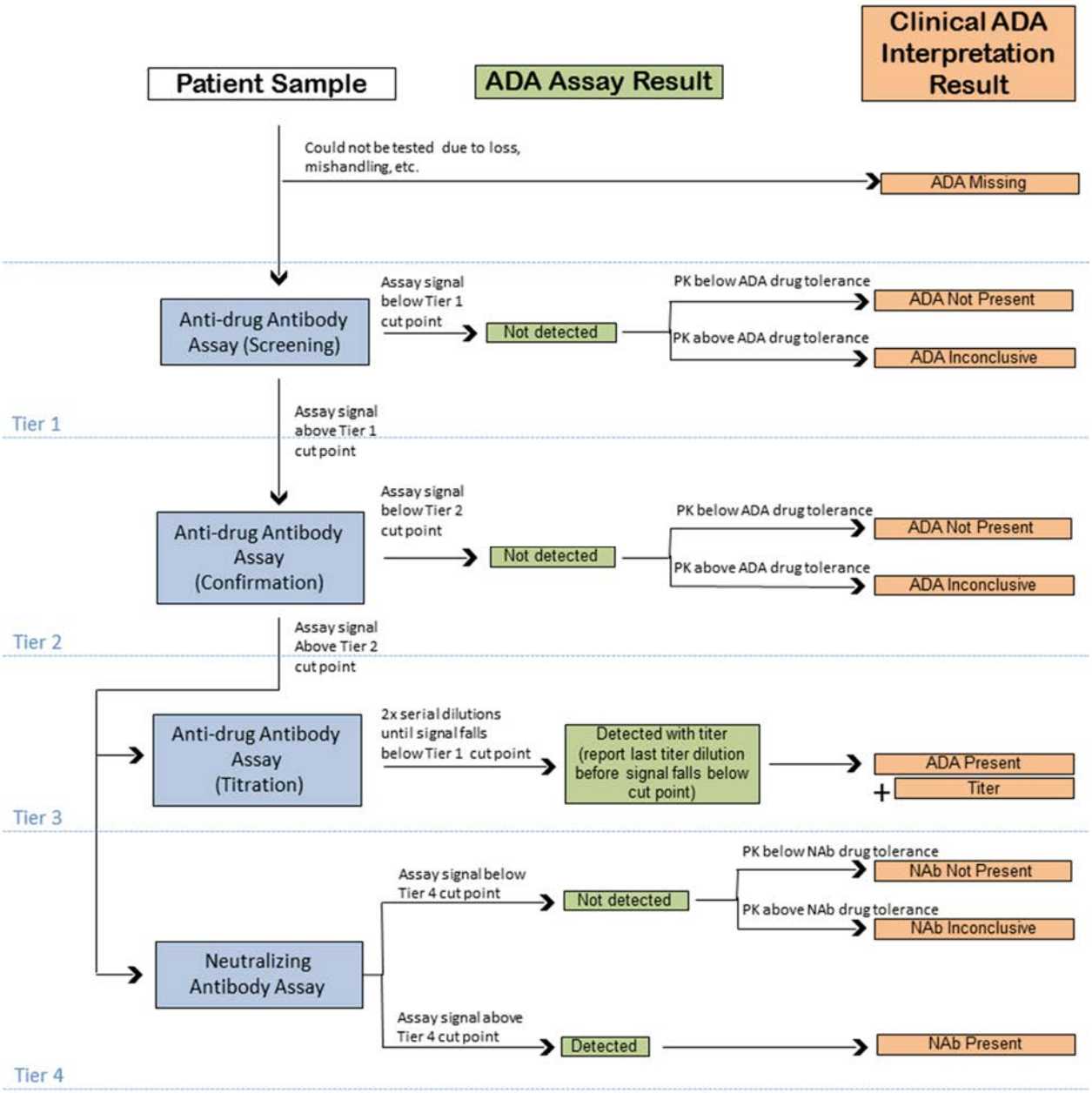
6.14.6. Immunogenicity

Figure AMAG.6.1 provides an overview of the immunogenicity assay process.

At a high level, an individual sample is potentially examined multiple times in a hierarchical procedure to produce a sample anti-drug antibodies (ADA) assay result and potentially a sample neutralizing antibody (NAb) assay result. The cut points used, the drug tolerance of an assay, and the possible values of titers are operating characteristics of the assay , which will be study specific.

It can be the case that the presence of high concentrations of LY will affect the measurements of the presence of ADA or NAb, and conversely high levels of ADA or NAb may affect the measurement of LY concentration. Thus, an LY drug concentration, assessed from a sample drawn at the same time as the ADA sample, plays a key role in clinical interpretation of a sample when the laboratory result is Not Detected, as shown in Figure AMAG.6.1.

The rest of this section defines the component concepts of Figure AMAG.6.1 in greater detail.



Abbreviations: ADA = anti-drug antibodies; NAb = neutralizing antibody; PK = pharmacokinetics.

Figure AMAG.6.1. Flow chart of ADA sample assessment with clinical interpretation.

6.14.6.1. Definitions of Sample ADA Status

Table AMAG.6.13. Sample ADA Assay Results

Sample Laboratory Result	Explanation
Detected	ADA are detected and confirmed.
Not Detected	The raw result as reported from the laboratory indicates Not Detected. The clinical interpretation of such results depends on other factors (see below).
No Test, QNS, etc.	Sample exists but was unevaluable by the assay.

Abbreviations: ADA = anti-drug antibodies; QNS = quantity not sufficient.

Table AMAG.6.14. Sample Clinical ADA Interpretation Results

Sample Clinical Interpretation	Explanation
ADA Present	ADA assay result is Detected.
ADA Not Present	ADA assay result is Not Detected and simultaneous drug concentration is at a level that has been demonstrated to not interfere in the ADA detection method (ie, drug concentration is below the assay's drug tolerance level). If drug concentration is not available for a treatment-period sample, the sample is inconclusive (see below). For subjects receiving placebo, drug concentration is not assessed and is assumed to be below the assay's drug tolerance level.
ADA Inconclusive	ADA assay result is Not Detected but drug concentration in the sample is at a level that can cause interference in the ADA detection method, or drug concentration is planned per protocol but is not available.
ADA Not Detected with Drug Concentration Not Available	If drug concentration analysis was planned but result is not available for a treatment-period sample, a Not Detected sample will be declared ADA Not Detected with Drug Concentration Not Available. In the computation of Subject ADA status (see below, Section 6.14.6.3), these samples will be considered ADA Not Present, on the basis of prior knowledge that the drug tolerance level of the ADA assay is high relative to the expected drug concentration levels.
ADA Missing	ADA sample not drawn, QNS, not tested, etc, causing there to be no laboratory result reported or the result is reported as No Test.

