



## 2.0 Synopsis

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| <b>Abbott Laboratories</b>  | <b>Individual Study Table Referring to Part of Dossier:</b><br><br><b>Volume:</b><br><br><b>Page:</b> | <b>(For National Authority Use Only)</b> |
| <b>Name of Study Drug:</b><br>Adalimumab  |   |  |
| <b>Name of Active Ingredient:</b><br>Adalimumab   |   |  |
| <b>Title of Study:</b><br>Open-label Study of Adalimumab in Subjects Who Have a Sub-optimal Response to Systemic Therapy or Phototherapy  |   |  |
| <b>Coordinating Investigator:</b><br>[REDACTED] MD, PhD redacted information 19Nov2014  |   |  |
| <b>Study Sites:</b><br>This study was conducted at 24 sites in the US and Canada.   |   |  |
| <b>Publications:</b><br>1 abstract  |   |  |
| <b>Studied Period (Years):</b><br>First Subject First Visit: 14 January 2008<br>Last Subject Last Visit: 14 April 2009  | <b>Phase of Development:</b> 3b   |  |
| <b>Objectives:</b><br>The objective of this study was to determine the efficacy and safety profile of switching to adalimumab after experiencing a sub-optimal response to prior systemic therapy of etanercept, methotrexate (MTX) or narrow band ultraviolet – B (NB-UVB) phototherapy. |   |  |



### **Methodology:**

This 16-week multicenter, open-label study consisting of 3 substudies was designed to evaluate the efficacy and safety of adalimumab 40 mg every other week (eow) in the treatment of psoriasis (Ps) in subjects with a suboptimal response to etanercept, MTX, or NB-UVB phototherapy. One hundred-fifty subjects were planned to be enrolled into three sub-studies as follows: Substudy E - approximately 80 subjects with sub-optimal response to etanercept, Substudy M - 40 subjects with sub-optimal response to MTX, and Sub-study P - 30 subjects with sub-optimal response to NB-UVB phototherapy.

Subjects were to have a diagnosis of chronic plaque Ps with disease duration of  $\geq 6$  months, and Physician Global Assessment (PGA) of mild or worse (for subjects with sub-optimal response to prior etanercept or MTX therapy), or moderate or worse (for subjects with sub-optimal response to prior NB-UVB phototherapy). Sub-optimal response to treatment with etanercept, MTX, or NB-UVB phototherapy was defined as follows:

#### **Etanercept**

- Treatment was to be administered for at least 6 consecutive months prior to Screening, with no treatment interruptions except for toxicity or intolerability, at doses of 50 mg biw (biweekly), 50 mg qw (every week), or 25 mg biw. If there was a treatment interruption due to toxicity or intolerability, the length of treatment interruption was not to have exceeded 14 days. If there was  $> 1$  treatment interruption due to toxicity or intolerability (regardless of the length of the treatment interruptions), the subject was not to be considered eligible.
  - The last dose of etanercept was to be  $\geq 11$  days and  $\leq 17$  days before the first dose of adalimumab.
- OR
- Treatment was to be administered for  $\geq 3$  consecutive months prior to Screening, with no treatment interruptions except for toxicity or intolerability, at doses of 50 mg biw, 50 mg qw, or 25 mg biw, and the subject had a deterioration of efficacy observed during the 3 month etanercept treatment period as determined and documented by the treating physician. If there was a treatment interruption due to toxicity or intolerability, the length of treatment interruption was not to have exceeded 14 days. If there was  $> 1$  treatment interruption due to toxicity or intolerability (regardless of the length of the treatment interruptions), the subject was not to be considered eligible.
  - The last dose of etanercept must have been  $\geq 11$  days and  $\leq 17$  days before the first dose of adalimumab.

#### **MTX**

- Treatment was to be administered for at least 4 consecutive months prior to Screening, with no treatment interruptions except for toxicity or intolerability. If there was a treatment interruption due to toxicity or intolerability, the length of treatment interruption was not to have exceeded 14 days. If there was  $> 1$  treatment interruption due to toxicity or intolerability (regardless of the length of the treatment interruptions), the subject was not to be considered eligible.
- The last dose of MTX was to be  $\geq 4$  days and  $\leq 10$  days before the first dose of adalimumab.



