Name of Finished Product	REMICADE
Name of Active Ingredient(s)	REMICADE (infliximab)

Protocol No.: P05088

Title of Study: The Efficacy of Open-Label Infliximab for the Induction and Maintenance of Mucosal Healing in Small Bowel Crohn's Disease Assessed Through Wireless Camera Endoscopy (the ICE study)

NCT No.: NCT01181765

Clinical Registry No.: CR100747

Principal Investigator: Lawrence B. Cohen, MD, Sunnybrook Health Sciences Centre, Division of Gastroenterology, 2075 Bayview Avenue, Toronto, ON M4N 3M5

Study Centers: Planned (5 centers in Canada) and Active (2 centers in Canada). A list of sites is provided in Appendix 3.

Publication (Reference): None

Study Period: 11 May 2011 to 17 January 2013.

Phase of Development: 4

OBJECTIVES

The primary objective was to assess the impact of infliximab, using wireless camera endoscopy, on the mean change in Lewis score at Week 26, relative to baseline, in moderate to severe Crohn's disease subjects with small bowel involvement.

The secondary objectives were:

- To assess the impact of infliximab on the mean change in Crohn's Disease Activity Index (CDAI) score at Week 26, relative to baseline, as assessed by CDAI score determined in moderate to severe Crohn's disease subjects with small bowel involvement.
- To determine if infliximab led to rapid symptomatic improvement at Week 10, relative to baseline, based on the mean changes in CDAI score in moderate to severe Crohn's disease subjects with small bowel involvement.
- To determine if infliximab led to early mucosal healing at Week 10, relative to baseline, based on the mean changes in Lewis score, in moderate to severe Crohn's disease subjects with small bowel involvement.
- To assess the impact of infliximab on the mean change in quality of life at Week 26, relative to baseline, as assessed by Inflammatory Bowel Disease Questionnaire (IBDQ) score determined in moderate to severe Crohn's disease subjects with small bowel involvement.

Hypothesis:

- We hypothesize that the effect size showed at least a 50% improvement in small bowel Lewis score in subjects taking infliximab for 26 weeks.

METHODS

This was a prospective Phase 4, multicenter, open-label, non-randomized, interventional study investigating the efficacy of infliximab treatment in adults with moderate to severe active small bowel Crohn's disease.

Five study centers were involved in the study. The study was expected to include approximately 20 subjects with small bowel Crohn's disease (with or without colonic involvement), a Lewis score of at least 790, and a CDAI score between 220 and 450. These subjects had to give written informed consent and had to be subsequently evaluated to meet all inclusion criteria and none of the exclusion criteria in order to enter the study. Each subject was to participate in the study for a maximum of 35 weeks from the time the subject signed the Informed Consent Form through the last study visit. Sample electronic case report form pages are located in Appendix 2.

This study consisted of 10 scheduled visits (prescreening (visit 1), screening (visit 2), baseline (Week 0-visit 3), Week 2 (visit 4), Week 6 (visit 5), Week 10 (visit 6), Week 14 (visit 7), Week 22 (visit 8), Week 26 (visit 9), and a follow-up at Week 30 (visit 10). Additional unscheduled visit(s) could occur if clinically indicated (eg, if study drug was interrupted or discontinued, new or worsening Crohn's disease symptoms occurred, a serious adverse event was reported, laboratory monitoring was required or the wireless camera capsule ingested by the subject did not appear to have passed through the system 30 hours postingestion). All subjects were to undergo wireless camera endoscopy at 3 visits, namely: at screening, Week 10, and Week 26. The wireless camera endoscopy procedure involved ingesting a pill-sized wireless camera, which passed naturally through the gastrointestinal tract while capturing images of the intestines and saving them onto a data recorder. At the prescreening visit, a patency capsule was administered to ensure compatibility of the subject's bowels with wireless camera endoscopy. Infliximab was administered at a dose of 5 mg/kg at 5 visits, namely: at baseline (Week 0), Week 2, Week 6, Week 14, and Week 22. The capsule was to be ingested and excreted prior to the administration of infliximab.

Number of Subjects (planned and analyzed):

Planned: Twenty subjects were planned to be enrolled in the study.

