2.0 Synopsis

<table>
<tr><td>Abbott Laboratories</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
HUMIRA</td></tr>
<tr><td>Name of Active Ingredient:
Adalimumab</td></tr>
<tr><td colspan="3">Title of Study:
Humira 40mg/0.8ml for Subcutaneous Injection-Drug Use Investigation (All Patient Investigation) for Rheumatoid Arthritis</td></tr>
<tr><td colspan="3">Investigator:
Not applicable</td></tr>
<tr><td colspan="3">Study Site(s):
1722 sites in Japan</td></tr>
<tr><td colspan="3">Publications:
No publications provided</td></tr>
<tr><td colspan="2">Studied Period (Years): 2 years
First Subject First Visit: 18Jun2008
Last Subject Last Visit: 30Jun2011</td><td>Phase of Development:
Post Marketing Surveillance</td></tr>
<tr><td colspan="3">Objective(s):
To clarify the following matters:
1) Unknown adverse reactions (especially clinically significant adverse reactions)
2) Incidence and conditions of occurrence of adverse reactions in the clinical setting
3) Factors that may affect the safety and effectiveness of Humira</td></tr>
<tr><td colspan="3">Methodology:
This survey was non-interventional, open-labeled, all-case, central registration method, post marketing observational study in which Humira was prescribed for Rheumatoid Arthritis in the routine medical practice</td></tr>
</table>

Number of Subjects (Planned and Analyzed):

Planned: As a result of discussion with Pharmaceuticals and Medical Devices Agency (PMDA), Abbott committed to report with a minimum of 3000 patients to complete the study at which time the results were submitted for PMDA review. The PMDA required that all additional RA patients who started to receive Humira during this review period be also enrolled in the study. The study ended when the PMDA had completed their review and then had lifted up this all-case study. At that time a total of 7740 patients had been recruited.

Analyzed: 7740

Diagnosis and Main Criteria for Inclusion:

All patients with Rheumatoid Arthritis who receive Humira

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

Marketed product of Humira, 40mg/0.8ml for subcutaneous injection

Duration of Treatment:

24 weeks

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

Not applicable

Criteria for Evaluation

Primary Outcome Measures:

- Total number of patients with Adverse Events [Time Frame: at week 24]
- Improvement rating on the basis of Disease Activity Score28 [Time Frame: at week 4, 12, 24]

Secondary Outcome Measures:

- Effectiveness evaluation by the investigator [Time Frame: at week 24]

Criteria for evaluation

Effectiveness:

Primary Outcome Measure

Clinical effectiveness was assessed using EULAR (European League Against Rheumatism) response criteria*. Patients were classified as good, moderate or non-response based on both the present DAS28 (Disease Activity Score 28) and DAS28 improvement (defined as the change of DAS from baseline DAS). For instance, when present DAS28 is <3.2 and the DAS28 improvement is >1.2, it is considered as Good response. Scores of good and moderate response were considered to have therapeutic response (Effective rate).

DAS missing data were processed using the last observation carried forward method, except for baseline values.

* EULAR response criteria

DAS28 improvement / present DAS28	> 1.2	0.6 - 1.2	< 0.6
<3.2	Good response	Moderate response	No response
3.2−5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

Secondary Outcome Measure

Overall improvement rating done by each physician was defined as the Secondary Outcome Measure. The level of overall improvement rating was categorized into “Markedly improved”, “Improved”, “Not changed” or "Not assessable", comparing clinical conditions at week 24 or at discontinuation with baseline conditions. Investigators could describe the reasons for the rating.

Safety:

Adverse events (AEs) were coded with the Medical Dictionary for Regulatory Activities (MedDRA/J Version 14.0). The frequency of AEs was analyzed by System Organ Class (SOC) and Preferred Terms (PTs). The incidence of AEs was expressed as number and percentage, and these were further expressed as serious adverse events (SAEs) and non-SAEs.

When a patient experienced more than one episode of AEs coded to a single PT of MedDRA, the episodes were counted as one case of the relevant PTs.

Summary/Conclusions

Patients Characteristics:

In total, 7740 patients were treated with Humira. The majority of patients were women (82.5%, n=6388). Patient age was 60.1 ± 13.0 years (mean ± SD). Disease duration was 10.5 ± 9.6 years (mean ± SD). Patients with prior treatment with biologics or DMARDs were 42.1% (n=3260) and 94.2% (n=7289), respectively. Concomitant use of methotrexate was 71.1% (n=5503) and that of glucocorticoids was 67.4% (n=5215).

Reasons for discontinuation:

The total number of discontinuing patients was 2250 (2250/7740, 29.1%) before the 24-week observation period. Lack of efficacy (849/7740, 11.0%) and AEs (767/7740, 9.9%) were the most common reasons for discontinuation.

Effectiveness Results:

Effectiveness of Humira treatment was assessed for 6802 of 7740 patients. A total of 938 patients were excluded due to diagnose other than RA (n=16), lack of assessable data (n=812) and too short treatment period (less than 2 weeks, n=254). The total number is not matched because of multiple counting.

The EULAR response was evaluated as a Primary Outcome Measure at week 4, 12 or 24. The number of patients who had enough data to calculate the DAS28 for EULAR response criteria was limited to 3341 at week 4, 3927 at week 12 and 4410 at week 24 respectively. The reason why the number of eligible patients for EULAR response decreased was because effectiveness data (a set of Tender Joint Counts, Swollen Joint Counts, patient Visual Analog Scale and Erythrocyte Sedimentation Rate) at each point was not obtained for all patients. Thus, 3341, 3927 and 4410 were used as the denominator to calculate the EULAR response at the respective time points. See note under Table 3

At week 4, 681 patients (681/3341, 20.4%) had achieved a good response. At week 12, 1036 patients (1036/3927, 26.4%) and at week 24, 1356 patients (1356/4410, 30.7%) had achieved a good response. At week 4, 2209 patients (2209/3341, 66.1%) had achieved a good or moderate response. At week 12, 2707 patients (2707/3927, 68.9%) and at week 24, 3091 patients (3091/4410, 70.1%) had achieved a good or moderate response.

Physicians' overall response rating was assessed as Secondary Outcome Measure for all 6802 patients. At week 24 or at discontinuation, 1979 patients (1979/6802, 29.1%) were "markedly improved", and 3077 patients (3077/6802, 45.2%) were "improved". On the other hand, 1333 patients (1333/6802, 19.6%) were "not changed" and 413 patients (413/6802, 6.1%) were "not assessable".

Effective rate of the combined "markedly improved" and "improved" was 74.3%.

Safety Results:

Safety analysis was performed in 7740 patients.

Total number of patients with AEs was 2155 patients (27.8%). The incidence of SAEs and non-SAEs were 6.1% (n=469) and 23.2% (n=1796). There were patients who experienced both a SAE and a non-SAE. The most frequent SAE was pneumonia (0.5%, n=41) followed by interstitial lung disease (0.5%, n=40). Among these 40 patients, 13 patients had documented pre-existing interstitial lung disease. Rash was the most frequently observed as non-SAE (3.3%, n=255), followed by Injection site erythema (2.1%, n=160). No overall safety profile change of Humira was seen and unknown clinically significant adverse events were not detected.

Conclusions:

It was concluded that no revisions of the Precautions or other sections of the Package Insert for Humira are required based on the results of 7740 patients analysis.

The results of the survey suggest that there was no new concern with either the "Indications" or "Dosage Administration" currently approved for Humira.