London, 22 April 2004
Product name: **HUMIRA**
Procedure No: EMEA/**H/C/481/II/06**

SCIENTIFIC DISCUSSION

1. Introduction

In this variation procedure, the MAH applied to introduce the extension of the therapeutic indication for Humira to include inhibition of structural damage in rheumatoid arthritis patients.

Consequential changes to section 5.1 of the SPC and section 2 of the PL were also proposed.

2. Background

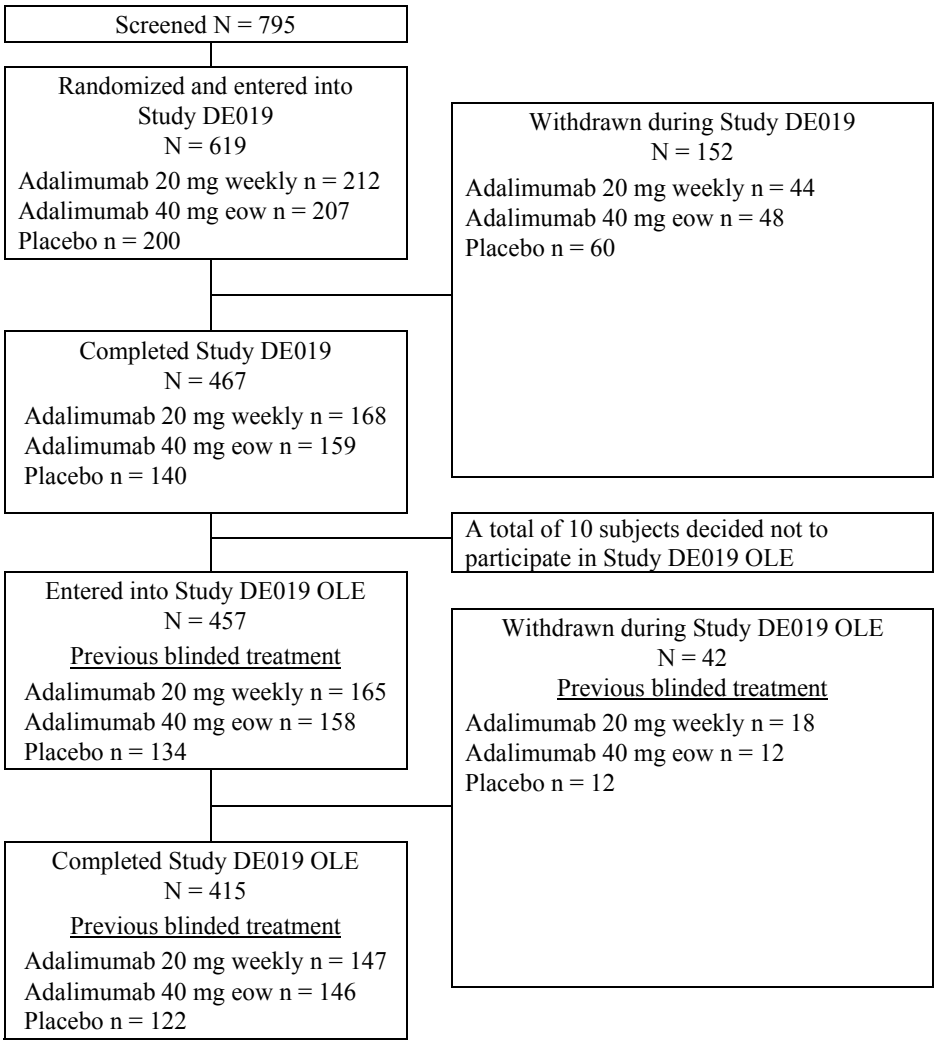
The dossier consisted of two-year open-label extension (DE019 OLE) data from the previously assessed pivotal trial DE019.

3. Efficacy

Study design

Twelve-month data from the DE019 trial were assessed for the Marketing Authorisation (MA) of the currently approved indication. Briefly, DE 019 enrolled adult patients (mean age 56 years) with chronic (mean disease duration 130 months), moderate to severe, active RA. With few exceptions, patients had failed on at least one previous DMARD, including methotrexate (MTX). The first 12 months were a double blind phase, where adalimumab (20 mg weekly or 40 mg every other week) was compared with placebo as add-on to MTX. During the extension period of up to two years (DE019OLE), all patients received open-label adalimumab, 40 mg eow. Study flow and subject disposition are given in Figure 1.

Figure 1. Subject Disposition DE019 / DE019OLE



Methods

Trial **DE019** had three co-primary endpoints, hierarchically arranged as follows, to preserve overall α=0.05:

1. ACR20 responder rate at 24 weeks
2. Change from baseline in modified total Sharp X-ray score (TSS) at week 52
3. Change from baseline in disability by HAQ (Health Assessement Questionnaire) at week 52

Significance testing was done following the closure principle (overall effect followed by individual doses *vs.* placebo).