Analyzed: One subject was enrolled and included in the safety and efficacy analysis data set.

Diagnosis and Main Criteria for Inclusion:

Subjects (male and female ≥18 years) were to have an established diagnosis of Crohn's disease and evidence of small bowel involvement based on appropriate radiologic modalities (eg, CT enterography/enteroclysis, wireless camera endoscopy, small bowel follow-through, colonoscopy, etc) within the 6 months prior to prescreening. In addition, they must have had a baseline Lewis score of at least 790, and a CDAI score between 220 and 450 inclusively. Refer to the study protocol (Appendix 1) for a complete list of inclusion and exclusion criteria.

Test Product, Dose and Mode of Administration, Batch No.:

REMICADE (infliximab) (Lot No: 0RMKA80401) was administered intravenously at 5 mg/kg body weight, rounding up to the full 100 mg vial. Intravenous infusions were to be given at Weeks 0, 2, 6, 14, and 22.

Reference Therapy, Dose and Mode of Administration, Batch No.:

There was no reference therapy in this study.

Duration of Treatment:

Subjects were to be treated with 5 doses of infliximab over a 22-week period. The total study duration was 30 weeks in addition to a screening phase of up to 5 weeks. The study was to begin when the first subject was screened and end when the last subject had completed or was discontinued from the study.

Criteria for Evaluation:

Primary Endpoints:

- To assess the impact of infliximab, using wireless camera endoscopy, on the mean change in Lewis score at Week 26, relative to baseline, in moderate to severe Crohn's disease subjects with small bowel involvement.

Secondary Endpoints:

- To assess the impact of infliximab on the mean change in CDAI score at Week 26, relative to baseline, as assessed by CDAI score determined in moderate to severe Crohn's disease subjects with small bowel involvement.
- To determine if infliximab led to rapid symptomatic improvement at Week 10, relative to baseline, based on the mean changes in CDAI score in moderate to severe Crohn's disease subjects with small bowel involvement.
- To determine if infliximab led to early mucosal healing at Week 10, relative to baseline, based on the mean changes in Lewis score, in moderate to severe Crohn's disease subjects with small bowel involvement.
- To assess the impact of infliximab on the mean change in quality of life at Week 26, relative to baseline, as assessed by IBDQ score determined in moderate to severe Crohn's disease subjects with small bowel involvement.

Exploratory Analysis:

- To assess complete mucosal healing of the small bowel (no visible ulcerations remaining in subjects that had any mucosal breaks at Screening capsule endoscopy) in subjects that had lesions at baseline (as collected at screening).
- To assess large bowel healing in subjects that had evidence of pre-existing lesions at prescreening.

Statistical Methods:

Data Sets: All subjects who received at least one dose of study medication were to be included in the safety population.

All subjects who received at least one dose of study medication were to be included in the intent-to-treat (ITT) population. The ITT population was to be used for efficacy analysis and constituted the primary analysis population for efficacy for all pre-specified comparisons.

Determination of Sample Size/Power/Level of Significance: The primary efficacy analysis was carried out using a paired t-test to compare the mean Lewis score at Week 26 to the mean Lewis score at baseline (as collected at screening). A sample size of 20 subjects, conservatively, had 56% power to detect a clinically relevant 50% decrease in Lewis score, assuming a standard deviation of measurement of 100% of the score[1] and liberally had 97% power to detect a clinically relevant 50% decrease in Lewis score, assuming a standard deviation of measurement of 50% of the score.[2] The Lewis score of the subjects withdrawing from the study were to be carried forward from their last wireless camera endoscopy procedure.

The secondary efficacy analysis was carried out using a paired t-test to compare the mean CDAI score at Week 26 to the mean CDAI score at baseline. A sample size of 20 subjects had 78% power to detect a clinically relevant 70 point change in CDAI score, assuming a standard deviation of measurement of 108 points[3] The CDAI score of the subjects withdrew from the study was to be carried forward from their discontinuation visit. Assuming a 25% rate of discontinuation, a sample size of 15 points had 64% power to detect a clinically relevant 70 point difference in CDAI score.

Demographic and Other Baseline Characteristics: Demographic variables (sex, race, age, weight, etc) were to be summarized.

