28 July 2008

Abbott's response to the consultation on the West Midlands Health Technology Assessment Collaboration (WMHTAC) Technology Assessment Report 2: Use of tumour necrosis factor alpha (TNF α) inhibitors adalimumab and infliximab for Crohn's Disease (CD) received on 30 June 2008.

Executive Summary

Abbott welcomes the opportunity to comment on the revised West Midlands Health Technology Assessment Collaboration (WMHTAC) report for the appraisal of adalimumab and infliximab for the treatment of Crohn's disease (CD). Abbott welcomes the WMHTAC conclusion that adalimumab is highly cost-effective for the induction of remission in CD. However, Abbott considers that the modelling of maintenance therapy of adalimumab and infliximab, while it is acknowledged to be exploratory in nature, presents an inaccurate estimate of the cost-effectiveness of these agents in severe disease. This is based on a number of factors, with the most important being the overestimation of the long-term effectiveness of Standard Care therapy in severe CD patients eligible for biologic therapy. Abbott's response considers first the issues regarding the clinical effectiveness of adalimumab, then issues regarding the WMHTAC model, before considering issues that were raised in the WMHTAC's critique of the model submitted by Abbott.

Of particular concern to Abbott is the report's conclusion based on the WMHTAC economic modelling that standard care therapy dominates maintenance therapy with adalimumab or infliximab. Abbott's response considers the validity of the WMHTAC model in a variety of dimensions; by reviewing the underlying interaction between data and methods, the use of the Silverstein Markov framework, the model's external predictive power, assumptions about input values, and finally errors identified in the TreeAge software and related computations.

The conclusion of dominance for Standard Care therapy implies that anti-TNF agents are more costly and less effective than Standard Care when used for maintenance therapy. Abbott agrees with the conclusion that maintenance anti-TNF therapy will be more costly than Standard Care therapy, however, we strongly believe that the available evidence does not support the WMHTAC model results that maintenance anti-TNF therapy would be less effective than Standard Care therapy. In all clinical trials to date, adalimumab-treated CD patients have had higher rates of remission, lower CDAI scores, and higher IBDQ measures than patients receiving Standard Care. Furthermore, in the CHARM maintenance study, the placebo arm patients all received induction doses of adalimumab—boosting their remission rate significantly. Upon being randomised to placebo at week four, the remission rates of the placebo treated patients monotonically declined, compared with either flat or slightly decreasing remission rates for adalimumab every other week or adalimumab given weekly.

There is therefore no evidence that Standard Care treated patients would have higher rates of remission than adalimumab treated patients. Abbott considers that the conclusion that Standard Care maintenance therapy is less costly and more effective than anti-TNF therapy cannot be relied upon by the Appraisal Committee when making recommendations on the role of adalimumab and infliximab in the treatment of severe Crohn's disease.

Table of Contents

Section 1: Issues relating to the clinical efficacy and safety of adalimumab

1.1 CHARM study design

1.1.1 Rationale for why CHARM was designed with the format of a responder group randomised to placebo rather than with a 'true' placebo arm.

An anti-TNF agent, infliximab, was already licensed at the time of study start, therefore it was considered unethical to conduct a study with a long-term true placebo arm. This would withhold anti-TNF from patients potentially eligible for such agents for a considerable period of time. The purpose of the CHARM study was to evaluate maintenance of remission therefore it was essential to have selected out those patients who were initial responders, in order to evaluate this group at the later timepoints for long term response/ remission.

1.1.2 Rationale for why week 4 was used for randomisation in CHARM and definition of response in the UK SmPC at 12 weeks

Week 4 was selected *a priori* as the point of randomisation based on pharmacokinetic model estimates for when maximal drug concentrations should be present. The 4-week timepoint was not chosen for efficacy reasons. In the adalimumab SmPC the point of assessment of patients is up to 12 weeks for Crohn's disease:

> *"Some patients who have not responded by week 4 may benefit from continued maintenance therapy through week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period."*

This statement is based on data from the randomised non-responder (RNR) analysis set in CHARM, which shows that a high proportion of patients who did not achieve clinical response at week 4 did ultimately achieve remission or clinical response (with data focused on timepoints used in co-primary endpoint of the trial, at weeks 26 and 56). A total of 279 subjects were randomised at week 4 who had not achieved CR-70 after OL adalimumab 80/40 mg induction therapy; these were the randomised non-responders (RNR). The RNR patients were randomised in a 1:1:1 ratio to one of three blinded treatment groups (40mg EOW, 40mg weekly or placebo). The proportions of RNR subjects who achieved clinical remission at weeks 26 and 56 were numerically greater in the adalimumab 40 mg EOW (22% and 16%, respectively) and 40 mg weekly (9% and 13%, respectively) groups compared to the placebo group (8% and 8%, respectively), however the differences were not statistically significant. The only statistically significant difference was between the RNR group who received adalimumab 40 mg EOW and the RNR group who received placebo at week 26. The regulatory agency noted that the fact that there was a statistically significant difference between placebo and adalimumab 40 mg EOW in this non-responder analysis might indicate that two induction doses and evaluation after 4 weeks may be a too short time for some subjects to respond in [1]. As a consequence, the adalimumab SmPC has been worded to reflect this.

1.1.3 WMHTAC critique of the adaptive trial design of CHARM

The WMHTAC report criticises the design of the maintenance trials for both adalimumab and infliximab:

"ACCENT I, CHARM and CLASSIC II trials had adaptive trial design of the type described as "drop-the-loser" with in some cases "adaptive treatment switching". An inherent problem of "drop-the-loser" design is that groups that are dropped may contain valuable information regarding the response to treatment under study. A further problem concerns how such studies should be powered; whether for the interim analysis at the point when "losers" are dropped, or for the final analysis involving winners only." (Page 136 of the WMHTAC report)

The report argues that this type of trial design selects out the 'winners' for analysis and is therefore not a true reflection of real clinical practice. However in the manufacturer submission, Abbott also presented combined results for the severe cohort from both the 'randomised responders' (RR) and RNR patients who had a baseline CDAI score $\geq$ 300 – i.e. the specific target population for which adalimumab is expected to be used in clinical practice. Table 1.1.3.1 shows that when all patients with severely active Crohn's disease are analysed, irrespective of their clinical response status at week 4, then statistically significantly more patients receiving 40mg adalimumab EOW achieve clinical remission or a clinically meaningful response at week 26 and 56 compared to placebo (P<0.001 for all timepoints vs. placebo). Furthermore, the percentage of patients with severe baseline disease achieving remission and/or clinical response in the combined RR and RNR group is comparable to the RR group only. Therefore, the adaptive trial design of CHARM does not preclude generalising the results to clinical practice as the patient population in the table below (all severe patients from CHARM) reflects patients that would be treated in real clinical practice in the UK.

Table 1.1.3.1: Subgroup analysis of patients in the CHARM trial with a baseline CDAI score ≥ 300

Patients with CDAI ≥ 300 – week 4 randomised responders and non-responders								
	Remission (CDAI < 150) n/N	**%**	**CDAI decrease > 70 n/N**	**%**	**CDAI decrease > 100 n/N**	**%**	**IBDQ score (change from baseline)**	**N**
Week 26								
Adalimumab 40mg EOW	41/135	30%	67/135	50%	64/135	47%	48	104
Placebo	16/149	11%	34/149	23%	32/149	21%	33	92
P values for Wk 26	P<0.0001		P<0.0001		P<0.0001		P=0.003	
Week 56								
Adalimumab 40mg EOW	36/135	27%	50/135	37%	49/135	36%	48	104
Placebo	12/149	8%	20/149	13%	19/149	13%	34	92
P values for Wk 56	P<0.0001		P<0.0001		P<0.0001		P=0.009	
Patients with CDAI ≥ 300 – week 4 "randomised responders" only *								
	Remission (CDAI < 150) n/N	**%**	**CDAI decrease > 70 n/N**	**%**	**CDAI decrease > 100 n/N**	**%**	**IBDQ score (change from baseline)**	**N**
Week 26								
Adalimumab 40mg EOW	35/96	36%	56/96	58%	54/9	56%	55	79
Placebo	13/96	14%	28/96	29%	27/95	28%	39	64
P values for Wk 26	P=0.0002		P<0.0001		P<0.0001		P=0.005	
Week 56								
Adalimumab 40mg EOW	33/96	34%	43/96	45%	42/96	44%	56	79
Placebo	9/96	9%	17/96	18%	16/96	17%	39	64
P values for Wk 56	P<0.0001		P<0.0001		P<0.0001		P=0.004	

