

Official Title: An Open-Label Extension and Safety Monitoring Study of Patients With Moderately to Severely Active Crohn's Disease Previously Enrolled in the Etrolizumab Phase III Protocol GA29144

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STATISTICAL ANALYSIS PLAN

STUDY TITLE: AN OPEN-LABEL EXTENSION AND SAFETY MONITORING STUDY OF PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE PREVIOUSLY ENROLLED IN THE ETROLIZUMAB PHASE III PROTOCOL GA29144

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PLAN PREPARED BY: [REDACTED], Ph.D.
[REDACTED], M.Sc.

STATISTICAL ANALYSIS PLAN APPROVAL

SPONSOR: F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS: Grenzacherstrasse 124
4070 Basel, Switzerland
DATE FINAL: See electronic date stamp on the last page of this document

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
5-ASAs	5-aminosalicylic acid
AE	adverse event
AEGT	Adverse Events Group Terms
AESI	adverse event of special interest
ALT	alanine aminotransferase
AP	abdominal pain
AST	aspartate aminotransferase
ATA	anti-therapeutic antibodies
BMI	body mass index
CCOD	clinical cutoff date
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CD-PRO/SS	Crohn's Disease- Patient Reported Outcome/ Signs and Symptoms
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
CS	corticosteroids
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
e-CRF	electronic Case Report Form
EQ-5D	EuroQL 5 Dimension Questionnaire
HLGT	High Level Group Terms
HLT	High Level Term
IBDQ	Inflammatory Bowel Disease Questionnaire
ICE	intercurrent event
iDMC	independent Data Monitoring Committee
IS	immunosuppressant
IxRS	interactive voice/Web based response system
LOCF	last-observation-carried-forward
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MICE	multivariate imputation by chained equations
mITT	modified intent to treat

MMRM	mixed models for repeated measures
NRI	non-responder imputation
OLE	open label extension
PD	pharmacodynamics
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PRO2	patient-reported outcomes-2
PT	preferred term
Q4W	every 4 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SES-CD	simplified endoscopic score for Crohn's disease
SF	stool frequency
SM	safety monitoring
SOC	system organ class
TNF	tumor necrosis factor
TNF-IR	TNF-inadequate responder
ULN	upper limit of normal
WOCF	worst-observation-carried-forward

1. INTRODUCTION

The analyses described in this Statistical Analysis Plan (SAP) will supersede those specified in Protocol GA29145 for the purposes of reporting.

The purpose of this document is to describe the analyses for reporting out Part 1 of the Open-Label-Extension Safety Monitoring (OLE-SM) study for GA29145. This SAP will solely focus on reporting data collected during Part 1 (OLE) of GA29145.

This OLE-SM study is composed of two parts:

1. Part 1 is the OLE for eligible patients, during which etrolizumab, 105 mg SC, will be administered Q4W followed by a 12-week safety follow-up post-treatment.
2. Part 2 is the 92-week PML SM for all patients, during which no etrolizumab will be administered.

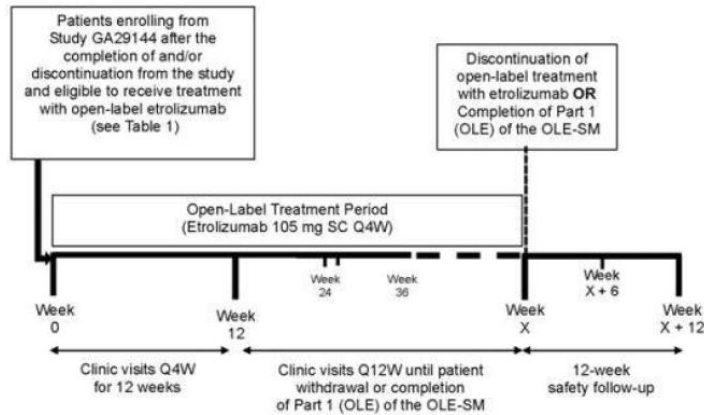
Patients who are enrolled in Part 1 (OLE) should participate in Part 2 (SM).

There may be patients from Study GA29144 who are ineligible for or choose not to participate in Part 1 (OLE) who will be asked to directly enroll in Part 2 (SM).

