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Dear Sally

Re: Golimumab for the treatment of rheumatoid arthritis – Response to request for clarification from the ERG

Please find our response to the request for clarification below.

'Please provide the 104 week radiographic, SF-36, HAQ and ACR data for the GO-BEFORE trial which are referred to on page 7 of the response'

The 104 week radiographic, SF-36, HAQ and ACR data as extracted from the Clinical Study Report (CSR) is presented in appendix 1.

'Please provide the 104 week radiographic, SF-36, HAQ and ACR data for the GO-FORWARD trial which are referred to on page 8 of the response'

The 104 week data from the GO-FORWARD trial for SF-36, HAQ and ACR were presented at the bottom of tables 3, 9 and 8 respectively of our response to the request for re-modelling and additional information.

The data extracted from the CSR is presented in appendix 2 along with the 104 week radiographic data.

'For the DMARD-experienced and TNF-experienced models submitted, please provide a full list of all changes made (comparing to the original submitted models)'

For the DMARD-experienced model, the following changes (comparing to the original submitted model) have been made:

Table 1: Changes to the DMARD-experienced model (HAQ utilities)

Change	Model Sheet	Change from original submitted model	Rationale
1	Throughout	Updated unit costs included	Per request of ERG in clarification questions
2	Throughout	ACR70 data included	Per request of ERG for ACD2
3	Model Control*	Efficacy estimates returned to indirect comparison	Per comments of ERG at ACD2 to ensure consistency with original submitted model
4	First Line Efficacy	Kay et al (2008) included	Per question of ERG in follow-up clarification questions
5	First Line Efficacy*	Formulae for transition probabilities corrected for double counting	ERG stated this as an issue at ACD2
6	Indirect Comparison	Meta-Analysis data updated so all values taken from fixed effects model	At ACD2 the ERG commented that the meta-analysis data had not been consistently selected
7	Indirect Comparison	Meta-analysis ACR70 data updated for etanercept	ACR70 including TEMPO trial used for consistency
8	HAQ score*	Base HAQ returned to 1.41	Per comments of ERG at ACD2
9	HAQ score	Rate of HAQ progression on palliative care updated from 0.09 to 0.06	In the evaluation report the ERG commented that the rate of 0.09 was inconsistent with the rate of 0.06 used in TA130.
10	Current model inputs	Various changes in values	The changes in values come as a result of the inclusion of ACR70 data and the updating of the MTC and Meta-analysis inputs

11	Markov Sheets	Internal inconsistencies across sheets corrected. i.e. etanercept sheet (blank cells), infliximab sheets (costs in death state), certolizumab sheet (modelling of HAQ decrements).	Many of these resulted from the attempt to include ACR70, but a number were present in the original model and identified by the ERG at ACD1
12	PSA Macro	Updated to include ACR70 data	For completeness
*These changes relate to differences between the first model submitted with ACR70 included and the latest model, not between the original model and the latest model.			

Table 2: Changes to the DMARD-experienced model (SF-36 utilities)

Change	Model Sheet	Change from original submitted model	Rationale
1	Throughout	Changes 1 to 12 described for the HAQ model in table 1 also applied to this model	Those stated above
2	HAQ score	SF-36 data included	Per request of ERG at ACD2
3	Utilities	SF-36 data included	Per request of ERG at ACD2
4	PSA Macro	Updated to include SF-36 data	For completeness
4	PSA Macro^	Limited to prevent draws above 1	To prevent the maximum possible utility value being exceeded in a small minority (approximately 2%) of draws
^A BETA-distribution version of the model also supplied			

For the TNF-experienced model, the following changes (comparing to the original submitted model) have been made:

Table 3: Changes to the TNF-experienced model

Change	Model Sheet	Change from original submitted model	Rational
1	Throughout	Changes 1,5,6 and 9 described for the HAQ (DMARD–experienced) model in table 1 also applied to this model	Those stated above
2	Model Control	tocilizumab and abatacept added as comparators	Per requests of ERG for ACD1 and at ACD2
3	First Line Efficacy	tocilizumab and abatacept data added	Per requests of ERG for ACD1 and at ACD2
4	HAQ score	tocilizumab and abatacept data added	Per requests of ERG for ACD1 and at ACD2
5	Cost data	tocilizumab and abatacept data added using assumptions quoted in the document provided by MSD on 28th Jan 2011	Per requests of ERG for ACD1 and at ACD2
6	Current Model inputs	Updated to ensure the tocilizumab and abatacept data is being referenced	So that the model references the correct data
7	Markov Sheets	Updated to ensure the tocilizumab and abatacept data is being referenced	So that the model references the correct data
8	Comp 6 Markov Sheet	Formulae in range ET21:EX102 found to be inconsistent with other comparators. Updated to match formulae used in Comp 4 (tocilizumab)	For consistency
9	PSA Macro	Updated to include abatacept and tocilizumab	For completeness

'Please can you provide full details and results, including all outcome measures, from the phase II trial referred to on page 17 of the response'

The dose ranging trial referred to on page 17 of the response has been published in Arthritis and Rheumatism[1]. From this publication the main table of results has been reproduced below.

Table 4: Results of the dose-ranging study

		Golimumab + MTX				
	Placebo + MTX (n = 35)	50 mg every 4 weeks (n = 35)	50 mg every 2 weeks (n = 34)	100 mg every 4 weeks (n = 34)	100 mg every 2 weeks (n = 34)	Combined (n = 137)
ACR20, no. (%) [*P*]	13 (37.1)	21 (60.0) [0.056]	17 (50.0) [0.281]	19 (55.9) [0.119]	27 (79.4) [<0.001]	84 (61.3) [0.010]
ACR50, no. (%) [*P*]	2 (5.7)	13 (37.1) [0.001]	8 (23.5) [0.036]	10 (29.4) [0.009]	11 (32.4) [0.005]	42 (30.7) [0.003]
ACR70, no. (%) [*P*]	0 (0.0)	3 (8.6) [0.077]	5 (14.7) [0.018]	6 (17.6) [0.009]	3 (8.8) [0.072]	17 (12.4) [0.028]
ACR-N						
Mean ± SD	−2.4 ± 50.0	22.7 ± 46.8	16.2 ± 57.4	24.8 ± 41.7	30.4 ± 42.3	23.5 ± 47.2
Median (IQR) [*P*]	0.0 (−12.5, 28.6)	37.4 (0.0, 54.4) [0.006]	19.4 (−1.0, 49.0) [0.095]	22.3 (0.0, 55.6) [0.010]	35.6 (20.0, 56.6) [<0.001]	33.3 (0.0, 54.4) [0.001]
DAS28 using CRP level						
Mean ± SD change from baseline	−0.9 ± 1.0	−1.9 ± 1.3	−1.4 ± 1.3	−1.9 ± 1.5	−1.9 ± 1.1	−1.8 ± 1.3
Median (IQR) change from baseline [*P*]	−1.0 (−1.8, −0.2)	−1.8 (−2.5, −1.3) [0.004]	−1.3 (−1.9, −0.6) [0.162]	−2.2 (−3.2, −0.9) [0.006]	−1.8 (−2.5, −1.1) [0.002]	−1.7 (−2.5, −1.0) [0.002]
Good response, no. (%)	7 (20.0)	13 (37.1)	10 (29.4)	12 (35.3)	17 (50.0)	52 (38.0)
Moderate response, no. (%)	12 (34.3)	13 (37.1)	13 (38.2)	11 (32.4)	12 (35.3)	49 (35.7)
No response, no. (%)	16 (45.7)	9 (25.7)	11 (32.4)	11 (32.4)	5 (14.7)	36 (26.8)
P†		0.081	0.256	0.256	0.005	0.025
Remission, no. (%) [*P*]‡	2 (5.7)	7 (20.0) [0.074]	9 (26.5) [0.019]	11 (32.4) [0.005]	9 (26.5) [0.019]	36 (26.3) [0.009]
DAS28 using ESR						
Mean ± SD change from baseline	−1.0 ± 1.1	−2.1 ± 1.4	−1.9 ± 1.5	−2.1 ± 1.7	−2.3 ± 1.2	−2.1 ± 1.4
Median (IQR) change from baseline [*P*]	−1.0 (−2.0, 0.0)	−2.2 (−2.8, −1.5) [0.003]	−1.6 (−2.6, −1.0) [0.059]	−2.7 (−3.6, −0.9) [0.015]	−2.2 (−2.9, −1.5) [<0.001]	−2.1 (−3.0, −1.2) [<0.001]
Good response, no. (%)	2 (5.7)	3 (8.6)	5 (14.7)	9 (26.5)	8 (23.5)	25 (18.2)
Moderate response, no. (%)	13 (37.1)	22 (62.9)	17 (50.0)	13 (38.2)	21 (61.8)	73 (53.3)
No response, no. (%)	20 (57.1)	10 (28.6)	12 (35.3)	12 (35.3)	5 (14.7)	39 (28.5)
P†		0.016	0.069	0.069	<0.001	0.001
Remission, no. (%) [*P*]‡	0 (0)	2 (5.7) [0.151]	4 (11.8) [0.037]	3 (8.8) [0.072]	4 (11.8) [0.037]	13 (9.5) [0.058]