1.2 Benefits of adalimumab maintenance therapy over episodic therapy

The WMHTAC report suggests that induction therapy with adalimumab is a highly cost-effective use of NHS resources, but argues that maintenance therapy is neither a clinical- or cost-effective option:

"*These results imply that a short burst of treatment is likely to be more clinically and cost-effective than prolonged treatment and that after about 12 weeks the likelihood the intervention will be clinically and cost effective will steadily diminish as treatment is extended unless other favourable outcomes additional to*

those based on CDAI measures are delivered later than 10-12 weeks." (Page 144 of the WMHTAC report)

However, Abbott does not believe the available clinical evidence supports this conclusion. Not only are there convincing data showing that CDAI based outcomes, e.g. clinical remission, are significantly better for those patients receiving continuous maintenance therapy vs. episodic use, but there are also data demonstrating a number of other favourable outcomes regarding disease progression that maintenance therapy confers over episodic use.

1.2.1 'All comer' analysis from CHARM shows adalimumab maintenance therapy is significantly better than intermittent use for a number of outcomes

A subanalysis of the 'All comer' data from CHARM supports maintenance over 'intermittent' therapy: Comparison of adalimumab efficacy as continuous maintenance therapy (CMT) vs. Induction Only/ Reinitiation (IO/R) therapies [2]. In this post-hoc analysis, the data were analysed regardless of week 4 response status. The patients originally randomised to placebo, here called the IO/R group (for induction only/ reinitiation of therapy), form a proxy for an intermittent therapy group, as they received open label adalimumab for the 1st two weeks of CHARM, then therapy was withdrawn when they were randomised to placebo at week 4. Per the design of CHARM, at or after week 12, patients with flare or non-response could leave the randomised arm and receive open label (OL) adalimumab, and randomised placebo patients who reinitiated on OL adalimumab also are included in the proxy intermittent therapy group (IO/R).

For clarity, the IO/R group included patients who received induction only therapy (IO) for the 1st two weeks of CHARM, and who were subsequently randomised to placebo and who remained on randomised placebo. The IO/R group also includes patients randomised to placebo and later reinitiated on OL adalimumab. The CMT group included pts on randomised adalimumab who either remained on blinded therapy or subsequently went to OL adalimumab. In this sub-analysis of continuous maintenance adalimumab therapy (CMT) versus intermittent therapy, multiple efficacy endpoints were studied, including the following: remission [CDAI<150], total IBDQ, fistula closure, flare occurrence, and hospitalisation risk. These endpoints were evaluated by comparing CMT vs. IO/R patients. A Cox proportional hazard model, after stepwise confounder selection, estimated the effect of adalimumab on hospitalisation risk, controlling for week-4 responder status, stenosis/ stricture history, and age.

Disease flare was defined as an increase in CDAI of =>70 points compared with week 4 and a CDAI score > 220. Sustained non-response was defined as not attaining a CDAI decrease of $\geq$ 70 points compared with baseline.

Table 1.2.1.1 demonstrates that continuous maintenance therapy with adalimumab results in statistically significantly greater remission rates, quality of life improvements, fewer flares, and reduction in all-cause and CD-related hospitalisations vs. induction only/ reinitiation therapy.

Table 1.2.1.1: Comparison of adalimumab efficacy as continuous maintenance therapy (CMT) vs. Induction Only/ Reinitiation (IO/R) therapies

	IO/R	CMT-EOW	CMT-EW
WK 56 CDAI (median)	183	147*	154*
Remission, n/N (%)	99/261 (38)	132/260 (51)*	125/257 (49)*
Total IBDQ, n (median)	261 (159)	260 (168)*	257 (168)*
Complete fistula closure, n/N (%)	6/47 (13)	11/30 (37)*	12/40 (30)*
CD-related hospitalization***	Reference group (1)	0.62 (0.40–0.97)*	0.52 (0.33–0.82)**
All-cause hospitalization***	Reference group (1)	0.55 (0.38–0.80)**	0.55 (0.38–0.80)**
Flares (mean)	0.98	0.80*	0.85*

LOCF. *p<0.05 and **p<0.01 vs. IO/R. ***Hazards Ratio (95% CI).

Thus, the preponderance and consistency of these all comer analyses across a variety of clinically relevant endpoints collectively suggest that continuous maintenance therapy with adalimumab yields superior results for patients with moderate to severe CD when compared with induction only/ reinitiation dosing over one year. Furthermore, these findings are also consistent with data for infliximab showing superior patient outcomes with maintenance therapy compared to intermittent therapy [24].

1.2.2 Reduction in the risk of all-cause hospitalisation

A subanalysis from CHARM based on a Poisson regression with time offset, evaluated the risk of all-cause hospitalisation after week 12, which showed that treatment with 40mg adalimumab EOW [redacted] or 40mg adalimumab weekly [redacted] significantly reduced the risk of all-cause hospitalisation compared to treatment with placebo [redacted]. These data demonstrate that maintenance treatment with adalimumab gives rise to favourable benefits, i.e. reduction in all-cause hospitalisation that are realised past 10-12 weeks of treatment.

Furthermore, a Kaplan Meier analysis of the risk of all-cause hospitalisation after week 12 (Figure 1.2.2.1) clearly shows a significant reduction in the risk of all-cause hospitalisation for those patients receiving adalimumab compared to the placebo group. Moreover, this analysis suggests that the greatest difference in the risk of hospitalisation between the adalimumab groups and the placebo group occurs around 300 days after randomisation, and therefore also supports the premise that favourable outcomes other than CDAI are achieved by patients on adalimumab maintenance therapy later than 10-12 weeks after treatment initiation.

Figure 1.2.2.1: Kaplan Meier Analysis of All-Cause Hospitalisation in CHARM

1.2.3 Long-term fistula data from CHARM and its open-label extension [3]

Two post-hoc analyses were performed. The first post-hoc analysis pooled data from both adalimumab doses and evaluated the subgroup of patients from CHARM who had fistulas at baseline (in keeping with the statistical analysis plan from CHARM where both adalimumab dose groups were pooled). Patients were analysed for the percentage of healed fistulas and the percentage with ≥50% fistula response at 6,12, 18, and 24 months of adalimumab treatment.

A total of 117 patients had fistulas at baseline of CHARM (47 randomised to placebo, 70 randomised to EOW or EW). At least half of the patients receiving adalimumab showed sustained fistula healing across Months 12, 18, and 24 (Table 1.2.3.1). The majority of patients (64-71%) experienced ≥50% response in fistulas across all time points.

Table 1.2.3.1: Fistula Response and Healing Rates at 6, 12, 18, and 24 Months of Adalimumab Treatment

Months	Fistula Healing, n (%)	≥50% Fistula Response, n (%)
6	35 (50)	45 (64)
12	35 (50)	41 (59)
18	39 (56)	50 (71)
24	42 (60)	50 (71)

LOCF analysis

In a follow up analysis, all patients with healed fistulas at the end of CHARM (including placebo patients) were studied two-years after the initiation of the study. The results demonstrated that fistula healing was sustained with adalimumab treatment, as 76% (29/38) of patients who had healing at month 12 continued to experience fistula healing at month 24 (non-responder imputation). Therefore, these data show that adalimumab confers considerable efficacy for healing fistulas in Crohn's disease, furthermore these benefits continued during the open label extension with a sustained response after 2 years of adalimumab treatment. Further information regarding fistula healing is detailed in Appendix 3.