Key characteristics of the GA29145 OLE-SM are provided in [Table 1](#). Treatment arms and rollover of patients from induction/maintenance to GA29145 OLE-SM from parent CD studies are depicted in [Figure 1](#) and [Figure 2](#).

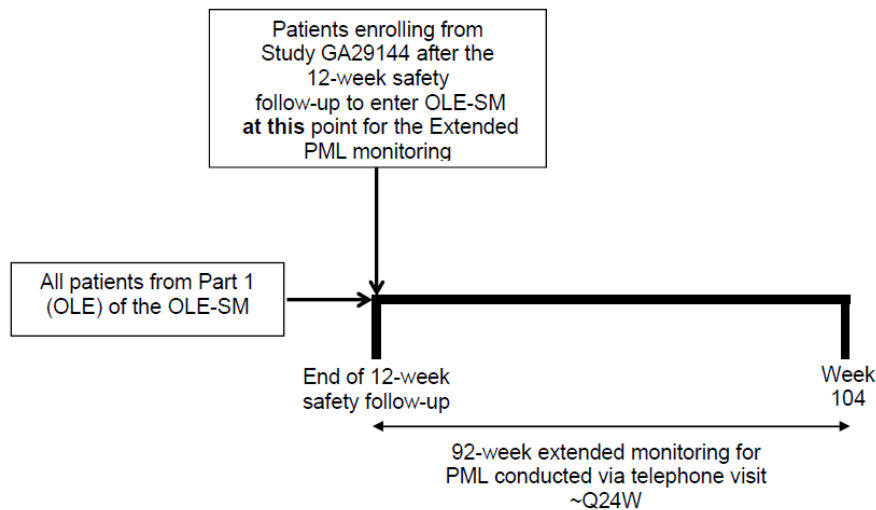
The maximum number of patients enrolled in GA29145 OLE-SM is approximately 1150 (i.e., all patients enrolled in Study GA29144). No formal sample size calculations were performed.

Figure 1 Study Schema for Part 1 (Open-Label Extension; OLE) of the OLE-SM Study



OLE=open-label extension; OLE-SM=open-label extension—safety monitoring; Q4W=every 4 weeks; Q12W=every 12 weeks; SC=subcutaneous.

Figure 2 Study Schema for Part 2 (Safety Monitoring; SM) of the OLE-SM Study



OLE=open-label extension; OLE-SM=open-label extension—safety monitoring; PML=progressive multifocal leukoencephalopathy; ~Q24W=approximately every 24 weeks.

Table 1 Key Characteristics of GA29145 OLE-SM in CD (Juniper)

Study	GA29145 (Phase III)	
Treatment (Number Exposed)	Open-label etrolizumab 105 mg SC Q4W (n= up to ~1150)	
Study Phases	OLE up to 10 years from FPI 12-week safety follow-up 92-week PML monitoring	
Key Eligibility Criteria	Part 1 (OLE)	Part 2 (SM)**
	<ul style="list-style-type: none"> • Previously enrolled in Study GA29144 • Starting at Week 10, CDAI > patient's baseline CDAI • Not eligible for maintenance* • A clinical relapse during the Maintenance Phase[^] • Complete the Maintenance Phase including the Week 66 or Week 74 	<ul style="list-style-type: none"> • Previously enrolled in Study GA29144 and are not eligible or chose not to enroll in Part 1 (OLE) and completed the 12-week SFU • Participated in Part 1 (OLE) and completed the 12-week SFU

CD= Crohn's disease; CDAI =Crohn's Disease Activity Index; FPI=first patient in; OLE=open- label extension; PML=progressive multifocal leukoencephalopathy; Q4W=every 4 weeks; SC=subcutaneous; SM=safety monitoring; SFU = safety follow-up.

*Including patients who completed the Week 14 visit in Study GA29144 and could not subsequently enter the Maintenance Phase, because the sample size was achieved and enrollment into the Maintenance Phase was closed.

**All patients must have completed the 12- week safety follow-up in either GA29144 or GA29145, Part 1 (OLE), as applicable, prior to entering Part 2 (SM).