**Methodology (Continued):**

**NB-UVB Phototherapy**

- Therapy was to be administered for at least 2 consecutive months prior to Screening, with no treatment interruptions except for toxicity or intolerability. If there was a treatment interruption due to toxicity or intolerability, the length of treatment interruption was not to have exceeded 14 days. If there was > 1 treatment interruption due to toxicity or intolerability (regardless of the length of the treatment interruptions), the subject was not to be considered eligible.
- The last treatment with NB UV-B was to be  $\geq 4$  days and  $\leq 10$  days before the first dose of adalimumab.

The study consisted of a screening period, a 16 week treatment period, and a follow-up assessment 70 days after the last dose of study drug. Subjects were to have a follow-up phone call 70 days after the last administration of study drug to obtain information on any new or ongoing adverse events (AEs)/serious adverse events (SAEs). The 70-day follow-up phone call was not required for any subject that continued on adalimumab therapy (switch to commercial adalimumab) after the end of study participation. For subjects who switched to commercial adalimumab, new AEs were to be captured through the standard Abbott post marketing mechanism of reporting.

At Baseline (Week 0), subjects were to receive an initial subcutaneous (SC) dose of 80 mg adalimumab (loading dose). Injections of adalimumab 40 mg adalimumab SC were to be given eow starting at Week 1 through Week 15. Study visits occurred at Baseline, Week 2, Week 4, Week 8, and Week 16 or Early Termination. PGA, Psoriasis Area and Severity Index (PASI), Patient's Global Assessment of Ps Severity, Visual Analogue Scale (VAS) for Plaque Ps and Psoriatic Arthritis Pain (PsA), and Ps-related Pruritus Assessment were assessed at each visit. Patient-reported outcomes included Dermatology Life Quality Index (DLQI), Medical Outcomes Study (MOS) Sleep Scale, and Work Productivity and Activity Impairment Questionnaire: Specific Health Problems (WPAI: SHP) and were assessed at Week 16 or Early Termination. Additionally, DLQI was assessed at Week 4.

**Number of Subjects (Planned and Analyzed):**

Planned: 150; Analyzed: 152

**Diagnosis and Main Criteria for Inclusion:**

See above.

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

Adalimumab 40 mg eow, SC injection

Lot number: [REDACTED] redacted information 19Nov2014

**Duration of Treatment:**

16 weeks

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

None; this was an open-label study.



### **Criteria for Evaluation**

#### **Efficacy:**

The primary efficacy variable was the proportion of subjects who achieved a PGA of clear or minimal at Week 16.

Secondary efficacy variables included:

- Proportion of subjects who achieved a PGA of clear or minimal at each visit
- Proportion of subjects who achieved a PGA of clear at each visit
- Proportion of subjects who achieved at least one grade of improvement in PGA relative to Screening Visit, at each visit
- Change from Screening Visit in DLQI at Week 4 and Week 16
- Proportion of subjects achieving a DLQI score of 0 at Week 4 and Week 16
- Proportion of subjects achieving a DLQI score of 0 or 1 at Week 4 and Week 16
- Time to achieving PGA of clear or minimal
- Percent change from Screening Visit in PASI at each visit
- Change from Screening Visit in PASI at each visit
- Proportion of subjects who achieved 'good or complete disease control' in the Patient's Global Assessment at each visit
- Change from Screening Visit in Ps-related Pruritus Assessment at each visit
- Change from Screening Visit in VAS for Ps/PsA Pain at each visit
- Change from Screening Visit in MOS Sleep Scale at Week 16
- Change from Screening Visit in WPAI-SHP at Week 16

Tertiary endpoints included:

- Proportion of subjects who achieved at least 50%, 75%, 90%, and 100% improvement in PASI from Screening Visit
- Change from Screening Visit in body surface area (BSA) affected by Ps

#### **Safety:**

Safety was assessed from AE monitoring and results from laboratory tests and vital signs testing.



## Statistical Methods

### Efficacy:

Efficacy summaries were provided overall, for each substudy, and for each dosing subgroup in Substudy E. Frequencies, percentages, and 95% confidence intervals (CIs) of the percentages were provided for discrete variables. Mean, standard deviation (SD), median, minimum, maximum, and 95% CIs of the mean were provided for continuous variables. The number of subjects achieving the outcomes of interest and 25<sup>th</sup>/50<sup>th</sup>/75<sup>th</sup> percentiles in time to event and the associated 95% CIs were provided from survival analysis. The time origin for time to event variables was the first date of the first dose.

