2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-874	**Volume:**	
Name of Active Ingredient: briakinumab	**Page:**	

Title of Study:

A Phase 2B, Multi-center, Randomized, Double-Blind, Parallel Group, Placebo-controlled, Dose Ranging Study Comparing the Efficacy, Safety, and Pharmacokinetics of Intravenous Infusions of ABT-874 vs. Placebo in Subjects with Moderately to Severely Active Crohn's Disease

Coordinating Investigator:

Remo Panaccione, MD

Study Sites: 60 sites in Australia, Canada, Europe, and the United States

Publications: 1 abstract

Studied Period (Years):	**Phase of Development:** 2b
First Subject First Visit: 05 December 2007 Last Subject Last Visit: 29 April 2010	

Objective: The objective of this study was to compare the efficacy, safety, and pharmacokinetics (PK) of ABT-874 200, 400, or 700 mg intravenous (IV) dosing every 4 weeks (q4wks) with placebo in subjects who had moderately to severely active Crohn's disease (CD).

Methodology:

This was a Phase 2b, multicenter, randomized, DB, parallel group, placebo-controlled, dose ranging, efficacy, safety, and PK study designed to demonstrate the effectiveness of ABT-874 in the treatment of moderately to severely active CD. Approximately 246 subjects with a diagnosis of CD for greater than 4 months and a Crohn's Disease Activity Index (CDAI) score of ≥ 220 and ≤ 450 at Week 0 were enrolled in the study at approximately 60 sites located throughout Australia, Canada, Europe, and the US.

At Week 0, subjects were randomized 1:1:1:3 according to stratification by prior anti-TNF use and prior anti-TNF response (anti-TNF naïve, anti-TNF responder, and anti-TNF non-responder) to receive one of the following doses of study drug:

- Placebo by IV infusion at Weeks 0, 4, and 8
- 200 mg of ABT-874 by IV infusion at Weeks 0, 4, and 8
- 400 mg of ABT-874 by IV infusion at Weeks 0, 4, and 8
- 700 mg of ABT-874 by IV infusion at Weeks 0, 4, and 8

Methodology (Continued):

Beginning with protocol Amendment 3, no subjects were randomized to ABT-874 200 mg IV dose at Week 0. With the removal of the 200 mg dosing group, a greater proportion of total study subjects were exposed to the 2 highest doses versus the originally planned proportion. This allowed the investigation of exposure response relationships in CD at higher exposures and did not have a significant impact on the scientific output of the study.

At Week 12, subjects who achieved clinical response (decrease in CDAI score of ≥ 70 points compared to the Week 0 score) continued into the Maintenance period. Subjects in the Induction period treatment who received placebo or either 200 mg or 400 mg ABT-874, who achieved clinical response, received the same dosage from the Induction period q4 wks (Continuing on Dose [CID] analysis set). Subjects in the Induction period who received 700 mg ABT-874, who achieved clinical response, were re-randomized in a 1:1:1 ratio into 1 of 3 treatment groups (Re-randomized [RR] analysis set) according to a stratification by prior anti-TNF use and prior anti-TNF response (anti-TNF naïve, anti-TNF responder, and anti-TNF non-responder) to receive one of the following doses of study drug:

- Placebo by IV infusion at Weeks 12, 16, and 20
- 200 mg of ABT-874 by IV infusion at Weeks 12, 16, and 20
- 700 mg of ABT-874 by IV infusion at Weeks 12, 16, and 20

Subjects who did not achieve a clinical response at Week 12 were able to enter the Open-Label (OL) period. A subject who relapsed (defined as CDAI increase of ≥ 70 points compared to the CDAI score at Week 12 and a CDAI ≥ 220 points) at any time point after Week 12 also had the option to enter the OL period.

At Week 24, subjects were assessed for clinical response and remission (defined as a decrease in CDAI score of ≥ 70 points compared to the Week 0 score). Subjects who achieved clinical remission entered the Withdrawal period and stopped receiving study drug until there was a relapse. When subjects relapsed, they had the option to enter the OL period. Non-remitters at Week 24 had the option to enter the OL period.