[^] A clinical relapse during the Maintenance Phase of Study GA29144 is defined as meeting at least one of the following criteria on two consecutive visits (may include unscheduled visits), with at least one of the two consecutive CDAI scores \geq 220: CDAI score \geq the baseline (Week 0) score, or CDAI score \geq 100 points higher than the Week 14 score

Changes to the protocol-planned analyses are described in [Section 4.4](#).

1.1 OBJECTIVES AND ENDPOINTS

The objectives of this OLE-SM study are as follows:

Part 1 (OLE)

- To assess the long-term safety and efficacy of etrolizumab in patients eligible for Part 1 (OLE)

Part 2 (SM)

- PML safety monitoring in patients who have stopped study treatment

This SAP will only cover analyses for GA29145 Part 1 (OLE) objective.

Other Safety Objectives

- To evaluate the incidence, rate per subject-year, and severity of infection-related adverse events
- To evaluate the incidence and rate per subject-year of malignancies
- To evaluate the incidence and severity of hypersensitivity reactions

Exploratory Objectives

- To assess endoscopic appearance at Week 108

The following endpoint was de-prioritised as a safety objective to an exploratory objective from Protocol GA29145, version 6. Rationale for this is detailed in Section 4.4:

- To evaluate the incidence and the clinical significance of anti-therapeutic antibodies (ATAs)

1.2 STUDY DESIGN

Details of the Part 1 (OLE) study design can be found in the Protocol Synopsis section, Section 3 and Study Schema in Figure 1 of Protocol Version 6.

1.2.1 Protocol Synopsis

The Protocol Synopsis is in Protocol Synopsis Section of study GA29145 Protocol Version 6. For additional details, see the Schedule of Assessments in Appendices 1 and 2 of study GA29145 Protocol Version 6.

1.3 OUTCOME MEASURES FOR GA29145 PART 1 (OLE)

1.3.1 Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- Crohn's Disease Activity Index (CDAI) remission assessed at 12-week intervals during GA29145 Part 1 (OLE)
- Clinical remission assessed at 12-week intervals during GA29145 Part 1 (OLE), as defined by a stool frequency (SF) mean daily score ≤ 3 and an abdominal pain (AP) mean daily score ≤ 1 with no worsening in either subscore compared to baseline, averaged over 7 days prior to visit

- Simple Endoscopic Score for Crohn’s disease (SES-CD) score assessed at Week 108 or at early withdrawal, if prior to Week 108, during GA29145 Part 1 (OLE)

The efficacy outcome definitions are provided below.

Table 2 Efficacy Outcome Definitions

Outcome Term	Definition
CDAI	CDAI is a composite of eight assessments: number of liquid or soft stools, abdominal pain, general well-being, presence of complications, taking Lomotil (diphenoxylate/atropine) or other opiates for diarrhea, presence of an abdominal mass, hematocrit, and percentage deviation from standard weight
SES-CD	SES-CD is an endoscopic score derived from four variables (ulcers, ulcerated surface, inflamed surface, and presence of narrowing) that are scored in five ileocolonic segments.
CDAI Remission	CDAI Score < 150
Clinical Remission	An SF mean daily score ≤3 and an AP mean daily score ≤1 with no worsening in either subscore compared to baseline, where the average is taken over 7 days prior to visit

AP= abdominal pain; CDAI = Crohn’s Disease Activity Index; SES-CD= Simple Endoscopic Score for Crohn’s disease; SF = liquid/soft stool frequency.

1.3.2 Safety Outcome Measures

The safety outcome measures for GA29145 Part 1 (OLE) of this study are as follows:

- Incidence and severity of adverse events
- Incidence of serious adverse events
- Incidence, rate per subject-year, and severity of infection-related adverse events
- Incidence of serious infection-related adverse events
- Incidence and severity of injection-site reactions
- Incidence of adverse events leading to etrolizumab discontinuation
- Incidence of laboratory abnormalities
- Incidence and rate per subject-year of malignancies
- Incidence and severity of hypersensitivity reactions

1.3.3 Exploratory Outcome Measures

The exploratory outcome measures for GA29145 Part 1 (OLE) of this study are as follows:

- SES-CD ≤ 4 (≤ 2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is > 1 , at Week 108
- Change in SES-CD score between Week 0 (Study GA29144) and Week 108 or early withdrawal (Study GA29145, Part 1; OLE)

Incidence of ATAs to etrolizumab (*de-prioritised from a safety outcome measure and will not be analysed or reported in primary Clinical Study Report [CSR] for GA29145 Part 1 (OLE). See Section 4.4 for details).*

1.4 ANALYSIS TIMING

GA29145 Part 1 (OLE) will be formally analyzed and reported in a primary CSR after the last patient has completed the 12-week safety follow up, following last dosing on 15th May 2022. Note that a database snapshot rather than a database lock for reporting Part 1 (OLE) of GA29145 will take place.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

Due to the non-comparative character of the study, no statistical tests or hypotheses are planned; all efficacy parameters will be summarized descriptively.

2.2 SAMPLE SIZE DETERMINATION

The maximum number of patients that could be enrolled into the GA29145 OLE-SM study is approximately 1150 (i.e., all patients enrolled in Study GA29144). No formal sample size calculations were performed.

3. ANALYSIS SETS

The analysis population for the purposes of analyses are presented in below:

Table 3 Analysis Population

Open-Label Extension	Patients who receive at least one dose of study drug in Study GA29145 Part 1 (OLE)
	Timeframe is from first dose of study drug in the GA29145 Part 1 (OLE) to the patient's last visit in GA29145 Part 1 (OLE), or safety follow-up, whichever is latest. Summaries will primarily focus on safety events arising after first dose of study drug in Study GA29145 Part 1 (OLE)

4. STATISTICAL ANALYSES

For reporting, a synoptic CSR will be reported. Due to this synoptic nature, limited efficacy data will be reported and all safety outcome measures will be reported in the CSR.

4.1 GENERAL CONSIDERATIONS

4.1.1 Analysis of Study Conduct

The number of patients who discontinued early (early discontinuation of OLE treatment or early termination from the study) or completed the study will be tabulated.

Reasons for early discontinuation of treatment or early termination from the study will be listed and summarized. Any eligibility criteria exceptions and other major protocol deviations will also be summarized.

Since Part 1 (OLE) of GA29145 was terminated by the Sponsor on 15th February 2022, no patients are expected to reach treatment completion. As a result of this, the end of Part 1 (OLE) of GA29145 is defined from the last dose date in GA29145 on 15th May 2022.

In summary, the following will be summarised for GA29145 Part 1 (OLE):

- Analysis populations
- Patient disposition
- Study treatment completion/discontinuation
- Study completion/discontinuation
- Major protocol deviations
- Exposure

Treatment Labels

For the OLE population, the only treatment arm to be summarized is:

Group	Patients Included
OLE Etrolizumab	Patients in the OLE population who receive at least one dose of etrolizumab in Study GA29145 Part 1 (OLE)

All tables should be presented by treatment group only.

Part 1 (OLE) Day 1

OLE Study Day 1 is defined as the day patient has the first receipt of study drug in GA29145 Part 1 (OLE).

Baseline

Baseline is defined as the last available assessment prior to first receipt of study drug in the Induction Phase of the parent study, GA29144.

4.1.2 Analysis of OLE Treatment

The following variables collected at baseline will be summarized for the OLE population. No treatment comparisons will be made since GA29145 is a single-arm open-label study.

For continuous variables, descriptive statistics including n, mean, median, standard deviation, minimum, and maximum will be calculated. For categorical variables, number and percentage in each category will be displayed.

