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 3, Multi-center, Open-label Continuation Study in Moderate to Severe Chronic Plaque Psoriasis Subjects Who Completed a Preceding Psoriasis Study With ABT-874		
Coordinating Investigator: Kenneth Gordon, MD		
Study Sites: 150 sites in the United States, Canada, and European Union		
Publications: None		
Studied Period (Years): First Subject First Visit: 07 Feb 2008 Last Subject Last Visit: 14 November 2011	**Phase of Development:** 3	
Objectives: The objectives of this study were to assess the long-term safety, tolerability, and efficacy, of ABT-874 in adults who had either completed or had demonstrated a loss of response (as defined in the original ABT-874 protocol) to treatment in a preceding ABT-874 study in the treatment of subjects with moderate to severe chronic plaque psoriasis (Ps).		
Methodology: Study M10-016 was to be a 208-week open-label study designed to evaluate the safety, tolerability, and clinical efficacy of long-term administration of ABT-874 in the treatment of adult subjects with moderate to severe plaque Ps who had participated in an ABT-874 Phase 2 Ps study (Study M05-736) or Phase 3 Ps study (Studies M06-890, M10-255, M10-114, and M10-315). All subjects from these 5 studies who had either completed or had demonstrated a loss of response to treatment, as defined in the original ABT-874 protocol, were eligible to enroll from sites in North America and Europe. Subjects who prematurely discontinued in any preceding Ps study with ABT-874 (other than due to loss of response as defined in the original ABT-874 protocol) were not eligible for this study. Each subject received 100 mg ABT-874 administered subcutaneously (SC) at Baseline (Week 0) and every 4 weeks thereafter. The Psoriasis Area and Severity Index (PASI), Physician's Global Assessment (PGA), and Patient's Global Assessment (PTGA) responses were determined every 12 weeks. A qualified investigator or designee from the site was responsible for performing the PGA and PASI evaluations at all appropriate study visits. The site was to make every attempt to have the same investigator or designee perform these assessments throughout the study for each subject. Subjects were to be discontinued from the study if they had a PGA score of ≥ 3 at any time on or after Week 24 during the study, and if the investigator and subject agreed that the risks outweighed the benefits.		

Methodology (Continued):

Blood samples for measurement of serum ABT-874 pharmacokinetics (PK) and anti-drug antibodies (ADAs) were collected prior to dosing every 24 weeks throughout the duration of the study.

During the study, subjects were evaluated every 12 weeks to assess safety, tolerability, and efficacy parameters. Following the implementation of Amendment 4 dated 14 May 2010, a cardiovascular (CV) risk assessment was conducted at Baseline and/or all study visits. This assessment included evaluation of CV risk factors, measurement of blood pressure (BP), weight, and body mass index (BMI) calculation. Subjects who had or developed 2 or more of the following 4 CV risk factors [1. history of atherosclerotic CV disease as manifested by any of the following: MI, stroke or transient ischaemic attack, angina (cardiac chest pain) requiring hospitalization, coronary artery disease requiring revascularization (stents, bypass surgery, or angioplasty), peripheral artery disease (intermittent claudication), or congestive heart failure requiring hospitalization; 2. history of diabetes mellitus; 3. BMI $\geq$ 30; or 4. Blood pressure (BP) elevation: systolic BP $\geq$ 140 and/or diastolic BP $\geq$ 90] were required to be discontinued from the study. However, subjects with 2 or more CV risk factors could continue in the trial if they had:

- Experienced failure to (i.e., failed to respond or lost response) or intolerance to tumor necrosis factor inhibitor therapy AND
- For whom treatment with other systemic therapies were deemed medically inappropriate in the opinion of the investigator, AND
- For whom, in the opinion of the investigator, treatment with ABT-874 continued to have a positive individual benefit: risk profile, as these subjects may not have had other options to treat their Ps.

However, these subjects were required to return to the site every 4 weeks for the duration of the study for BP, weight, BMI and CV risk factor assessments. All subjects who began an every 4 week visit schedule for CV risk factor assessments were required to remain on a 4 week schedule for the remainder of the trial, regardless of whether or not the number of risk factors was reduced.