Abbreviations: ADA = anti-drug antibodies; QNS = quantity not sufficient.

Parallel terminology applies for NAb Detected, NAb Not Detected, NAb Present, NAb Not Present, NAb Inconclusive, NAb Not Detected with Drug Concentration Not Available, and NAb Missing. ADA and NAb are distinct assays and have different assay operating characteristics.

6.14.6.2. Definitions of Immunogenicity Assessment Periods

Immunogenicity Baseline Observations: Baseline period for immunogenicity assessment for each subject includes all observations on or prior to the date of the first administration of study drug (whether LY3074828 or comparator). In instances where multiple baseline observations are collected, the last non-missing value prior to study drug is used as baseline. For studies

where applicable, subjects who receive LY3074828 subsequent to receiving Placebo, the original pre-Placebo baseline value is used.

Immunogenicity Postbaseline Period Observations: Postbaseline period observations for each subject include all observations after the first administration of study drug. As mentioned in the previous section, for subjects who receive LY3074828 subsequent to receiving Placebo, the baseline is the original pre-Placebo baseline. However, the analysis uses only the postbaseline observations after receiving LY3074828.

6.14.6.3. Definitions of Subject ADA Status

Subject evaluable for treatment-emergent ADA: A subject is evaluable for treatment-emergent ADA if the subject has a non-missing baseline ADA result, and at least 1 non-missing postbaseline ADA result.

Treatment-emergent ADA positive (TE ADA+) subject: A subject who is evaluable for treatment-emergent ADA is TE ADA+ if either of the following holds:

a. The subject has baseline status of ADA Not Present and at least 1 postbaseline status of ADA Present with titer ≥2 * minimum required dilution (MRD) of the ADA assay (Treatment Induced).
b. The subject has baseline and postbaseline status of ADA Present, with the postbaseline titer being 2 dilutions (4-fold) greater than the baseline titer. That is, the subject has baseline status of ADA Present, with titer 1:B, and at least 1 postbaseline status of ADA Present, with titer 1:P, with P/B ≥4 (Treatment Boosted).

Treatment-emergent ADA Inconclusive subject: A subject who is evaluable for TE ADA is TE ADA Inconclusive if ≥20% of the subject's postbaseline samples, drawn pre-dose, are ADA Inconclusive and the subject is not otherwise ADA+.

Treatment-emergent ADA negative (TE ADA-) subject: A subject who is evaluable for TE ADA is TE ADA- when the subject is not TE ADA+ and the subject is not TE ADA Inconclusive.

6.14.6.4. Analyses to Be Performed

Analyses will be performed for Safety Population Period 1 and Safety Population All LY (see Section 6.1.2).

A listing will be provided of all immunogenicity assessments for those subjects who at any time had ADA Present. This includes the laboratory ADA assay result (Detected or Not Detected), LY concentration from a simultaneous PK sample, and the clinical interpretation result that combines these (ADA Present, ADA Not Present, ADA Inconclusive, Missing). When detected, a titer will be included, and TE ADA+ observations will be flagged. Also included will be the laboratory NAb assay result (Detected or Not Detected) and the NAb clinical interpretation result (NAb Present, NAb Not Present, NAb Inconclusive, Missing) when the NAb assay was performed.

For the remainder of this section, "ADA result" will refer to the clinical interpretation result. "NAb result" will be handled similarly.

The number and proportion of subjects who are TE ADA+ will be tabulated by treatment group, where proportions are relative to the number of subjects who are TE ADA evaluable, as defined above. The tabulation will include all postbaseline observations, the number and proportion of subjects with ADA Present at baseline, and the number and proportion of TE ADA+ subjects exhibiting NAb+.

For each TE ADA+ subject, a plot will be constructed of titer values from individual samples over time. Samples that are ADA Not Present or ADA Inconclusive will also be indicated.

A summary will be provided of the number and percentage of LY-treated subjects experiencing TEAEs (overall and by PT) by subject TE ADA status (TE ADA+, TE ADA-, TE ADA Inconclusive). The PT will be ordered by decreasing incidence in TE ADA+ status group.

A listing will be provided that includes any subject who has ADA Detected at any time, OR who reports specific TEAEs (see Table AMAG.6.15). This listing includes a time course of ADA (clinical interpretation result plus flags for samples meeting TE ADA+ criteria and for NAb+ samples) along with the AE.

Table AMAG.6.15. TEAEs for Listing with ADA/NAb Results

Events satisfying Anaphylaxis SMQ (narrow or broad)
Events satisfying Hypersensitivity SMQ (narrow or broad)
Events satisfying Angioedema SMQ (narrow or broad)
Events mapping to HLT of Injection site reaction
Events mapping to HLT of Infusion site reaction
Events mapping to HLT of Administration site reaction

Abbreviations: ADA = anti-drug antibodies; HLT = high level term; MedDRA = Medical Dictionary for Regulatory Activities; NAb = neutralizing antibody; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.

6.14.7. Histopathology

Biopsies will be collected during endoscopy procedures at Screening, Week 12, and Week 52. The Central Readers will review the images in a blinded fashion and determine the following scores:

- Global Histologic Disease Activity Score (GHAS; D'Haens et al. 1998): assesses the extent and severity of histologic inflammation in colonic or ileal biopsy samples in CD. Factors include epithelial and architecture changes, inflammatory cell infiltrates, erosions or ulcers, granulomas, and an adjustment for the number of biopsy samples affected.
- Robarts Histopathology Index (RHI; Mosli et al. 2017): a new evaluative index that is designed to be reproducible and responsive to clinically meaningful change in disease activity over time. The total RHI score ranges from 0 (no disease activity) to 33 (severe disease activity).

Descriptive statistics will be presented for the changes from baseline in GHAS and RHI for Safety Population Periods 1 and 2. The definition for histological mucosal healing based on GHAS and RHI (that is, the cut-off for CD) has not been determined; details of the analyses will be documented when specified by Robarts Clinical Trials (ROBARTS).