Tests for homogeneity across the substudies were performed by Fisher's Exact test for categorical variables, by one-way ANOVA for continuous variables, and by Log-rank test for time-to-event variables. If the heterogeneity was not detected (at alpha level of 0.2), the overall summaries and the 95% CIs were reported in addition to the results of the substudies.

Missing data were imputed using the following:

Non-responder imputation (NRI) - The NRI categorized any subject who had a missing value at a specific visit as a non-responder for that visit. The NRI is the primary approach in the analysis of categorical values.

Lost observation carried forward (LOCF) - The LOCF analyses used the completed evaluation from the previous visit for efficacy measures assessed to impute missing data at later visits. LOCF was the primary approach in the analysis of continuous variables and the secondary approach in the analysis of categorical values.

In the time to event variables, subjects who discontinued or completed the study prior to reaching the outcome of interest were censored in the analysis.

### Safety:

Safety analyses were carried out on the intent-to-treat population. The Baseline for all safety variables was the last measurement obtained prior to the subject receiving the first dose of study drug. Final assessment or evaluation is defined as the last assessment up to 70 days after the last dose of adalimumab for laboratory and vital signs variables. The Baseline value, minimum, maximum, and final value means were presented for subjects who had both the Baseline and post-Baseline visits. Frequencies, percentages, and 95% CIs for the percentages were provided. Mean, SD, median, minimum, maximum, and 95% CIs of the mean were provided.

The incidence and prevalence of treatment-emergent AEs (TEAEs) were summarized for each Medical Dictionary for Drug Regulatory Affairs (MedDRA v11.0) system organ class and preferred term. In addition to the evaluation of TEAEs, deaths, and SAEs, the following categories of TEAEs of special interest were specifically examined: AEs leading to premature discontinuation from the study, infections, serious infections, opportunistic infections, malignancies, injection site reactions, hepatic AEs, congestive heart failure (CHF), demyelinating disorders, allergic reactions, and lupus like syndrome. These events are of special interest because they have been identified as safety concerns for the anti-TNF agent class of drugs. Clinical laboratory data were summarized with mean change from Baseline to the minimum, maximum, and final values during adalimumab treatment, and with the proportion of subjects who changed to potentially clinically significant (PCS) values from Baseline values that were not PCS. Vital signs were analyzed similarly.



| <b>Summary/Conclusions</b>   |          |            |           |                |                           |
|--|----------|------------|-----------|----------------|---------------------------|
| <b>Efficacy Results:</b>   |          |            |           |                |                           |
| <p>The primary efficacy variable was the proportion of subjects who achieved a PGA of clear (0) or minimal (1) at Week 16. Subjects with missing PGA response were counted as not achieving PGA of clear or minimal. Primary efficacy results are consistent across all substudies and demonstrated substantial improvement for subjects upon switching to adalimumab, indicating that irrespective of which previous treatment subjects failed (etanercept, MTX, or NB-UVB phototherapy), subjects gained benefit from treatment with adalimumab.</p>   |          |            |           |                |                           |
| <b>Proportions of Subjects Achieving PGA of 0 or 1 at Week 16, n (%)</b>   |          |            |           |                |                           |
| <b>Group</b>   | <b>N</b> | <b>Yes</b> | <b>No</b> | <b>Missing</b> | <b>95% CI<sup>a</sup></b> |
| All subjects   | 152      | 79 (52.0)  | 59 (38.8) | 14 (9.2)       | 43.7, 60.1                |
| Substudy M <sup>b</sup>  | 41       | 25 (61.0)  | 14 (34.1) | 2 (4.9)        | 44.5, 75.8                |
| Substudy P <sup>c</sup>  | 29       | 14 (48.3)  | 10 (34.5) | 5 (17.2)       | 29.4, 67.5                |
| Substudy E <sup>d</sup>  | 82       | 40 (48.8)  | 35 (42.7) | 7 (8.5)        | 37.6, 60.1                |
| E5 <sup>e</sup>  | 38       | 18 (47.4)  | 17 (44.7) | 3 (7.9)        | 31.0, 64.2                |
| E6 <sup>f</sup>  | 44       | 22 (50.0)  | 18(40.9)  | 4 (9.1)        | 34.6, 65.4                |
| <p>Note: Subjects with missing PGA responses were counted as not achieving PGA of clear (0) or minimal (1).</p> <p>a. Exact 95% CI for the proportion of responders.</p> <p>b. Substudy M: Subjects with sub-optimal response to MTX.</p> <p>c. Substudy P: Subjects with sub-optimal response to NB-UVB phototherapy.</p> <p>d. Substudy E: Subjects with sub-optimal response to etanercept.</p> <p>e. E5: etanercept 50 mg per week at study entry.</p> <p>f. E6: etanercept 100 mg per week at study entry.</p>  |          |            |           |                |                           |
| <p>The results of the following secondary and tertiary endpoints are consistent with the primary endpoint results demonstrating that subjects gained benefit from treatment with adalimumab with 95% CIs for the continuous variables excluding 0, irrespective of previous treatment with MTX, etanercept, or NB-UVB phototherapy:</p> <ul style="list-style-type: none"> <li>• Change from Screening at Week 16 in VAS for Ps/PsA pain</li> <li>• Proportion of subjects who achieved at least 50% reduction from Screening in PASI at Week 16</li> <li>• Percent change from Screening at Week 16 in PASI score</li> <li>• Improvement from Screening to Week 16 in BSA affected by Ps</li> <li>• Proportion of subjects with DLQI of 0 at Week 16</li> </ul> |          |            |           |                |                           |