1.2.4 Mucosal healing data

Abbott is currently conducting M05-769, a phase III trial evaluating the safety and efficacy of adalimumab in the healing of mucosal ulcerations in moderate to severe ileocolonic Crohn's disease. In the same vein as the fistula healing data, this trial will aim to show that adalimumab maintenance therapy provides favourable outcomes in the long-term, other than CDAI based measures, that may help attenuate disease progression. In a trial with another anti-TNF agent, Rutgeerts *et al.* [4] demonstrated that scheduled maintenance treatment with infliximab resulted in more improvement in mucosal ulceration and higher rates of mucosal healing than those patients receiving episodic therapy. Complete mucosal healing by week 10 occurred in significantly more week 2 responders who had received 3 doses of infliximab compared with a single dose (31% vs. 0%, p=0.01). Furthermore, a significantly higher proportion of week 2 responders in the combined scheduled maintenance group had complete mucosal healing at week 54 compared with the episodic group (50% vs. 7%, p=0.007)[4]. Moreover, mucosal healing appeared to correlate with fewer hospitalisations.

1.2.5 Summary of benefits for maintenance therapy over intermittent use

To summarise, Abbott argues that the significantly greater remission rates, quality of life improvements and fewer flares reported for continuous therapy over episodic use; coupled with the significant reduction in all-cause hospitalisation, the fistula healing data, and evidence of greater mucosal healing observed for patients receiving continuous maintenance therapy compared to episodic use, clearly demonstrate that maintenance treatment with an anti-TNF is superior to intermittent therapy.

1.3 Sustained long-term remission data from CHARM maintenance trial of adalimumab

Analysis of those patients from CHARM who were in remission at week 4 and continued to be in remission at any visit through to week 56 demonstrate that treatment with adalimumab offers sustained response over placebo in the long-term. In this analysis, if at any time point through to week 56 a patient was no longer in clinical remission (even if they were to regain remission at another visit) they were considered to be a non-responder for the remainder of the survival analysis. This sustained long-term remission is evidenced by the fact that a statistically significantly greater proportion of patients receiving adalimumab remained in clinical remission at every visit from week 4 through to week 56 compared to the placebo group.

Therefore, it can be concluded that adalimumab maintenance therapy provides long-term sustained clinical remission in patients with moderate-to-severe Crohn's disease.

1.4 Two-year data from CHARM demonstrating maintenance of efficacy [5]

At the end of CHARM (56 weeks), patients were eligible to enrol in an ongoing open label extension trial (OLE), during which patients who completed CHARM on blinded randomised therapy received adalimumab 40 mg EOW OL, and patients who completed CHARM while receiving OL adalimumab EOW or EW continued their existing open label regimens. Patients could switch to EW dosage for flares/non-response once in the OLE, but could not decrease to EOW.

Post-hoc analyses of maintenance of remission (CDAI<150) and response (drop in CDAI >70 [CR-70] or 100 [CR-100] points) were performed for patients initially randomised to adalimumab who were in remission at CHARM Week 56. Both intention-to-treat (ITT) and randomised responder (RR) [CR-70 at Week 4] populations were evaluated. Patients randomised to placebo were not analysed in this instance, as they had not had 2 years of continuous therapy.

Remission rates were calculated using non-responder imputation (NRI) and last observation carried forward (LOCF). A total of 467 patients enrolled in the OLE. Remission results are shown in Table 1.4.1. Of the 145 ITT patients initially randomised to adalimumab who were in remission at the end of CHARM, 111 (77%) were still in remission 2 years after CHARM enrolment (12-month OLE visit), and 97 (79%) of the 123 RRs maintained remission at 2 years (NRI).

Table 1.4.1: Remission Rates for Adalimumab-Treated Patients Through 2 Years

Population	Months since CHARM baseline*	Remission, NRI n (%)	Remission, LOCF n (%)
ITT N=145	18	113 (78)	118 (81)
	24	111 (77)	123 (85)
RRs N=123	18	99 (80)	103 (84)
	24	97 (79)	107 (87)

Months 18 and 24 represent OLE months 6 and 12, respectively.

Adalimumab shows sustained efficacy in maintaining CD remission through 2 years of therapy. The majority of adalimumab-treated patients in remission after 1 year in CHARM maintained remission for an additional year in an OLE. Data on long-term improvements in quality of life are available in Appendix 3.

1.5 Dropout rates of interventional trials in Crohn's disease

In the discussion of clinical evidence in the WMHTAC report (page 145), it is stated that the initial good response of anti-TNFs is not well maintained with extended treatment, which can be evidenced in three ways. One of the three points raised was the large numbers of patient dropouts in ACCENT I and CHARM. However, a review of the literature of CD interventions other than anti-TNF agents, clearly shows that the high dropout rates observed for ACCENT I and CHARM are not as a result of anti-TNF use, but are instead indicative of the disease itself. In a clinical study of azathioprine (AZA), Candy *et*

al.[6] demonstrated statistically significantly higher rates of remission after 15 months of treatment with AZA vs. placebo, however the overall dropout rate for all randomised patients was 74.6% (58% receiving AZA and 93% receiving placebo). In a study of 40 patients, evaluating methotrexate in comparison to placebo for the maintenance of remission in Crohn's disease, Feagan *et al.* [7] found that 42% of patients receiving methotrexate and 64% receiving placebo dropped out of the study before the 40-week study period ended. Furthermore, in a retrospective study Lemann *et al*.[8] found that only 12.2% patients were still on methotrexate after 3 years. Thus, the available literature suggests that there is an abnormally high dropout rate in trials observed for all interventions indicated for Crohn's disease. The fact that the high dropout is not due specifically to anti-TNF treatment is further supported by the high-level of compliance in clinical trials of adalimumab in other indications, for example: psoriasis, rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis.

1.6 Long-term steroid-free remission in Crohn's patients receiving adalimumab in CHARM [9]

In CHARM, adalimumab demonstrated a steroid-sparing effect. Steroid-free remission was maintained through 1 year of adalimumab therapy in patients who were receiving steroids at baseline (a stable dosage of ≤30 mg/day prednisone/equivalent for ≥2 weeks prior to screening). Described below are the rates of steroid-free remission among patients who continued treatment with adalimumab for an additional year (total length of therapy 2 years) in an ongoing, OLE of CHARM. This post-hoc sub-analysis evaluated data from the intention-to-treat population of patients receiving steroids at baseline who were randomised to adalimumab and assessed for steroid-free remission at 12, 18, and 24 months from the start of CHARM. Patients with missing data were considered non-responders, i.e. not in steroid-free remission, regardless of the reason for the absence of data, including failure to enroll in the OLE. In CHARM, 206 pts were receiving steroids at baseline and were randomised to EOW or EW adalimumab treatment.

Table 1.6.1: Steroid-free remission through 2 years of adalimumab therapy among randomised patients receiving steroids at baseline

Timepoint	Adalimumab N (%)	Placebo N (%)
12 months	44/206 (21)	6/107 (6)
18 months	45/206 (22)	Not applicable
24 months	52/206 (25)	

Adalimumab therapy resulted in clinically meaningful rates of steroid-free remission in patients who were receiving stable doses of steroids when they entered the CHARM study. Responses were sustained over 2 years.

1.7 Evidence indicates that the natural history of CD may lead to patients not reverting to full remission spontaneously after a flare

The evidence that 50% of patients with CD need surgery in the first 10 years of disease, 70-80% require surgery during their lifetime, and that surgery is not curative [10], indicate that over time, the majority of patients will not be controlled on their conventional therapy and require surgical intervention. Agents that could reduce the potential risk of surgery would therefore clearly be of benefit. Indeed, Vermeire *et al*.[11] showed that approximately 75% of patients had new lesions on endoscopy one year after surgery and the reported re-operation risk varies between 20-70% dependent mainly on the follow-up time of the patients. The authors conclude that these data taken together strongly indicate the need for strategies aimed at interrupting or delaying the natural evolution of the disease.

