Abbott's response to the report authored by the Decision Support Unit (DSU) regarding the cost-effectiveness of adalimumab and infliximab for the treatment of Crohn's disease

Abbott welcomes the opportunity to comment on the report authored by the DSU, "Use of tumour necrosis factor alpha (TNF a) inhibitors (adalimumab and infliximab) for Crohn's disease" (the DSU Study), received June 17, 2009. DSU reviewed the Leeds model and analysis (referred to as the West Midlands Health Technology Assessment Committee or WMHTAC Report in previous Abbott comments), as well as the model and analysis submitted by Abbott on July 2007 and subsequent comments submitted on February 2008, July 2008, and September 2008.

Executive Summary

Abbott considers that the analyses conducted by the DSU provide support for the following propositions:

1. Adalimumab 80/40mg induction and every-other-week (eow) maintenance therapy is cost-effective versus both non-biologic standard of care and episodic adalimumab for treatment of severe, active Crohn's disease (CD);
2. The Leeds Model should not be considered as a source of valid information regarding the cost-effectiveness of adalimumab; and
3. Adalimumab is a more cost effective option than infliximab for the treatment of CD, based on a comparison of costs and efficacy performed by the DSU and published, peer-reviewed analysis by Bodger *et al*.

We describe our rationale and evidence base for these conclusions in the next section.

We agree with DSU that the Leeds Model is based on an unrepresentative sample, lacks transparency, and uses invalid transitional probabilities.

DSU recognised that the Leeds model is "*derived from a single study (Silverstein et al., 1999) which reports a retrospective cohort study of all patients diagnosed with Crohn's Disease (CD) between 1970 and 1993, resident in Olmsted County, Minnesota*" (page 6, DSU Study). We also agree that this Olmsted cohort is not comparable to patients enrolled in the Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) trial who were indicated for adalimumab. DSU stated, "*the focus of the [Silverstein et al.] study is not moderate to severe, refractory patients indicated for biologic therapy*" (page 12, DSU Study), and that therefore "*the Leeds model relies almost exclusively on data derived from a cohort of patients that may be substantially different from those indicated for anti-TNF therapy*" (page 42, DSU Study). Since the Leeds model is derived from this single, unrepresentative study, it cannot be considered as a valid source for assessing the cost-effectiveness of adalimumab for CD in patients with severe disease.

The DSU report also indicated that the rationale for the parameters of the Leeds Model lacked transparency. For example, "*As stated in our previous report, we were unable to replicate the transition probabilities used in the Leeds model from the published paper*" (page 6, DSU Study). Accordingly, this lack of transparency in the calculations means that the parameters and structure of the Leeds Model cannot be properly assessed.

DSU also recognised that the ICER produced by the Leeds model is highly sensitive to the remission-to-relapse transition probability (as well as other transition probabilities). As such, they conducted a systematic review of published evidence relating to this transition probability. After reviewing 249 articles, four of which were deemed appropriate for complete review, the DSU stated, "*we find trial evidence to suggest that the [true remission-to-relapse] rate may far exceed*

that used in the Leeds base case, with estimates of the 4 week transition probability between 0.07 and 0.14 compared to 0.0059 used in the Leeds base case model" (page 42, DSU Study). Accordingly, DSU found that there are substantial differences in the predicted proportion of patients in remission between the Leeds model and the published literature throughout the first year of therapy. DSU also considered the analysis that Abbott conducted on the CHARM patient-level data (see Abbott 7th October 2008 and previous responses). DSU acknowledged the analysis and stated, "*this probability could be as high as 0.42*" (page 11, DSU Study). DSU amended the Leeds model in twelve different ways, details of which are described in their technical documentation.

In summary, the DSU report implies that the Leeds model applying the Silverstein relapse rate results in predictions that are not credible.[a] For these reasons, as well as others articulated in Abbott's previous comments, we strongly consider that NICE should not base its recommendations on an unadjusted version of the Leeds model when developing guidance for anti-TNF biologics for CD. Alternatively, DSU's amendments to the Leeds model were based on appropriate sources, including randomised clinical trials that include CD patients with baseline Crohn's Disease Activity Index (CDAI) score of 220-450 points. DSU's amended model is, therefore, a more appropriate source for NICE's guidance.