All subjects, whether they completed the study or terminated early, were to have a telephone follow-up call approximately 45 days after the last dose of study drug to determine the occurrence of AEs and changes in concomitant medications. In addition, it was planned for all subjects who agreed to be contacted, whether they terminated early or completed the study, to be called at Weeks 12 and 24 after the last dose of study medication to capture possible occurrences of the following: myocardial infarction (MI), stroke or transient ischaemic attack, angina (cardiac chest pain) requiring hospitalization, coronary artery disease requiring revascularization (stents, bypass surgery, or angioplasty), peripheral artery disease (intermittent claudication), or congestive heart failure requiring hospitalization.

Number of Subjects (Planned and Analyzed):

Planned: Up to 2500 subjects

Analyzed: 2300 (2300 for safety, 627 for efficacy)

Diagnosis and Main Criteria for Inclusion: Subjects were males and females aged 18 years or older who participated in a prior ABT-874 Phase 2 or Phase 3 Ps study and who did not prematurely discontinue the previous ABT-874 study (other than protocol required discontinuation due to loss of response as defined in the original ABT-874 protocol). Criteria for inclusion in the preceding studies included a clinical diagnosis of Ps for at least 6 months, stable plaque Ps for at least 2 months before Screening and at Baseline (Week 0), moderate to severe plaque Ps (≥ 10% Body Surface Area [BSA] at Baseline [Week 0]), a PGA of at least moderate (defined as a score ≥ 3) disease at Baseline (Week 0), a PASI score ≥ 12 at Baseline (Week 0), being candidates for systemic therapy or phototherapy and having active Ps despite treatment with topical agents.

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

Test Product: 100 mg/mL of ABT-874

Test Dose/Strength/Concentration: 100 mg ABT-874/mL at Week 0 and every 4 weeks thereafter.

Mode of Administration: SC injection

Bulk Product Lot Numbers: 07-013252, 07-013788, 08-015184, 08-017707, 08-017003, 08-017708, 08-020315, 08-020321

Duration of Treatment: 208 weeks planned. Maximum 180 weeks due to termination by the sponsor.

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

Reference Therapy: None

Dose/Strength/Concentration: Not applicable

Mode of Administration: Not applicable

Bulk Product Lot Numbers (placebo matching ABT-874): Not applicable

Criteria for Evaluation

Efficacy: The following efficacy variables were summarized by visit:

- Proportion of subjects achieving PASI 50 response
- Proportion of subjects achieving PASI 75 response
- Proportion of subjects achieving PASI 90 response
- Proportion of subjects achieving PASI 100 response
- Change from Baseline in PASI score
- Percent change from Baseline in PASI score
- Proportion of subjects achieving PGA of "clear" (PGA 0)
- Proportion of subjects achieving PGA of "clear" or "minimal" (PGA 0/1)
- Proportion of subjects achieving PGA of "clear," "minimal," or "mild" (PGA 0/1/2)
- Proportion of subjects achieving a PTGA of "complete or good disease control."

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

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

Statistical Methods

Efficacy: Efficacy analyses were performed on the Maintenance of Efficacy (ME) Population and included data starting from the first dose date of ABT-874 during Study M10-016. The ME Population consisted of all subjects who received at least one dose of ABT-874 during Study M10-016 and also had a PGA score of 0 (clear) or 1 (minimal) at the last evaluation on or before the date of the first dose of ABT-874 in Study M10-016, and who also satisfied either of the following two conditions:
(a) randomized to the ABT-874 arm during Study M10-114, Study M10-315, or Study M10-255, or
(b) randomized to the ABT-874 treatment group during the Induction Phase of Study M06-890.
Summary statistics were presented using the observed and last observation carried forward values.

Pharmacokinetic: Serum ABT-874 concentrations were summarized at each time point using descriptive statistics; results are presented in a separate report ([redacted]).