6.14.8. Special Safety Topics

6.14.8.1. Abnormal Hepatic Tests

Analyses for laboratory analyte measurements are described in Section 6.14.3. This section describes additional analyses for the topic.

The percentages of subjects with the following elevations in hepatic laboratory tests at any time will be summarized between treatment groups:

- The percentages of subjects with a alanine aminotransferase (ALT) measurement greater than or equal to 3 times (3X), 5 times (5X), and 10 times (10X) the performing lab ULN during the treatment period will be summarized for all subjects with a postbaseline value and for subsets based on various levels of baseline value.
    - The analysis of 3X ULN will contain 4 subsets:
        - subjects whose non-missing maximum baseline value is less than or equal to 1X ULN
        - subjects whose maximum baseline is greater than 1X ULN but less than 3X ULN
        - subjects whose maximum baseline value is greater than or equal 3X ULN
        - subjects whose baseline values are missing
    - The analysis of 5X ULN will contain 5 subsets:
        - subjects whose non-missing maximum baseline value is less than or equal to 1X ULN
        - subjects whose maximum baseline is greater than 1X ULN but less than 3X ULN
        - subjects whose maximum baseline is greater than or equal to 3X ULN but less than 5X ULN
        - subjects whose maximum baseline value is greater than or equal to 5X ULN
        - subjects whose baseline values are missing
    - The analysis of 10X ULN will contain 6 subsets:
        - subjects whose non-missing maximum baseline value is less than or equal to 1X ULN
        - subjects whose maximum baseline is greater than 1X ULN but less than 3X ULN
        - subjects whose maximum baseline is greater than or equal to 3X ULN but less than 5X ULN
        - subjects whose maximum baseline is greater than or equal to 5X ULN but less than 10X ULN

    - subjects whose maximum baseline value is greater than or equal to 10X ULN
    - subjects whose baseline values are missing
- The percentages of subjects with an aspartate transaminase (AST) measurement greater than or equal to 3X, 5X, and 10X the performing lab ULN during the treatment period will be summarized for all subjects with a postbaseline value and for subsets based on various levels of baseline, as described above for ALT.
- The percentages of subjects with a total bilirubin measurement greater than or equal to 2 times (2X) the performing lab ULN during the treatment period will be summarized for all subjects with a postbaseline value, and subset into 4 subsets:
    - subjects whose non-missing maximum baseline value is less than or equal to 1X ULN
    - subjects whose maximum baseline is greater than 1X ULN but less than 2X ULN
    - subjects whose maximum baseline value is greater than or equal to 2X ULN
    - subjects whose baseline values are missing

Maximum baseline will be the maximum non-missing observation in the baseline period. The maximum value will be the maximum non-missing value from the treatment period. Planned and unplanned measurements will be included.

These analyses will be conducted for Safety Population Period 1, Safety Population Period 2, Safety Population All SC LY, and Safety Population All LY.

Individual graphical subject profiles will be prepared for subjects with an ALT or AST measurement greater than or equal to 5X ULN or with an alkaline phosphatase (ALP) measurement greater than or equal to 2X ULN. A graphical subject profile will be created for any subject meeting the criteria from the Safety Population (any phase, any medication). The graphical subject profile will include demographics, disposition, and a display of study drug exposure, AEs, medications, and liver-related measurements over time. The review for these subjects includes an assessment of the proximity of any ALT or AST elevation to any total bilirubin elevation, ALP levels, gamma-glutamyl transpeptidase (GGT) levels, other potential causes, and the temporal association with events such as nausea, vomiting, anorexia, abdominal pain, or fatigue.

A plot of maximum postbaseline ALT versus maximum postbaseline total bilirubin will be created that includes all subjects from the Safety Population (any phase, any medication). Each subject with at least 1 postbaseline ALT and total bilirubin contributes 1 point to the plot. The maximum ALT measurement divided by ULN and the maximum total bilirubin measurement divided by ULN during the treatment period are used. The measurements do not need to be taken at the same blood draw. Symbols will be used to indicate treatments (concentrated when multiple treatments are taken).

6.14.8.2. Infections

Infections will be defined using the PTs from the MedDRA Infections and Infestations SOC.

Treatment-emergent infections will be analyzed according to various groups of infectious events including:

- all infections
  - all PTs in the Infections and Infestations SOC by maximum severity,
- serious infections
  - all PTs in the Infections and Infestations SOC that are SAEs,
- Opportunistic infections (OIs), as described below.

The MedDRA terms used to identify infections typically considered to be potential OIs are based on Winthrop et al. (2015) and are listed in Appendix 7. The list contains relevant groupings of PTs, that is, narrow search terms and broad search terms, which together can assist in identifying subjects of interest. The list of terms is currently based on MedDRA version 19.1, but the list will be updated with each new version of MedDRA, including versions released after finalization of the statistical analysis plans but before database lock. For each of all infections and serious infections, the number and percentage of subjects overall and for each specific PT will be summarized by treatment, with specific event terms ordered by decreasing frequency in the total LY treatment group.

The number and percentage of subjects with TEAEs that are considered as OIs will be summarized by using PT nested within categories. For these TEAEs, the summary table will pool the narrow and broad terms together. Events will be ordered by decreasing frequency in the total LY treatment group.

These summaries will be presented for Safety Population Period 1, Safety Population Period 2, Safety Population All SC LY, and Safety Population All LY.

Visual techniques will be used to examine subjects experiencing treatment-emergent infectious AEs in the context of subject demographics, treatment group, treatment start and stop dates, infectious event, event start and stop dates, event severity and possible relationship to the study drug, total leukocytes, total lymphocytes, absolute neutrophils, event seriousness, event outcome, whether the subject was immunized for tuberculosis and/or herpes zoster, infecting agent, infection site, and whether anti-microbial treatment was recorded.

6.14.8.3. Hypersensitivity Reactions

Two main analyses are performed in support of assessment of potential immediate hypersensitivity, including anaphylaxis and infusion-related reactions (IRR), as well as potential non-immediate hypersensitivity. These analyses will be conducted for Safety Population Period 1, Safety Population Period 2, Safety Population All SC LY, and Safety Population All LY.