For **DE019OLE**, the following primary criteria relevant to the current application were prospectively defined in the analysis plan:

✓ Sustained inhibition of structural damage for subjects originally receiving adalimumab in DE019

This was evaluated by changes in TSS during the second year of treatment compared to Week 52. The Week 104 TSS change was defined as Week 104 TSS minus Week 52 TSS. The primary measure was the percentage of subjects with no progression, defined as a change in TSS ≤0 during the second year of treatment with adalimumab. If ≥50% of subjects observed a difference of ≤0 units in Week 104 TSS change, or if the lower confidence limit of the observed percentage of subjects with no Week 104 TSS change is ≥37%, the two-year open-label TSS data demonstrate sustained inhibition of radiographic structural damage.

- ✓ Maintenance of improved physical function for subjects originally receiving adalimumab in DE019

Maintenance of improved physical function during Study DE019 OLE was defined as the percentage of subjects who achieved a 0.5 units or greater improvement in Week 52 HAQ DI (*i.e.*, HAQ DI 0.5 responder), and then maintained an improvement of at least 0.5 units in HAQ DI through Week 104. Maintenance of improved physical function was demonstrated if 75% of HAQ DI 0.5 responder subjects (with lower confidence limit ≥60%) at Week 52 maintained responder status at Week 104 (LOCF, Last Observation Carried Forward).

A number of secondary efficacy assessments relating to ACR, TSS and HAQ were predefined.

Results

Results from **DE019** are summarised in Table 1. The findings had been discussed in greater detail in the initial assessment for the Marketing Authorisation.

Table 1. Efficacy Endpoints of Study DE019 by Randomised Treatment Group (FAS)

	Adalimumab		
	20 mg weekly	**40 mg eow**	**Placebo**
ACR20 responders (as observed)			
Week 24 N (%)	**129 (60.8%)** [a]	**131 (63.3%)** [a]	**59 (29.5%)**
Week 52 N (%)	116 (54.7%) [a]	122 (58.9%) [a]	48 (24.0%)
Modified Total Sharp X-ray Score (extrapolated) Mean Change From Baseline			
Change at Week 52			
Mean ± SD	**0.8 ± 4.9**	**0.1 ± 4.8**	**2.7 ± 6.8**
Median (Range)	**0.0 (-14.5-50.5)**[c]	**0.0 (-37.0-23.5)**[c]	**1.0 (-25.0-39.0)**
Percentage with ΔTSS ≤0	58%	62%	46%
Disability Index of the HAQ Mean Change From Baseline (as observed)			
Change at Week 52			
Mean ± SD	**-0.69 ± 0.55** [a]	**-0.64 ± 0.57** [a]	**-0.34 ± 0.54**
Percentage with HAQ ≥0.5 response	66%	60%	35%

[a] Statistically significantly different from placebo (p≤0.001).

[b] Statistically significantly different from placebo (p≤0.01) based on median values.

[c] Statistically significantly different from placebo (p≤0.001) based on median values.

Bolded parameters represent the primary efficacy endpoints of the study.

The effects on TSS components joint space narrowing and erosion on score were consistent.

It was noted that the population studied in DE019 had rather low ongoing erosion activity, with 46% of patients in the placebo group showing no deterioration in TSS M0-M12. The CPMP opinion during the initial assessment was that two-year data would be necessary for reassurance regarding maintenance of clinically relevant effect.

Efficacy on HAQ was considered clinically relevant and was already mentioned in section 5.1 of the SPC.

Results from **DE019OLE** are discussed below.

Radiographic progression

Analysis according to the primary endpoint is summarised in Table 2 (all treated subjects set = all subjects treated during DE019OLE).

Table 2. Sustained Inhibition of Structural Damage as Measured by the change in TSS between Week 52 and Week 104 (All Treated Subjects)

	Treatment Assignment in Study DE019		
Total Sharp Score	**20 mg weekly (N = 165) n (%)**	**40 mg eow (N = 158) n (%)**	**All Adalimumab (N = 323) n (%, 95% CI)**
Subjects with no change or decreased score	87 (52.7)	88 (55.7)	175 (**54.2**, 48.7-59.6)
Subjects with increased score	65 (39.4)	64 (40.5)	129 (39.9, 34.6-45.3)
Missing	13 (7.9)	6 (3.8)	19 (5.9, 3.3-8.4)

eow: every other week

Criteria for "sustained inhibition of radiographic progression" were, thus, fulfilled. An analysis including only patients with X-rays available during DE019OLE (N=304) produced similar results (ΔTSS $\leq$0 in 175/304, 57.6%)

Change in TSS from DE019 baseline through Week 104 is given in Table 3

Table 3. Summary of change from baseline in modified TSS (All treated subjects)