Demography

- Age
- Age category (≥ 18 to < 40 , ≥ 40 to < 65 , ≥ 65)
- Sex
- Race
- Ethnicity
- Region
- Smoking status history
- Body mass index
- Weight

Disease Characteristics

- Duration of disease (years)
- Duration of disease (years) category (< 3 , ≥ 3 to < 8 , ≥ 8)
- Disease location (Ileum only, Colon only, Ileum + Colon)
- Number of affected ileo-colonic segments
- Ulcerations at baseline
- Mean SF score
- Mean AP score (4-point scale)
- CDAI score
- CDAI Category (≤ 330 , > 330) (IxRS and Rave)
- SES-CD score
- CD-PRO/SS – Functional score

- CD-PRO/SS – Bowel score
- Inflammatory Bowel Disease Questionnaire (IBDQ) total score
- Fecal calprotectin ($\mu\text{g/g}$)
- Fecal calprotectin category ($<250 \mu\text{g/g}$, $\geq 250 < 500 \mu\text{g/g}$, $\geq 500 \mu\text{g/g}$)
- C-reactive protein (CRP) levels (mg/L)
- CRP category ($\leq 2.87 \text{ mg/L}$, $> 2.87 \text{ to } \leq 10 \text{ mg/L}$, $> 10 \text{ mg/L}$)
- Albumin

Baseline Treatments

- Use of oral CS at Baseline (yes vs. no) (IxRS and Rave)
- Use of IS at Baseline (yes vs. no) (IxRS and Rave)
- Prior anti-TNF exposure (yes vs. no) (IxRS and Rave)

The patients with prior anti-TNF exposure at baseline will be further evaluated to include the number of TNFs previously received and status (e.g., primary non-responder, secondary non-responder, Intolerant, etc).

4.1.3 Primary Efficacy Analysis

To evaluate the efficacy of etrolizumab during long-term open-label treatment, efficacy will be summarized within the population of patients who enroll into the Study GA29145. Both endoscopic improvement and clinical remission will be summarized in two separate analyses. Due to the open-label nature of the study, no treatment comparisons will be made.

Concerning missing data and treatment withdrawal imputation, there will be 3 strategies employed, described below.

Hybrid LOCF

Within this strategy, at each visit only patients who had the possibility of reaching the visit will be considered in the analysis for that specified visit. Patients will be deemed evaluable at a visit if it was possible for them to have reached this visit based on their enrollment date and the date of the closure of Part 1 of the study.

- Patients for whom it is not possible to have reached the visit at the time of the clinical cut off are termed non-evaluable and will not be included in the analysis at that visit.
- For evaluable patients with missing data, Last Observation Carried Forward (LOCF) will be used from their most recent available data.

- For evaluable patients who previously withdrew from treatment, they will be imputed as a non-responder until their maximum hypothetical visit (i.e., the maximum visit that they could have attended if they had remained within the study).
 - For visits after a patient's maximum hypothetical evaluable visit, they will be removed from the analysis.

As Observed

Within this analysis only the available data at each visit will be summarized. No imputation will be performed for missing data or treatment withdrawals.

Non-Responder

Within this strategy, at each visit only patients who had the possibility of reaching the visit will be considered in the analysis for that specified visit. Patients will be deemed evaluable at a visit if it was possible for them to have reached this visit based on their enrollment date and the date of the closure of Part 1 of the study.

- Patients for whom it is not possible to have reached the visit at the time of the clinical cut off are termed non-evaluable and will not be included in the analysis at that visit.
- Evaluable patients with missing data will be set as a non-responder.
- For evaluable patients who previously withdrew from treatment, they will be imputed as a non-responder until their maximum hypothetical visit (i.e., the maximum visit that they could have attended if they had remained within the program).
 - For visits after a patient's maximum hypothetical evaluable visit, they will be removed from the analysis.

Maximum Hypothetical Evaluable Visit

A patient's maximum hypothetical study day (i.e., the maximum visit that they could have attended if they had remained within the study) is calculated as follows:

Maximum hypothetical study day = (15th May 2022 - Patient's Day 1 OLE enrollment date)

For the hybrid LOCF analysis and non-responder analyses, this will impute patients who have withdrawn as a non-responder until the 15th May 2022, which was the latest day of dosing reported in the closure of the study announcement. This excludes patients who withdrew from study drug with reason being stated as "study terminated by sponsor" after 15th February 2022, these patients will not be imputed as non-responders and will be considered 'treatment completers' for the efficacy analysis with data included "as observed".

