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A Phase 2, Multi-Center, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Induction Therapy with PRA023 in Subjects with Moderately to Severely Active Ulcerative Colitis

STATISTICAL ANALYSIS PLAN
Addendum to SAP V01

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APPROVAL

A Phase 2, Multi-Center, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Induction Therapy with PRA023 in Subjects with Moderately to Severely Active Ulcerative Colitis

STATISTICAL ANALYSIS PLAN
Primary Analysis (Induction Period)

Addendum to SAP V01
Version/Date: 01 / 29 November 2022

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[1] Author, signs for correctness and completeness
[2] Reviewer, signs for correctness and completeness
[3] Approver, signs for the release of the document

DEFINITIONS / ABBREVIATIONS

CDx	companion diagnostic
CI	confidence interval
CMH	Cochran–Mantel–Haenszel test
DMC	Data Monitoring Committee
FAS	full analysis set
GM	geometric mean
hsCRP	high sensitivity C-reactive protein
LS	least square
IBDQ	Inflammatory Bowel Disease Questionnaire
SAP	statistical analysis plan
TL1A	tumor necrosis factor-like cytokine 1A

Table of Contents

1 INTRODUCTION

This statistical analysis plan (SAP) addendum describes the additions or modifications to the approved SAP V01 dated 10 August 2022 and is based on the study protocol version 4.0.

The SAP addendum covers the following topics of statistical analyses of the Induction Period for Cohort 1 following the corresponding database lock:

- Modification of Section 6.10, for the approach to multiplicity adjustment.
- Addition of an interim analysis for subjects with CDx+ based on protocol specified algorithm and the alternative algorithms.

2 MODIFICATION TO APPROACH FOR MULTIPLICITY

The following text will replace the content of Section 6.10 of the SAP V01.

A closed hierarchical procedure will be used to control for multiple comparisons of primary and key secondary endpoints. The order of testing will be primary endpoint, followed by the key secondary endpoints in the order as displayed in Table 1. If at any point in this sequential procedure the null hypothesis is not rejected, the testing procedure will be terminated. All subsequent analyses would be considered exploratory.

The primary endpoint will be analyzed and compared between PRA023 and placebo treatment groups in FAS from Cohort 1. The primary endpoint, the proportion of subjects achieving clinical remission, will be tested between the 2 treatment groups at 1-sided significance level of 0.025 using CMH. If significant, the secondary endpoints will be tested sequentially between the 2 treatment groups at significance level indicated in the table.

Table 1 Primary and Key Secondary Endpoints in Cohort 1

Endpoints	**Analysis Population (1-sided alpha)**
Primary	
Proportion of subjects in 3-component Modified Mayo Score clinical remission (as defined by endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and stool frequency subscore of 0 or 1 and not greater than Baseline) at Week 12	FAS (0.025)
Secondary	
• Proportion of subjects with endoscopic improvement (as defined by endoscopy subscore ≤ 1 with no friability) at Week 12	FAS (0.025)
• Proportion of subjects in 3-component Modified Mayo Score clinical response (as defined by a reduction from Baseline ≥ 2 points and ≥ 30% in 3-component Modified Mayo Score, accompanied by a reduction ≥ 1 in rectal bleeding subscore or absolute rectal bleeding subscore ≤ 1) at Week 12	FAS (0.025)

Endpoints	Analysis Population (1-sided alpha)
• Proportion of subjects with symptomatic remission (as defined by stool frequency (SF) subscore = 0 and rectal bleeding (RB) subscore = 0) at Week 12	FAS (0.025)
• Proportion of subjects with histologic-endoscopic mucosal healing (defined as Geboes score ≤ 2B.1 **and** endoscopy subscore ≤ 1 with no friability) at Week 12	Histology Analysis Set (0.025)
• Proportion of subjects with histologic improvement (defined as Geboes score ≤ 3.1) at Week 12	Histology Analysis Set (0.025)
• Proportion of subjects with histologic-endoscopic mucosal improvement (defined as Geboes score ≤ 3.1 and endoscopy subscore ≤ 1 with no friability) at Week 12	Histology Analysis Set (0.025)
• Proportion of subjects with IBDQ response, as defined by ≥ 16-point increase from Baseline at Week 12	FAS (0.025)
• Proportion of subjects in 3-component Modified Mayo Score clinical remission at Week 12 in CDx+ subjects (Cohort 1 + Cohort 2)	CDx+ FAS (0.0245)
• Proportion of subjects with endoscopic improvement, as defined by endoscopy subscore ≤ 1 with no friability) at Week 12 in CDx+ subjects (Cohort 1 + Cohort 2)	CDx+ FAS (0.0245)
• Proportion of subjects in 3-component Modified Mayo Score clinical response at Week 12 in CDx+ subjects (Cohort 1 + Cohort 2)	CDx+ FAS (0.0245)
• Proportion of subjects with symptomatic remission (as defined by rectal bleeding score = 0 and stool frequency score = 0) at Week 12 in CDx+ subjects (Cohort 1 + Cohort 2)	CDx+ FAS (0.0245)
• Proportion of subjects with histologic-endoscopic mucosal healing (defined as Geboes score ≤ 2B.1 **and** endoscopy subscore ≤ 1 with no friability) at Week 12 in CDx+ subjects (Cohort 1 + Cohort 2)	CDx+ Histology Analysis Set (0.0245)
• Proportion of subjects with histologic improvement (defined as Geboes score ≤ 3.1) at Week 12 in CDx+ subjects (Cohort 1 + Cohort 2)	CDx+ Histology Analysis Set (0.0245)
• Proportion of subjects with histologic-endoscopic mucosal improvement (defined as Geboes score ≤ 3.1 and endoscopy subscore ≤ 1 with no friability) at Week 12 in CDx+ subjects (Cohort 1 + Cohort 2)	CDx+ Histology Analysis Set (0.0245)
• Proportion of subjects with IBDQ response, as defined by ≥ 16-point increase from Baseline at Week 12 in CDx+ subjects (Cohort 1 + Cohort 2)	CDx+ FAS (0.0245)