Week 104 TSS	Visit	Treatment	N	Mean (95% CI)	Median
Change from baseline	Week 52	Adalimumab	305	-0.4 (-1.1;0.4)	0.0
		Placebo	123	3.0 (1.8;4.3)*	0.5
	Week 104	Adalimumab in DE 019	304	0.4 (-0.5;1.4)	0.0
		Placebo in DE019	121	3.8 (2.1;5.5)*	0.5
Change from Week 52	Week 104	Adalimumab in DE 019	304	0.8 (-0.2;1.8)	0.0
		Placebo in DE019	121	0.9 (0.0;1.7)*	0.0

* Statistically significant based on 95% CI (paired t-test)

Effects on TSS components erosion score and JSN were consistent with those for overall TSS. Subgroup analyses did not reveal clinically important differences with regard to sex, age, race, corticosteroid use, or duration of RA.

The CPMP considered that the interpretation is hampered by the lack of a placebo control group for the second year. The MAH justifies this by reference to ethical and feasibility aspects. Considering the low underlying progression rate in the population studied (46% non-progressors for TSS in the placebo group during M0-M12), the outcome in the primary analysis may not provide very impressive support for sustained effect. Second-year data for patients treated with adalimumab in DE019 suggest some resumption of erosive activity.

On the other hand, DE019OLE findings for the original placebo group support efficacy of adalimumab on progression of joint damage as noted in DE019. Differences between groups treated with adalimumab M0-M24 and M12-M24, respectively, remain significant at the two-year evaluation and do not appear reduced, compared with at one year. Overall, sustained effects of adalimumab on the rate of progression of joint damage are considered acceptably documented.

Disability by HAQ

As described above effects of adalimumab *vs.* placebo on disability by HAQ were reasonably convincing at 12 months in DE019. Similar findings were made in other trials. The 0.5 MCID criterion chosen for analysis in DE19OLE is considered relevant. Outcome for the primary analysis is given in Table 4 and supports maintained response in a relevant fraction of patients. Similar conclusions could be made for other HAQ MCIDs (0.22, 0.75, 1.0).

Table 4. Maintenance of Improved Physical Function: Preservation of the HAQ DI for 0.50 Responders (Week 52 HAQ DI 0.50 Responder Subset Subjects)

	Treatment Assignment in Study DE019		
	20 mg weekly n (%)	**40 mg eow n (%)**	**All Adalimumab n (%, 95% CI)**
0.50 HAQ DI responders at Week 52	109	95	204
0.50 responders at Week 104 (LOCF)	87 (79.8)	80 (84.2)	167 (**81.9**, 76.6 - 87.2)
0.50 responders at Week 104 (as observed)	76 (69.7)	76 (80.0)	152 (**74.5**, 68.5 - 80.5)

eow: every other week, LOCF: last observation carried forward

ACR

ACR responder data from DE019OLE are summarised in Table 5 and support class-typical maintenance of efficacy.

Table 5. ACR Responses (All Treated Subjects)

		Treatment Assignment in Study DE019		
ACR Response		**20 mg weekly (N = 165) n (%)**	**40 mg eow (N = 158) n (%)**	**All Adalimumab (N = 323) n (%)**
ACR20 Responder	Week 54 [a]	107 (64.8)	109 (69.0)	216 **(66.9)**
	Week 104	99 (60.0)	101 (63.9)	200 **(61.9)**
ACR50 Responder	Week 54 [a]	78 (47.3)	83 (52.5)	161 **(49.8)**
	Week 104	67 (40.6)	75 (47.5)	142 **(44.0)**
ACR70 Responder	Week 54 [a]	47 (28.5)	38 (24.1)	85 **(26.3)**
	Week 104	45 (27.3)	47 (29.7)	92 **(28.5)**

[a] Week 54 is entry visit for Study DE019 OLE

Subjects who withdrew prematurely, or who took additional DMARDs during the study, were counted as non-responders.

As observed data is presented.

4. Safety

Patient exposure
Exposure data from DE019 plus DE019OLE are summarised in Table 6.

Table 6. Extent of Exposure (Safety Set)