Simple Endoscopic Score for Crohn's disease (SES-CD) score: Handling of Partially Available Segments

Note that in the OLE study GA29145, no central adjudication took place and therefore only a local score will be available for the Week 108 assessment. This differs from Study GA29144, which utilized central adjudication and up to 3 readers provided a score. To overcome differences in reader availability between studies the following approach will be used:

Baseline score will utilize data from all available readers with adjudication applied to determine the final total SES-CD score. This aligns with the original Day 1 Baseline score in study GA29144 and ensures that the central readers are retained in the Baseline score derivation, as reported in the CSR analysis.

The determination of segment availability will use the Local reader only for both the baseline and post-baseline time points, as follows:

- any segment(s) missing by the local reader at baseline will not be considered in the Week 108 visit total SES-CD total score calculation
- any segments(s) available at baseline that are not available at Week 108 will result in a non-responder status for the patient for endoscopic improvement/remission. For continuous data the patient's baseline segment score will be carried forward (BOCF) to impute the Week 104 segment score when calculating the total SES-CD score.

4.1.3.1 Endoscopic Improvement and Remission at Week 108

As endoscopy data is only collected at a common time point of Week 108 during the OLE Study GA29145, the endpoints of endoscopic improvement and endoscopic remission will be summarized only at this time point. These endpoints will be examined overall and separated by their previous endoscopic improvement status at their latest visit prior to enrollment into GA29145 i.e., at the parent study's (GA29144) Week 14 or Week 66.

The handling of patients with partially available segments is detailed in Section [4.1.3](#), this is not considered as true missing data.

Population: All patients who enrolled into Part 1 of the OLE Study GA29145.

Baseline: The original baseline value from the parent study will be used to calculate improvement.

Sub-groups:

- All patients overall and split by prior endoscopic improvement status and their prior aTNF exposure status.

Analysis 1 - Non-Responder

Missing data: Patients who are non-evaluable at Week 108 (i.e., could not have reached the maximum visit if they had remained within the program as detailed in Section 4.1.3) will be removed from the analysis. Patients who remain in Study GA29145 but are missing endoscopy scores (i.e., the assessment was not done) will be imputed as non-responders within the analysis, as LOCF is not appropriate when endoscopy data is not collected routinely.

Intercurrent events: Patients who withdraw during Study GA29145 will be set to non-responders using the composite strategy if they could have reached OLE Week 108 at the time of the clinical cut-off date had they not withdrawn from treatment. This excludes patients who withdrew from study drug on or after 15th February 2022.

Analysis 2 - As Observed

Missing data: If a patient has missing data at a visit, they will be removed from the analysis and no imputation will be performed.

Intercurrent events: No imputation will be performed for treatment withdrawals

4.1.3.2 Simple Endoscopic Score for Crohn's disease (SES-CD) score at Week 108

As endoscopy data is only collected at a common time point of Week 108 during the OLE Study GA21945, continuous SES-CD score will be summarized only at this time point and at parent study Baseline. The handling of patients with partially available segments is detailed in Section 4.1.3, this is not considered as true missing data.

Population: All patients who enrolled into Part 1 of the OLE Study GA29145.

Baseline: The original baseline value from the parent study will be used as the baseline SES-CD score.

Analysis 1 - BOCF

Missing data: If a patient has missing data at a visit (i.e., the assessment was not done), they will be removed from the analysis and no imputation will be performed.

Intercurrent events: No imputation will be performed for treatment withdrawals

4.1.3.3 CDAI Remission and Clinical Remission Every 12 Weeks

The percentage of patients in CDAI remission or clinical remission as defined in the Efficacy Derivations Section 1.3.1 will be summarized for each OLE visit for patients who entered Study GA29145. All OLE visits will be summarized until a minimum of 20 evaluable patients overall remain within the analysis (i.e., an evaluable patient either reached the visit or could have reached the visit if they had remained within the OLE).

Population: Patients who enroll into Part 1 of Study GA29145.

Baseline: The original baseline value from the parent study will be used to calculate remission, where applicable.

Sub-groups:

- Table outputs: All patients overall, split by aTNF exposure status and by OLE Day 1 CDAI remission or clinical remission status, as appropriate.
- Figure outputs: All patients overall and split by OLE Day 1 CDAI remission or clinical remission status.

Analysis 1 - Hybrid LOCF

Missing data: If patients who remain in Study GA29145 at the specified visit are missing data then LOCF will be used to impute. For visits where patients are non-evaluable (i.e. it is not possible for them to have reached the specified visit at the time of the clinical cut-off date) they will be removed from the analysis.

Intercurrent Events: Using the composite strategy in the case where patients have withdrawn from the Study GA29145, they will be set to non-responders for all visits where they are evaluable. This excludes patients who withdrew from study drug with reason being stated as “study terminated by sponsor” after 15th February 2022.

Analysis 2 - As Observed

Missing data: If a patient has missing data at a visit, they will be removed from the analysis and no imputation will be performed.

Intercurrent events: No imputation will be performed for treatment withdrawals

4.2 SAFETY ANALYSES

Safety data will be assessed through descriptive summaries using the OLE population. All data available up until the clinical cut-off date (CCOD) will be reported.

Safety evaluations for the OLE population will include data from the first dose of treatment in Part 1 (OLE) until the patient completes/withdraws from the Part 1(OLE) of the study GA29145, this includes any 12-week safety follow-up data.

4.2.1 Extent of Exposure

Exposure to study treatment will be summarized by:

- treatment duration (weeks)
- number of patients receiving a dose at each visit
- number of doses received/missed for a patient

4.2.2 Adverse Events

Verbatim descriptions of AEs will be mapped to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events (AEs) will include all terms recorded on the AE Case Report Form (CRF) pages (except pregnancies). For each recorded AE, the term entered by the investigator describing the event (the “reported term”) will be assigned a standardized term (the “preferred term”) and assigned to a superclass term on the basis of the Medical Dictionary for Regulatory Activities (MedDRA) World Health Organization (WHO) dictionary of terms. All analyses of AE data will be performed using the preferred terms and system organ class unless otherwise specified.

For the etrolizumab program, the adverse events of special interest (AESIs) are the following:

- Systemic hypersensitivity reactions and anaphylactic and anaphylactoid reaction which will be reported using the MedDRA anaphylactic reaction Standard MedDRA Query (SMQ) algorithmic and Hypersensitivity SMQ narrow.
- Neurological signs, symptoms, and AEs that may suggest possible progressive multifocal leukoencephalopathy (see Appendices 5 and 6 of Protocol)
- Suspected transmission of an infectious agent by the study drug
- Cases of potential drug-induced liver injury that include an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy’s Law

Specific AEs listed below will also be reported:

- Serious infections
- Gastrointestinal Infections
- Opportunistic infections
- Malignancies

- Injection site reactions

A listing or, summary table (e.g., n > 10) of all AEs suspected or confirmed, and AEs associated with COVID-19 will be generated. Associated AEs are defined as all AEs reported within a time window of 7 days prior and 30 days after the confirmed COVID-19 start date (dates inclusive). Additionally, a listing of patients experiencing 'long COVID-19' will be generated. This listing will include all AEs with a duration >30 days occurring after a confirmed COVID-19 infection or a positive PCR test.

All AESIs and specific AEs will be determined using a selection of eCRF tick box or MedDRA SMQs, Adverse Events Group Terms (AEGTs), High Level Term (HLTs), High Level Group Terms (HLGTs), System Organ Class (SOC), as appropriate.

Summary tables will be generated for AEs, serious adverse events (SAEs), deaths, AEs leading to discontinuation of study drug, and AESIs. A listing will be generated for AEs, deaths, selected AESIs/specific AEs, and COVID-19 AEs. Pregnancies will be reported as narratives in the study CSR.

Summary tables of AEs will summarize the incidence of treatment-emergent AEs only. Treatment-emergent events are defined as any new AE reported on or after the first dose of OLE study drug or any worsening of an existing condition. Note that worsening of existing conditions include AEs ongoing from the parent study, GA29144. Otherwise, only AEs reported on or after the first dose of OLE study drug are included. If the onset date of the AE is prior to the day of first dose, the AE will be considered treatment emergent only if the most extreme intensity is greater than the initial intensity (i.e., the intensity for a given AE increases and its end date is on or after the date of the first dose). For all summary tables, the AEs will be sorted by SOC (in decreasing order of overall incidence) and then by preferred term (PT) (in decreasing order of overall incidence).