Time Period A, of potential immediate hypersensitivity, includes all TEAEs occurring on the day of study drug administration.

Time Period B, of potential non-immediate hypersensitivity, includes all TEAEs occurring strictly after the day of study drug administration (but prior to subsequent drug administration).

Analyses for both time periods are based on the following:

- Anaphylactic reaction standardized MedDRA query (SMQ) (20000021; narrow, algorithm per MedDRA Maintenance and Support Services Organization [MSSO] SMQ guide, and broad)
- Hypersensitivity SMQ (20000214; narrow and broad)
- Angioedema SMQ (20000024; narrow and broad)
- Event maps to PT of Infusion-related reaction (10051792).

The number and percentage of subjects who experienced a TEAE for the following will be analyzed for each of the 2 time periods:

- Any narrow or algorithmic term from any one of the 3 SMQs indicated above or the PT of Infusion-related reaction (ie, combined search across narrow and algorithmic portions of all 3 SMQs plus PT of Infusion-related reaction)
- Any narrow scope term within each SMQ separately (that is, narrow SMQ search)
- Any term within each SMQ separately (that is, broad SMQ search).

Within query, individual PTs that satisfied the queries will be summarized. For Infusion-related reaction (PT), the individual LLTs will be summarized.

For Time Period A only, the number and percentage of each PT that is not in any of the 3 SMQs, and is not the PT Infusion-related reaction (ie, other events occurring on the day of study drug administration) will be summarized overall and by individual PT. Only PTs that occur in at least 3 subjects on LY will be displayed in this portion of the table.

The PT and LLT will be listed as a summary in decreasing order of incidence for LY-treated subjects. Note that an individual subject may contribute multiple events. Also, a single event may satisfy multiple SMQs, in which case the event contributes to every applicable SMQ.

6.14.8.4. Injection Site Reactions

A summary will be provided for Safety Population Period 1, Safety Population Period 2, Safety Population All SC LY, and Safety Population All LY, by treatment group (where applicable), of the number of subjects with reported events that map to any one of the following:

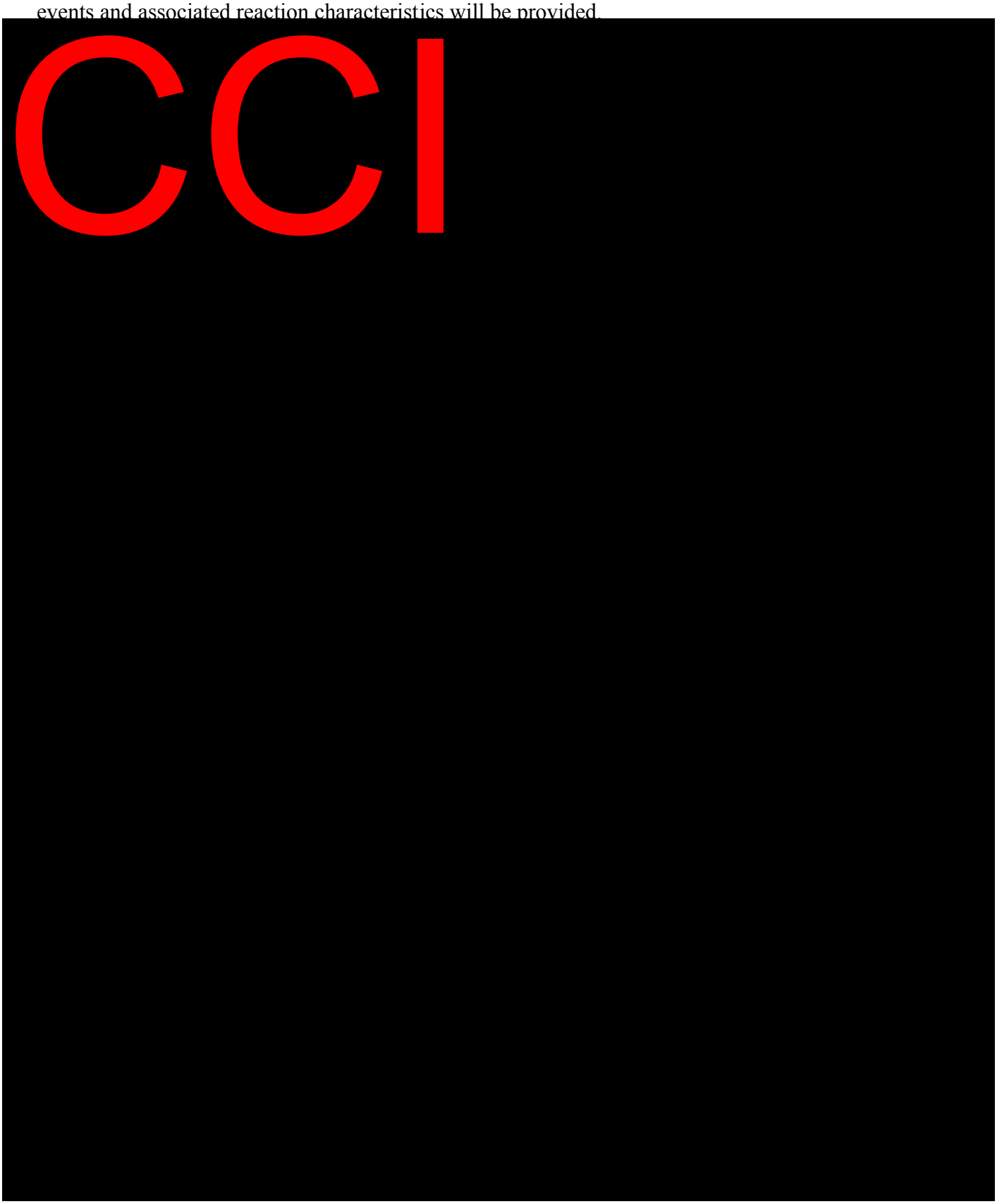
- MedDRA high level term (HLT) of Injection site reaction
- HLT of Administration site reaction
- HLT of Infusion site reaction

The summaries will include the following:

- An integrated search using all terms from all of the above categories (3 HLTs) combined
- A summary rolling up all terms within each of the above categories separately
- Within each of the above categories, the associated PTs that were reported will be summarized

The PTs will be listed for summary within each category in decreasing order of incidence for LY-treated subjects.

