2.0 Synopsis

<table>
<tr><td>Abbott Laboratories</td><td>Individual Study Table Referring to Part of Dossier:</td><td>(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug: ABT-874</td><td rowspan="2">Volume:
Page:</td><td rowspan="2"></td></tr>
<tr><td>Name of Active Ingredient: ABT-874</td></tr>
<tr><td colspan="3">Title of Study: A Phase 3, Multicenter, Randomized, Double-blind Study Comparing the Safety and Efficacy of ABT-874 to Methotrexate in Subjects with Moderate to Severe Chronic Plaque Psoriasis</td></tr>
<tr><td colspan="3">Coordinating Investigator: Kristian Reich, MD</td></tr>
<tr><td colspan="3">Study Sites: 43 sites in Europe and Canada</td></tr>
<tr><td colspan="3">Publications: None</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 27 May 2008
Last Subject Last Visit: 26 November 2009</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="3">Objectives: The objectives of this study were to compare the short-term and long-term clinical efficacy, safety and tolerability of ABT-874 to MTX in the treatment of moderate to severe chronic plaque Ps over a 24- and 52-week period.</td></tr>
<tr><td colspan="3">Methodology: The study was a 52-week double-blind treatment study designed to evaluate the safety, tolerability, and clinical efficacy of one ABT-874 dosing regimen versus MTX in the treatment of adult subjects with moderate to severe plaque psoriasis (Ps). Three hundred seventeen adults were enrolled from 43 sites in Europe and Canada.

At Week 0, subjects were randomized 1:1 to receive one of the following doses of study drug:
• Treatment A (ABT-874 subcutaneous [SC] injection): 200 mg ABT-874 administered SC at Baseline (Week 0) and Week 4, followed by 100 mg ABT-874 SC at Week 8 and a maintenance dose of 100 mg ABT-874 SC every 4 weeks starting at Week 12 and continuing through Week 48.
• Treatment B (MTX capsules): 5 to 25 mg weekly dosing per titration schedule at Weeks 0 to 51. Subjects in Treatment B also received oral folate, 5 mg weekly at Weeks 0 to 51.

At Week 24, subjects who achieved a 75% or greater reduction in Psoriasis Area and Severity Index (PASI) (PASI ≥ 75) and Physicians Global Assessment (PGA) 0 or 1 maintained the current MTX dose (active or placebo) from Week 24 through Week 51. Adjustments were made only for laboratory abnormalities.</td></tr>
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Methodology (Continued):

At Week 24, subjects who did not achieve a treatment success, defined as having achieved both PASI ≥ 75 and PGA 0/1, were discontinued from the study and were eligible to roll into the open label extension study M10-016 and receive treatment with SC injections of ABT-874, at a dose of 100 mg every 4 weeks.

To maintain the blind, subjects in Treatment A also received placebo capsules to match MTX and placebo tablets to match folate at Weeks 0 to 51. Subjects randomized to Treatment B received weekly capsules of MTX (weekly dose of 5 to 25 mg per titration schedule) and weekly doses of 5 mg oral folate at Weeks 0 to 51. To maintain the blind, subjects randomized to Treatment B also received 2 SC injections of placebo to match ABT-874 at Week 0 and Week 4 and 1 SC injection of placebo to match ABT-874 at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.

After Week 24, subjects who lost response, defined as PASI < 50% reduction from Baseline (Week 0) PASI score and PGA ≥ 3, were discontinued from the study and were eligible to roll into the open-label extension Study M10-016 and to receive treatment with SC injections of ABT-874, at a dose of 100 mg every 4 weeks.

Efficacy and safety measurements were performed throughout this study.

Blood samples for measurement of serum ABT-874 concentration were to be collected prior to dosing at Baseline (Week 0) and at Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, and 52, or if applicable, the Early Termination Visit.

Blood samples for measurement of serum anti-drug antibodies (ADA) were to be collected prior to dosing at Baseline (Week 0) and at Weeks 8, 12, 16, 24, 32, 40, 48, and 52, or if applicable, the Early Termination Visit.

Subjects who did not enter the open-label study (M10-016) were to have had a follow-up visit approximately 45 days following drug discontinuation to determine the occurrence of Adverse Events (AEs), changes in concomitant medications, and urine pregnancy test, if applicable.

Subjects who successfully completed the study through Week 52 were eligible to receive treatment with ABT-874 in the open-label extension Study M10-016.

Subjects who discontinued from the study prematurely for reasons other than loss of response to treatment were not eligible for the open-label extension Study M10-016.