A study by Cosnes demonstrated over time the natural history of the disease often changes, moving from purely inflammatory in nature, to the more complex stricturing disease and then penetrating/fistulising disease[12]. 1,199 patients (60%) developed a stricturing (n = 254) or a penetrating (n= 945) complication. Twenty-year actuarial rates of inflammatory, stricturing, and penetrating disease were 12, 18, and 70%,

respectively. Most patients with CD will eventually develop a stricturing or perforating complication. Therefore it is clear, as the disease progresses, the needs of the patient and need for more complex intervening management may also increase.

A recent review evaluated agents' efficacy in terms of altering the natural history of CD [13]. It indicated that corticosteroids do not alter the disease course and maintenance therapy with corticosteroids should be avoided given their side effects. Population-based data from Denmark showed that after the first year of diagnosis, 55% of CD patients are in remission and 15% only have mild disease. Nevertheless, up to a third of patients will have highly active disease. In addition this review also states that biologicals have been shown to alter the natural history of immune-mediated diseases other than CD. Adalimumab has demonstrated this for both Rheumatoid Arthritis and Psoriatic Arthritis – leading to a reduction in the structural damage occurring in the joints. Therefore, although the natural course of CD is characterised in many patients by flare-ups alternating with periods of remission, it can be postulated that a significant proportion of patients may still have highly active disease, patients may be steroid dependent (with the ensuing steroid related problems), and a large proportion of patients will need to undergo surgery.

A study conducted by Lemann et al aimed to evaluate the usefulness of infliximab combined with azathioprine (AZA) or 6-mercaptopurine (6-MP) in steroid-dependent CD patients [14]. It demonstrated that infliximab+azathioprine/6-MP is more effective in maintaining remission and being off steroids than placebo+azathioprine/6-MP over 1 year. Data also demonstrated better remission with infliximab in those patients who were naïve to AZA/6MP in the preceding 2 years and those who had failed it. Results were better in the AZA/6-MP naïve population compared to the failures.

It is also noted that when reviewing the results of the placebo+AZA/6-MP arm, there is a steady decrease in the percentage achieving remission over time; this is more apparent in the AZA/6-MP failure stratified arm than AZA/6-MP naïve arm. This therefore suggests that remaining on conventional therapy (particularly those who have failed conventional therapy), leads to a reduction of patients in remission over time. This refutes the notion that, when followed over a significant amount of time, high percentages of patients on conventional therapy will revert back to remission after a flare.

Figure 1.7.1a: Remission status of patients from Lemann et al.

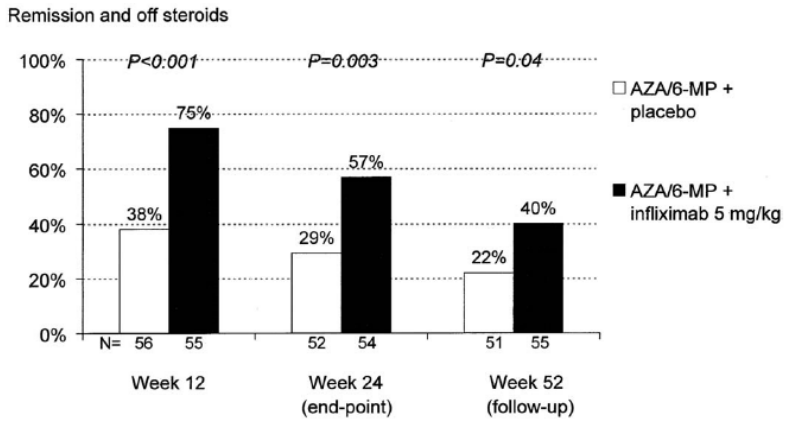
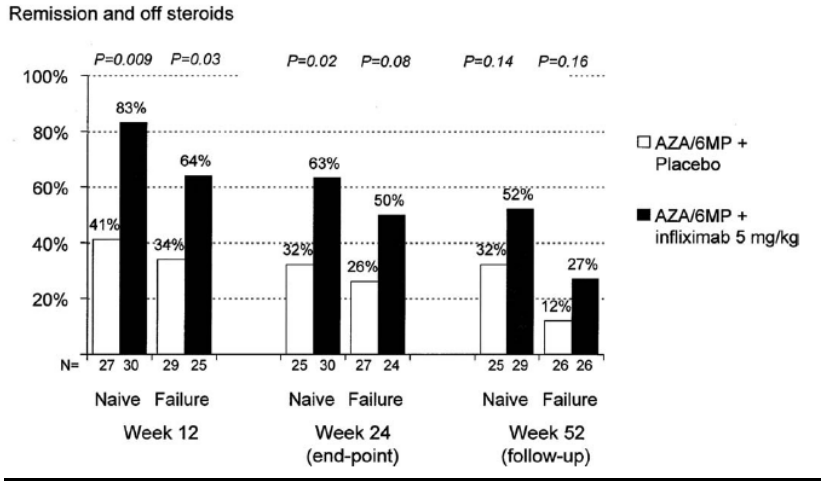


Figure 1.7.1a: Remission status of patients from Lemann et al.



1.8 Safety of adalimumab

The Yellow Card reporting system is a UK initiative for reporting spontaneous adverse drug reactions (ADRs) and counts for a relatively small contribution to the overall safety profile of a medicine, which is based on the global safety profile and is developed through the review of global spontaneous ADRs (involving Yellow Card reports in the UK but also spontaneous reports collected using alternative methods) as well as adverse events collected in clinical trials and literature review. It would therefore be misleading to assess the safety of a medicine based purely on UK Yellow Card reporting data alone. Abbott considers that the SmPC for adalimumab provides a more robust overview of the rates of adverse events as well as warnings and precautions.

There is a large volume of long-term clinical trial safety data for adalimumab in RA, and recently updated data specifically for CD as indicated in the section below.

Table 1.8.1: Adalimumab Safety Profile in Global Clinical Trials and Reduction in Standardised Mortality Ratios (SMR) Across Multiple Indications [15]

	RA	PsA	AS	JRA	Ps	CD
N	12,202	395	393	171	290	1,459
Total PY of exposure	16,973.2	756.5	558.8	278.5	470.5	1,520.1
Serious infections	4.65	2.51	0.89	3.59	0.85	5.92
Tuberculosis	0.28	0.26	0	0	0.20	0.20
Opportunistic infections	0.09	0	0	0	0	0.13
Histoplasmosis	0.03	0	0	0	0	0
Malignancies other than lymphomas and NMSC	0.85	0.26	0	0	0.85	0.53
Lymphomas	0.10	0.26	0.18	0	0	0.07
NMSC	0.18	0	0	0	0.42	0
Demyelinating disease	0.05	0	0	0	0	0.13
Lupus-like syndrome	0.06	0	0	0	0	0.07
Congestive heart failure	0.22	0	0	0	0	0

PY=patient-years, NMSC=non-melanoma skin cancer.

Global Safety of Adalimumab in CD Clinical Trials [16]

An analysis was conducted of overall adalimumab safety across CD randomised pivotal trials, open-label extensions, and phase IIIb studies CHOICE (US) and CARE (EU).

All participants in these trials were evaluated for safety at regular intervals. Rates of adverse events of interest to physicians prescribing anti-TNF therapy were assessed per 100-patient-years (E/100-PY). Standardised mortality ratios were calculated using the World Health Organization 2002 US mortality data as comparator.

As of April 15, 2007 the adalimumab CD clinical trial safety database contained data for 2,228 patients [2,373.7 patient-years (PYs) of adalimumab exposure]. Table 1.8.2 compares rates observed in all CD clinical trials as of Apr 15, 2007 to those from the February 14, 2006 safety update. The rate of serious infection was comparable to those observed in February 2006 and to rates in published reports of other TNF antagonists. Adverse event rates in adalimumab CD and rheumatoid arthritis clinical trials were comparable. In CD trials, the calculated standardised mortality ratio, 0.31 (95% CI, 0.03, 1.11), was lower than published rates.