In the OL period, all subjects received cyclical dosing of 700 mg ABT-874 by IV infusion q4wks for 3 doses followed by a withdrawal period. At the discretion of the investigator, the subject started additional 3-dose and withdrawal cycles. Throughout the OL period, subjects may have undergone multiple 3-dose and withdrawal cycles. The minimum duration of time between the third dose of an OL cycle and the first dose of a new cycle was 4 weeks (less 3 days if necessary to accommodate the allowed ± 3-day visit window). The OL study visits occurred at 4-week intervals and were to have continued until the subject had completed 2 years of treatment (defined as 104 weeks post Week 0). Study M10-222 was discontinued due to a lack of efficacy and all remaining subjects were terminated from the study.

Methodology (Continued):

Blood samples for the evaluation of ABT-874 concentrations and anti-drug antibodies (ADA) were collected throughout the study. Following International Review Board (IRB) approval of Amendment 2, blood samples for measuring IL-22 and other mediator levels were collected at Week 0 and Week 6. Following IRB approval of Amendment 5, a blood sample for the measurement of total hemolytic complement, complement 3 (C3), and complement 4 (C4) was collected at each subject's next visit immediately prior to and after study drug infusion. In the event of an acute systemic infusion reaction (occurring during or after an infusion), blood samples for the determination of anti ABT-874 IgE, total IgE, tryptase, other pro-inflammatory cytokine markers, total hemolytic complement, C3, and C4 were collected. Within this study, there was also a substudy for pharmacogenomic and pharmacogenetic testing. Blood samples for the pharmacogenomic testing were collected at Week 0 and Week 6. Blood samples for the pharmacogenetic testing were collected at Week 0. Subjects were required to sign a consent form indicating their intent to participate in the substudy.

Number of Subjects (Planned and Analyzed):

Planned: 420 subjects changed to 225 subjects per Protocol Amendment 3

Induction Period:

Analyzed: 246 subjects analyzed for safety (139 subjects on 700 mg ABT-874; 45 subjects on 400 mg ABT-874; 16 subjects on 200 mg ABT-874; and 46 subjects on placebo); 230 subjects analyzed for efficacy (139 subjects on 700 mg ABT-874; 45 subjects on 400 mg ABT-874; and 46 subjects on placebo).

Maintenance Period:

Analyzed: 99 subjects (14 subjects on placebo/placebo [CID]; 21 subjects on 400 mg ABT-874/400 mg ABT-874 [CID]; 21 subjects on 700 mg ABT-874/700 mg ABT-874 [CID]; 21 subjects on 700 mg ABT-874/200 mg ABT-874 [RR]; and 22 subjects on 700 mg ABT-874/placebo [RR]).

OL Period:

Analyzed: 202 subjects (37 subjects previously on placebo, 12 subjects on 200 mg ABT-874, 35 subjects on 400 mg ABT-874, and 118 subjects on 700 mg ABT-874).

Diagnosis and Main Criteria for Inclusion: Subjects were males and females aged 18 years to < 75 years who had a diagnosis of CD for greater than 4 months, confirmed by endoscopy or radiologic evaluation, and a CDAI score of ≥ 220 and ≤ 450 at Week 0.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Test Product: 100 mg/mL of ABT-874

Test Dose/Strength/Concentration: 200 mg, 400, or 700 mg ABT-874/mL at Weeks 0, 4, and 8 and 200 mg or 700 mg ABT-874/mL at Weeks 12, 16, and 20.

Mode of Administration: IV infusion

Bulk Product Lot Numbers: 06-004555, 05-003264, 06-005517, and 06-009405

Duration of Treatment: 115 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Reference therapy: Placebo

Dose/Strength/Concentration: not applicable

Mode of Administration: IV infusion

Bulk Product Lot Numbers (placebo matching ABT-874): 01479605-003623 and 06-009192

Criteria for Evaluation

Efficacy: The primary efficacy variable was the proportion of subjects achieving clinical remission, defined as CDAI score of < 150 points, at Week 6.