The alpha reduction by 0.001 (2-sided) is due to the added Sponsor unblinded interim analysis of CDx+ population based on Cohort 1. This analysis of the CDx based on Cohort 1 is considered interim because data from Cohort 1 CDx+ subjects are considered interim results of CDx+ FAS (Cohort 1 + Cohort 2). While Section 3 of this addendum will detail the analyses, the interim analysis intends to estimate the effect size of PRA023 comparing to the placebo in CDx+ subjects. A minimal alpha level is allocated to the interim analysis, as no efficacy early stopping is expected.

3 ANALYSIS OF CDX+ SUBPOPULATIONS IN COHORT 1

3.1 DEFAULT CDX+

The protocol specified CDx status, called default UC algorithm, was used for stratification of the randomization in Cohort 1. As designed, CDx+ subjects will be enrolled in Cohort 2 following the completion of Cohort 1 enrollment. The analysis for CDx+ related secondary endpoints will be analyzed when all subjects in Cohort 2 complete Week 12 or early discontinue. The combined CDx+ subjects across Cohort 1 and Cohort 2 will consistitute the CDx+ FAS for these secondary endpoints.

At the time of this SAP addendum, the planned interim analysis when approximately 80% of subjects in Cohort 1 (i.e., ~96 subjects) have reached Week 12 or early terminated from the study has been completed. DMC reviewed the unblinded interim efficacy and safety data for all available subjects and CDx+ subjects on 19 October 2022. Following the review, DMC recommended to continue the enrollment of Cohort 2, and informed a total sample size of 48 for the cohort.

Based on the emerging information related to CDx development and validation, the Sponsor has made the decision to conduct an additional analysis for CDx+ subpopulation based on Cohort 1 data to assess the effect size of PRA023 in CDx+ subjects. In addition to the subgroup analysis based on CDx status for the primary endpoint, Table 2 lists endpoints that will be assessed for the Cohort 1 CDx+ subpopulation. The methods of analysis are similar to those specified in SAP V01, with the following exceptions:

- The analysis sets are defined as CDx+ subjects who are randomized and treated in Cohort 1.
- No statistical hypothesis testing will be performed between PRA023 and Placebo treatment groups, while 95% confidence intervals will be presented for the estimation of treatment difference.

Table 2 Analyses for CDx+ Population in Cohort 1

Endpoints	Treatment Difference
Proportion of subjects in 3-component Modified Mayo Score clinical remission at Week 12	Included in subgroup analysis of the primary endpoint
Proportion of subjects with endoscopic improvement, as defined by endoscopy subscore ≤ 1 with no friability) at Week 12	Risk difference and 95% CI
Proportion of subjects in 3-component Modified Mayo Score clinical response at Week 12	Risk difference and 95% CI
Mean change in Partial Mayo Score over time Mean change in PRO-2 Score over time	Difference of LS mean and 95% CI
Fold change in hsCRP over time Fold change in fecal calprotectin over time	Ratio of geometric means and 95% CI

3.2 CDX+ BASED ON ALTERNATIVE ALGORITHMS

To evaluate whether a CDx call can render a different treatment effect of PRA023 comparing to placebo, alternative algorithms (Table 3) will also be assessed.

Table 3 Alternative CDx Algorithms

Algorithm Name	Description
entrocyte.RDS	Score and predicted label (high/low) based on Ileum-derived entrocytes from subject's germline genetics
colon.bma.model.cluster Resident.macrophages.RDS	Score and predicted label (high/low) based on Colon-derived resident macrophages from subject's germline genetics
colon.bma.model.cluster.TA.RDS	Score and predicted label (high/low) based on Colon-derived Transit-Amplifying (TA) cells from subject's germline genetics
colon.bma.model.cluster.Goblet.cell.RDS	Score and predicted label (high/low) based on Colon-derived Goblet cells from subject's germline genetics
modc.RDS	Score and predicted label (high/low) based on Ileum-derived monocyte-derived dendritic cells (moDC) from subject's germline genetics

For each CDx+ call, descriptive statistics for the endpoints listed in Table 2 will be provided by treatment group. Additionally, the point estimate and multiplicity controlled 95% CI for the treatment difference in clinical remission at Week 12 will be plotted against the estimated overall treatment effect in Cohort 1. Given the number of alternative CDx algorithms to be evaluated, the conventional confidence intervals are subject to an inflation of the alpha. A re-sampling based method [1] will be used to construct the 95% CI for each CDx+ call subpopulation with an overall alpha level of 0.05 (2-sided) across alternative algorithms.

4 CHANGES FROM PROTOCOL

The analyses outlined in Section 3 of this addendum are additions to the analyses defined by the protocol.

5 REVISION HISTORY

Version	Reason
V01	New

6 REFERENCES

1. Westfall, P. H., & Young, S. S. (1993). *Resampling-based multiple testing: Examples and methods for p-value adjustmen*. John Wiley & Sons.