Table 1.8.2: Rates of Adverse Events (AE) of Interest

Events of Interest (E/100-PY)	Feb 14, 2006 N=1,459 (1,506.0 PY)	Apr 15, 2007 N=2,228 (2,373.7 PY)
Any AE	805.0	631.1
Any SAE	32.3	30.0
AE leading to discontinuation	21.6	16.6
Infection	142.5	118.8
Serious infection	6.0	5.2
Opportunistic infection	2.1	1.8
Injection-site reaction	36.7	24.9
Malignant neoplasm	1.1	1.3
Demyelinating disease	0.1	0.2
Any fatal AE	<0.1	0.1

The safety profile of adalimumab in the Crohn's clinical trials was similar to that reported previously and to safety reports of other TNF antagonists in CD populations. Rates of adverse events were stable or lower over time, adalimumab was well-tolerated, and no new safety signals were identified.

1.9 Miscellaneous comments on the clinical effectiveness and safety of anti-TNF agents

1.9.1 Infliximab dosing

It should be noted that the SmPC for infliximab has recently been amended to include the option to dose escalate to 10mg/ kg. This is in line with the dosing options included in the infliximab clinical trials and expected UK clinical practice.

1.9.2 Immunogenicity for adalimumab

> *"The development of anti-TNF antibodies may be associated with a decrease in efficacy and predispose the patient to an additional risk of recurrent delayed or acute allergic reactions."* Page 25 WMHTAC report

Please note that the SmPC for adalimumab states in the immunogenicity section: "*Formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of adalimumab.*

There is no apparent correlation between the presence of anti-adalimumab antibodies and adverse events."

1.9.3 Immunogenicity for infliximab

> *"Based on the results from the ACCENT I trial, it appeared that "episodic" treatment lead to the formation of fewer antibodies than scheduled treatment (28% in placebo/episodic treatment arm, 9% in 5 mg/kg scheduled arm and 6% in 10 mg/kg scheduled arm)."* Page 130 WMHTAC report.

This conclusion is not in line with the evidence presented and should be changed to indicate that episodic treatment led to the formation of greater levels of antibodies than scheduled treatment.

Section 2: Issues relating to the cost effectiveness of anti-TNF therapy

2.1 Independent Research in the Cost-effectiveness of adalimumab versus Standard Care (and infliximab) for CD

Bodger et al. have recently presented independent research on the cost effectiveness of adalimumab and infliximab in CD[17].

- Bodger et al. find that adalimumab maintenance therapy is very cost effective versus STANDARD CARE at one and two years after initiating therapy (£7,190/QALY and £10,310/QALY).
- The Silverstein data and Markov-based methods used by Bodger et al. are the same as those used by WMHTAC: however, the conclusions are very different;
- While the results of the Bodger et al. analysis closely follow our own, Abbott considers that use of the Silverstein Markov framework overestimates the effectiveness of Standard Care therapy in the cohort of severe patients eligible for adalimumab.

2.2 Overview of the WMHTAC Model

The WMHTAC independently assessed the cost-effectiveness of adalimumab maintenance therapy in moderately and severely active CD using a Markov model with four primary states – remission, relapse, surgery, and post-surgery remission – and a one-year time horizon. The model starts with an expected patient in the relapse state. Monthly transitions to the other states under Standard Care are then based on a modified version of the 8-state transition matrix of the Silverstein et al. [18] cohort model. Modifications to the Silverstein et al. [18] transition matrix include collapsing the "drug-responsive" and "drug-dependent" states into a broader "remission" state, and systematically removing the "mild" and "death" states. The resulting 4-state transition matrix for Standard Care appears in Table 2.1.1a below.

The impact of anti-TNF therapy was *initially* incorporated into the model by modifying the relapse-to-remission and remission-to-relapse transition probabilities with a remission rate ratio and its inverse, respectively, assumed by the WMHTAC based on their clinical effectiveness review. However, in their revised model – described in 'Assessment Report 2' – the WMHTAC instead used "observed events as estimate of effectiveness, not risk-ratios". A variable called "Charm_active" with the value 0.3385 was used. The inverse of "Charm_active", or 1-0.3385=0.6615, was used for the effectiveness of adalimumab in preventing relapse from remission. In addition, they implemented a 2-month stopping rule (i.e., stopping adalimumab after two monthly cycles in relapse) by adding two new health states: Relapse Standard Care and Relapse 2. The resulting 6-state transition matrix for adalimumab, as obtained from the TreeAge model, appears in Table 2.1.1b below.

Table 2.1.1a: Standard Care transition probabilities from the WMHTAC Model

		Subsequent state			
		Remission	Relapse	Surgery	Post-surgery remission
Initial State	Remission	0.9837	0.0059	0.0069	0.0035
	Relapse	0.0713	0.8749	0.0348	0.0189
	Surgery	0.0521	0.0158	0.6709	0.2613
	Post-surgery remission	0.0054	0.0011	0.0026	0.9909

Note: Table 52 from the WMHTAC report (p. 176) and also obtained from the TreeAge model.

Table 2.1.1b: Adalimumab transition probabilities from the WMHTAC maintenance Model

		Subsequent state					
		Remission	Relapse	Surgery	Post-surgery remission	Relapse 2	Relapse Standard Care
Initial State	Remission	0.3281	**0.6615****	0.0069	0.0035	--	--
	Relapse	**0.3385***	--	0.0348	0.0189	0.6078	--
	Surgery	0.0521	0.0158	0.6709	0.2613	--	--
	Post-surgery remission	0.0054	**0.6615****	0.0026	0.3305	--	--
	Relapse 2	**0.3385***	--	0.0348	0.0189	--	0.6078
	Relapse Standard Care	0.0713	--	0.0348	0.0189	--	0.8749

Note: All values obtained from the TreeAge model
*Variable "Charm_active" in the TreeAge model
**(1 – Charm_active) in the TreeAge model

2.2 Critique of the WMHTAC Independent Economic Assessment ("WMHTAC Model")

Abbott considers that the cost-effectiveness results of the WMHTAC Model do not accurately reflect the cost-effectiveness of adalimumab when used in severe CD patients who are indicated for biologics. The basis for this consideration is three-fold.

2.2.1 Methodology and Data:

- Biased characterisation of the clinical course of patients indicated for biologics due to use of Markov methods on a population-based sample of CD patients.

2.2.2 External Validity:

- The effectiveness of Standard Care to elicit remission and prevent relapse is overestimated and not supported by the available clinical evidence.
- The probability of relapse from post-surgery remission under Standard Care (0.0011) is underestimated and not supported by the available clinical evidence. Conversely, the probability of remaining in post-surgery remission under Standard Care (0.9909) is overestimated and not supported by the available clinical evidence.
- The probability of relapse from remission/post-surgery remission under adalimumab (0.6615) is grossly overestimated compared to Standard Care, and not supported by the available clinical evidence. Furthermore, it is unclear how this estimate has been calculated.
- The assumed lack of differentiation in outcomes for moderate versus severe CD is invalid and not supported by the available clinical evidence.
- The number of surgical hospitalisations predicted for adalimumab-treated CD patients is overestimated and not supported by the available clinical evidence.
- The number of medical hospitalisations is not modelled at all.

2.2.3 Internal Validity:

- Imprecise surgery and relapse cost estimates used.
- Errors in the construction of the model.

The following sections provide further detail on the above three critiques of the WMHTAC Model.

2.2.1 Methodology and Data:

- ***Biased characterisation of the clinical course of patients indicated for biologics due to use of Markov methods on a population-based sample of CD patients***

While the methodology (i.e., Markov modelling) and data (i.e., Silverstein et al. [18] cohort model) that the WMHTAC Model employs are valid in and of themselves, they become invalid when used together to characterize the CD clinical course under Standard Care of severe patients indicated for biologics. Below we describe how the data, methods, and Markov states that the WMHTAC Model employs together lead to biased results.

✶ **Data**

The Markov transition matrix estimated by Silverstein et al. [18] is based on a population-based cohort of Olmsted County, Minnesota, residents with a CD diagnosis from 1970 through 1993. As a population-based sample, the Olmsted cohort includes a preponderance of patients with sub-clinical, remitted, or mild disease over the course of their lifetimes. The Olmsted cohort is also incidence-based, such that it includes patients with new CD diagnoses who often are naïve to even first-line conventional therapies, like 5-ASA, azathioprine, or steroid treatments. The inclusion of these patients, who on average are very different in terms of disease severity and expected clinical course from the patients enrolled in the CHARM trial or otherwise indicated for biologics, makes the Olmsted cohort a biased sample for the purpose of characterising the CD clinical course under Standard Care of patients indicated for biologics.