Secondary efficacy variables for the Induction period were:

- Proportion of subjects achieving clinical remission at Week 12 in the ABT-874 treatment groups versus the placebo group.
- Proportion of subjects achieving clinical remission at both Week 6 and Week 12 in the ABT-874 treatment groups versus the placebo group, by anti-TNF stratification status.
- Proportion of subjects achieving a CDAI 100 clinical response at Week 6, defined as a decrease in CDAI score of ≥ 100 points compared to the CDAI score at Week 0.
- Proportion of subjects achieving a CDAI 100 clinical response at Week 6, defined as a decrease in CDAI score of ≥ 100 points compared to the CDAI score at Week 0, by anti-TNF stratification status.
- Proportion of subjects achieving a CDAI 70 clinical response at Week 6, defined as a decrease in CDAI score of ≥ 70 points compared to the CDAI score at Week 0.
- Proportion of subjects achieving a CDAI 70 clinical response at Week 6, defined as a decrease in CDAI score of ≥ 70 points compared to the CDAI score at Week 0, by anti-TNF stratification status.
- Proportion of subjects achieving a CDAI 100 clinical response at Week 12, defined as a decrease in CDAI score of ≥ 100 points compared to the CDAI score at Week 0.
- Proportion of subjects achieving a CDAI 100 clinical response at Week 12, defined as a decrease in CDAI score of ≥ 100 points compared to the CDAI score at Week 0, by anti-TNF stratification status.
- Proportion of subjects achieving a CDAI 70 clinical response at Week 12, defined as a decrease in CDAI score of ≥ 70 points compared to the CDAI score at Week 0.
- Proportion of subjects achieving a CDAI 70 clinical response at Week 12, defined as a decrease in CDAI score of ≥ 70 points compared to the CDAI score at Week 0, by anti-TNF stratification status.
- Change from Week 0 to Week 12 in total CDAI scores between the ABT-874 treatment groups versus placebo.
- Change from Week 0 to Week 12 in total IBDQ scores between the ABT-874 treatment groups versus placebo.

Efficacy (Continued):

- Change from Week 0 to Week 12 in EQ-5D index scores between the ABT−874 treatment groups versus placebo.
- Change from Week 0 to Week 12 in WPAI Questionnaire scores (absenteeism, presenteeism, total work impairment, and activity impairment) between the ABT-874 treatment groups versus placebo.
- Cumulative number of unscheduled outpatient visits (physician visits, ER visits, hospital admissions, and days of hospitalization) by Week 12 were was tabulated for the ABT-874 treatment groups and placebo. Information was adjusted for health utilization values collected at Week 0.
- Proportion of subjects who were remitters at both Week 12 and Week 24.

Secondary efficacy variables for the Maintenance period (CID) were:

- Among subjects in CID analysis set, proportion of subjects with clinical remission at Week 24 visit.
- Assuming that subjects who do not enter the Maintenance period are non-remitters at Week 24, proportion of subjects with clinical remission at Week 24 visit. [Note: since not all subjects in ABT-874 700 mg group in Induction period reach Week 12 visits, it is not possible to determine the denominator (same as the total number of subjects in this treatment group that would have been randomized to ABT-874 700 mg group in Maintenance period) for ABT-874 700 mg group in Maintenance period. Therefore, this analysis will not use the ABT-874 700 mg group.]
- Among subjects in the CID analysis set, proportion of subjects with clinical remission at both Week 6 and Week 24 visits.
- Assuming that subjects who do not enter Maintenance period are non-remitters at Week 24, proportion of subjects with clinical remission at both Week 6 and Week 24 visits [Note: this analysis will not use the ABT-874 700 mg group.]
- Among subjects in the CID analysis set, proportion of subjects with clinical remission at both Week 12 and Week 24 visits.
- Assuming that subjects who do not enter Maintenance period are non-remitters at Week 24, proportion of subjects with clinical remission at both Week 12 and Week 24 visits [Note: this analysis will not use the ABT-874 700 mg group.]
- Among subjects in the CID analysis set, proportion of subjects with CDAI 100 clinical response at Week 24.
- Among subjects in the CID analysis set, proportion of subjects with CDAI 70 clinical response at Week 24.
- Among subjects in the CID analysis set, proportion of subjects who relapse by Week 24.