Efficacy: The primary efficacy variable was Lewis score. The analyses were to be performed using paired t-test. The secondary variables were: CDAI score, modified Lewis score (average of 3 tertiles, as opposed to worst tertile), complete mucosal healing and IBDQ. Modified Lewis score and complete mucosal healing were not validated in the small bowel, and therefore these analyses were exploratory in nature.

Safety: Descriptive statistics were to be provided for safety data. No formal analysis of safety data was planned. The number of subjects reporting any adverse events, the occurrence of specific adverse events, and discontinuation due to adverse events were to be tabulated.

Interim and Other Analysis: There was no interim analysis for the study. All capsule videos were to be read by a single independent external reader who was blinded to the study design.

RESULTS

STUDY POPULATION

This study was conducted from 11 May 2011 to 17 January 2013. Five centers were planned to screen and enroll subjects, however only 2 centers were active. Twenty subjects were planned to be enrolled in the study. However, 7 subjects were screened, of whom 6 were not enrolled due to not meeting protocol eligibility. One subject (Subject 5005), a 48-year-old white female with weight 56.5 kg, and height 157 cm was enrolled and completed the study. This subject was the only subject included in the efficacy and safety analysis set. The summary for prescreening, laboratory data, inclusion exclusion criteria, study completion data, screen failure are provided in Attachment Plate001, Attachment Plate002, Attachment Plate004, Attachment Plate009, Attachment Plate016, respectively. The investigator statement is provided in Attachment Plate010.

The subject's prior medical history included intermittent heart palpitations, occasional heart burn, cyst in the right kidney, previous kidney stones, and total hysterectomy and bilateral salpingo-oophorectomy. The summary for medical history is provided in Attachment Plate003.

The subject's prior medications included vitamin D and Tylenol extra strength. The subject's concomitant medication included vitamin E ointment and hydrochlorothiazide. The summary for prior and concomitant medication is provided in Attachment Plate012.

There is no evidence of large bowel involvement on colonoscopy. The subject was infused with 3 vials of infliximab dose (5 mg/kg – rounded up to the full 100 mg vial) each on Week 0 (visit 3), Week 2 (visit 4), Week 6 (visit 5), Week 14 (visit 7), and Week 22 (visit 8). The summary of pregnancy test and infusion is provided in Attachment Plate007.

Subject 1001 had an additional history, which included myopia and kidney stone. The summary for additional history is provided in Attachment Plate013. The subject's prior medications included prednisone, vitamin D, and calcium. The summary for prior and concomitant medication is provided in Attachment Plate012.

EFFICACY RESULTS

A summary of the Lewis scores is provided in Attachment Plate015. There was a substantial decrease in mean Lewis score for Subject 5005 from 4846 at Visit 2 to 168 at Visit 6 and was maintained through Visit 9 at 225.

A summary of the CDAI Scores for the subject is provided in Attachment Plate005. The calculated mean CDAI score for Subject 5005 ranged from 111 to 256. There was a substantial decrease in mean CDAI scores from 240 at Visit 1 to 111 at Visit 6 and was maintained through Visit 9 at 135.

A summary of the IBDQ Scores for the subject is provided in Attachment Plate006. The calculated mean IBDQ for Subject 5005 ranged from 103 to 192. There was a slight increase in the mean IBDQ score from 122 at Visit 1 to 192 at Visit 6, which subsequently decreased to 175 at Visit 9.

SAFETY RESULTS

The subject experienced adverse events of flank pain – bilateral, rash - right hand - ring finger, occasional dizziness, occasional nausea, and blisters on hands – bilateral. All adverse events were mild to moderate in severity, not related to the study drug, and were resolved. The dose of the study drug was not changed due to the adverse events.

No serious adverse events were reported and the subject did not discontinue the study drug prematurely.

The changes from reference in vital sign parameters were generally small throughout the study and were not considered clinically relevant. There were no abnormal findings during physical examination.

The summary of pregnancy test and infusion, capsules administration, and adverse event are provided in Attachment Plate007, Attachment Plate008, and Attachment Plate011, respectively.

STUDY LIMITATIONS

The study was stopped after the enrollment of 1 subject due to slow enrollment.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.