Evidence exists from published literature for the heterogeneity of CD clinical course in population-based samples of CD patients and the presence of a subgroup of patients with consistently active disease and lower probability of being in remission, a subgroup that would be indicated for biologics. For example, Munkholm and colleagues [19] studied the clinical course over a continuous 5-year period of CD patients (n=171) who have been followed up for at least 7 years after being diagnosed in Copenhagen, Denmark. During years 3 to 7 after diagnosis, 25% of all patients had active disease every year, 22% had inactive disease, and 53% fluctuated between active and inactive disease, thus illustrating the heterogeneity of CD clinical course in this sample (Figure 2.2.1a). The subgroup (44%) of patients with constant active disease during years 0 to 3 after diagnosis – the group that would be indicated for biologics – fared worse during years 3 to 7 after diagnosis; 45% of these patients had active disease every year, 5% had inactive disease, and 50% fluctuated between active and inactive disease (Figure 2.2.1b). In contrast, of the subgroup (29%) of patients with active disease during only 1 of the first 3 years after diagnosis, 8% had active disease during years 3 to 7 after diagnosis, 44% had inactive disease, and 48% fluctuated between active and inactive disease. Thus, the course of CD is dependent on a patient's prior history, particularly in the subgroup having aggressive disease. The Munkholm et al. study illustrates the bias that using the entire population-based Olmsted cohort to predict the clinical course of CD patients indicated for biologics would introduce.

Figure 2.2.1: Graphic presentation of the prevalence figures of 5-year activity courses for 171 patients 3-7 years after diagnosis (Munkholm et al. [2])

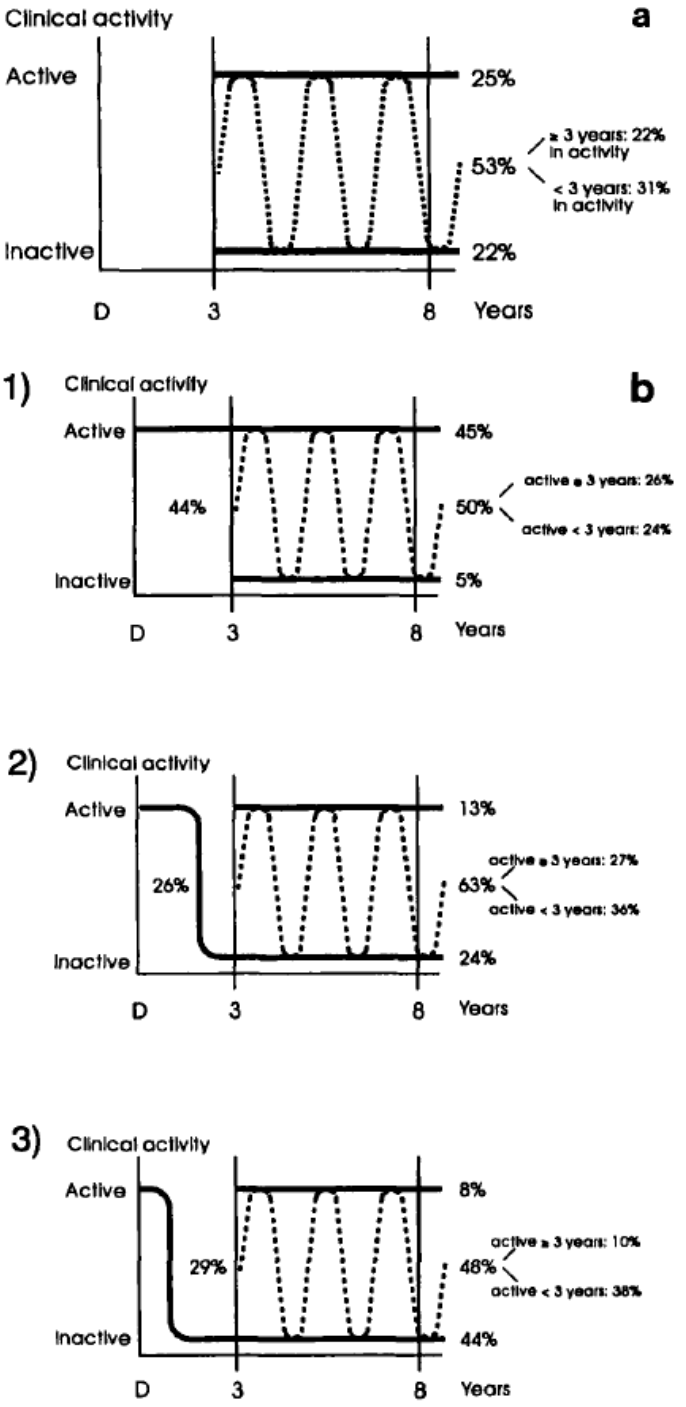


Fig. 5a. Graphic presentation of the prevalence figures of 5-year activity courses for 171 patients 3–7 years after diagnosis. 5b. Disease activity courses in the 5-year period, years 3–7, in relation to the initial disease activity course: 1) 44% had active disease each of the preceding 3 years; 2) 26% had active disease in 2 of the preceding 3 years; and 3) 29% had active disease in 1 of the preceding 3 years.

5-year disease activity courses for 171 patients 3-7 years after diagnosis: 25% with active disease every year, 22% with inactive disease every year, and 53% fluctuated between active and inactive diseases. Represents the clinical course for entire sample.

5-year disease activity courses for the 44% of 171 patients that had active disease each of the preceding 3 years: 45% with active disease every year, 5% with inactive disease every year, and 50% fluctuated between active and inactive diseases. Represents the relationship between having severe disease for first three years with CD and outcomes over next five. Demonstrates that CD patients are not homogenous, and sub-groups exist with a propensity for severe disease. Also demonstrates that "zero memory" assumption, necessary in Markov modelling, is invalid.

5-year disease activity courses for the 29% of 171 patients that had active disease in 1 of the preceding 3 years: 8% with active disease every year, 44% with inactive disease every year, and 48% fluctuated between active and inactive diseases.

- **Methods**

The use of Markov methods on the entire population-based sample renders the results invalid. Specifically, the Markov modelling method employed by the WMHTAC Model makes two strong assumptions, both of which are violated in the WMHTAC Model. First, it assumes "population homogeneity" or that the expected course of disease is the same for every patient starting in the relapse state regardless of differences in individual characteristics such as presence of risk factors. Second, the Markov modelling method also assumes "zero memory" (page 159 in the WMHTAC report) or that regardless of different disease histories every patient faces the same expected course of disease at any given point in time.

The violation of the population homogeneity assumption is two-fold. First, as described in the "Data" section, the clinical characteristics of the Olmsted cohort and CD patients indicated for anti-TNF therapy are very different and assuming homogeneity between the two cohorts as in the WMHTAC model would produce biased results. Second, there is significant heterogeneity even just among patients in the CHARM trial, including important clinical characteristics such as baseline CDAI score [mean (SD); 313.1 (62.0)] and previous anti-TNF exposure [n (%); 414 (49.6)] [20].

The violation of the "zero memory" assumption is likewise two-fold. First, as described in the "Data" section, the CD treatment history of the Olmsted cohort and CD patients indicated for biologics are very different, such that the "zero memory" assumption, even if valid within the Olmsted cohort itself, would not translate to patients indicated for biologics. Second, just as the WMHTAC had suggested, both past disease severity and response to prior treatments are significant predictors of future disease progression in CD, such that the assumption of "zero memory" is not a realistic one among CD patients [19]. The Munkholm et al. figure demonstrates that this assumption is invalid (Figure 2.2.1).