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**Efficacy Results (Continued):**

The results for the following secondary and tertiary endpoints all demonstrated a benefit of switching to Humira for each substudy, with 95% CIs for the continuous variables excluding 0; however, the magnitude of the benefit was not consistent across the substudies.

- Proportion of subjects achieving PGA of clear (0) at Week 16.
- Proportion of subjects achieving DLQI of 0 at Week 16.
- The proportion of subjects achieving good/complete disease control in the Patient Global Assessment for Ps at Week 16.
- Proportion of subjects achieving at least 75%/90%/100% reduction from Screening in PASI at Week 16.
- Change from Screening at Week 16 in PASI.
- Change from Screening at Week 16 in DLQI.
- Change from Screening at Week 16 in pruritus.

In addition, for MOS Sleep Scale, the mean change from Screening in the sleep problems index I and II, sleep adequacy, sleep disturbance scale, sleep quantity, somnolence, and snoring all trended beneficially; however, the 95% CIs included 0 either overall or in some substudies, therefore failed to show consistent significant benefit across all substudies. The overall mean change from Screening in shortness of breath is 0, which failed to show a trend in benefit of switching to Humira in this measurement.

No consistent benefit was observed across subscales of the four impairment percentages of WPAI for subjects who switched to adalimumab in their work productivity.

Further, the treatment strategy of discontinuing the prior, sub-optimal therapies abruptly and commencing adalimumab after a washout period of 11 – 17 days for etanercept or 4 – 10 days for MTX or NB-UVB phototherapy was associated with a low risk of disease flare during the transition.



**Safety Results:**

Adalimumab was generally safe and well-tolerated in subjects with a sub-optimal response to etanercept, MTX, or NB-UVB phototherapy.

No deaths occurred during the study and the number of subjects who reported serious TEAEs was few (5 subjects). No serious TEAEs were considered by the Investigator to be probably related to study drug.

TEAEs most frequently reported were few, mild to moderate in severity, and infrequently considered probably or possibly related to study treatment.

One subject prematurely discontinued from the study due to a TEAE [REDACTED]

[REDACTED] redacted information 19Nov2014

Infections were reported by 33 subjects (21.7%) and most were considered by the Investigator not probably related to study drug. The most frequently reported infectious event was upper respiratory tract infection. One subject experienced a serious infectious TEAE during this study (cellulitis). No opportunistic infections were reported. No cases of tuberculosis were reported.

No demyelinating disorders, malignancies, CHF, lupus-like syndromes, allergic reactions, or hematologic events were reported during this study.

No clinically meaningful changes in mean laboratory values were observed. Shifts to high or low were generally infrequent.

Changes in vital signs were clinically unremarkable.

In conclusion, no new safety findings were observed during this open-label study of adalimumab.

**Conclusions:**

Adalimumab was generally efficacious, safe, and well-tolerated in subjects with a sub-optimal response to etanercept, MTX, or NB-UVB phototherapy who switched to adalimumab. Further, the treatment strategy of discontinuing the prior, sub-optimal therapies abruptly and commencing adalimumab after a washout period of 11 – 17 days for etanercept or 4 – 10 days for MTX or NB-UVB phototherapy was associated with a low risk of disease flare during the transition.