Title of Research
Evaluating the Placebo Endoscopic Response in Crohn’s Disease Clinical Trials

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Data Sharing Agreement Date
Not provided

Summary of Research
Understanding the magnitude of placebo response and associating factors in inflammatory bowel disease (IBD) clinical trials is important for trial design and interpretation. Factors affecting the placebo response include patient expectations of treatment benefits, response to observation and assessment (Hawthorne effect), 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 Crohn’s Disease Activity Index (CDAI) has been used as the basis for approval of many treatments over the past four decades. The CDAI’s properties are well defined, but subjective components of the score may contribute to measurement error. In contrast, endoscopic activity is a more objective measurement of disease activity, and mucosal healing—which may reduce relapse, hospitalization and surgery rates in CD patients—has emerged as an important therapeutic endpoint in CD clinical trials.

An understanding of the evolution of endoscopic activity in trial subjects randomized to placebo will help inform design of randomized trials, particularly in calculating sample sizes.

Study Design
This study is a retrospective analysis of three existing datasets from completed clinical trials of induction therapy for CD. Data will be analyzed for research subjects who had baseline endoscopy, received placebo treatment, and then underwent a second colonoscopy after 10-12 weeks. All three trials have ileo-colonoscopy videos recorded at baseline and follow-up for outcome assessment, read by a local and central reader blinded to treatment allocation and study visit. The study objectives will be to describe changes in endoscopic scores (measured using the Simplified Endoscopy Score for CD or SES-CD) in participants randomized to placebo in the three completed trials; provide a pooled estimate of the endoscopic placebo response rate; and identify factors associated with spontaneous improvement in endoscopic mucosal healing in CD patients randomized to placebo treatment.

Study Population
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. Descriptive statistics will be used to report demographic information including: age, sex, smoking status, duration of CD, location of CD, and use of concomitant immunomodulators and concomitant corticosteroids.
Funding Source of Research
Not provided

Requested Study
NCT01466374: A Phase IIa, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Clinical Efficacy and Safety of Induction and Maintenance Therapy with BMS-936557 in Subjects With Active Crohn's Disease

Statistical Analysis Plan
Data will be collected from 3 existing study databases of completed clinical trials. No personally identifiable information will be included and study data will already be coded by unique patient identifier numbers.

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. 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), concomitant immunomodulators (%), concomitant corticosteroids (%).

The following will be reported at baseline (week 0) and at the primary endpoint assessment (week 11 for BMS-936557): 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).

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).

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.

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. 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.
Publication Citation
Added after the research is published