We agree with DSU's analysis that outcomes based on the Abbott CHARM-based remission-to-relapse transitional probability (i.e., 0.4213) "*is compatible with substantial evidence from systematic reviews of clinical trials.*"

DSU commented briefly on Abbott's estimation of the four-week probability of transitioning from remission to relapse (i.e., 0.4213) using CHARM patient-level data (see Abbott 7th October 2008 and previous responses). This probability far exceeds the 0.0059 derived by Silverstein et al. (1999) that the Leeds model used. It also exceeds the probabilities reported by DSU (i.e., between 0.07 and 0.14). DSU recognised that the discrepancy could be due to the method of analysis, stating "*these estimates are substantially lower than those proposed by Abbott based on their analysis of the CHARM data. In part this may be due to the patient level analysis conducted by Abbott*" (page 21, DSU Study). We agree that the primary difference between the Abbott estimate and the literature review derived estimates is likely due to the Abbott analysis using primary patient-level data from the randomised controlled trial.

Furthermore, the Abbott CHARM analysis that estimated the transitional probability to be 0.4213 limited the CHARM sample to only those with CDAI > 300, as per the licensed indication of severe patients in the UK. DSU stated that they included studies in their literature review that selected patients with moderate-to-severe Crohn's disease (CD) defined as a baseline Crohn's Disease Activity Index (CDAI) score of 220-450 points. This may have contributed to the different relapse rate estimates.

Another means of assessing model validity is by examining its predicted rates of remission. DSU indicated that the 0.4213 rate parameter led to remission estimates that were in line with those observed in their literature review, stating "*using the CHARM based estimates does reduce the proportions of standard care patients in remission to a degree that is compatible with substantial evidence from systematic reviews of clinical trials*" (page 43, DSU Study). Abbott considers that this validity checking by the DSU is important as the predictions based on the 0.4213 estimate are in line with the observed data from the randomised controlled trials.

[a] On page 43, DSU stated, "when a relapse rate was used [in the Leeds base case model] that produced more *credible* model outputs in terms of the proportion of patients in remission, the ICER for episodic infliximab rose to in excess of £200k per QALY" (our italics). We interpret this to mean that the DSU does not consider the base case in the Leeds Model to produce credible outputs.

While we agree with DSU overall, some of the critiques in earlier Abbott comments were left unaddressed and some advantages of the Abbott modelling approach have perhaps been under recognised.

DSU addressed most of the pertinent issues with the Leeds Model. However, not all issues were resolved. For example, the costs of surgery and relapse for the CD patient population were changed but were still too low. We believe the estimates that the Leeds Model, as well as the Schering Plough (SP) Model and amended Leeds Model used for surgery and relapse state costs are biased downwards. This is because either they are not CD-specific but rather are general costs for inflammatory bowel diseases, as per the Leeds Models; or are derived from data published more than ten years ago, as per the SP Model. Abbott's model uses the more appropriate, CD-specific estimate for the costs available from Bassi et al. (2004),[1] a NHS hospital-based, peer-reviewed micro-costing study. Bassi et al provided details of regression model coefficients, from which costs for CD-only patients could be estimated.

Also, the Abbott model should be recognised as the only model that fully captured the benefits of anti-TNF treatment, which was one of the issues to be addressed by DSU. The Leeds and SP models operate based on difficult to validate assumptions regarding Markov structure and definition of the Markov states, including states that were derived from Silverstein et al. who defined such states based on practice patterns from 1970-1993. Alternatively, Abbott's model used CDAI data directly sourced from a randomised trial to map patients into four exclusive and comprehensive disease activity-based states. While DSU stated that "*it is also worth noting that the [Abbott] model distinguishes remission and other intermediate health states and thereby allows treatment benefits other than full remission to be reflected*" (page 10, DSU Study), it is important to emphasise that the Abbott model is the only model that reflected the comprehensive benefits of anti-TNFs rather than reflecting solely the benefits of being in remission.

We agree with the analysis in DSU's Conclusions section, specifically that adalimumab maintenance therapy is cost-effective versus standard and episodic care for patients with severe active CD when using valid parameter estimates and modelling methods.

