Evaluating the Placebo Endoscopic Response in Crohn's Disease Clinical Trials

RP1621

STATISTICAL ANALYSIS PLAN

Version 01

Status: Effective

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APPROVAL

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1 INTRODUCTION

The placebo response in clinical trials is a complex phenomenon that is influenced by multiple factors including the type of intervention, the method and frequency of treatment, response expectancy, patient-provider interactions, behavioral conditioning and the clinical context.[1, 2] Understanding the magnitude of placebo response and the associating factors in inflammatory bowel disease (IBD) trials is important for the design and interpretation of efficient clinical trials.

Factors affecting the placebo response include natural variation in underlying disease, regression toward the mean and the "true" placebo effect which is likely attributable to interrelated environmental and psychosocial factors. In clinical trials these factors include patient expectations of treatment benefits, the response to observation and assessment (Hawthorne effect), the response to administration of a therapeutic ritual, the patient-physician relationship and intrinsic features of trial design.

In clinical trials for Crohn's disease (CD), the CDAI (Crohn's Disease Activity Index) has been used as the basis for approval of many treatments over the past 4 decades.[3] Although its operating properties are well defined there are subjective components of the score which may contribute to measurement error. In contrast endoscopic activity is a more objective measurement of disease activity, and mucosal healing has emerged as an important therapeutic endpoint in clinical trials involving subjects with CD. There is evidence to suggest that mucosal healing, defined as the complete healing of ulcers in the small intestine and the colon on endoscopy, may change the natural course of the disease by reducing relapse, hospitalization and surgery rates in patients with CD.[4]

Evolving trial endpoints and use of endoscopic mucosal healing as an endpoint requires an understanding of the evolution of endoscopic activity in trial subjects randomized to placebo, in order to help inform design of randomized trials, particularly in calculating sample sizes.

2 SUMMARY OF THE STUDY

2.1 STUDY OBJECTIVES

The objectives of this study are to:

1. Describe the evolution of endoscopic mucosal healing through change in the endoscopic scores (Simplified Endoscopy Score for CD [SES-CD], Crohn's Disease Endoscopic Index of Severity [CDEIS]) in patients with CD who participated in a clinical trial and were randomized to placebo treatment.
2. Provide a pooled estimate of the endoscopic placebo response rate in CD trials.
3. Identify factors associated with spontaneous improvement in endoscopic mucosal healing in patients with CD who participated in a clinical trial and were randomized to placebo treatment.

2.2 STUDY DESIGN

This study is a retrospective analysis of 3 existing datasets. Changes in endoscopic scores (SES-CD and CDEIS) will be evaluated from participants randomized to placebo arm in 3 completed clinical trials of induction therapy for CD. All 3 trials have ileo-colonoscopy videos recorded at baseline and then at follow-up for outcome assessment, read by a local and central reader blinded to treatment allocation and study visit. For the pooled placebo rate, results will be provided for the central reader primarily and, where both are available, for the central and local reader. These 3 completed trials are described below.

2.3 DATA SOURCES

2.3.1 GLPG0634 (FILGOTINIB)

The GLPG0634-CL-211 trial of GLPG0634 (filgotinib) was a double-blind, randomized, placebo-controlled, multi-center phase 2 study.[5] GLPG0634 is a selective inhibitor of JAK1. Janus kinases (JAKs) are intracellular cytoplasmic tyrosine kinases (TYKs) that transduce cytokine signaling from membrane receptors through signal transducer and activator of transcription (STAT) to the nucleus of cells. JAK inhibitors block the signaling of various cytokines, growth factors, and

hormones, including the pro-inflammatory cytokine interleukin (IL)-6. Four different types of JAKs are known, JAK1, JAK2, JAK3, and TYK2 which (co-)interact with different sets of membrane receptors.

The primary objective of this study was to demonstrate efficacy in terms of the percentage of subjects achieving clinical remission (CDAI score < 150) following 10 weeks of treatment with GLPG0634. Subjects were randomized to receive orally-administered GLPG0634 or placebo in addition to their stable background treatment (e.g., corticosteroids, aminosalicylates, or CD-related antibiotics).

The study consisted of two parts. Part 1 consisted of a 10-week treatment period followed by colonoscopy at week 10. Subjects were randomized in 3:1 ratio to receive either once daily GLPG0634 200 mg or placebo. Maintenance of the clinical remission was assessed during Part 2 of the study; no endoscopy was performed in the second part of the trial. Therefore, for the current study, the data from the week 10 endpoint will be used.