Number of Subjects (Planned and Analyzed):

Planned: 250 subjects (125 MTX and folic acid and 125 ABT-874)

Analyzed: 317 subjects (163 MTX and folic acid and 154 ABT-874)

Diagnosis and Main Criteria for Inclusion: Subjects were males and females aged 18 years or older who had 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), and were candidates for systemic therapy or phototherapy and had active Ps despite treatment with topical agents.

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

Test Product: 100 mg ABT-874

Test Dose/Strength/Concentration: 200 mg ABT-874 administered SC at Baseline (Week 0) and Week 4, followed by 100 mg ABT-874 SC at Week 8 and a maintenance dose of 100 mg ABT-874 SC every 4 weeks starting at Week 12 and continuing through Week 48.

Mode of Administration: Subcutaneous

Lot Number: 07-012983, 08-015184, and 08-017707

Placebo Lot Numbers: 07-012409 and 08-015127

Duration of Treatment: 52 weeks

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

Test Product: 5 to 25 mg MTX capsules weekly dosing per titration schedule at Weeks 0 to 51 and oral folate, 5 mg weekly at Weeks 0 to 51.

Test Dose/Strength/Concentration: 5 to 25 mg MTX; 5 mg oral folate

Mode of Administration: Capsules

Lot Numbers – MTX: 07-010822, 07-010843, 07-010845, 07-010847, 08-017113, 08-016718, and 08-016719

Lot Numbers – oral folate: 07-013132, 08-017329, and 08-018991

Placebo Lot Numbers - MTX: 07-010823, 07-010874, 07-010876, 07-010878, 08-017114, 08-016720, 08-016721, and 08-016722

Placebo Lot Numbers – oral folate: 07-012763, 07-013296, and 09-021125

Criteria for Evaluation

Efficacy:

The primary efficacy variables were:

1. The proportion of subjects who achieved a PASI 75 response defined as at least 75% reduction in PASI score relative to Baseline at Week 24.
2. The proportion of subjects who achieved a PGA score of 0 or 1 at Week 24.
3. The proportion of subjects who achieved a PASI 75 response defined as at least 75% reduction in PASI score relative to Baseline at Week 52.
4. The proportion of subjects who achieved a PGA score of 0 or 1 at Week 52.

Criteria for Evaluation – Efficacy (Continued):

The ranked secondary efficacy variables were:

1. Proportion of subjects who achieved PASI 100 response at Week 24.
2. Proportion of subjects who achieved PASI 90 response at Week 24.
3. Changes from Baseline in DLQI total score at Week 24.
4. Proportion of subjects who achieved PASI 100 response at Week 52.
5. Proportion of subjects who achieved PASI 90 response at Week 52.
6. Changes from Baseline in DLQI total score at Week 52.
7. Percent change from Baseline in Nail Psoriasis Severity Index (NAPSI) score at Week 52.
8. Proportion of subjects who achieved PASI 75 response at Week 12.
9. Proportion of subjects who achieved a PGA score of 0 or 1 at Week 12.
10. Percent change from Baseline in NAPSI score at Week 24.

Non-ranked secondary efficacy variables were:

- Proportion of subjects achieving a DLQI Total score = 0 by visit.
- Change from Baseline in EQ-5D scores by visit.
- Change from Baseline in VAS for Ps pain by visit.
- Change from Baseline in VAS for PsA pain by visit.
- Change from Baseline in Ps related pruritus by visit.
- Proportion of subjects achieving a clinical response defined as ≥ PASI 50 by visit.
- Proportion of subjects achieving a clinical response defined as ≥ PASI 75 by visit.
- Proportion of subjects achieving a clinical response defined as ≥ PASI 90 by visit.
- Proportion of subjects achieving a clinical response defined as ≥ PASI 100 by visit.
- Proportion of subjects achieving a PGA of "clear" or "minimal" by visit.
- Proportion of subjects with improvement in PGA by visit.
- Proportion of subjects with improvement in Patient's Global Assessment (PTGA) of Ps severity by visit.
- Proportion of subjects achieving a PTGA of "0" or "1" by visit.
- Percent change from Baseline in PASI score by visit.
- The median time to achieve PASI 50/75/90/100 response by Week 52.
- The median time to achieve PGA "clear" or "minimal" status by Week 52.
- Percent change from Baseline in NAPSI score by visit.
- Proportion of subjects with improvement in Nail Physician Global Assessment (NPGA) by visit.