Efficacy (Continued):

- Assuming that subjects who do not enter Maintenance period will relapse by Week 24, proportion of subjects with relapse by Week 24 [Note: this analysis will not use the ABT-874 700 mg group.]
- Among subjects in CID analysis set who are on steroid at Week 12, proportion of subjects who become steroid free by Week 24.
- For subjects in the CID analysis set, compare the time to loss of CDAI 70 (or 100) response during the period Week 12 to Week 24. The time to loss of CDAI 70 (or 100) response will be described with the Kaplan-Meier survival curve using the pooled date from the three strata.
- Time to onset of relapse during the Withdrawal period (Week 24 to the end of Withdrawal period) by treatment regimen. Relapse defined as a gain of ≥ 70 points in CDAI compared to Week 24 and CDAI ≥ 220 points.
- Change and percent change from baseline in CDAI scores at Week 24.
- Change and percent change from baseline in Harvey-Bradshaw (H-B) scores at Week 24.
- Change and percent change from baseline in total IBDQ scores at Week 24.
- Change and percent change from baseline in EQ-5D scores at Week 24.
- Change and percent change from baseline in WPAI scores at Week 24.
- Cumulative number of unscheduled outpatient visits (physician visits, emergency room visits, hospital admissions, and days of hospitalization) by Week 24 using the pooled data from the three strata.

Secondary efficacy variables for the Maintenance period (RR analysis set) were:

- Among subjects in re-randomized analysis set, proportion of subjects with clinical remission at Week 24 visit.
- Among subjects in re-randomized analysis set, proportion of subjects with clinical remission at both Week 6 and Week 24 visits.
- Among subjects in re-randomized analysis set, proportion of subjects with clinical remission at both Week 12 and Week 24 visits.
- Among subjects in re-randomized analysis set, proportion of subjects with CDAI 100 clinical response at Week 24.
- Among subjects in re-randomized analysis set, proportion of subjects with CDAI 70 clinical response at Week 24.
- Among subjects in re-randomized analysis set, proportion of subjects who relapse by Week 24.
- Among subjects in re-randomized analysis set who are on steroid at Week 12, proportion of subjects who become steroid free by Week 24.
- Change and percent change from baseline in CDAI scores at Week 24.
- Change and percent change from baseline in Harvey-Bradshaw (H-B) scores at Week 24.
- Change and percent change from baseline in total IBDQ scores at Week 24.

Efficacy (Continued):

- Change and percent change from baseline in EQ-5D scores at Week 24.
- Change and percent change from baseline in WPAI scores at Week 24.
- Cumulative number of unscheduled outpatient visits (physician visits, emergency room visits, hospital admissions, and days of hospitalization) by Week 24 (no *P* values will be provided).
- For subjects in the re-randomized analysis set, compare (using Log-rank test) the time to loss of CDAI 70 (or 100) response during the Maintenance period. Kaplan-Meier curves will be used to show the survival curves for time to loss of clinical response during the Maintenance period. The analysis will be performed using the pooled data from the three strata.
- Within-group summary statistics are presented for those subjects that continued on their original Induction treatment - Placebo, ABT-874 400 mg or ABT-874 700 mg.
- Between-group comparisons are presented for those subjects in the re-randomized group - Placebo, ABT-874 200 mg, or ABT-874 700 mg.
- Cumulative number of unscheduled outpatient visits (physician visits, emergency room visits, hospital admissions, and days of hospitalization) by Week 24.

Secondary efficacy variables for the Withdrawal period were:

- Time to onset of relapse during the Withdrawal period (Week 24 to end of the Withdrawal period) by treatment groups in Maintenance period. Relapse defined as a gain of ≥ 70 points in CDAI compared to Week 24 and CDAI ≥ 220 points.
- Time to onset of relapse during the Withdrawal period (Week 24 to end of the Withdrawal period) by treatment groups in Maintenance period. Relapse defined as a gain of ≥ 70 points in CDAI compared to Week 24 and CDAI ≥ 220 points, by anti-TNF stratification status.
- Time to onset of relapse during the Withdrawal period (Week 24 to the end of Withdrawal period) by treatment regimen. Relapse is defined as a gain of ≥ 70 points in CDAI compared to Week 24 and CDAI ≥ 220 points.
- Change from Week 0 to the end of Withdrawal period in total CDAI scores by treatment regimen.
- Change from Week 0 to the end of Withdrawal period in total IBDQ scores by treatment regimen.
- Change from Week 0 to the end of Withdrawal period in EQ-5D index scores by treatment regimen.
- Change from Week 0 to the end of Withdrawal period in WPAI Questionnaire scores (absenteeism, presenteeism, total work impairment, and activity impairment) by treatment regimen.