At baseline, included subjects had CDAI scores ranging from 220 to 450 with evidence of active inflammation demonstrated by endoscopic confirmation of active disease (based on central reading), with evidence of ulceration corresponding to a score of 1 in at least 1 of the 5 ileocolonic segments on the Presence of Ulcers subscore of the SES-CD, and total SES-CD score of at least 7 (See Appendix A).

Concomitant medication was allowed with oral steroids (≤ 30 mg prednisolone equivalent/day or budesonide dose ≤ 9 mg/day, at a stable dose ≥ 2 weeks prior to the first dose of study drug), mesalazine and olsalazine (stable dosage ≥ 4 weeks prior to screening and same dosage to be maintained throughout the study) and CD-related antibiotics (stable dosage ≥ 4 weeks prior to screening and no discontinuation in the 14 days prior to the first dose of study drug). Previous exposure to immunomodulators (e.g., thiopurines and methotrexate) was permitted, but discontinued at least 25 days prior to the first dose of the study drug. Previous exposure to anti-TNF agents was allowed, and had to be discontinued at least 8 weeks before baseline.

Each patient underwent an ileocolonoscopy at baseline and week 10. All ileocolonoscopies were recorded with the use of a standard protocol and interpreted by a single central reader, who was blinded to treatment allocation and timing of the procedure (baseline or week 10). Endoscopic response was defined as a reduction of SES-CD score by at least 50% from screening. Endoscopic remission was defined as a SES-CD score ≤ 4, with ulcerated surface subscore no greater than 1 in any segment. Mucosal healing was defined as a SES-CD score equal to 0.

2.3.2 BMS-936557 (ELDELUMAB)

The IM129-008 study of BMS-936557 (Eldelumab) was a phase IIa, randomized, placebo-controlled evaluation of the efficacy and safety of induction therapy with Eldelumab (Anti-interferon-γ-inducible protein-10 [anti-IP-10] Antibody) in subjects with active CD. Eldelumab is a fully human monoclonal antibody to IP-10 (Interferon-γ-inducible protein-10), which is involved in inflammatory cell recruitment and the survival and migration of gut epithelial cells.[6, 7] The primary objective of this study was to assess the efficacy of BMS-936557 for induction of clinical remission (CDAI score < 150) at week 11. Adult subjects with CDAI scores ranging from 220 to 450 were randomly assigned 1:1:1 to placebo or Eldelumab 10 or 20 mg/kg IV and received study drug on Days 1 and 8 and every other week thereafter. Subjects on a stable dose of immunomodulators or aminosalicylates were eligible to participate. Concomitant medication was allowed. Aminosalicylates (5-ASA) had to remain stable throughout the induction period (starting at least 2 weeks prior to entry into the induction period). Low-dose oral corticosteroids were permitted (≥20 to ≤ 30 mg/day prednisone or equivalent: or ≤ 9mg/day budesonide) and had to remain stable during the induction period (starting at least 2 weeks prior to entry into the induction period). Permitted immunosuppressants (azathioprine ≥ 2 mg/kg/day or 6-mercaptopurine ≥ 1.0 mg/kg/day, or documentation of a therapeutic concentration of 6-thioguanine nucleotide, or methotrexate ≥ 15mg/week for at least 12 weeks) had to remain stable throughout the induction period. Antibiotics, for the treatment of CD, were to remain stable throughout the induction period.

Ileocolonoscopy was performed at baseline. At week 11 only subjects in the Ileocolonoscopy Cohort underwent another endoscopy. Entrance criteria into the Ileocolonoscopy Cohort were defined as a score of 2 to 3 on the Ulcerated Surface subscore of the SES-CD (≥ 10% of surface covered by ulcers) in at least 1 of 5 segments (rectum, descending colon/sigmoid, transverse colon,

ascending colon, or ileum) during the screening ileocolonoscopy. Endoscopies were videotaped and read in a blinded fashion by one central reader using the SES-CD.

