Official Title: An Open-Label Extension and Safety Monitoring Study of Moderate to Severe Ulcerative Colitis Patients Previously Enrolled in Etrolizumab Phase II/III Studies

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STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**AN OPEN-LABEL EXTENSION AND SAFETY MONITORING STUDY OF PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS PATIENTS PREVIOUSLY ENROLLED IN THE ETROLIZUMAB PHASE II/III STUDIES**
STUDY NUMBER:	GA28951
STUDY NAME:	COTTONWOOD
VERSION NUMBER:	1
ROCHE COMPOUND(S):	Etrolizumab (PRO145223, RO5490261)
EUDRACT NUMBER:	2013-004435-72
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STATISTICAL ANALYSIS PLAN APPROVAL

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This SAP was developed based on Roche SAP model document v2.0, Revised 28 Feb 2022.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	see electronic date stamp on the last page of the document	V9, 12 February 2019

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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
BMI	body mass index
CCOD	clinical cutoff date
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 Terms
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
MCS	Mayo Clinical Score
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
SMQ	Standard MedDRA Query
SOC	system organ class
TNF	tumor necrosis factor
TNF-IR	TNF-inadequate responder
UC	Ulcerative Colitis
UC-PRO/SS	Ulcerative Colitis- Patient Reported Outcome/ Signs and Symptoms
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 GA28951 for the purposes of reporting.

The purpose of this document is to describe the definitions and data handling rules for producing outputs to report out Part 1 of the Open-Label-Extension Safety Monitoring (OLE-SM) study for GA28951 (Cottonwood).

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.

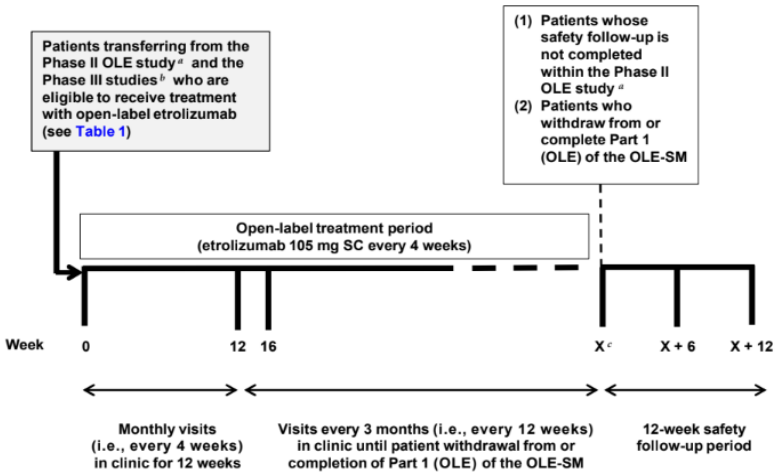
Patients who are enrolled in Part 1 (OLE) should participate in Part 2 (SM).

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

Key characteristics of the GA28951 OLE-SM are provided in Table 1. Treatment arms and rollover of patients to GA28951 OLE-SM from their parent UC study are depicted in Figure 1 and Figure 2.

The OLE-SM study will be conducted in centers that have participated in the Phase II OLE Study GA27927 and/or the double-blinded Phase III Studies GA28948, GA28949, GA28950, GA29102, and GA29103. The maximum number of patients potentially enrolling in this study will be all patients from the studies; approximately 2100 patients. Patients will be allocated the same subject number they had in the initial Phase II OLE study or Phase III study.