Safety: Safety data were summarized for the All ABT-874 Treated Population, which included subjects who received at least one injection of ABT-874 in Study M10-016. Safety analyses using this population include data starting from the first dose date of ABT-874 during Study M10-016 or the preceding studies, whichever was earlier. Safety analyses were also performed for the ME Population.

For the All ABT-874 Treated Population, treatment-emergent adverse events (TEAEs) were defined as AEs with an onset date on or after the first ABT-874 dose (whether received in a preceding study or in Study M10-016) and up to 45 days after the last dose of ABT-874. For the ME Population, TEAEs were defined as any AE with an onset date on or after the first dose of ABT-874 in Study M10-016. Adverse events that started more than 45 days after the last dose during a protocol-defined gap or during a gap between studies were excluded.

In addition to the evaluation of AEs, deaths, SAEs, and AEs leading to premature study discontinuation, a total of 22 AEs of special interest categories were specifically examined. These categories included TEAEs which were of special interest based on the immunomodulating mechanism of action of ABT-874 (e.g., infections, including opportunistic infections, tuberculosis [TB]) or due to potentially higher rates of some events in the Ps population.

In addition, major adverse cardiovascular events (MACE) and serious non-MACE cardiovascular events for analysis were identified based on a review of all investigator reported SAE terms by a blinded independent external adjudication committee (CV Endpoints Committee [CEC]). The CEC adjudicated the SAEs using the endpoint definitions defined in the protocol to identify MACE and serious non-MACE CV events for analysis. MACE events included non-fatal MI, non-fatal stroke, and all CV deaths. Serious non-MACE CV events included unstable angina; coronary revascularization; transient ischaemic attack; cerebral revascularization; venous and peripheral arterial vascular thrombotic events; congestive heart failure; cardiac arrhythmia, no evidence of ischemia; and other serious non-MACE CV events.

Adverse event data were summarized and presented by severity and the investigator's assessment of relationship to study drug using primary Medical Dictionary for Regulatory Activities (MedDRA) system organ classes and preferred terms according to MedDRA Version 12.0.

Laboratory values and vital signs were displayed over time, and analyses included comparisons of changes from last observation prior to the first ABT-874 dose (either in Study M10-016 or the preceding study, whichever was earlier) and the occurrence of marked laboratory abnormalities.

Summary/Conclusions

Demographic and Baseline Characteristics: Subjects in the All ABT-874 Treated Population were predominantly white (2103/2300; 91.4%), male (1582/2300; 68.8%), and had a mean age of 45.2 years and mean weight of 93.1 kg. Demographic characteristics were comparable for the ME Population.

The All ABT-874 Treated Population consisted of subjects with moderate to severe plaque Ps disease activity at Baseline (of the preceding study) as characterized by having a PGA of at least moderate disease severity (defined as ≥ 3), BSA with Ps at least 10% (mean Baseline BSA of 24.80%), and PASI at least 12 (mean Baseline PASI score of 18.90). In the ME Population, the mean Baseline BSA affected was 22.77% and the mean Baseline PASI score was 18.13.

Medical histories reported for at least 10% of subjects in the All ABT-874 Treated Population included hypertension, hyperlipidemia, and depression. A majority (2152/2300; 93.6%) of subjects received previous topical treatment for Ps prior to study entry.

Efficacy Results: By definition, all subjects in the ME Population (N = 627) had a PGA score of clear (0) or minimal (1) at the last evaluation on or before the first dose of ABT-874 in Study M10-016 (i.e., Week 0). The proportion of subjects who had a PGA score of clear (0) or minimal (1) and the proportion who had a PASI 75 remained above 94% at all visits through Week 144.