To see the impact of these assumptions, consider two CD patients refractory to their current immunosuppressant therapy. The WMHTAC Model would assign them both the same probability of remission on continued Standard Care, even if one patient was failing his/her first course of immunosuppressant therapy and the other patient had been treated with immunosuppressant therapy for several years. Past disease severity and treatment history are likely associated with the future course of disease and response to Standard Care. Therefore, patients with severe CD who are indicated for anti-TNF therapy cannot be modelled by starting the patients in the refractory state of a Markov model built from the on average much healthier Olmsted cohort. The conditional probabilities of transitioning out of the drug-refractory state would be from two different patient types.

- **States**

The Markov states used in the WMHTAC Model are problematic for two reasons. First, the Silverstein et al. [18] Markov states on which they are based are entirely a function of practice patterns and responsiveness to conventional drugs in Olmsted County from 1960 to 1996, instead of disease activity. Second, the assumptions that WMHTAC used in collapsing the eight Silverstein et al. [18] Markov states into four states are problematic.

The interpretation of these Markov models would be difficult because the definitions of the disease states by Silverstein et al. [18] are no longer applicable to UK clinical practice in 2008. Disease states in the Silverstein et al. [18] publication are based on practice patterns regarding patient responsiveness to conventional drugs (i.e., Standard Care) and are a function of practice patterns over the study period, 1960 to 1996. They are not a function of disease activity, unlike CDAI, which is measured in clinical trials and provides more actionable information for physicians in 2008. For example, the "remission" state is not a function of low disease activity (i.e., Silverstein et al. "remission" is not CDAI < 150), but a function of not receiving any conventional drugs. Patients who were refractory to all therapies could be considered in remission. Since practice patterns change over time, these states would not even apply to the current practice of medicine in Olmsted County, Minnesota, in 2008, much less to other parts of the United States or the world. Further, these states were more clinically relevant prior to the advent of anti-TNF agents; no state exists in the framework for anti-TNF responsive or anti-TNF refractory.

Additionally, it is unclear what clinical or theoretical basis was used by WMHTAC to combine the Silverstein et al. states into their four-state framework. The WMHTAC removed the mild state, and combined the drug responsive and drug dependent states into one remission state. These changes effectively remove any means for the model to include patients who have moderate disease (CDAI between 150 and 300). Assuming that adalimumab therapy shifts the CDAI distribution of CD patients downward, a large component of its therapeutic effect is thus structurally removed from the model.

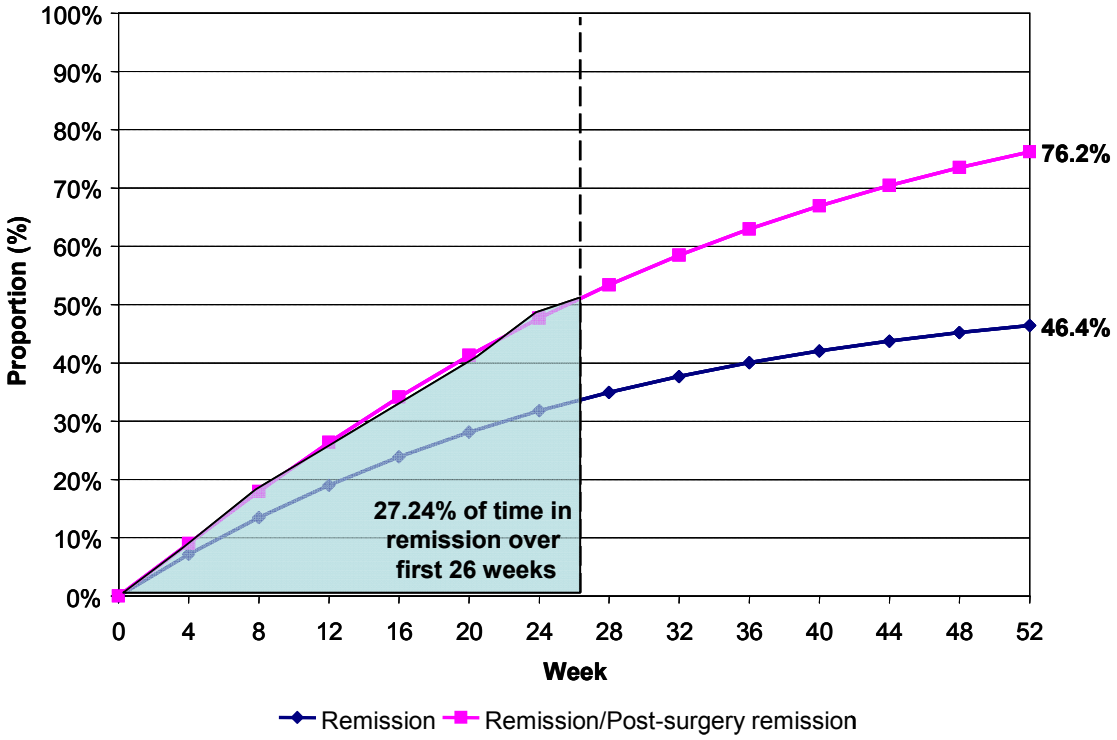
Finally, on page 196 of their report, the WMHTAC admits that invalid transitions are possible in their Silverstein-based, four-state Markov model: "[In] common with the Silverstein et al. analysis, the matrix includes transitions [to] post-surgery remission from relapse and remission states. These transitions are most likely an artefact of the maximum likelihood method used to estimate the Silverstein transition matrix". Although Silverstein and colleagues [18] never acknowledged the presence of these impossible transitions in their publication, the fact that they exist demonstrates that the use of a Silverstein-based Markov model by the WMHTAC is problematic.

2.2.2 External Validity:

- ***The effectiveness of Standard Care to elicit remission and prevent relapse is overestimated and not supported by the available clinical evidence.***

Abbott considers that the WMHTAC Model's characterisation of the clinical course under Standard Care for CD patients indicated for biologics resulted in the overestimation of the effectiveness of Standard Care to elicit remission and prevent relapse. Based on the Markov trace obtained from the electronic version of the WMHTAC "Adalimumab maintenance severe" model received by Abbott on July 10, 2008, the estimated proportions of moderate to severe patients in remission and post-surgery remission over one year (i.e., 13 cycles in the model) under Standard Care monotonically increase from 0% to 46.4% and 39.8%, respectively (Figure 2.2.2.1). Thus, the model predicts the combined proportion in remission (i.e., remission and post-surgery remission) at the end of one year to be 76.2%, a proportion that is not supported by the available clinical evidence. Also, Standard Care-treated patients would spend an average of 27.24% of time in remission over a 26-week period according to the WMHTAC Model.

Figure 2.2.2.1: WMHTAC Model predictions of the proportions of moderate to severe patients in remission and post-surgery remission over one year under Standard Care



To validate the remission figures predicted by the WMHTAC Model against peer-reviewed published data, Abbott conducted a systematic literature review of all clinical trials of biologic agents involving Standard Care-treated patients published after 1990. The full description of this research can be found in Appendix 1.

To summarise the research, as shown in Table 2.2.2.1, we present the 21 placebo arms of randomised clinical trials (RCTs) evaluating biologics (i.e., monoclonal antibodies and recombinant proteins) without crossover with the following characteristics for comparison versus the WMHTAC Model predictions.