* All *P* values are versus placebo. ACR20 = American College of Rheumatology 20% improvement criteria; ACR-N = numeric index of the ACR response; IQR = interquartile range (see Table 1 for other definitions).
† By chi-square test, for the proportion of patients with good or moderate response versus the proportion with no response, for each treatment group versus placebo.
‡ DAS28 <2.6.

'Please can you provide actual references to the particular trials/data sources referred to throughout the document (e.g. what tocilizumab trial was used?)'

A number of trials were referred to in the main body of the document provided by MSD on 28th Jan 2011 and a few additional data sources were used in the modelling. These are listed below and referenced in full in the reference list.

- GO-FORWARD trial[2],
- GO-BEFORE trial[3],
- TEMPO trial[4],
- GO-AFTER study[5],
- Phase II dose-ranging study[1],
- Tocilizumab data source (TNF exp model)[6],
- Abatacept data source (TNF exp model)[7].

References

1. Kay J, Matteson E, Dasgupta B, Nash P, Durez P, Hall S, Hsia E, Han J, Wagner C, Xu Z, Visvanathan S & Rahman M. Golimumab in Patients With Active Rheumatoid Arthritis Despite Treatment With Methotrexate: A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study. *Arthritis & Rheumatism.* 2008; **58**(4) 964-975

2. Keystone E, Genovese M, Klareskog L, Hsia E, Hall S, Miranda P, Pazdur J, Bae S, Palmer W, Zrubek J, Wiekowski M, Visvanathan S, Wu Z & Rahman M. Golimumab, a Human Antibody to TNF-α Given by Monthly Subcutaneous injections, in Active Rheumatoid Arthritis Despite Methotrexate: The GO-FORWARD Study. *Ann Rheum Dis*. 2008; **70** 238-274

3. Emery P, Fleischman R, Moreland L, Hsia E, Strusberg I, Durez P, Nash P, Amante E, Churchill M, Park W, Pons-Estel B, Doyle M, Visvanathan S, Xu W & Rahman M. Golimumab, a human anti–tumor necrosis factor α monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: Twenty-four–week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis & Rheumatism*. 2009; **60**(8) 2272-2283

4. Van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, Tomero-Molina J, Wajdula J, Pedersen R & Fatenejad S. Comparison of Etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: Two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis & Rheumatism*. 2006; **54**(4) 1063-1074

5. Smolen J, Kay J, Doyle M, Landewé R, Matteson E, Wollenhaupt J, Galis N, Murphy F, Neal J, Zhou Y, Visvanathan S, Hsia E & Rahman M. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor α inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo controlled, phase III trial. *Lancet*. 2009; **374**(9685) 178-180

6. Emery P, Keystone E, Tony H-P, Cantagrel A, Vollenhoven R, Sanchez A, Alecock E, Lee J & Kremer J. IL-6 Receptor inhibition with Tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-TNF

biologics: results from a 24-week multicentre Randomised Placebo Controlled Trial. *Ann Rheum Dis*, 2008; **68** 296-313

7. Genovese M, Becker J, Schiff M, Luggen M, Sherrer Y, Kremer J, Birbara C, Box J, Natarajan K, Nuamah I, Li T, Aranda R, Hagerty D & Dougados M. Abatacept for Rheumatoid Arthritis Refractory to Tumor Necrosis Factor α Inhibition. *The New England Journal of Medicine*, 2005 **353**(11) 1114-1123