Figure 1 Study Schema for Part I (OLE) of the OLE-SM Study



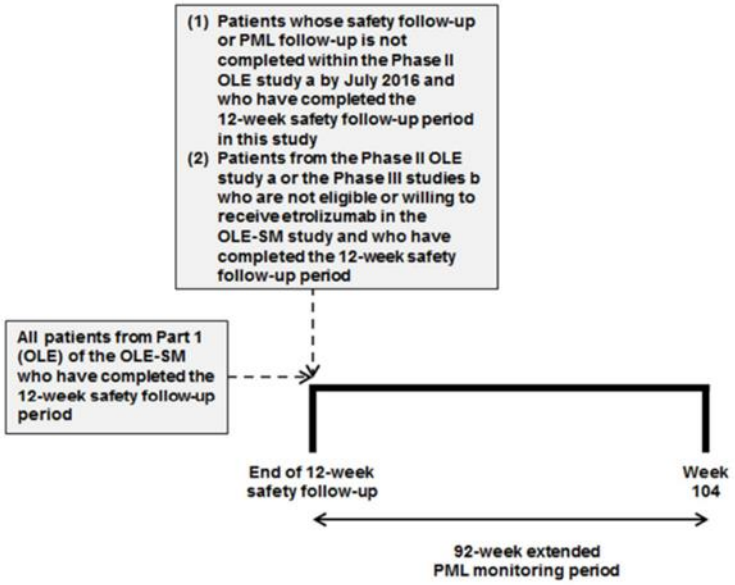
OLE = open-label extension; OLE-SM = open-label extension—safety monitoring study; SC = subcutaneous.

[a] Study GA27927.

[b] Studies GA28948, GA28949, GA28950, GA29102, and GA29103.

[c] Patients may continue to receive open-label etrolizumab in Part 1 (OLE) for up to *approximately 9 years* after the first patient is enrolled, until commercial availability, or until the Sponsor's decision to terminate the study, whichever is earlier.

Figure 2 Study Schema for Part II (SM) of the OLE-SM Study



OLE = open-label extension; OLE-SM = open-label extension – safety monitoring study; PML = progressive multifocal leukoencephalopathy; SM = safety monitoring.

[a] Study GA27927.

[b] Studies GA28948, GA28949, GA28950, GA29102, and GA29103.

Table 1 Key Characteristics of GA28951 OLE-SM Study in UC (Cottonwood)

Study	GA28951 (Phase III)	
Treatment (Number Exposed)	Open-label etrolizumab 105 mg SC Q4W (n=up to ~2100)	
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)**
	• Patients who were previously enrolled in the Phase II OLE study or a Phase III controlled study and meet the eligibility criteria for treatment with open-label etrolizumab as described in the GA28951 protocol in Table 1 may enroll in Part 1 (OLE) of the study.	• Patients whose safety follow-up or PML follow-up is not completed within Study GA27927 and patients who had their last dose of etrolizumab in July 2016 in Study GA27927 and are not eligible or choose not to enroll in Part 1 (OLE) • Patients who participated in one of the etrolizumab Phase III studies (GA28948, GA28949, GA28950, GA29102, and GA29103) and are not eligible or chose not to enroll in Part 1 (OLE) • Participated in Part 1 (OLE) and completed the 12-week SFU

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, UC = Ulcerative Colitis.

**All patients must have completed the 12- week safety follow-up in either the parent study or GA28951 Part 1 (OLE), as applicable, prior to entering Part 2 (SM).

Outputs for this primary CSR will solely focus on reporting data collected during Part 1 (OLE) of GA28951.

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

This SAP will only cover analyses for the GA28951 Part 1 (OLE) objective.

Other Safety Objectives:

- To evaluate the incidence and severity of infection-related adverse events
- To evaluate the incidence of malignancies
- To evaluate the incidence and severity of hypersensitivity reactions

Exploratory:

- To evaluate histology at Week 108

The following endpoint was de-prioritised as a safety objective to an exploratory objective from Protocol GA28951, version 9. 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 Section 3 and Study Schema in Figure 1 of Protocol Version 9.

1.2.1 Protocol Synopsis

The Protocol Synopsis is in Protocol Synopsis Section of Protocol Version 9. For additional details, see the Schedule of Assessments in Appendices 1 and 2 of Protocol Version 9.