DSU's analysis indicates that adalimumab maintenance therapy is likely to be a cost effective use of NHS resources. After updating the Leeds model with credible parameter estimates, the DSU stated that adalimumab maintenance therapy generates an ICER of below £10k (page 43, DSU Study). DSU stated, "*Adapting the Leeds model to more closely reflect the manufacturer analyses, by incorporating values from the SP model, suggests that episodic adalimumab dominates standard care and maintenance adalimumab is cost effective compared to episodic adalimumab (ICER = £7445)*" (page 43, DSU Study). This is similar to Abbott's original model estimated ICER for maintenance versus standard of care in severe patients of around £11k per QALY. Of note, the Abbott model and analysis has recently been published in a peer-reviewed publication.[2]

Adalimumab represents better value than infliximab for the NHS.

Based on our review of the data, we believe that adalimumab is likely to be more cost effective than infliximab for the treatment of severe CD. We base this on three arguments. First, adalimumab is less expensive than infliximab. Second, the trial evidence indicates that adalimumab is more efficacious at inducing and maintaining remission. Third, we reviewed the existing literature for evidence of comparative costs and effectiveness of adalimumab and infliximab for first line therapy for moderate to severe active CD and found that the published evidence on cost effectiveness of adalimumab and infliximab supports the superior value of adalimumab. We elaborate on these points further in the following sections.

Comparisons of drug acquisition and administration costs between adalimumab eow maintenance and infliximab 5mg/kg maintenance therapies indicate that adalimumab is the lower cost option.

A simple comparison of costs of the adalimumab and infliximab biologic regimens is informative in the cost-effectiveness assessment, especially given that there was a lack of clarity in the costs of infliximab in the review. For example, DSU noted after revising the Leeds model that the SP analysis models biologic costs to be less than half of what their own analysis indicated, stating "*it is interesting to note that whilst the costs of (infliximab) episodic and standard care are closer to those in the SP model, maintenance care is more than double the estimated SP cost*" (page 21, DSU Study).

In the table below, we present a cost comparison of every other week (eow) maintenance adalimumab (with 80/40mg induction) and 5mg/kg infliximab. We assume perfect adherence to a 52 week maintenance regimen for both drugs. We also assume a 70 kg patient for infliximab based on average trial weights, and create three scenarios for infliximab costs - the first where infliximab drug acquisition costs are the only costs considered; the second where administration costs are also included (assumed to be £124 per administration); and the third where vial wastage occurs, averaging one-half vial per infusion, based on the assumption that the excess infliximab in each 100 mg vial that is not used in an infusion is wasted.

Table 1. Dose and cost comparison of 40mg adalimumab eow maintenance and 5mg/kg infliximab maintenance, assuming perfect adherence

	ADA EOW (80/40 induction)		IFX 5 mg/kg			
Week	Doses	Cost	Infusions	IFX Costs Only no wastage[1]	IFX + Administration Costs[2]	IFX + Administration + Wastage Costs[3]
0	2	£715.00	1	£1,468.67	£1,592.67	£1,802.48
2	1	£357.50	1	£1,468.67	£1,592.67	£1,802.48
4	1	£357.50				
6	1	£357.50	1	£1,468.67	£1,592.67	£1,802.48
8	1	£357.50				
10	1	£357.50				
12	1	£357.50				
14	1	£357.50	1	£1,468.67	£1,592.67	£1,802.48
16	1	£357.50				
18	1	£357.50				
20	1	£357.50				
22	1	£357.50	1	£1,468.67	£1,592.67	£1,802.48
24	1	£357.50				
26	1	£357.50				
28	1	£357.50				
30	1	£357.50	1	£1,468.67	£1,592.67	£1,802.48
32	1	£357.50				
34	1	£357.50				
36	1	£357.50				
38	1	£357.50	1	£1,468.67	£1,592.67	£1,802.48
40	1	£357.50				
42	1	£357.50				
44	1	£357.50				
46	1	£357.50	1	£1,468.67	£1,592.67	£1,802.48
48	1	£357.50				
50	1	£357.50				
One-year Total	27	£9,652.50	8	£11,749.36	£12,741.36	£14,419.84

Notes:

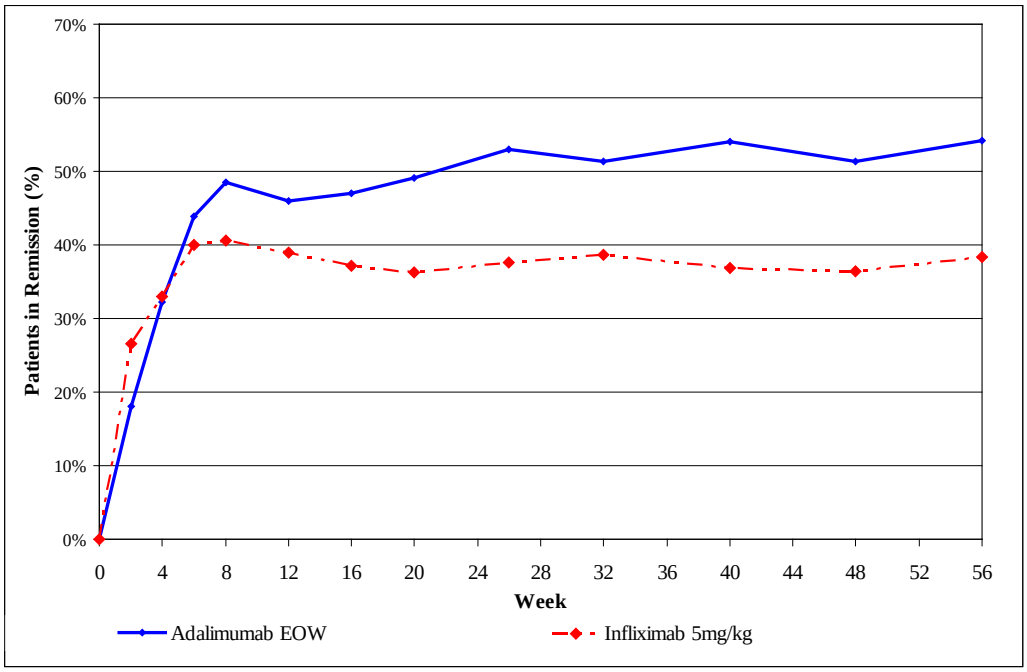
1. Infliximab cost scenario 1 assumes a 70 kg patient and no vial wastage.
2. Infliximab cost scenario 2 assumes a 70 kg patient and a 124 GBP administration fee.
3. Infliximab cost scenario 3 assumes a 70 kg patient, a 124 GBP administration fee and 1/2 vial wastage.

As Table 1 demonstrates, adalimumab is £2,097 to £4,767 less expensive than infliximab based on the three scenarios.

Evidence of comparative efficacy of adalimumab and infliximab

There have been no head-to-head randomised controlled trials comparing adalimumab and infliximab for CD. However, overlaying the published remission percentages over time from the intention-to-treat analyses for the ACCENT I and CHARM trials could be helpful in forming an initial understanding of the relative efficacies of the two biologics. In figure 1, we have overlaid the two published remission curves. Of note, the ITT analyses should be used in the comparison.[3,4] This figure demonstrates that adalimumab patients spend more time in remission than infliximab patients. While this analysis does not explore differences with statistical methods and the baseline patient samples could be argued to be different, this is a useful first approximation of the comparative efficacy of the two biologics. Of note, CHARM patients had higher CDAI at baseline on average than did ACCENT I patients, and about 50 percent of CHARM patients had previously received infliximab therapy. A detailed comparison on the matched samples between adalimumab and infliximab was presented in Abbott's original submission and will be published shortly[5].

Figure 1. Comparison of Remission Rates after Overlaying Rates Published in Rutgeerts et al. (2004) and Colombel et al. (2009)



Literature review of cost-effectiveness of adalimumab and infliximab

A search was undertaken to identify literature that analysed the cost effectiveness of adalimumab versus infliximab. Databases searched included Pubmed and Google scholar, the latter of which encompasses many other search engines including Informa, Elsevier, Ingenta and Wiley Interscience. Further searches for conference abstracts were completed on the Digestive Disease Week (DDW) and American College of Gastroenterology (ACG) websites. Article searches were not restricted by publication type, but must have been published in English after 2007. The search criteria were as follows: must include the words adalimumab, infliximab, and Crohn's Disease, and could include the words "cost-effectiveness", "cost", "efficacy", and/or "comparative".

Two articles were identified which considered the cost effectiveness of both adalimumab and infliximab. Kaplan et al (2007) is not reviewed in detail here as the study was US-based and considered the decision problem of whether to escalate infliximab dose in infliximab non-responders to 10mg/ kg or switch to adalimumab[6]. Bodger et al. considered the cost effectiveness of maintenance therapy with adalimumab or infliximab from the UK NHS perspective[7]. As such, Bodger et al. was considered appropriate for further review.

Bodger et al. (2009) finds that the mean lifetime ICER for one or two years of infliximab therapy was £19,050 and £21,300, respectively. Meanwhile, the same measure for one or two years of adalimumab therapy was £7,190 and £13,310, respectively. The incremental costs and QALYs imply that adalimumab is both less costly and more effective. These results implicitly demonstrate that adalimumab is dominant over infliximab. As previously noted, Abbott considers that the application of the Silverstein transition probabilities by Bodger et al will provide an inflated estimate of the long term cost per QALY of anti-TNF therapy versus standard care, however this would not affect the estimated cost effectiveness of adalimumab versus infliximab over 1-2 years.

In addition, Abbott has previously presented data on the comparison between adalimumab and infliximab in our original evidence submission. The detailed data on the estimated effectiveness of adalimumab versus infliximab based on matched samples from the trials are due to be published shortly.

Table 2. Overview of Bodger et al. study

Study	Method	Population & Data	Intervention	Costs	QALYs	ICER
K. Bodger, T. Kikuchi and D. Hughes (2009)	Lifetime Markov cohort analysis comparing one or two years of infliximab or adalimumab therapy to standard care from the perspective of the UK NHS	Adult patients with moderate to severely active Crohn's disease Uses data from the ACCENT I clinical trial for infliximab and the CHARM clinical trial for adalimumab	Infliximab: 5mg/kg intravenous infusions at week 0, 2 and 6 for induction of remission; then 8-weekly infusions for maintenance therapy Adalimumab: 80mg subcutaneously at week 0, 40mg at week 2 for induction of remission; 40mg every other week for maintenance therapy	<u>Mean Lifetime Costs</u> (2006/2007 GBP) Standard Care: £43,490 Infliximab: 1 year of tx – £50,330 2 years of tx – £58,230 Adalimumab: 1 year of tx – £46,730 2 years of tx – £53,090 *Note: 1 or 2 years of tx denotes one or two years of biologic therapy followed by standard of care for the rest of a patient's lifetime*	<u>Mean Lifetime QALYs</u> Standard Care: 14.209 Infliximab: 1 year of tx – 14.568 2 years of tx – 14.901 Adalimumab: 1 year of tx – 14.682 2 years of tx – 15.156 *Note: 1 or 2 years of tx denotes one or two years of biologic therapy followed by standard of care for the rest of a patient's lifetime*	<u>Mean Lifetime ICER vs. standard care</u> (2006/2007 GBP) Infliximab: 1 year of tx – £19,050 2 years of tx – £21,300 Adalimumab: 1 year of tx – £7,190 2 years of tx – £13,310 (adalimumab was associated with lower costs and greater QALY gain)

References

[1] Bassi A., Dodd S., Williamson P., Bodger K. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. *Gut* 2004; 53:1471-1478.

[2] Loftus E, Johnson S, Yu A, Wu E, Chao J, Mulani P. Cost-effectiveness of adalimumab for the maintenance of remission in patients with Crohn's disease. *Eur J Gastroenterol Hepatol*. 2009 May 21. Epub ahead of print: http://www.ncbi.nlm.nih.gov/pubmed/19465858.

[3] Rutgeerts P., Feagan B., Lichtenstein G., Mayer L., Schreiber S., Colombel J.F., et al. Comparison of Scheduled and Episodic Treatment Strategies of Infliximab in Crohn's Disease. *Gastroenterology* 2004;126:402–413.

[4] Colombel JF., et al. Comparison of two adalimumab treatment schedule strategies for moderate to severe Crohn's disease: results from the CHARM trial. *American Journal of Gastroenterology* 2009;104:1170-1179.

[5] Yu A, Johnson S, Wang S-T, Atanasov P, Tang J, Wu E, Chao J, Mulani PM. Cost Utility of Adalimumab versus Infliximab Maintenance Therapies in the United States for Moderately to Severely Active Crohn's Disease. PharmacoEconomics: in press.

[6] Kaplan, G. et al. Infliximab dose escalation vs. initiation of adalimumab for loss of response in Crohn' disease: a cost effectiveness analysis. *Alimentary Pharmacology & Therapeutics* 2007; 26(11-12): 1509-1520.

[7] Bodger et al. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient level cost data. *Alimentary Pharmacology & Therapeutics*; May 5, 2009.