2.3.3 BI 655066 (RISANKIZUMAB)

The 1311.6 study was a phase II, multicenter, randomized, double-blind, multiple dose, placebo-controlled, parallel-group study in which the efficacy, pharmacokinetics, and safety of BI 655066 (Risankizumab), a humanized antagonist monoclonal antibody specific to IL-23p19.[8]

At baseline, included subjects had moderate to severe active CD (defined as CDAI scores in the range of 220 to 450) and presence of mucosal ulcers in at least one segment of the ileum or colon and a CDEIS score ≥ 7 (for subjects with isolated ileitis ≥4). 120 subjects were randomly assigned 1:1:1 to placebo or Risankizumab 200 mg or 600 mg intravenously (IV). Permitted concomitant medications were oral 5-aminosalicylate (5-ASA) compounds, the immunomodulators azathioprine, 6-mercaptopurine, and methotrexate, oral corticosteroids, and antibiotics on a stable dose. Ileocolonoscopy/biopsy was performed at baseline and week 12 and the SES-CD and CDEIS were calculated by the study site endoscopist and central reader.

2.3.4 OVERVIEW OF THE 3 TRIALS

Trial ID	**Study Drug *(Mechanism of Action)***	**Patient Population**	**Concomitant Medication**	**Primary Objective**	**Endoscopic Evaluation (Week)**	**Endoscopic Score**	**No. of Placebo Subjects**
GLPG0634-CL-211	GLPG0634/ Filgotinib *(JAK1 inhibitor)*	CDAI ≥ 220 to ≤ 450 and evidence of ulceration including SES-CD ≥7	immunosuppressants, corticosteroids, 5-ASA, CD-related antibiotics	clinical remission (CDAI < 150)	10	SES-CD (central reader)	45
IM129-008	BMS-936557/ Eldelumab *(Anti-IP-10 Antibody)*	CDAI ≥220 and ≤450	corticosteroids, 5-ASA, antibiotics	clinical remission (CDAI < 150)	11*	SES-CD (central reader)	40
1311.6	BI 655066 / Risankizumab *(IL-23p19 antagonist monoclonal antibody)*	CDAI ≥220 and ≤450 and CDEIS score ≥ 7 (isolated ileitis ≥4)	oral 5-ASA, AZA, 6- MP, MTX, oral corticosteroids, antibiotics	clinical remission (CDAI < 150)	12	SES-CD and CDEIS (local and central readers)	40

* only subjects who qualified for the endoscopy cohort
5-ASA=5-aminosalicylate; AZA=azathioprine; 6-MP=6-mercaptopurine; MTX=methotrexate

3 STATISTICAL ANALYSIS

3.1 METHODS

Data will be collected from 3 existing study databases of completed clinical trials (see Appendix 2). No personally identifiable information will be included and study data will already be coded by unique patient identifier numbers.

3.1.1 BASELINE DEMOGRAPHIC INFORMATION

An overview of data that will be extracted from 3 clinical trial databases for research subjects who had baseline endoscopy, received placebo treatment, and then underwent a second colonoscopy after 10-12 weeks is provided in Appendix B. Descriptive statistics will be used to report demographic information including: age (median, interquartile range [iqr]), % female, smoking status, duration of CD (median, iqr), location of CD (% each of ileal/colonic/ileo-colonic), disease behavior (% inflammatory/stricturing/fistulizing), concomitant immunomodulators (%), concomitant corticosteroids (%).

3.1.2 DISEASE ACTIVITY INDICES

The following will be reported at baseline (week 0) and at the primary endpoint assessment (week 10 for GLPG0634; week 11 for BMS-936557 and week 12 for BI 655066): CDAI (median, iqr), CRP (median, iqr), SES-CD (median, iqr), SES-CD each sub-component, change in SES-CD overall, change in each component of SES-CD. A statistical comparison will be made for the change in CDAI (PRO-2, if components available), CRP, overall SES-CD and each component of the SES-CD from baseline to primary endpoint assessment. A graph will be plotted of baseline entry SES-CD against the change in SES-CD (from baseline to primary assessment).

3.1.3 IMPROVEMENT IN SES-CD ON PLACEBO TREATMENT

Improvement in SES-CD from baseline to primary endpoint assessment will be dichotomized into a binary response (yes/no). Improvement in SES-CD will be assessed based on alternate definitions:

(a) 25% reduction in the total SES-CD score;

(b) 50% reduction in the total SES-CD score;

(c) reduction of at least 5 points (or score of 0) AND minimum of 50% in the total SES-CD score (since this was predictive of corticosteroid free remission in post-hoc analysis of the SONIC trial[9]).

Furthermore, change in SES-CD from baseline in the subjects who have total SES-CD of at least 4 at baseline (current analyses have >2 at baseline), and the percent of patients with 50% decrease in SES-CD from baseline in the subjects who have total SES-CD of at least 4 at baseline will be calculated. Similarly, change in SES-CD from baseline in the subjects who have total SES-CD of at least 6 at baseline and the percent of patients with 50% decrease in SES-CD from baseline in the subjects who have total SES-CD of at least 6 at baseline.