		ME Population (N = 627) **Observed Data**	
Visit	**n**	**PGA of Clear (0) or Minimal (1) n (%)**	**PASI 75 Response n (%)**
Week 0	627	627 (100)	620 (98.9)
Week 12	622	605 (97.3)	615 (98.9)
Week 24	603	584 (96.8)	597 (99.0)
Week 36	592	562 (94.9)	583 (98.5)
Week 48	574	544 (94.8)	565 (98.4)
Week 72	533	513 (96.2)	528 (99.1)
Week 96	467	442 (94.6)	460 (98.5)
Week 120	366	354 (96.7)	363 (99.2)
Week 144	22	22 (100)	21 (95.5)

- At Baseline of Study M10-016 (Week 0), 66.7% of subjects in the ME Population had a PGA of clear; at Week 144, 81.8% had achieved this score.
- At Baseline of Study M10-016 (Week 0), 100% of subjects in the ME Population had a PASI 50 response and 98.9% had a PASI 75 response. At Week 144, 100% had a PASI 50 response and 95.5% had a PASI 75 response. The proportion of subjects who achieved a PASI 90 response increased from 87.2% at Week 0 to 95.6% at Week 120 and was 86.4% at Week 144; the proportion who achieved a PASI 100 response increased from 65.4% at Week 0 to 81.8% at Week 144.

Efficacy Results (Continued)

- The mean change and mean percent change in PASI score from Baseline of the preceding study were –17.6 and –96.7%, respectively, at Week 0 for subjects in the ME Population (observed data). During open-label ABT-874 treatment in Study M10-016, a sustained reduction in mean PASI score was observed at all visits through Week 144.
- At Week 0, 95.5% of subjects in the ME Population had a PTGA score of complete (0) or good (1) disease control. This percentage remained above 97% at all visits through Week 120, and was 91.3% at Week 144.

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

Safety Results: Except where otherwise noted, results presented are for the All ABT-874 Treated Population. A total of 2,300 subjects received at least 1 dose of ABT-874 in Study M10-016. The following results were observed based on 5950.4 patient-years (PYs) of exposure in the All ABT-874 Treated Population, starting with each subject's first dose of ABT-874, and 1274.7 PYs in the ME Population, starting with each subject's first dose of ABT-874 in Study M10-016:

- Treatment-emergent AEs were reported by 88.3% of subjects in the All ABT-874 Treated Population. Events in 43.1% of subjects were assessed by the investigator as at least possibly related to study drug. The majority of subjects who experienced TEAEs had events that were mild or moderate in severity. Overall, the most frequently reported TEAEs were upper respiratory tract infection (20.0%), nasopharyngitis (19.1%), hypertension (10.9%) arthralgia (9.6%), and headache (8.7%).
- The incidence of AEs was lower in the ME Population (82.3% overall, 30.0% at least possibly related to study drug) than in the All ABT-874 Treated Population, although the types and patterns of AEs were comparable between the two analysis populations.
- A total of 14 deaths (9 treatment-emergent) occurred in Study M10-016. The PTs for the fatal events were completed suicide (2 subjects), completed suicide/gunshot wound, accidental overdose, cardiac failure, cardiac arrest, pancreatic carcinoma, euthanasia/oesophageal adenocarcinoma metastatic, small cell lung cancer stage unspecified, bronchopneumonia, cardio-respiratory arrest/acute MI, cardiomyopathy, and death (due to unknown causes) (2 subjects).
- Treatment-emergent SAEs were reported for 228 of the 2,300 subjects (9.9%) during ABT-874 treatment in either a preceding study or in Study M10-016. Of these, SAEs in 63 subjects (2.7%) were considered at least possibly related to study drug according to the investigator. All other SAEs were assessed as not or probably not related to study drug per the investigator. The most common of the possibly or probably related SAEs were cellulitis (8 subjects, 0.3%), pneumonia (6 subjects, 0.3%), and sepsis (4 subjects, 0.2%). Coronary artery disease and MI were reported in 3 subjects (0.1%) each. In the ME Population, 42 subjects (6.7%) had SAEs; in 15 subjects (2.4%), these were assessed as at least possibly related to study drug.

Safety Results (Continued)

- Neurological SAEs considered at least possibly related to study drug by the investigator included events of convulsion, loss of consciousness, cervical myelopathy, thalamic infarction, syncope (2 subjects) and amyotrophic lateral sclerosis (ALS). One additional subject experienced an SAE of ALS, which was considered not related to study drug, and 1 additional subject had a non-serious TEAE of ALS considered not related to study drug.
- A total of 135 subjects (5.9%) had TEAEs leading to discontinuation, the most common of which were blood CPK increased (10 subjects, 0.4%), psoriatic arthropathy (8 subjects, 0.3%), MI (4 subjects, 0.2%), and Ps (4 subjects, 0.2%).
- Among the AEs of special interest that were analyzed, infections were reported by 61.3% of subjects. The most frequently reported infectious TEAEs were upper respiratory tract infection (20.0%) and nasopharyngitis (19.1%). A mycobacterium marinum infection considered possibly related to study drug was reported by a subject with a history of cleaning a fish tank, a known risk factor for mycobacterium marinum infections. Serious infections were reported for 34 subjects (1.5%); 5 of these subjects discontinued treatment because of these events. Treatment-emergent opportunistic infections, all of which were non-serious, were reported in 16 subjects (0.7%) in the All ABT-874 Treated Population, including 14 subjects with candidiasis, 1 with coccidioidomycosis, and 1 with a fungal ear infection. Eight of these subjects had opportunistic infections that were considered at least possibly related to study drug (4 with oral candidiasis, 2 with unspecified candidiasis, and 1 each with coccidioidomycosis and ear infection). Two TB events were identified by a TB Company Medical Dictionary for Regulatory Activities query, including 1 with a positive skin test and 1 with a pulmonary granuloma.
- Treatment-emergent malignancies were reported by 85 subjects (3.7%), including 54 subjects (2.3%) with non-melanoma skin cancer (NMSC); 4 subjects (0.2%) each with prostate cancer, dysplastic naevus syndrome, and malignant melanoma in situ; 3 subjects (0.1%) with lung neoplasm; and 2 subjects each (< 0.1%) with breast cancer and transitional cell carcinoma; the remaining malignancies occurred in only 1 subject each. Of the 54 subjects with events of NMSC (including 6 subjects who experienced more than 1 tumor type), 35 subjects had basal cell carcinoma, 21 subjects had squamous cell carcinomas, 5 subjects had squamous cell carcinoma of skin, and 1 subject had lip neoplasm. In addition to solid tumors and NMSC, hematologic malignancies were reported in 1 subject each with nodal marginal zone B cell lymphoma, hairy cell leukemia, and plasmacytoma. Malignancies in 36 of these 85 subjects were considered possibly related to study drug; 12 of these were assessed as serious and 12 led to study drug discontinuation. Skin malignancies were reported in 43 subjects (1.9%), including 1 subject who discontinued from the study due to a severe SAE of malignant melanoma assessed as possibly related to study drug.
- Treatment-emergent premalignant skin disorders were reported for 82 subjects (3.6%), including 12 subjects with events considered at least possibly related to study drug. A total of 54 subjects (2.3%) experienced events of NMSC, including 6 events in 4 subjects reported as SAEs: squamous cell carcinoma and basal cell carcinoma.
- Four subjects developed melanoma in situ, one of which was assessed as possibly related to study drug and one of which was serious and assessed as probably not related to study drug.

Safety Results (Continued)

- Injection site reaction TEAEs were reported by 245 subjects (10.7%). Allergic reactions were reported by 732 subjects (31.8%), the most common of which was nasopharyngitis (440 subjects, 19.1%). Events in 140 subjects were considered possibly or probably related to study drug. Eleven subjects had serious allergic reactions including 1 subject who had an anaphylactoid reaction that occurred 15 minutes after the subject took an antibiotic and was assessed by the investigator as not related to study drug
- TEAEs in the category of angioedema were reported in 45 subjects (2.0%), including 33 subjects with urticaria. TEAEs in the category of asthma (predominantly asthma or wheezing) were reported by 50 subjects (2.2%). Three events of asthma and 1 event of wheezing were reported as SAEs, and 1 led to study drug discontinuation.
- Hepatic-related TEAEs were experienced by 83 subjects (3.6%). The most frequently reported hepatic events were ALT increased (30 subjects, 1.3%) and AST increased (23 subjects, 1.0%). Hepatic TEAEs in 37 subjects were assessed by the investigator as possibly or probably related to study drug, and one event (jaundice) was reported as serious. Hepatic TEAEs led to study drug discontinuation in 8 subjects.
- Hematopoietic cytopenia-related TEAEs were experienced by 25 subjects (1.1%). The most frequent of these were platelet count decreased (10 subjects, 0.4%), lymphocyte count decreased (5 subjects, 0.2%), neutropenia (5 subjects, 0.2%), and white blood cell count decreased (3 subjects, 0.1%).
- Four subjects had an event related to CNS hemorrhages and cerebrovascular accidents. Three of the events were serious: 2 events of cerebrovascular accident, both of which were assessed as not related to study drug and led to study drug discontinuation; and one event of thalamic infarction, assessed as possibly related to study drug, which was suspended.
- Treatment-emergent AEs in the category of ischaemic heart disease were experienced by 122 subjects (5.3%). The most frequent of these events were blood CPK increased (80 subjects, 3.5%), angina pectoris (16 subjects, 0.7%), MI (9 subjects, 0.4%), coronary artery disease (9 subjects, 0.4%), and acute MI (7 subjects, 0.3%). No subject with an AE of blood CPK increased had a MACE reported. Events in 31 subjects were assessed by the investigator as possibly or probably related to study drug, events in 27 subjects were SAEs, and 19 subjects discontinued from study drug due to ischaemic heart disease AEs. One subject experienced a non-serious TEAE of ventricular extrasystoles, assessed as probably not related to study drug.
- Depression-related TEAEs were reported by 100 subjects (4.3%), including depression (84 subjects, 3.7%), depressed mood (5 subjects, 0.2%), suicidal ideation (3 subjects, 0.1%), mood swings (2 subjects, < 0.1%), and completed suicide (2 subjects, < 0.1%). Events in 7 subjects were assessed by the investigator as possibly related to study drug. Depression-related SAEs occurred in 7 subjects, two of whom discontinued study drug due to the events.

Safety Results (Continued)

- Thirty events assessed by the CEC as MACE (0.50 events per 100 PYs) occurred in 29 subjects, including 18 non-fatal MIs (0.30 events per 100 PYs), 6 non-fatal strokes (0.10 events per 100 PYs), and 6 CV deaths. Twenty-five of the MACEs in 24 subjects were treatment-emergent, including 18 non-fatal MIs, 4 non-fatal strokes, and 3 CV-related deaths. Seven of these events were assessed by the investigator as possibly related to study drug, and 11 of the events led to study drug discontinuation. Serious treatment-emergent non-MACEs occurred in 22 subjects. The most frequent categories of these were coronary revascularization (9 subjects, 0.4%) and venous thromboemobolism (5 subjects, 0.2%).
- Laboratory parameters for which ≥ 1% of CTC grade 3 or 4 included elevated glucose (114 subjects, 5.0%), CPK (66 subjects, 2.9%), triglycerides (31 subjects, 1.4%), and inorganic phosphate (27 subjects, 1.2%). Thirty-eight subjects had maximum ALT elevations ≥ 3 × ULN, 43 subjects had maximum AST elevations ≥ 3 × ULN, and 3 subjects had total bilirubin ≥ 3 × ULN after Baseline. No other clinically meaningful changes in hematology, clinical chemistry, urinalysis parameters, or vital signs were observed.

Conclusions: Results of this open-label extension study of subjects with moderate to severe chronic plaque Ps who had achieved a PGA score of clear or minimal in a previous Ps study demonstrate that continuing treatment with briakinumab 100 mg every 4 weeks for up to 3 years maintains a very high efficacy response rate that is clinically meaningful. Overall, the incidence rate of previously identified potential risks of serious infections, malignancies, and serious cardiovascular events remained similar with longer dosing in Study M10-016. An increased prevalence of depression and completed suicide as well as rare hematologic malignancies and serious neurological conditions was of unclear relationship to briakinumab.