1.3 OUTCOME MEASURES FOR GA28951 PART 1 (OLE)

1.3.1 Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- pMCS remission assessed at Weeks 0, 4, 8 and then in 12-week intervals during GA28951 Part 1 (OLE)
- MCS remission assessed at Week 108 during GA28951 Part 1 (OLE)
- Endoscopic remission at Week 108 during GA28951 Part 1 (OLE)

The efficacy outcome definitions are provided below:

Outcome Measure	Definition
Mayo Clinic Score (MCS)	MCS (0−12) is a composite of 4 assessments, each rated from 0-3: stool frequency, rectal bleeding, endoscopy, and PGA
Partial Mayo Clinic Score (pMCS)	pMCS (0−9) is a composite of 3 assessments, each rated from 0-3: stool frequency, rectal bleeding, and PGA

MCS Remission	MCS ≤ 2 with individual subscores ≤1 and a rectal bleeding subscore of 0
MCS Clinical Response	MCS with ≥ 3-point decrease and 30% reduction from baseline as well as ≥ 1-point decrease in rectal bleeding subscore or an absolute rectal bleeding score of 0 or 1
pMCS Remission	pMCS ≤ 2, with, rectal bleeding score of 0, PGA 0−1 and stool frequency subscore 0−1
Improvement in endoscopic appearance of the mucosa	Endoscopy subscore ≤ 1
Endoscopic Remission	Endoscopy subscore = 0

ES= Endoscopic Subscore; PGA = Physician's Global Assessment.
Endoscopy Score=1 includes mild friability criteria unless identified in the description of an endpoint above.

1.3.2 Safety Outcome Measures

The safety outcome measures for GA28951 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 GA28951 Part 1 (OLE) are as follows:

- Histologic appearance of mucosa at Week 108
- Incidence of ATAs to etrolizumab *(de-prioritised from a safety outcome measure. See* Section 4.4 *for details)*

Due to termination of study GA28951, exploratory outcome measures will **not** be reported in the Primary CSR.

1.4 ANALYSIS TIMING

GA28951 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 GA28951 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 have been enrolled in the OLE-SM study is approximately 2100 (i.e., all patients enrolled in the Phase II OLE protocol and the five UC Phase III protocols). No formal sample size calculations were performed.

3. ANALYSIS SETS

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

Table 2 Analysis Populations

Open-Label Extension	**Patients** who receive at least one dose of study drug in Study GA28951 Part 1 OLE
	Timeframe is from first dose of study drug in the GA28951 Part 1 (OLE) to the patient's last visit in GA28951 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 GA28951 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. 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 enrolled in Part 1 (OLE) and Part 2 (SM) will be tabulated 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. The data will also be summarized by origin of the patient (i.e., by original Phase II OLE protocol or Phase III controlled protocol).

Since Part 1 (OLE) of GA28951 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 GA28951 is defined from the last dose date in GA28951 on 15th May 2022.

In summary, the following will be summarized for GA28951 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 GA28951 Part 1 (OLE)

OLE = Open-Label-Extension

Part 1 (OLE) Day 1

OLE Study Day 1 is defined as the day patient has the first receipt of study drug in GA28951 Part 1 (OLE).

Baseline

For patients who were previously enrolled in one of the Phase III studies, baseline is defined as the last available assessment prior to first receipt of study drug in the Induction Phase of the parent studies: GA28948, GA28949, GA28950, GA29102, and GA29103.

For patients who were previously enrolled in the Phase II trial GA27927, baseline is defined as the last available assessment prior to first receipt of study drug in their parent trial ABS4986g.

4.1.2 Analysis of OLE Treatment

The following demographic and baseline disease characteristics will be summarized for

the OLE population using baseline from the original parent studies. No treatment comparisons will be made since GA28951 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 category (years) (< 3, ≥ 3 to < 8, ≥ 8)
- Disease extent (Left-sided colitis, Extensive/Pancolitis, Other)
- MCS score
- MCS score category (MCS ≤ 9, MCS ≥ 10) (IxRS and Rave)
- Mean Stool Frequency (SF)
- Worst Rectal Bleeding (RB)
- Physician's Global Assessment (PGA)
- pMCS score
- Endoscopic Subscore
- Ulcerative Colitis Patient-Reported Outcomes, Signs and Symptoms (UC-PRO/SS) – Functional score
- UC-PRO/SS – Bowel score
- UC-PRO/SS – Systemic score
- Inflammatory Bowel Disease Questionnaire (IBDQ) total score
- Extraintestinal Manifestations

- Fecal calprotectin (μg/g)
- Fecal calprotectin category (<250 μg/g, ≥250 to <500 μg/g, ≥500 μg/g)
- C-reactive protein (CRP) levels (mg/L)
- CRP category (≤2.87 mg/L, >2 .87 to ≤10 mg/L, >10 mg/L)

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)
- Prior anti-TNF History
- Corticosteroid and Immunosuppressant categories
- Prior Corticosteroid (CS) History

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 GA28951. All data available up until the clinical cut-off date (CCOD) will be reported. The endpoints to be summarized are described below. 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 non-responders 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"

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 GA28951, the endpoints of endoscopic improvement and remission will be summarized at this time point. These endpoints will be examined overall and also with patients separated by their previous endoscopic improvement status at their latest visit prior to OLE (e.g., at Week 10/14 or Week 54/62/66 in their parent study).

Population: All patients who enrolled into Part 1 of the OLE Study GA28951.

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

Sub-groups:

- Table outputs: 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., it is not possible for them to have reached this visit at the time of the clinical cut-off date) will be removed from the analysis. Patients who remain in Study GA28951 Part 1 (OLE) but are missing endoscopy scores 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 GA28951 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 with reason being stated as “study terminated by sponsor” after 15th February 2022.

Analysis 2 - As Observed

Intercurrent events: No imputation will be performed for treatment withdrawals

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

4.1.3.2 MCS Remission at Week 108

As endoscopy data is only collected at a common time point of Week 108 during the OLE Study GA28951, a full MCS score can only be calculated at this visit. Therefore, the endpoint of MCS remission (clinical remission, response?) will be summarized at this time point. These endpoints will be examined overall and also with patients separated by their previous MCS remission status at their latest visit prior to OLE at Week 10/ 14 or Week 54/62/66 in their parent study.

Population: All patients who enrolled into Part 1 of the OLE Study GA28951.

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

Sub-groups:

- Table outputs: All patients overall and split by prior MCS remission status and their prior aTNF exposure status.

Analysis 1 - Non-responder

Missing Data: Patients who are non-evaluable at Week 108 (i.e., it is not possible for them to have reached this visit at the time of the clinical cut-off date) will be removed from the analysis. Patients who remain in Study GA28951 but are missing MCS scores will be imputed as non-responders within the analysis, as LOCF is not appropriate when endoscopy data, which comprises part of the MCS score, is not collected routinely.

Intercurrent events: Patients who withdraw during Study GA28951 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 with reason being stated as “study terminated by sponsor” after 15 February 2022.

Analysis 2 - As Observed

Missing data: No imputation will be performed for missing data

Intercurrent events: No imputation will be performed for treatment withdrawals

4.1.3.3 pMCS Remission

The percentage of patients in remission defined using the pMCS will be summarized for each OLE visit for patients who entered Study GA28951. 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 GA28951.

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

Sub-groups:

- Table outputs: All patients overall, split by aTNF exposure status and by OLE Day 1 pMCS remission status.
- Figure outputs: All patients overall and split by OLE Day 1 pMCS remission status.

Analysis 1 - Hybrid LOCF

Missing data: If patients who remain in Study GA28951 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 GA28951, 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 until the patient completes/withdraws from the Part 1 (OLE) of the study GA28951, 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 UC parent studies (GA28948, GA28949, GA28950, GA29102, and GA29103). 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:

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

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 etrolizumab in GA28951 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 GA28951 Part 1 (OLE). The end of the time-frame coincides with the last patient's last visit, this includes safety follow-up in Study GA28951 Part 1 (OLE).

All outputs focus only on safety events after first dose in Study GA28951; these can be handled by flagging events that arise during the OLE treatment period in a manner similar to the identification of treatment-emergent AEs.

4.3 INTERIM ANALYSES

There are no planned interim analyses for study GA28951.

4.4 CHANGES TO PROTOCOL-PLANNED ANALYSES

The incidence of ATAs to etrolizumab was extensively evaluated in the 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 GA28951 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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