Additionally, an Injection Site Reaction follow-up CRF form will collect more information on the events identified by the investigator as injection site reactions. A by-subject listing of these events and associated reaction characteristics will be provided.



6.17. Protocol Deviations

Review of all major and minor protocol deviations will be performed on an ongoing basis during the conduct of the study. All protocol deviations identified during clinical monitoring visits or data validation will be tracked in the Clinical Trial Management System (CTMS) software. Pre-defined types of protocol deviations are listed in Appendix 1 of this document. Other deviation types may be added to this list. The pre-defined protocol deviation list will be given to the clinical team, and will also be programmed and verified by statistics when possible and reasonable to do so. The CTMS and programmed deviation data will be merged together and utilized in all protocol deviation outputs.

No subject will be excluded from the ITT Population due to any protocol deviations. There is no Per-Protocol Population in this plan. If deemed necessary, an exploratory analysis of the primary endpoint may be added based on a Per-Protocol Population.

Protocol deviations will be tabulated for the ITT population (Period 1) and EHO Group 2 (Periods 1, 2, 3, and follow-up). A listing will also be provided of all protocol deviations through the end of the study.

6.18. Interim Analyses and Data Monitoring

The following interim (and final) data locks are planned for this study:

- 50% of all subjects complete Week 12 or ETV (First Interim)
- 100% of all subjects complete Week 12 or ETV (Primary Endpoint)
- 50% of all subjects complete Week 52 or ETV
- 100% of all subjects complete Week 52 or ETV (End of Blinded Study Periods)
- 100% of all subjects complete Week 120 or ETV (End of Study])

The purpose of all interim analyses will be to support further development planning. No modifications or adaptations to the study are planned to coincide with the interim analysis. The study will not be stopped for futility or efficacy and, as such, will not incorporate an alpha penalty. Changes to the timing and number of interim analyses may occur. Any changes to the planned analyses will be fully captured in the unblinding plan (see Section 7).

6.19. DSUR

Based on regulatory requirements for the Development Safety Update Report (DSUR), reports will be produced (if not already available from the study CSR) for the reporting period covered by the DSUR.

6.20. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset that will be converted to an XML file. Both Serious Adverse Events and "Other" Adverse Events are summarized by treatment group, by MedDRA PT.

- An AE is considered "Serious" whether or not it is a TEAE.
- An AE is considered in the "Other" category if it is both a TEAE and is not serious. For each SAE and "Other" AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced
- Consistent with www.ClinicalTrials.gov requirements, "Other" AEs that occur in fewer than 5% of subjects/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).

- AE reporting is consistent with other document disclosures, for example, the CSR, manuscripts, and so forth.

7. Unblinding Plan

The unblinding plan will be a separate document from this SAP.

8. References

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9. Appendices

Appendix 1. Protocol Deviations

The following is a list of pre-defined protocol deviations that will be reported. Additional protocol deviations may also be added to this list if discovered during the course of site monitoring and data review.

Visit	Number	Deviation
Screening	1	Site fails to obtain informed consent from subject.
Randomization	2	Subject age <18 or >75 years at randomization.
Screening and Randomization	3	Subject fails to meet inclusion criteria.
Screening and Randomization	4	Subject fails to meet exclusion criteria.
Treatment Periods 1, 2, and 3	5	Noncompliance with study regimen (failure to attend for administration of study medication within the required treatment window).
Treatment Periods 1, 2, and 3	6	Administration of the incorrect treatment.
Treatment Periods 1, 2, and 3, and Follow-up Period	7	Subject has taken prohibited concomitant medications during treatment or follow-up periods.
Enrollment, Randomization, Treatment Periods 1, 2, and 3, and Follow-up Period	8	During the course of this study, the subject enrolls in a clinical trial involving an investigational product or nonapproved use of a drug or device, OR enrolls in any other type of medical research not scientifically or medically compatible with this study, per investigator judgment.
Enrollment, Randomization, and Treatment	9	Subject visits are outside of visit windows.

Appendix 2. Algorithm for Calculating the SES-CD

The Simple Endoscopic Score for Crohn's Disease (SES-CD) is based on 4 endoscopic variables (presence and size of ulcers, proportion of surface covered by ulcers, proportion of surface affected by disease, and presence and severity of stenosis), which are assessed in 5 ileocolonic bowel segments. Each of the 4 endoscopic variables is scored from 0 to 3 (Daperno et al. 2004).

Presence and size of ulcers: • 0 = None • 1 = Diameter 0.1-0.5 cm • 2 = Diameter 0.5-2 cm • 3 = Diameter >2 cm	Extent of ulcerated surface • 0 = None • 1 = <10% • 2 = 10%-30% • 3 = >30%
Extent of affected surface • 0 = None • 1 = <50% • 2 = 50%-75% • 3 = >75%	Presence and type of narrowings • 0 = None • 1 = Single, can be passed • 2 = Multiple, can be passed • 3 = Cannot be passed

These scores should be entered into the table below. The SES-CD is obtained by summing all of the endoscopic scores across all bowel segments.

	Ileum	**Right colon**	**Transverse colon**	**Left colon**	**Rectum**	**Row Total**
Presence and size of ulcers		+	+	+	+	=
Extent of ulcerated surface		+	+	+	+	=
Extent of affected surface		+	+	+	+	=
Presence and type of narrowing		+	+	+	+	=
Grand Total						=

Appendix 3. IBDQ

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a 32-item self-administered questionnaire. The IBDQ has 4 dimensions: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items) (Feagan 2011). Responses are graded on a 7-point Likert scale in which 7 denotes "not a problem at all" and 1 denotes "a very severe problem." Scores range from 32 to 224; a higher score indicates a better quality of life.

The 4 dimensions are defined as:

- Bowel symptoms: Questions 1, 5, 9, 13, 17, 20, 22, 24, 26, 29
- Systemic symptoms: Questions 2, 6, 10, 14, 18
- Emotional function: Questions 3, 7, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32
- Social function: Questions 4, 8, 12, 16, 28

Rules for handling missing data:

1. If no response is given for a particular question and only 1 response per dimensional score is missing, impute the missing value to be equal to the mean score for the other items of the subscore.
2. If 2 or more questions are unanswered for a particular domain, then the subscore will be set to missing.
3. If after steps 1 and 2, more than 4 questions are missing for the full IBDQ, then the total IBDQ will be set to missing.