Efficacy (Continued):

Secondary efficacy variables for the OL period were:

- Change and percent change in CDAI scores from Week 0 (Induction period) to final value (last non-missing value in Open-Label period).
- The above analysis will be repeated for IBDQ, EQ-5D and WPAI scores.
- Cumulative number of unscheduled outpatient visits (physician visits, emergency room visits, hospital admissions, and days of hospitalization) by the end of the study.

Pharmacokinetic: Blood samples for ABT-874 and ADA assays were obtained and are described in a separate report.

Safety: Adverse events (AEs), serious adverse events (SAEs), laboratory data, ADA, and vital signs were assessed throughout the study.

Summary/Conclusions

Demographic and Baseline Characteristics:

The study population was similar across treatment groups. No statistically significant differences in demographics, medical history, Baseline disease conditions, ECG, TB skin test for positivity, CXR and prior and concomitant medications were observed between treatment groups. At study entry, subjects who participated in the study were predominantly white (217/246; 94.3%), female (122/246; 53.0%), with a mean age of 38.8 years, and mean weight of 77.0 kg across treatment groups.

The study population consisted of subjects who had a diagnosis of CD for greater than 4 months, confirmed by endoscopy or radiologic evaluation, and a CDAI score of ≥ 220 and ≤ 450 at Week 0. At Screening, mean duration of CD was 11.63 years, with a range from 0.3 to 43.2 years across all groups with no statistically significant differences observed. The total mean score of total CDAI at Baseline was 318.6 across all groups and mean CRP was 1.72 mg/dL. Most of the subjects had used prior anti-TNF therapy and over half had responded to the prior treatment.

Efficacy Results: While a greater proportion of subjects in the 700 mg and 400 mg ABT-874 treatment groups achieved clinical remission, defined as CDAI score of < 150 points at Week 6, no statistically significant differences were observed when each was compared to placebo.

Study M10-222 was terminated by the Sponsor due to a lack of efficacy and all remaining subjects were discontinued from the study.

Efficacy Results (Continued):

The following results were observed for secondary variables in the Induction period:

- While a greater proportion of subjects in the 700 mg and 400 mg ABT-874 treatment groups achieved clinical remission, defined as CDAI score of < 150 points at Week 6, no statistically significant differences were observed when each treatment group was compared to placebo (24/139 subjects [17.3%], 6/45 subjects [13.3%], and 4/46 subjects [8.7%], respectively).
- A greater proportion of subjects in the 700 mg and 400 mg ABT-874 treatment groups achieved clinical remission (CDAI < 150) at both Week 6 and Week 12 compared to subjects in the placebo group (20/139 subjects [14.4%], 6/45 subjects [13.3%], and 2/46 subjects [4.3%], respectively). However, no statistically significant differences were observed when each ABT-874 treatment group was compared to placebo or between treatment groups by strata.
- At Week 12, few subjects were in clinical remission (43/139 subjects [30.9%], 16/45 subjects [35.6%], and 8/46 subjects [17.4%] for subjects in the 700 mg and 400 mg ABT-874 treatment groups and subjects in the placebo group, respectively.) and the results were not statistically significant.
- At Week 6 (52/139 subjects [37.4%] versus 8/46 subjects [17.4%], respectively; $P = 0.013$) and at Week 12 (55/139 subjects [39.6%] versus 9/46 subjects [19.6%]; respectively; $P = 0.013$), a statistically significantly greater proportion of subjects in the ABT-874 700 mg treatment group achieved a CDAI 100 response compared to placebo subjects.
- At Week 12, a statistically significantly greater proportion of subjects in the 700 mg ABT-874 treatment group achieved a CDAI 70 response at Week 12 compared to placebo subjects (55/139 subjects [39.6%] versus 9/46 subjects [19.6%]; $P = 0.013$). At Week 12, statistically significant differences were observed in anti-TNF naïve subjects the 700 mg and 400 mg ABT-874 treatment groups when both were compared to placebo ($P = 0.015$ and $P = 0.027$, respectively).
- Mean changes in IBDQ score, EQ-5D VAS scores, and WPAI from Baseline to Week 12 were statistically significantly greater in both the 700 mg and 400 mg ABT-874 treatment groups than the placebo group.
- The majority of subjects had cumulative post-Baseline unscheduled outpatient visits during the study. ER visits, hospital admissions, and the length of stay in hospital were higher in the ABT-874 treatment groups compared to placebo by number of visits.