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

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

Statistical Methods

Efficacy: The primary efficacy analysis consisted of 4 comparisons performed in the ITT population; the analysis was carried out in the hierarchical order specified in the primary efficacy variable section above to address the issue of multiplicity. A *P* value ≤ 0.05 for comparison 1 was necessary to proceed to comparison 2, a *P* value ≤ 0.05 for comparison 1 and 2 was necessary to proceed to comparison 3, and a *P* value ≤ 0.05 for comparison 1, 2, and 3 was necessary to proceed to comparison 4. Because a step-down procedure was used, each comparison was tested at a significance level of 0.05 and an overall alpha level of 0.05 was preserved. For each primary efficacy variable, the superiority of ABT-874 over MTX was established by the Cochran Mantel-Haenszel (CMH) test adjusted for center (two-sided) at an alpha level of 0.05.

The primary method for dealing with missing values was non-responder imputation for categorical endpoints and last observation carried forward (LOCF) for continuous endpoints.

In analyzing categorical variables, the Chi-Square test or Fisher's exact test, as appropriate, were used to evaluate the superiority of ABT-874 versus MTX. Wilcoxon two-sample tests were used to compare the treatment difference in the percent change.

Mean change in laboratory variables and vital signs from Baseline were summarized for all subjects and compared between ABT-874 and MTX using a one-way ANOVA. The last evaluation prior to the first dose of study drug was used as Baseline in all analyses. For selected laboratory parameters, a listing of all subjects with any laboratory value that was above grade 2 of Common Toxicity Criteria (CTC) was provided. Shift tables for changes from Baseline according to the normal range were also provided for laboratory variables.

Pharmacokinetic: Serum ABT-874 concentrations were summarized by treatment group at each time point using descriptive statistics and used for the population PK analyses, results of which are presented in a separate report ([redacted]).

Safety: Safety data were summarized for subjects in the MTX/oral folate and ABT-874 populations according to the treatment a subject actually received. The safety analyses included all subjects who received at least 1 dose of study drug.

Pre-treatment SAEs (SAEs occurred before the first dose of study drugs) were summarized separately by randomized treatment group. A treatment emergent AE was defined as an event with onset or worsening after the first study dose of drug and, for subjects who did not enter M10-016, within 45 days after the last dose of study drug.

Statistical Methods

Safety: (Continued)

The number and percent of subjects experiencing treatment emergent AEs (TEAEs) were tabulated by Medical Dictionary for Regulatory Activities (MedDRA®) system organ class and MedDRA preferred term. In addition, a summary of TEAEs by severity and relationship to study drug was presented. Treatment-emergent AEs that were judged by the investigator to be probably or possibly related to study drug were summarized. A summary of SAEs, deaths, and TEAEs leading to discontinuation was also provided.

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

Summary/Conclusions

Efficacy Results: Demographic and Baseline Characteristics: Statistically significant differences between groups were observed at Baseline for PGA (9.1% of subjects in the ABT-874 treatment group had very severe disease compared to 2.5% of subjects in the MTX treatment group) and for VAS for EQ-5D (subjects in the ABT-874 treatment group had mean value of 60.0 compared to the mean = 65.4 for subjects in the MTX treatment group). No other 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 and male, with a mean age of 44.0 years and mean weight of 83.5 kg across the treatment groups. Overall mean PASI was 18.1, with mean PASI for the treatment groups of 17.8 (MTX) and 18.4 (ABT-874).

The study population consisted of subjects with moderate to severe plaque Ps disease activity at Baseline 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 26.1%), and PASI at least 12 (mean Baseline PASI score of 18.1). A majority (289/317; 91.2%) of subjects notably received previous topical treatment for Ps prior to study entry.

Efficacy Results: Treatment with ABT-874 was superior to MTX plus folic acid as demonstrated by the Week 24 and Week 52 primary endpoints, PGA (0/1) and PASI 75 response.

	Treatment Group	
Response Criteria at Week 24	**MTX N = 163**	**ABT-874 N = 154**
PASI 75 Responder, n (%)	65 (39.9)	126 (81.8)[a]
PGA 0/1 Responder, n (%)	56 (34.4)	124 (80.5)[a]
Response Criteria at Week 52		
PASI 75 Responder, n (%)	39 (23.9)	102 (66.2)[a]
PGA 0/1 Responder, n (%)	33 (20.2)	97 (63.0)[a]

a. $P < 0.001$ versus MTX group.

Summary/Conclusions (Continued)

Statistically significant results were achieved in all ranked secondary endpoints ($P < 0.001$ for all ranked secondary variables), indicating that the ABT-874 treatment group was superior to MTX plus folic acid.

- A statistically significantly greater proportion of subjects in the ABT-874 treatment group achieved a PASI 100 response at Week 24 (No. 1) and at Week 52 (No. 4) (42.2% and 45.5%, respectively) compared to the MTX treatment group (8.6% and 9.2% at Weeks 24 and 52, respectively).
- A statistically significantly greater proportion of subjects in the ABT-874 treatment group achieved a PASI 90 response at Week 24 (No. 2) and at Week 52 (No. 5) (63.6%and 59.7%, respectively) compared to the MTX treatment group (22.7% and 17.8% at Weeks 24 and 52, respectively).
- Subjects in the ABT-874 treatment group had statistically significantly greater decreases (improvement) from Baseline in DLQI Total scores at Week 24 (No. 3) and at Week 52 (No. 6) (means = –9.53 and –9.62, respectively) compared to the MTX treatment group (means = –6.53 and –6.54, respectively, at Weeks 24 and 52).
- Statistically significantly greater proportions of subjects in the ABT-874 treatment group had DLQI = 0 at Weeks 12, 24, 36, and 52 compared to the subjects in the MTX treatment group.
- Subjects in the ABT-874 treatment group had statistically significantly larger percent changes from Baseline, in the direction of improvement, in NAPSI score at Week 52 (No. 7) and at Week 24 (No. 10) (mean percent changes = –77.9 and –58.1, respectively) compared to the MTX treatment group (mean percent changes = –39.3 and –36.8 at Weeks 52 and 24, respectively).
- A statistically significantly greater proportion of subjects in the ABT-874 treatment group (76.6%) achieved a PASI 75 response at Week 12 (No. 8) compared to the MTX treatment group (36.2%).
- A statistically significantly greater proportion of subjects in the ABT-874 treatment group (68.2%) achieved a PGA of clear or minimal (0/1) at Week 12 (No. 9) compared to the MTX treatment group (22.1%).

Analysis of the non-ranked secondary endpoints also indicated that the ABT-874 treatment group was superior to the MTX treatment group.

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

Safety Results:

- Similar proportions of subjects in the 2 treatment groups had at least 1 TEAE, TEAEs that were at least possibly related to study drug, severe TEAEs, serious AEs, TEAEs that led to discontinuation of study drug, and SAEs that were at least possibly drug-related.
- Fourteen subjects (9.1%) in the ABT-874 treatment group and 10 subjects (6.1%) in the MTX reported treatment-emergent SAES; 4 subjects in the ABT-874 treatment group and 3 subjects in the MTX treatment group had SAEs that were considered at least possibly related to study drug.
- One subject in the MTX treatment group died during the study due to esophageal rupture.
- Nasopharyngitis was the most frequently reported TEAE (28.6% and 27.6% of subjects in the ABT-874 and MTX treatment groups, respectively), followed by headache (11.7% and 13.5% of subjects in the ABT-874 and MTX treatment groups, respectively).
- Twelve subjects (7.8%) in the ABT-874 treatment group and 10 subjects (6.1%) in the MTX treatment group had TEAEs that led to discontinuation of study drug.
- Nasopharyngitis, upper respiratory tract infection, and gastroenteritis were the most frequently reported infectious AEs. Four (2.6%) and 3 subjects (1.8%) in the ABT-874 and MTX treatment groups, respectively, had serious infections.
- Fifteen subjects (9.7%) in the ABT-874 treatment group had diarrhoea versus 6 subjects (3.7%) in the MTX treatment group ($P < 0.05$).
- Thirteen subjects (8.4%) in the ABT-874 treatment group had injection site related TEAEs compared to 3 subjects (1.8%) in the MTX treatment group ($P < 0.05$).
- Three subjects (1.9%) in the ABT 874 treatment group experienced a malignancy.
- No subjects experienced TEAEs in the special interest categories of TB, lymphoma, skin malignancy, premalignant skin disorder, nonmelanoma skin cancer (NMSC), melanoma, melanoma in-situ, CNS haemorrhages and cerebrovascular accidents, or ventricular tachyarrhythmia.
- Ten subjects (6 in the ABT-874 treatment group and 4 in the MTX treatment group) experienced ischaemic heart disease TEAEs.
- Fifty-six subjects (36.4%) in the ABT-874 treatment group and 68 subjects (41.7%) in the MTX treatment group had allergic reaction related TEAEs.
- Ten subjects (6.5%) in the ABT-874 treatment group and 16 subjects (9.8%) in the MTX treatment group had hepatic reaction related TEAEs.
- Six subjects (3.9%) in the ABT 874 treatment group and 9 subjects (5.5%) in the MTX treatment group had depression related TEAEs.

Safety Results: (Continued)

- Treatment group differences between ABT-874 and MTX for mean changes from Baseline were statistically significant at some time points for hematology parameters: hemoglobin, hematocrit, platelet counts, RBC counts, platelet counts, lymphocytes, eosinophils, and basophils. Differences in each instance were small and were considered not clinically significant.
- Nine subjects in the MTX treatment group had downward shifts in hematocrit, compared to 1 subject in the ABT-874 treatment group. Eighteen subjects in the MTX treatment group had downward shifts in RBC count, compared to 4 subjects in the ABT-874 treatment group. The treatment groups had similar numbers of shifts for other hematology parameters.
- Four subjects, 2 in each treatment group, had hematology results with CTC grade ≥ 3 during the study; all results were low lymphocyte values.
- Treatment group differences between ABT-874 and MTX for mean changes from Baseline were statistically significant at some time points for clinical chemistry parameters: ALT, AST, total bilirubin, BUN, potassium, chloride, triglyceride, carbon dioxide, and magnesium. Differences in each instance were small.
- Seven subjects in the ABT 874 treatment group shifted from low or normal to high for ALT versus 21 subjects in the MTX treatment group, 9 subjects in the ABT-874 treatment group shifted from low or normal to high for LDL cholesterol versus 20 subjects in the MTX treatment group, and 18 subjects in the ABT-874 treatment group shifted from low or normal to high for triglycerides versus 6 subjects in the MTX treatment group. The treatment groups had generally similar numbers of shifts for other chemistry parameters.
- Twenty subjects in the ABT-874 treatment group and 12 subjects in the MTX treatment group had clinical chemistry results with CTC grade ≥ 3 during the study. Four subjects had clinical chemistry results with CTC Grades of 4: 3 subjects in the ABT-874 (2 subjects experienced elevated creatine phosphokinase and 1 subject had hypoglycemia) and 1 subject in the MTX treatment group (elevated creatine phosphokinase). Twenty-six subjects (12 and 14 in the ABT-874 and MTX treatment groups, respectively) had abnormal post-Baseline liver function test results that were potentially clinically significant.
- The ABT-874 treatment group had statistically significantly great mean decreases from Baseline in urine pH at Weeks 24 and 36; the MTX treatment group had a mean decrease at Week 24 and a mean increase at Week 36. The MTX treatment group had a statistically significantly greater decrease from Baseline in urine specific gravity compared to the ABT-874 treatment group at Week 52. Similar numbers of subjects in the treatment groups shifted from low or normal at Baseline to high urine specific gravity values at the Final evaluation.
- No subjects changed from negative at Baseline to positive at final evaluation for ANA or anti-dsDNA.
- At Week 2; subjects in the MTX treatment group had a mean increase of 2.6 beats/min versus a mean decrease of 0.2 beats/min in the ABT 874 treatment group ($P < 0.05$). At Weeks 2, 8, and 10, subjects in the ABT-874 had statistically significantly greater mean increases in weight compared to subjects in the MTX treatment group. No other statistically significant differences between treatment groups were observed for any vital signs at any time point.

Conclusions: In this 52-week study, ABT-874 was superior to MTX in the treatment of subjects with moderate to severe chronic plaque Ps. The results of this study demonstrated the efficacy benefits of ABT-874 to reduce the signs and symptoms of plaque psoriasis, improve nail psoriasis, and favorably influence patient-reported measures such as DLQI, VAS for plaque Ps pain, VAS for Ps arthritis pain, and assessment of psoriasis-related pruritus. Treatment with ABT-874 produced a rapid clinical response that was maintained through 52 weeks when compared to MTX. No clinically important safety concerns were identified in the study.

The safety profile for ABT-874 was similar to that observed in the MTX treatment group in this study. The proportions of subjects with SAEs and the proportions of subjects discontinuing due to AEs were similar in the 2 treatment groups.

Based on the clinically significant improvements in psoriasis analyzed by multiple parameters and a safety profile without clinically significant findings compared to MTX, it is concluded that the results of this study support a favorable benefit-risk ratio for ABT-874 with respect to MTX as a therapeutic option for the treatment of moderate to severe psoriasis.