Appendix 4. FACIT-Fatigue

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

FACIT-Fatigue Subscale Scoring Guidelines (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X

2. Perform reversals as indicated, and sum individual items to obtain a score.

3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.

4. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
FATIGUE	HI7	4	-	_____	=_____
SUBSCALE	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores:_____

Multiply by 13: _____

Divide by number of items answered:

_____=Fatigue Subscale score

Source: FACIT.org website (http://www.facit.org/FACITOrg/Questionnaires)

Appendix 5. Algorithm for Calculating the QIDS-SR16 Total Score

The Quick Inventory of Depressive Symptomatology-Self Report (16 Items) (QIDS-SR16) is a 16-item self-report instrument intended to assess the existence and severity of symptoms of depression (Rush et al. 2003). The following table can be used to calculate the total score.

Enter the highest score recorded for the 4 sleep items (items 1 to 4) Enter score for item 5 Enter the highest score recorded for the appetite/weight items (items 6 to 9) Enter score for item 10 Enter score for item 11 Enter score for item 12 Enter score for item 13 Enter score for item 14 Enter the highest score recorded for the psychomotor items (items 15 and 16)	____ ____ ____ ____ ____ ____ ____ ____ ____
Sum the scores to obtain a total score (Total score range 0 – 27)	____

If any of the 9 items above are missing, the QIDS-SR16 total score will be considered missing.

Appendix 6. Algorithm for Calculating the CDAI Score

The Crohn's Disease Activity Index (CDAI) score is calculated for each week using the algorithm below (Best et al. 1976). The standard weights can be determined using the Standard Weight table on the following page.

FOR REVIEW PURPOSES ONLY

Questionnaire obtained by: Lilly	Study ID	Subject Number	Visit/Cycle Number	Signature of Individual Completing Form
	Investigator Number	Page 1 of 1		Date Signed by Individual Completing Form

Patient reported outcomes in Crohn's disease

(a) Crohn's Disease Activity Index (CDAI)

VARIABLE	DAY 1	2	3	4	5	6	7	7 Day Total	Weighting Factor	Total
1. Number of liquid or very soft stools									x 2 =	
2. Abdominal pain 0=none, 1=mild, 2=moderate, 3=severe									x 5 =	
3. General well-being 0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible									x 7 =	

4. Extra-intestinal manifestations, Current	Check all that apply	
a. Arthritis/arthralgia		
b. Iritis/uveitis		
c. Erythema nodosum, pyoderma gangrenosum,aphthous stomatitis		
d. Anal fissure, fistula, or abscess		
e. Other fistula		
f. Fever over 37.8C (100F) during past 7 days		
	Total number of checked boxes=	
	x 20 =	
5. Lomitil, Imodium, Opiates for diarrhea in the last 7 days	No = 0, Yes = 1	
	x 30 =	
6. Abdominal mass	None = 0, Questionable = 2, Definite = 5	
	x 10 =	
7. Local Haematocrit (%, rounded to whole)	If Male, 47-_____= If Female,42-_____= If negative, enter 0	
	x 6 =	
8. Body weight calculation	Percentage deviation from standard weight x 1 =	
	CDAI TOTAL=	

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Standard Weight Table Based on Height and Sex

WOMEN	
Height in cm *without shoes*	Standard Weight in Kg
148	53.1
149	53.6
150	54.1
151	54.5
152	55.0
153	55.4
154	55.9
155	56.4
156	57.0
157	57.5
158	58.1
159	58.6
160	59.1
161	59.6
162	60.2
163	60.7
164	61.3
165	61.9
166	62.4
167	62.9
168	63.4
169	63.9
170	64.5
171	65.0
172	65.5
173	66.0
174	66.6
175	67.2
176	67.7
177	68.3
178	68.8
179	69.3
180	69.8
181	70.3
182	70.9
183	71.5
184	72.1
185	72.7
186	73.4

MEN	
Height in cm *without shoes*	Standard Weight in Kg
158	62.6
159	62.9
160	63.3
161	63.7
162	64.1
163	64.6
164	65.0
165	65.5
166	66.0
167	66.6
168	67.1
169	67.6
170	68.1
171	68.7
172	69.2
173	69.7
174	70.3
175	70.8
176	71.3
177	71.9
178	72.4
179	73.0
180	73.6
181	74.3
182	74.8
183	75.5
184	76.2
185	76.9
186	77.6
187	78.2
188	78.8
189	79.6
190	80.4
191	81.0
192	81.6
193	82.2
194	82.8
195	83.4
196	84.0

Modified for height without shoes from the 1983 Metropolitan Life Insurance Ideal Weights for Height tables.