Efficacy Results (Continued):

The following results were observed for secondary variables in the Maintenance Period (CID):

- A greater proportion of subjects in the 700 mg and 400 mg ABT-874 treatment groups (NRI) achieved clinical remission (CDAI < 150) at Week 24 (12/21 subjects [57.1%; 700 mg ABT-874]; 10/21 subjects [47.6%; 400 mg ABT-874]; 4/14 subjects [28.6%; placebo]); at both Week 6 and 24 (9/21 subjects [42.9%; 700 mg ABT-874]; 5/21 subjects [23.8%; 400 mg ABT-874]; 2/14 subjects [14.3%; placebo]); and at both Weeks 12 and 24 (11/21 subjects [52.4%; 700 mg ABT-874]; 8/21 subjects [38.1%; 400 mg ABT-874]; 1/14 subjects [7.1%; placebo]) compared to placebo.
- At Week 24, a greater percentage of subjects in both the 700 mg (15/21 subjects; 71.4%) and 400 mg (13/21 subjects; 61.9%) ABT-874 treatment groups maintained a clinical response for CDAI 100 and in both the 700 mg (15/21 subjects; 71.4%) and 400 mg (14/21 subjects; 66.7%) ABT-874 treatment groups for CDAI 70 when both were compared to placebo (5/14 subjects; 35.7% for CDAI 100 and 6/14 subjects; 42.9% for CDAI 70).
- A greater mean reduction from Baseline in CDAI score was observed at Week 24 in subjects in the 700 mg and 400 mg ABT-874 treatment groups (LOCF) compared to the placebo group. Results for the OC analysis and by stratification for both the LOCF and OC analyses were similar.
- At Week 24, a smaller percentage of subjects in both the 700 mg and 400 mg ABT-874 treatment groups (4/21 subjects; 19.0% for both) relapsed compared to subjects in the placebo group (8/14 subjects; 57.1%); however, results were not statistically significant.
- All treatment groups (LOCF) had an improvement (increase) in mean IBDQ score and mean EQ-5D VAS score from Baseline and decreases in WPAI domains (within group change).
- The number of physician visits by Week 24 was greatest in the 700 mg ABT-874 treatment group. ER visits, hospital admissions, and the length of stay in hospital were higher in the ABT-874 treatment groups compared to placebo by number of visits.

Similar results were observed during the Maintenance period for the RR analysis set as those for the CID analysis set.

The following results were observed for secondary variables in the Withdrawal Period:

- Mean decreases in CDAI from Baseline were observed over time in all treatment groups; with the greatest mean decreases seen in subjects the placebo group and the ABT-874 400 mg treatment groups who continued on the same induction dose.
- During the Withdrawal period, no subjects completed the study without switching to the OL period, and all subjects in each treatment group experienced a relapse. The median time for relapse for subjects in the ABT-874 treatment groups ranged from 16 to 28 weeks.
- No statistically significant increases in IBDQ score or EQ-5D UK and VAS score from Baseline to final value by treatment group or by stratification level were observed in any treatment group.