3.2 ANALYSIS OF PLACEBO EVENTS

Rates of endoscopic response in the placebo arms of the 3 trials will be pooled using a weighted method with the inverse of variance for signal proportion as weights, the associated 95% confidence interval will be obtained using stratified Wilson method.[10] Endoscopic response (Yes/No) at patient level will be analyzed using a multivariable logistic regression model, with the focus of identifying important factors for the response. A liberal P-value of 0.10 will be used as a criterion to retain a factor. For ease of interpretation, risk ratios for factors retained in the final logistic model will be obtained using the modified Poisson regression model.[11]

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APPENDIX A: SES-CD

The score for each endoscopic variable is the sum of the values obtained for each of 5 segments. The SES-CD Total is the sum of the 4 endoscopic variable scores. The SES-score can range from 0-56, with a higher score indicating more severe disease.[12]

Simple Endoscopic Score for Crohn's Disease (SES-CD)				
	Score			
Variable	0	1	2	3
Size of ulcers	None	Aphthous ulcers (Ø 0.1 to 0.5 cm)	Large ulcers (Ø 0.5 to 2 cm)	Very large ulcers (Ø>2cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowings	None Single, can be	Single, can be passed	Multiple, can be passed	Cannot be passed

Ø, Diameter.

APPENDIX B: DATA VARIABLES

Data will be extracted from existing study databases of 3 completed clinical trials that included subjects with CD who had baseline endoscopy, received placebo treatment, and then underwent a second colonoscopy after 10-12 weeks. Variables to be extracted (***placebo arm only***):

Patient characteristics:

- Age
- Gender
- Date of birth (month/year)
- Age at diagnosis/year of diagnosis
- Disease duration at baseline endoscopy (months)
- Disease location based on Montreal criteria at diagnosis
- Disease location based on Montreal criteria at baseline endoscopy
- Prior bowel resections
- Prior perianal fistula/Abscess
- Disease behavior based on Montreal criteria at diagnosis
- Disease behavior based on Montreal criteria at baseline endoscopy
- Smoking (previous, current)

Previous medical treatments:

- Anti-TNF treatment infliximab (IFX): yes/no and from when to when (month/year)
    - Date of last dose of IFX
    - Reason for stop of IFX: inefficacy-loss of effect-side effects
- Anti-TNF treatment adalimumab (ADA): yes/no and from when to when (month/year)
    - Date of last dose of ADA
    - Reason for stop of ADA: inefficacy-loss of effect-side effects
- Vedolizumab (VEDO) treatment: yes/no and from when to when (month/year)
    - Date of last dose of VEDO
    - Reason for stop of VEDO: inefficacy-loss of effect-side effects
- Azathioprine (AZA) treatment: yes/no and from when to when (month/year)
    - Date of last dose of AZA or ONGOING
    - Reason for stop of AZA: inefficacy-loss of effect-side effects
- 6-mercaptopurine treatment (6-MP): yes/no and from when to when (month/year)
    - Date of last dose of 6-MP or ONGOING
    - Reason for stop of 6MP: inefficacy-loss of effect-side effects
- Methotrexate (MTX) treatment: yes/no and from when to when (month/year)
    - Date of last dose of MTX or ONGOING
    - Reason for stop of MTX: inefficacy-loss of effect-side effects
- Corticosteroids during induction treatment: yes/no, brand name and dose
    - Date of last date of corticosteroids
    - Reason for stop of corticosteroids: inefficacy-loss of effect-side effects
- Experimental treatment: yes/no, brand name and date of last dose

CD activity at baseline:

- Date of visit
- CDAI (if possible with individual diary components to allow calculation of PRO-2)
- SES-CD by local and central reader with details of the individual items
- CDEIS (when applicable) by local and central reader with details of the items
- C-reactive protein
- Serum albumin
- Hematocrit
- Fecal calprotectin

CD activity at end of induction:

- Date of visit
- CDAI (if possible with individual diary components to allow calculation of PRO-2)
- SES-CD by local and central reader with details of the individual items
- CDEIS (when applicable) by local and central reader with details of the items
- C-reactive protein
- Serum albumin
- Hematocrit
- Fecal calprotectin

Trial

- Number of study visits prior to second endoscopy