Appendix 7. Lilly-Defined MedDRA Preferred Terms for Opportunistic Infections

Opportunistic Infection	Preferred Term (MedDRA Version 19.1)	Lilly-Defined Classification
Pneumocystis jirovecii (II)	Pneumocystis jirovecii infection Pneumocystis jirovecii pneumonia	Narrow
	Blood beta-D-glucan Blood beta-D-glucan abnormal Blood beta-D-glucan increased Gomori methenamine silver stain Carbon monoxide diffusing capacity decreased Carbon monoxide diffusing capacity Pneumocystis test positive	Broad
Human Polyomavirus infection including BK virus disease and PVAN (V), and Progressive Multifocal Leukoencephalopathy (IV)	BK virus infection Human polyomavirus infection JC virus granule cell neuronopathy JC virus infection Polyomavirus-associated nephropathy Progressive multifocal leukoencephalopathy	Narrow
	JC virus test Polyomavirus test Polyomavirus test positive	Broad
Cytomegalovirus disease (V)	Cytomegalovirus chorioretinitis Cytomegalovirus colitis Cytomegalovirus duodenitis Cytomegalovirus enteritis Cytomegalovirus enterocolitis Cytomegalovirus gastritis Cytomegalovirus gastroenteritis Cytomegalovirus gastrointestinal infection Cytomegalovirus gastrointestinal ulcer Cytomegalovirus hepatitis Cytomegalovirus infection Cytomegalovirus mononucleosis Cytomegalovirus mucocutaneous ulcer Cytomegalovirus myelomeningoradiculitis Cytomegalovirus myocarditis Cytomegalovirus oesophagitis Cytomegalovirus pancreatitis Cytomegalovirus pericarditis Cytomegalovirus syndrome Cytomegalovirus urinary tract infection Cytomegalovirus viraemia Disseminated cytomegaloviral infection Encephalitis cytomegalovirus	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 19.1)	Lilly-Defined Classification
	Pneumonia cytomegaloviral	
	Cytomegalovirus test Cytomegalovirus test positive	Broad
Post-transplant lymphoproliferative disorder (EBV) (V)	EBV associated lymphoproliferative disorder Post transplant lymphoproliferative disorder	Narrow
	Epstein-Barr viraemia EBV associated lymphoma EBV infection Lymphoproliferative disorder Lymphoproliferative disorder in remission Oral hairy leukoplakia	Broad
Bartonellosis (disseminated disease only) (V)	Bacillary angiomatosis Trench fever	Narrow
	Bartonella test Bartonella test positive Bartonellosis Cat scratch disease Peliosis hepatis Splenic peliosis	Broad
Blastomycosis (IV)	Blastomycosis Epididymitis blastomyces Osteomyelitis blastomyces Pneumonia blastomyces	Narrow
	None	Broad
Toxoplasmosis (IV)	Cerebral toxoplasmosis Eye infection toxoplasmal Hepatitis toxoplasmal Meningitis toxoplasmal Myocarditis toxoplasmal Pneumonia toxoplasmal	Narrow
	Toxoplasma serology Toxoplasmosis	Broad
Coccidioidomycosis (II)	Coccidioides encephalitis Coccidioidomycosis Cutaneous coccidioidomycosis Meningitis coccidioides	
	None	Broad
Histoplasmosis (II)	Acute pulmonary histoplasmosis Chronic pulmonary histoplasmosis Endocarditis histoplasma Histoplasmosis Histoplasmosis cutaneous Histoplasmosis disseminated Meningitis histoplasma Pericarditis histoplasma Retinitis histoplasma	Narrow
	Presumed ocular histoplasmosis syndrome	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 19.1)	Lilly-Defined Classification
Aspergillosis (invasive disease only) (II)	Aspergillosis oral Cerebral aspergillosis Meningitis aspergillus Oro-pharyngeal aspergillosis	Narrow
	Aspergillus infection Aspergillus test Aspergillus test positive Bronchopulmonary aspergillosis Sinusitis aspergillus	Broad
Candidiasis (invasive disease, or oral not limited to the tongue) (II)	Candida endophthalmitis Candida osteomyelitis Candida pneumonia Candida retinitis Candida sepsis Cerebral candidiasis Endocarditis candida Fungal oesophagitis Gastrointestinal candidiasis Hepatic candidiasis Hepatosplenic candidiasis Meningitis candida Oesophageal candidiasis Oral candidiasis Oral fungal infection Oropharyngeal candidiasis Peritoneal candidiasis Splenic candidiasis Systemic candida	Narrow
	Bladder candidiasis Candida infection Candida test Candida test positive Mucocutaneous candidiasis[1] Respiratory moniliasis	Broad
Cryptococcosis (II)	Cryptococcal cutaneous infection Cryptococcal fungaemia Cryptococcosis Disseminated cryptococcosis Gastroenteritis cryptococcal Meningitis cryptococcal Neurocryptococcosis Pneumonia cryptococcal	Narrow
	Cryptococcus test Cryptococcus test positive	Broad
Other invasive fungi: Mucormycosis (=zygomycosis) [Rhizopus, Mucor, and	Allescheriosis Fusarium infection Mucormycosis	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 19.1)	Lilly-Defined Classification
Lichtheimia], Scedosporum/Pseudallescheria boydii, Fusarium (II)	Scedosporium infection Pseudallescheria infection Pseudallescheria sepsis	
	See "Non-specific terms" below	Broad
Legionellosis (II)	Legionella infection Pneumonia legionella Pontiac fever	Narrow
	Legionella test Legionella test positive	Broad
Listeria monocytogenes (invasive disease only) (II)	Listeria encephalitis Listeria sepsis Meningitis listeria	Narrow
	Listeria test Listeria test positive Listeriosis	Broad
Tuberculosis (I)	Adrenal gland tuberculosis Bone tuberculosis Choroid tubercles Conjunctivitis tuberculous Cutaneous tuberculosis Disseminated Bacillus Calmette-Guerin infection Disseminated tuberculosis Ear tuberculosis Epididymitis tuberculous Extrapulmonary tuberculosis Female genital tract tuberculosis Immune reconstitution inflammatory syndrome associated tuberculosis Intestinal tuberculosis Joint tuberculosis Lupus vulgaris Lymph node tuberculosis Male genital tract tuberculosis Meningitis tuberculous Oesophageal tuberculosis Oral tuberculosis Pericarditis tuberculous Peritoneal tuberculosis Prostatitis tuberculous Pulmonary tuberculoma Pulmonary tuberculosis Renal tuberculosis Salpingitis tuberculous Silicotuberculosis Spleen tuberculosis Thyroid tuberculosis Tuberculoma of central nervous system	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 19.1)	Lilly-Defined Classification
	Tuberculosis Tuberculosis bladder Tuberculosis gastrointestinal Tuberculosis liver Tuberculosis of central nervous system Tuberculosis of eye Tuberculosis of genitourinary system Tuberculosis of intrathoracic lymph nodes Tuberculosis of peripheral lymph nodes Tuberculosis ureter Tuberculous abscess central nervous system Tuberculous endometritis Tuberculous laryngitis Tuberculous pleurisy Tuberculous tenosynovitis	
	Interferon gamma release assay Interferon gamma release assay positive Mycobacterium tuberculosis complex test Mycobacterium tuberculosis complex test positive Tuberculid Tuberculin test Tuberculin test false negative Tuberculin test positive	Broad
Nocardiosis (II)	Nocardia sepsis Nocardiosis	Narrow
	Nocardia test positive	Broad
Nontuberculous mycobacterium disease (II)	Atypical mycobacterial infection Atypical mycobacterial lower respiratory tract infection Atypical mycobacterial lymphadenitis Atypical mycobacterium pericarditis Atypical mycobacterial pneumonia Borderline leprosy Bovine tuberculosis Indeterminate leprosy Leprosy Lepromatous leprosy Mycobacterial infection Mycobacterial peritonitis Mycobacterium abscessus infection Mycobacterium avium complex immune restoration disease Mycobacterium avium complex infection Mycobacterium chelonae infection Mycobacterium fortuitum infection Mycobacterium kansasii infection Mycobacterium marinum infection Mycobacterium ulcerans infection Superinfection mycobacterial	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 19.1)	Lilly-Defined Classification
	Tuberculoid leprosy Type 1 lepra reaction Type 2 lepra reaction	
	Atypical mycobacterium test positive Mycobacterial disease carrier Mycobacterium leprae test positive Mycobacterium test Mycobacterium test positive	Broad
Salmonellosis (invasive disease only) (II)	Aortitis salmonella Arthritis salmonella Meningitis salmonella Osteomyelitis salmonella Paratyphoid fever Pneumonia salmonella Salmonella bacteraemia Salmonella sepsis Typhoid fever	Narrow
	Salmonella test positive Salmonellosis	Broad
HBV reactivation (IV)	None	Narrow
	Asymptomatic viral hepatitis Chronic hepatitis B HBV-DNA polymerase increased Hepatitis B Hepatitis B antigen Hepatitis B antigen positive Hepatitis B core antigen Hepatitis B core antigen positive Hepatitis B DNA assay Hepatitis B DNA assay positive Hepatitis B DNA increased Hepatitis B e antigen Hepatitis B e antigen positive Hepatitis B surface antigen Hepatitis B surface antigen positive Hepatitis B virus test Hepatitis B virus test positive Hepatitis infectious Hepatitis post transfusion Hepatitis viral Withdrawal hepatitis	Broad
Herpes simplex (invasive disease only) (IV)	Colitis herpes Eczema herpeticum Gastritis herpes Herpes oesophagitis Herpes sepsis Herpes simplex colitis	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 19.1)	Lilly-Defined Classification
	Herpes simplex encephalitis Herpes simplex gastritis Herpes simplex hepatitis Herpes simplex meningitis Herpes simplex meningoencephalitis Herpes simplex meningomyelitis Herpes simplex necrotising retinopathy Herpes simplex oesophagitis Herpes simplex pneumonia Herpes simplex sepsis Herpes simplex visceral Meningitis herpes Meningoencephalitis herpetic Meningomyelitis herpes Pneumonia herpes viral	
	Genital herpes Genital herpes simplex Herpes dermatitis Herpes ophthalmic Herpes pharyngitis Herpes simplex Herpes simplex DNA test positive Herpes simplex otitis externa Herpes simplex pharyngitis Herpes virus infection Nasal herpes Ophthalmic herpes simplex Oral herpes Proctitis herpes	Broad
Herpes zoster (any form) (II)	Disseminated varicella zoster vaccine virus infection Encephalitis post varicella Genital herpes zoster Herpes zoster Herpes zoster cutaneous disseminated Herpes zoster disseminated Herpes zoster infection neurological Herpes zoster meningitis Herpes zoster meningoencephalitis Herpes zoster meningomyelitis Herpes zoster necrotising retinopathy Herpes zoster oticus Herpes zoster pharyngitis Necrotising herpetic retinopathy Ophthalmic herpes zoster Varicella Varicella keratitis Varicella post vaccine	Narrow