Efficacy Results (Continued):

- Subjects in the Withdrawal Period analysis set had fewer unscheduled outpatient visits during the study. One subject in the ABT-874 700 mg/ABT-874 700 mg treatment group reported a hospital admission and 1 subject each in the ABT-874 700 mg/ABT-874 200 mg treatment groups reported ER visits.

The following results were observed for secondary variables in the OL Period:

- A greater mean decrease in CDAI score from Baseline (Induction Period) was observed over time in subjects in the 700 mg and 400 mg ABT-874 treatment groups compared to placebo. Mean decreases in CDAI score from Baseline (Induction Period) were observed over time by stratification level in all treatment groups with the greatest mean reductions seen in subjects who were anti-TNF naïve and anti-TNF responders.
- Increases in IBDQ score and EQ-5D UK and VAS score from Baseline (Induction Period) to final value were observed in all treatment groups by treatment sequence and by stratification level. Mean decreases in WPAI from Baseline were observed over time in all treatment groups by treatment sequence and by stratification level.
- During the OL Period, physician visits, ER visits, hospital admissions, and the length of stay in hospital were higher in the ABT-874 treatment groups compared to placebo. No subjects in the 400 mg ABT-874 treatment group reported ER visits or hospital admissions during the OL Period.

Pharmacokinetic Results:

Pharmacokinetic results are presented and discussed in a separate report ([redacted]).

Safety Results:

ABT-874 was generally safe and well tolerated in subjects with moderate to severe CD and had an AE profile that was similar to placebo during the Induction and Maintenance Periods. One subject who received ABT-874 200 mg during the Induction and Maintenance Periods died 66 days after the last dose of study drug in the Maintenance Period from a fatal AE of respiratory distress secondary to acute pancreatitis.

The incidence of SAEs in subjects exposed to any ABT-874 up to 3 months during the Induction period was lower than placebo, 4.5% versus 8.7%, respectively. Similarly, the incidence of SAEs in subjects exposed to any ABT-874 up to 6 months during the Induction and Maintenance Period was lower than placebo, 6.7% versus 14.3%, respectively. As expected, the incidence of SAEs in subjects treated with any ABT-874 up to 2 years during the study increased along with exposure to 16.9%, slightly higher than the placebo rate observed over a maximum of 6 months. Overall, 8 serious infusion-related reactions, 7 reported as such and an additional event of anaphylaxis, were reported in subjects exposed to ABT-874 700 mg, the highest dose administered in the study. All events resolved. No serious infusion-related reactions occurred in subjects receiving ABT-874 200 or 400 mg.

Safety Results (Continued):

During the study, the overall occurrence of TEAEs leading to discontinuation of study drug was low (12.2%). The most frequently reported TEAEs by subjects who received any ABT-874 during the study were upper respiratory tract infection (20.7%), nausea (17.3%), abdominal pain (14.3%), and headache (14.3%). A similar incidence of infectious AEs was observed between placebo and ABT-874 during the Induction period (34.8% versus 33.0%, respectively) and during the Induction and Maintenance Periods (50.0% versus 46.7%, respectively). Approximately 59% of subjects who received any ABT-874 during the 2-year study reported infectious TEAEs; 2% of subjects had infections that were serious. All of the subjects with serious infectious TEAEs had events that resolved with continuous drug exposure. Two subjects exposed to ABT-874 and 2 subjects who received placebo experienced a malignancy. Seven subjects (3.0%) who received any ABT-874 during the study had asthma-related TEAEs considered unrelated to study drug by the investigator. All asthma-related events resolved. All subjects with asthma-related TEAEs had a documented medical history of asthma for years prior to the study, except 1 subject who experienced an event of wheezing. No clinically meaningful changes in hematology, clinical chemistry, urinalysis parameters, or vital signs were observed.

Conclusions:

ABT-874 Induction therapy in subjects with moderate to severe CD resulted in greater rates of remission and response than placebo at Weeks 6, 12, and 24; however, the primary endpoint of remission at Week 6 was not significant.

ABT-874 was generally safe and well-tolerated in subjects with moderate to severe CD. During the Induction and Maintenance Periods ABT-874 had an AE profile that was similar to placebo and little evidence of dose-related safety effects was apparent. Laboratory and vital sign findings were clinically unremarkable.