For OLE etrolizumab treatment, the incidence count for each AE PT will be defined as the number of patients reporting at least one treatment-emergent occurrence of the event (multiple occurrences of the same AE in 1 patient will be counted only once). The proportion of patients with an AE will be calculated as the incidence count divided by the total number of patients in the population. Each table will also present the total number of AEs reported where multiple occurrences of the same AE in an individual are counted separately.

Rate tables will be generated for selected AEs of interest. The rate per 100 patient years and 95% CIs will be summarized by treatment group and will be calculated by:

$$AE \text{ Rate (per 100 patient years)} = \frac{\text{Total number of AEs (in OLE only)}}{\text{Total number of patient years at risk (in OLE only)}} \times 100$$

where the total patient-years at risk is the sum over all patients of the time intervals (in years) from the first dose of study treatment in Part 1 (OLE) until the patient completes/withdraws from the study (including the 12-week safety follow-up, if applicable). Only treatment emergent AEs with an onset date after the first dose of open label Etolizumab in GA29145 will be included within these outputs.

All summary tables and listings will report AEs using the OLE population.

4.2.3 Additional Safety Assessments

4.2.3.1 Laboratory Data

Selected laboratory parameters for safety reporting will be described further in the OLE population by summarizing the marked abnormalities and shift tables. Marked abnormalities will be identified according to a Sponsor-defined standard, which generally captures post-baseline laboratory values both outside a reference range and achieving a threshold percent change from baseline. Where needed, laboratory values will be linearly transformed to a standard reference range in order to account for intrinsic differences between males and females or measurement differences between laboratory standards.

Laboratory abnormalities and the patient's worst Common Terminology Criteria for Adverse Events (CTCAE) grade during study will be summarized for hematology and serum chemistry parameters, in addition to change from Baseline summaries.

Elevated liver enzyme tests will be summarized by the following upper limit of normal (ULN) categories as these are indicators of severe liver injury:

- ALT or AST > 3ULN and total bilirubin > 2 ULN as defined by Hy's law
- ALT or AST > 3 ULN

4.2.3.2 Vital Signs

Vital signs will be summarized using summary statistics and change from baseline. The proportion of patients experiencing clinically significant changes relative to baseline will be reported if appropriate.

4.2.3.3 ECGs

A shift table for the qualitative ECG assessments will be produced, summarizing the Baseline and worst post-baseline results.

4.2.3.4 Medical History

Medical history data collected in the electronic-CRF (eCRF) from OLE Day 1 will be summarized using summary statistics, reporting the proportion of patients with at least one medical condition and the total number of medical conditions. The medical conditions will then be split out by type.

4.2.3.5 Concomitant Medications

Concomitant medications include any medication being used at any time from first dose of OLE study drug through to 7 days after last dose of OLE study drug. The data will be summarized, and report the total number of patients taking at least one medication, and total number of medications. Summaries will also be split by medication class and preferred medication. Medication terms will be mapped and reported using the WHO drug dictionary.

4.2.4 Open-Label Extension Timeframe

For the open-label extension population, the safety reporting timeframe is defined to capture safety information within the OLE treatment period only. It begins at first dose of study drug in Study GA29145 Part 1 (OLE). The end of the time-frame coincides with the last patient last visit, this includes safety follow-up in Study GA29145 Part 1 (OLE).

4.3 INTERIM ANALYSES

There are no planned interim analyses for study GA29145.

4.4 CHANGES TO PROTOCOL-PLANNED ANALYSES

The incidence of ATAs to etrolizumab was extensively evaluated in Ulcerative Colitis and Crohn's Disease within the phase 3 program, where no obvious impact on injection site reactions or other relevant safety parameters such as hypersensitivity was found. Following this evaluation, ATAs has been de-prioritised from a safety objective and outcome measure in GA29145 to an exploratory objective and outcome measure.


5. SUPPORTING DOCUMENTATION

This section is not applicable, since there is no additional supporting document.

6. REFERENCES

Not applicable.

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