	Treatment Assignment During Study DE019			Study DE019 OLE
	20 mg weekly (N = 165)	**40 mg eow (N = 158)**	**Placebo (N = 134)**	**40 mg eow (N = 457)**
Duration of Treatment During Study DE019 OLE (days)				
N	165	158	134	457
Mean ± SD	336.9 ± 79.5	350.7 ± 53.1	343.3 ± 73.5	343.6 ± 69.6
Median	365.0	365.0	365.0	365.0
Range	15.0 - 392.0	85.0 - 392.0	16.0 - 382.0	15.0 - 392.0
Number of Injections				
N	165	158	133	457[a]
Mean ± SD	23.6 ± 5.7	24.6 ± 3.9	23.6 ± 5.4	24.0 ± 5.1
Median	26.0	26.0	26.0	26.0
Range	1.0 - 26.0	6.0 - 26.0	1.0 - 26.0	1.0 - 26.0
Cumulative Dose of Adalimumab (mg)				
N	165	158	133	456
Mean ± SD	945.7 ± 229.1	983.8 ± 157.2	945.9 ± 215.2	958.9 ± 203.0
Median	1040.0	1040.0	1040.0	1040.0
Range	40.0 - 1040.0	240.0 - 1040.0	40.0 - 1040.0	40.0 - 1040.0

a Table 14.3__1 listed 456 subjects receiving drug because one subject did not have drug compliance entries in the database but participated in the study through Week 104.

eow: every other week; SD: standard deviation

Adverse events

An overview of most frequent treatment-emergent AEs is given in Table 7. There were no relevant differences between OLE period and DE019 as a whole.

Table 7. Number (%) of Subjects with Most Frequently Reported (≥ 5% of Subjects)Treatment-Emergent Adverse Events in Study DE019 OLE (Safety Set Subjects)

Treatment-Emergent[a] Adverse Event[b,c]	Study DE019 OLE Prior Adalimumab (N = 323) n (%)	Study DE019 OLE Prior Placebo (N = 134) n (%)	Study DE019 OLE All Subjects (N = 457) n (%)	Study DE019 All Adalimumab (N = 419) n (%)
Upper respiratory infection	48 (14.9)	18 (13.4)	66 (14.4)	82 (19.6)
Rhinitis	38 (11.8)	18 (13.4)	56 (12.3)	71 (16.9)
Clinical flare reaction	45 (13.9)	9 (6.7)	54 (11.8)	20 (4.8)
Accidental injury	39 (12.1)	14 (10.4)	53 (11.6)	57 (13.6)
Sinusitis	30 (9.3)	21 (15.7)	51 (11.2)	64 (15.3)
Arthralgia	27 (8.4)	8 (6.0)	35 (7.7)	43 (10.3)
Joint disorder	25 (7.7)	5 (3.7)	30 (6.6)	27 (6.4)
Flu syndrome	20 (6.2)	10 (7.5)	30 (6.6)	21 (5.0)
Urinary tract infection	22 (6.8)	7 (5.2)	29 (6.3)	38 (9.1)
Bronchitis	21 (6.5)	7 (5.2)	28 (6.1)	29 (6.9)
Infection	13 (4.0)	12 (9.0)	25 (5.5)	48 (11.5)
Rash	15 (4.6)	10 (7.5)	25 (5.5)	42 (10.0)
Hypertension	16 (5.0)	8 (6.0)	24 (5.3)	28 (6.7)
Asthenia	16 (5.0)	7 (5.2)	23 (5.0)	32 (7.6)
Back pain	16 (5.0)	7 (5.2)	23 (5.0)	32 (7.6)
Surgery	18 (5.6)	5 (3.7)	23 (5.0)	25 (6.0)

a Treatment-emergent AEs were defined as AEs that were reported between Week 52 through Week 104 for subjects still participating in the study at Week 104 and Week 52 through < 70 days after the last dose of study drug for those who prematurely withdrew from the study.

b Occurring in ≥ 5% of subjects in Study DE019 OLE.

c More than one AE category per subject possible.

Deaths and Adverse events of specific interest

There were three deaths during the OLE phase, one case each of interstitial pneumonia, sepsis, and small bowel infarction.

Serious infectious AEs occurred in similar proportions (3.8% *vs.* 3.7% of subjects) in adalimumab-treated patients in DB and OLE phases, respectively. There were three cases of granulomatous infection (one TB, two Histoplasmosis) during OLE, compared with two cases during DB.

Demyelinating disorder compatible with MS was diagnosed in one case during OLE and in one case during DB.

Malignancies were diagnosed in 1.9% and 2.0% during DB and OLE phases, respectively.

No case of autoantibody development was noted during DE019 plus DE019OLE.

5. Benefit-risk assessment

To document sustained benefit of Humira on progression of joint damage and disability, the MAH submitted 24month OLE data from the previously assessed trial DE019. Although the trial design with lack of control group during the second year is not ideal to assess long-term efficacy, the data presented provide acceptable reassurance that the effect of adalimumab on progression of joint damage, established at one year, is not lost with long-term treatment up to two years. Data on ACR and HAQ support continued efficacy for symptoms and signs and disability, respectively, as expected for this class of agents.

The safety data raise no new concerns.

III. CONCLUSION

The CPMP considered this Type II variation to be acceptable and agreed on the proposed wordings to be introduced into the Summary of Product Characteristics, Labelling and Package Leaflet based on the observations and the appropriate conclusions.

The CPMP adopted on 22 April 2004 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation.