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:
Adalimumab</td><td>Volume:</td><td rowspan="3"></td></tr>
<tr><td>Name of Active Ingredient:
Adalimumab</td><td>Page:</td></tr>
<tr><td colspan="3">Title of Study:
A Multi-center, Randomized, Vehicle-controlled study to Assess the Efficacy and Safety of Adalimumab in Combination with Topical Treatment (Calcipotriol/Betamethasone) in Subjects with Moderate to Severe Psoriasis and Insufficient Response to Classic Systemic Treatment (BELIEVE)</td></tr>
<tr><td colspan="3">Rationale for Abbreviated Clinical Study Report:
Study M10-060 was conducted to evaluate the use of adalimumab in the approved indication of plaque psoriasis in combination with an established and widely used topical therapy in a broader setting that mimics day-to-day clinical practice to obtain further efficacy and safety data.
Study M10-060 was not conducted for use in supporting a claim in labeling.</td></tr>
<tr><td colspan="3">Investigator:
Coordinating Investigator: Dr. Diamant Thaci, Frankfurt/Main, Germany</td></tr>
<tr><td colspan="3">Study Sites:
132 sites in 15 European countries (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, Switzerland, Turkey, UK) Note: Norway was planned but no subjects were enrolled.</td></tr>
<tr><td colspan="3">Publications:
None.</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 22 Nov 2007
Last Subject Last Visit: 29 Oct 2008</td><td>Phase of Development: 3b</td></tr>
<tr><td colspan="3">Objective:
The objective of this study was to assess the efficacy and safety of adalimumab in combination with topical psoriasis treatment, calcipotriol/betamethasone (C/B), versus adalimumab in combination with matching vehicle in adult subjects with moderate to severe chronic plaque psoriasis.</td></tr>
</table>

Methodology: Multicenter, double-blind

The study was designed to reflect daily clinical practice, using inclusion criteria consistent with national and reimbursement guidelines. Qualified subjects were randomized in a 1:1 ratio to receive adalimumab + topical active treatment (adalimumab + calcipotriol/betamethasone [C/B]) or adalimumab + topical vehicle (vehicle ointment). Adalimumab was administered via SC injection: an initial dose of 80 mg (2 injections) at Baseline followed by 40 mg (1 injection) every other week (eow) from Week 1 through Week 15. Topical ointment (C/B or matching vehicle) was applied once daily onto affected Ps skin portions of the trunk and extremities for the first 4 weeks and as needed thereafter (Weeks 5 through 16), with a maximum weekly dose of 100 g. Topical ointment was not to be used on the face, scalp, mouth, or eyes.

Efficacy was collected at Weeks 2, 4, 8, 12, and 16. Safety was collected throughout the 16 weeks of treatment and up to 70 days after the last adalimumab injection (via a follow-up phone call) for any subject who discontinued study treatment at Week 16 or before and did not continue on commercial Humira®.

Number of Subjects (Planned and Analyzed):

Planned: 658; Enrolled: 730

Randomized: 730 (364 randomized to adalimumab + vehicle; 366 randomized to adalimumab + C/B)

Analyzed (for both efficacy and safety): 730

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria were consistent with national and reimbursement guidelines. The main inclusion criteria were as follows:

Male and female subjects were included who were 18 years or older, with chronic plaque psoriasis (Ps) for at least 6 months duration who had been treated and failed to respond to, had a contraindication to, or were intolerant to at least 2 different prior systemic therapies, 1 of which had to be cyclosporine, methotrexate, or ultraviolet A with psoralen (PUVA). Subjects had to meet 2 of the following criteria: Psoriasis Area and Severity Index (PASI) ≥ 10; affected body surface area (BSA) ≥ 10%; Dermatology Life Quality Index (DLQI) ≥ 10. Subjects with concomitant Ps subjects Ps palmaris and plantaris were permitted to enter the study; subjects with prior tumor necrosis factor (TNF)-antagonist or other biologic therapy experience were permitted to enter the study if washout criteria were met.

Subjects were excluded who had previous exposure to: adalimumab, systemic corticosteroid for 4 weeks or topical corticosteroids for 2 weeks prior to Baseline; topical treatment with calcipotriol or C/B within 2 weeks prior to Baseline; had known overexposure to PUVA or ultraviolet B (UVB); a previous biologic agent (e.g., etanercept, infliximab, certolizumab) within the specified washout periods prior to Baseline. Subjects were also excluded who had other active skin diseases, skin infections, or skin manifestations that might interfere with the evaluation of Ps or who had a calcium metabolism disorder.

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

Test Product #1:

Adalimumab; sterile, preservative-free solution containing 40 mg/0.8 mL; SC injection using pre-filled pen (PEN)/ prefilled syringe (PFS); manufactured by Abbott Laboratories

Lot number	Description	Countries
07-013725	[redacted]	[redacted]
08-015743	[redacted]	[redacted]
08-016856	[redacted]	[redacted]
07-014053	[redacted]	[redacted]

[redacted]

Test Product #2:

Calcipotriol/betamethasone (Daivobet®) ointment in 100 g tubes; topical administration per Summary of Product Characteristics (SmPC); [redacted]

Lot number	Description	Countries[a]
07-013720	Ointment	[redacted]
07-013944	Ointment	[redacted]

[redacted]

Redacted information - 08Jun2012

Duration of Treatment:

16 weeks

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

Vehicle ointment

Criteria for Evaluation

Primary Endpoint: PASI75 response rates at Week 16 (PASI75 defined as at least a 75% reduction in Baseline [Week 0] PASI score).

Key Secondary Parameters: PASI 50/75/90/100 responses; time to PASI 50/75/90/100 responses; Physician's Global Assessment (PGA) of clear or clear/minimal; DLQI; NAPSI and PSSI (at Weeks 8 and 16); and HAQ in subjects with concomitant psoriatic arthritis (PsA).

Safety: Adverse events (AEs), clinical laboratory test values (hematology, chemistry, and urinalysis), physical examinations, and vital signs.

Statistical Methods

Efficacy: The primary and secondary efficacy variables were described by statistical characteristics which were presented by treatment group and overall.

The primary null hypothesis was that there was no difference in the proportion of subjects who achieve ≥ PASI75 response at Week 16 between the adalimumab + C/B group and the adalimumab + vehicle group. The primary confirmatory efficacy analysis (comparison of the proportion of subjects in each treatment group with a ≥ PASI75 response at Week 16) was performed using a two-sided Cochran-Mantel Haenszel test stratified by (pooled) country at the alpha level of 0.05, with subjects missing PASI assessments at Week 16 imputed as non-responders.

For secondary efficacy variables, categorical data and quantitative data were described using non-responder imputation and last observation carried forward (LOCF), respectively, as the primary approach for dealing with missing values.

Safety: Safety data was analyzed for subjects as they were treated, without any imputation strategies utilized. All safety variables were described using statistical characteristics and were presented by treatment group and overall.

The number/percentage of subjects who reported treatment-emergent AEs (TEAEs) were summarized using MedDRA system organ class and preferred term and included all TEAEs, TEAEs by maximum relationship to study drug (adalimumab and/or C/B), TEAEs by maximum severity, serious TEAEs, and TEAEs that led to discontinuation of adalimumab and/or C/B or led to death. AEs of special interest, those that are typically observed with TNF-antagonists were also summarized, including (serious) infectious AEs, opportunistic infections, tuberculosis [TB], malignancies, lupus and lupus-like reactions, demyelinating disease, congestive heart failure (CHF), and hematological events and hepatic events that led to discontinuation of adalimumab. All TEAEs, plus pretreatment serious AEs and AEs that started > 70 days after discontinuation of study drug or after the initiation of commercial Humira®, were listed.

Laboratory parameter values and vital signs assessed over time (minimum, maximum, and final values) and changes from Baseline to minimum, maximum, and Final Visit (Week 16/ET) were summarized. The quantitative laboratory parameter values were analyzed using shift tables, with liver function tests (ALT. AST, total bilirubin) analyzed separately using Baseline and maximum value after treatment. Select laboratory parameters were assessed for potentially clinically significant findings, using the Common Toxicity Criteria (CTC) Grades 3 and 4. All laboratory and vital sign values were listed.

Categorical urinalysis results were analyzed using frequency and percentage.

Summary/Conclusions

Efficacy Results (brief summary for this abbreviated clinical study report):

PASI75 at Week 16 did not demonstrate the superiority of adalimumab + C/B combination therapy versus adalimumab + vehicle monotherapy (64.8% versus 70.9%, respectively; $P = 0.086$). PASI75 response rates over the course of treatment showed that initial efficacy was superior in the adalimumab + C/B group at Weeks 2 and 4 (Week 2: 14.8% versus 5.8%; $P < 0.001$; Week 4: 40.7% versus 32.4%; $P = 0.021$), but this greater response rate was not sustained from Week 8 onward, where numerically greater percentages of responders were observed in the adalimumab + vehicle group (Week 8: 53.3% versus 59.9%, $P = 0.074$; Week 12: 57.9% versus 73.4%, $P < 0.001$). PASI50/90/100 response rates over time demonstrated the same general trends in efficacy as PASI75, with the greater response rates observed from Weeks 8 through 16 for the adalimumab + vehicle group (e.g., PASI90 at Week 16: 38.8% versus 50.3%; $P = 0.002$).

Other secondary endpoints demonstrated numerical advantage favoring adalimumab + vehicle at Week 16, including (presented as adalimumab + C/B versus adalimumab + vehicle):

- PGA of clear or minimal, response rates: 56.6% versus, 64.6%; $P = 0.028$
- PGA of clear, response rates: 18.0% versus 29.9%; $P < 0.001$
- DLQI, mean percent change from baseline: 67.2% versus 71.46%; $P = 0.228$

PSSI and NAPSI, for scalp psoriasis and nail psoriasis respectively, both demonstrated clinically relevant improvement with overall adalimumab therapy. At Week 16, a 100% improvement in PSSI values and a 39.5% improvement in NAPSI values were observed for more than half of the subjects. As topical C/B therapy was applied neither to scalp nor to nails, the results confirmed the expected finding that there was no difference in these indices between adalimumab + C/B and adalimumab + vehicle groups. HAQ scores in subjects with PsA also decreased over time with overall adalimumab treatment (74.2% improvement at Week 16).

Safety Results:

In general, AE incidences were similar between the adalimumab + C/B and adalimumab + vehicle groups. With overall adalimumab therapy, 61.8% of subjects reported treatment-emergent (TE) AEs, with the most frequently reported (≥ 2% of subjects in either treatment group) TEAEs being nasopharyngitis, headache, (worsening of) psoriasis, and pruritus. TEAEs were predominantly mild to moderate in severity and were assessed by the investigator as either not related or probably not related to adalimumab or to C/B. Nasopharyngitis, pruritus, and headache were most frequently assessed as possibly or probably related to adalimumab, and were reported by similar proportions of subjects in both treatment groups.

No deaths were reported during the study, and there was no clinically relevant difference between treatment groups in the incidence of subjects who reported SAEs, AEs leading to discontinuation of adalimumab, and other AEs (i.e., the AEs of special interest).

With overall adalimumab therapy, 31 subjects (4.2%) had TE SAEs, most of which were moderate or severe in intensity and were assessed by the investigator as not related or probably not related to adalimumab. The only SAEs considered probably related to adalimumab were a case of onycholysis of fingernails and toenails, an acute generalized exanthematous pustulosis, and a case of erysipelas; the first SAE led to discontinuation of both adalimumab and C/B while the latter 2 SAEs resolved within 2 weeks.

A total of 34 subjects (4.7%) discontinued adalimumab and/or C/B treatment due to TEAEs, which were serious for 11 of these subjects. Twenty-seven subjects who discontinued one or both study drugs due to AEs also permanently discontinued from the study.

No demyelinating diseases, TB, lupus and lupus-like reactions, CHF, or hematologic events were reported during the study. Small numbers of subjects in each treatment group reported serious infections, opportunistic infections, and hepatic events (note that only hepatic and hematologic events that were serious or led to discontinuation of adalimumab were analyzed). There were 4 malignancies, 3 of which were serious and considered by the investigator to be probably not related to adalimumab: 1 case of lymphoma that occurred after 7 weeks of adalimumab treatment; one non-melanoma skin cancer (a spinocellular carcinoma) that occurred after 2 weeks of adalimumab treatment in a subject who had received prior PUVA (for 3 years), UVB, cyclosporine, and MTX; and a malignant melanoma that occurred after 2 months of adalimumab treatment in a subject who had received > 11 years MTX therapy prior. An additional malignancy, that was not serious, was a lentigo maligna, stage unspecified, that occurred after 4 weeks of adalimumab treatment and was considered possibly related to adalimumab. Each case of malignancy led to discontinuation of study drugs (adalimumab and/or C/B) and to permanent discontinuation of the subject from the study.

Signs/symptoms of TB were reported in 1 subject who completed the study and had been receiving treatment with commercial Humira® for more than a month.

Two subjects became pregnant during the study. One of the subjects underwent an elective abortion subsequent to a cytomegalovirus infection, and the other subject delivered a healthy female, without birth defects, on 19 Feb 2009.

Changes from Baseline in clinical chemistry and hematologic parameters were few, small, and not clinically relevant.

Conclusions:

In this 16-week, multicenter double-blind study, adalimumab was generally safe and well tolerated in subjects with moderate to severe plaque psoriasis who received treatment with adalimumab with or without concomitant C/B as evaluated by the incidence and pattern of serious and non-serious TEAEs, AEs leading to discontinuation of adalimumab, TNF-inhibitor related AEs of special interest, laboratory results, and vital signs. Adalimumab alone or in combination with topical C/B demonstrated substantial efficacy in the PASI50/75/90/100 responses, PGA, and DLQI over 16 weeks. Adalimumab + C/B combination therapy generally demonstrated an early benefit in the study, but produced less favorable results compared with the adalimumab monotherapy treatment at later time points. Scalp psoriasis and nail psoriasis both demonstrated clinically relevant improvement with overall adalimumab therapy at Week 16 (a 100% improvement for scalp and a 39.5% improvement for nails were observed for more than half of the subjects).

Date of Report: 09Jun2009