Opportunistic Infection	Preferred Term (MedDRA Version 19.1)	Lilly-Defined Classification
	Varicella zoster gastritis Varicella zoster oesophagitis Varicella zoster pneumonia Varicella zoster virus infection	
	Varicella virus test Varicella virus test positive	Broad
Stronglyoides (hyperinfection syndrome and disseminated forms only) (IV)	None	Narrow
	Strongyloidiasis	Broad
Paracoccidioides infections (V)	Paracoccidioides infection	Narrow
	None	Broad
Penicillium marneffei (V)	Penicillium infection	Narrow
	None	Broad
Sporothrix schenckii (V)	Cutaneous sporotrichosis Sporotrichosis	Narrow
	None	Broad
Cryptosporidium species (chronic disease only) (IV)	Biliary tract infection cryptosporidial	Narrow
	Cryptosporidiosis infection Gastroenteritis cryptosporidial	Broad
Microsporidiosis (IV)	Microsporidia infection	Narrow
	None	Broad
Leishmaniasis (Visceral only) (IV)	Visceral leishmaniasis	Narrow
	Leishmaniasis	Broad
Trypanosoma cruzi infection (Chagas' Disease) (disseminated disease only) (V)	None	Narrow
	American trypanosomiasis Trypanosomiasis Meningitis trypanosomal	Broad
Campylobacteriosis (invasive disease only) (V)	Campylobacter sepsis	Narrow
	Campylobacter colitis Campylobacter gastroenteritis Campylobacter infection Campylobacter test positive	Broad
Shigellosis (invasive disease only) (V)	Shigella sepsis	Narrow
	Shigella infection Shigella test positive	Broad
Vibriosis (invasive disease due to *V. vulnificus*) (V)	None	Narrow
	Gastroenteritis vibrio Vibrio test positive	Broad
HCV progression (V)	None	Narrow
	Chronic hepatitis C Hepatitis C Hepatitis C RNA Hepatitis C RNA fluctuation Hepatitis C RNA increased Hepatitis C RNA positive Hepatitis C virus test	Broad

Opportunistic Infection	Preferred Term (MedDRA Version 19.1)	Lilly-Defined Classification
	Hepatitis C virus test positive	
Non-specific terms	None	Narrow
	Abscess fungal Alternaria infection Arthritis fungal Biliary tract infection fungal Central nervous system fungal infection Cerebral fungal infection Encephalitis fungal Erythema induratum Eye infection fungal Fungaemia Fungal abscess central nervous system Fungal endocarditis Fungal labyrinthitis Fungal oesophagitis Fungal peritonitis Fungal pharyngitis Fungal retinitis Fungal sepsis Hepatic infection fungal Meningitis fungal Mycotic endophthalmitis Myocarditis mycotic Oral fungal infection Oropharyngitis fungal Osteomyelitis fungal Otitis media fungal Pancreatitis fungal Pericarditis fungal Phaehyphomycosis Pneumonia fungal Pulmonary mycosis Pulmonary trichosporonosis Sinusitis fungal Splenic infection fungal Systemic mycosis	Broad

[1] Only oral or chronic

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