Table 2.2.2.1: Characteristics and outcomes of all clinical trials of biologic agents involving Standard Care-treated patients published after 1990

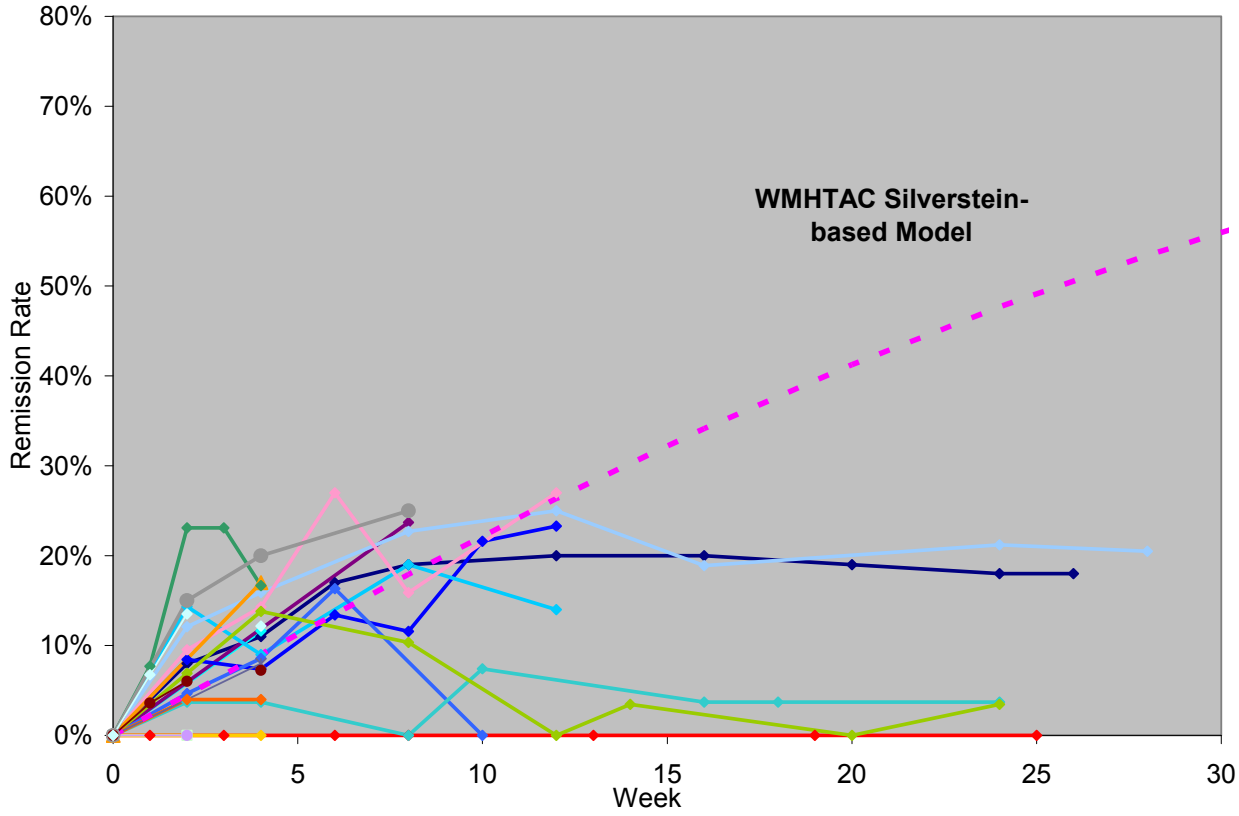
Source	N	Trial Duration (weeks)	Disease Duration (years)	Baseline CDAI	Anti-TNF Naïve Patients	Time Spent in Remission	Study Non-Completion
Sandborn et al., 2004	132	28	8	301	79%	19%	57%
Sandborn et al., 2007b	326	26	8	285	74%	17%	47%
Mannon et al., 2004	8	25	10	335	100%	0%	13%
Sandborn et al., 2001b	27	24	11	320	100%	4%	81%
Sandborn et al., 2001c	31	24	8	343	100%	5%	81%
Ghosh et al., 2003	63	12	9	300	100%	17%	16%
Korzenik et al., 2005	43	12	10	300	40%	13%	16%
Schreiber et al., 2005	73	12	8	NR	100%	12%	27%
Sands et al., 2002	49	10	11	310	100%	8%	49%
Rutgeerts et al., 2006	38	8	13	307	62%	12%	0%
Sandborn et al., 2001a	20	8	NR	265	60%	18%	45%
Fedorak et al., 2000	23	6	11	261	100%	0%	0%
Gordon et al., 2001	12	4	8	273	100%	4%	17%
Hanauer et al., 2006	74	4	NR	296	100%	10%	8%
Hommes et al., 2006	43	4	7	303	56%	6%	16%
Sandborn et al., 2007a	166	4	NR	313	0%	5%	6%
Sander et al., 1997	13	4	9	292	100%	16%	8%
Sands et al., 1999	15	2	NR	311	100%	0%	0%
Schreiber et al., 2000	66	4	8	271	100%	9%	14%
Targan et al., 1997	25	4	10	288	100%	3%	4%
Stack et al., 1997	10	2	8	253	100%	0%	0%
Biologic Placebo Arm Average	**1,257**	**15****	**8.7****	**296****	**72%****	**8.48%* 11.61%** 14.57%*****	**30%****

* Mean time in remission across all 21 placebo arms
** Mean time in remission weighted by sample size
*** Mean time in remission weighted by sample size and duration of trial (weeks)
NR: Not Reported.

The mean time spent in remission for patients observed in the systematic literature review of biologic RCTs was calculated in three different ways (Table 2.2.2.1). The mean time in remission across all 21 arms was 8.48%, the mean weighted by sample size was 11.61%, and the mean weighted by sample size and duration of the trial in weeks was 14.57%. Weighting by the duration of trials increases the effect of any bias caused by early drop-out, which we discuss in Appendix 1 as well as in the following paragraphs, but we use this as a conservative estimate of the true remission rate.

In Figure 2.2.2.2, we present a scatter plot of all of the reported remission observations for the sample of RCT placebo arms from the biologic studies. The maximum published remission rate was 27% and none of the biologic trial placebo arms exhibited monotonically increasing remission rates after week 12. Most remission curves were concave, indicating diminishing remission rates over time. This directly contradicts the predictions of the WMHTAC Model.

Figure 2.2.2.2: Remission rate over trial duration of placebo arms in all RCTs of biologic agents involving Standard Care-treated CD patients published after 1990



The biologic RCT arms identified in the systematic literature review with the longest durations (i.e., longer than 12 weeks) include Sandborn et al., 2007, Sandborn et al., 2004, Mannon et al., 2004, Sandborn et al., 2001b, and Sandborn et al., 2001c. Sandborn et al., 2007 and Sandborn et al., 2004 lasted 26 and 28 weeks, had samples of 326 and 132 patients, enrolled 74% and 79% of patients who were anti-TNF naïve at baseline, and had average remission times of 16.8% and 19%, respectively. Observed remission rates in both arms were declining from week 12 onward. Further, 47% and 57% of patients dropped out of the trials by the final observation date. Mannon et al., 2004, Sandborn et al., 2001b, and Sandborn et al., 2001c had smaller samples (N=8, 27, and 31, respectively) and average remission rates below 5% (0%, 3.7%, and 4.9%, respectively).

As described in Appendix 1, the earlier observations in the biologic RCT arms are susceptible to upward bias because of potential for a placebo effect[i], and the later observations are also susceptible to upward bias because of relatively high rates of drop-out. The average study drop-out rate was 30%, and the two

[i] The placebo effect has been documented in IBD clinical trials to increase relative remission rates by an additional 60 percent, as discussed in Janowitz et al. In a MEDLINE search yielding 38 clinical trials of active UC, the placebo remission rate was found to be approximately 10% and the placebo effect approximately 30%. In another evaluation of the placebo effect in gastrointestinal clinical trials, Musial et al. found that placebo effects are common in gastrointestinal diseases and there seems to be no clear difference between placebo effects in functional gastrointestinal diseases and organic gastrointestinal disease like IBD. For more on the placebo effect in CD trials see Appendix 1.

longest studies had drop out rates of 47% and 57%. As we demonstrate in Appendix 1 based on Sutherland et al., 1991, placebo patients who drop out tend to have statistically significantly higher CDAIs at the end of the trial than patients who complete the trial. Therefore, it is reasonable to consider all systematic literature review values as upper bounds on the true rate of remission.

According to the WMHTAC Model, patients would spend an average of 27.24% of time in remission over a 26-week period, as opposed to 8.48% to 14.57% observed in the systematic literature review. Table 2.2.2.2 summarises the 26-week comparisons.

Table 2.2.2.2: Percentage of time spent in remission over 26 weeks from placebo arms from biologic trials versus WMHTAC Model estimates

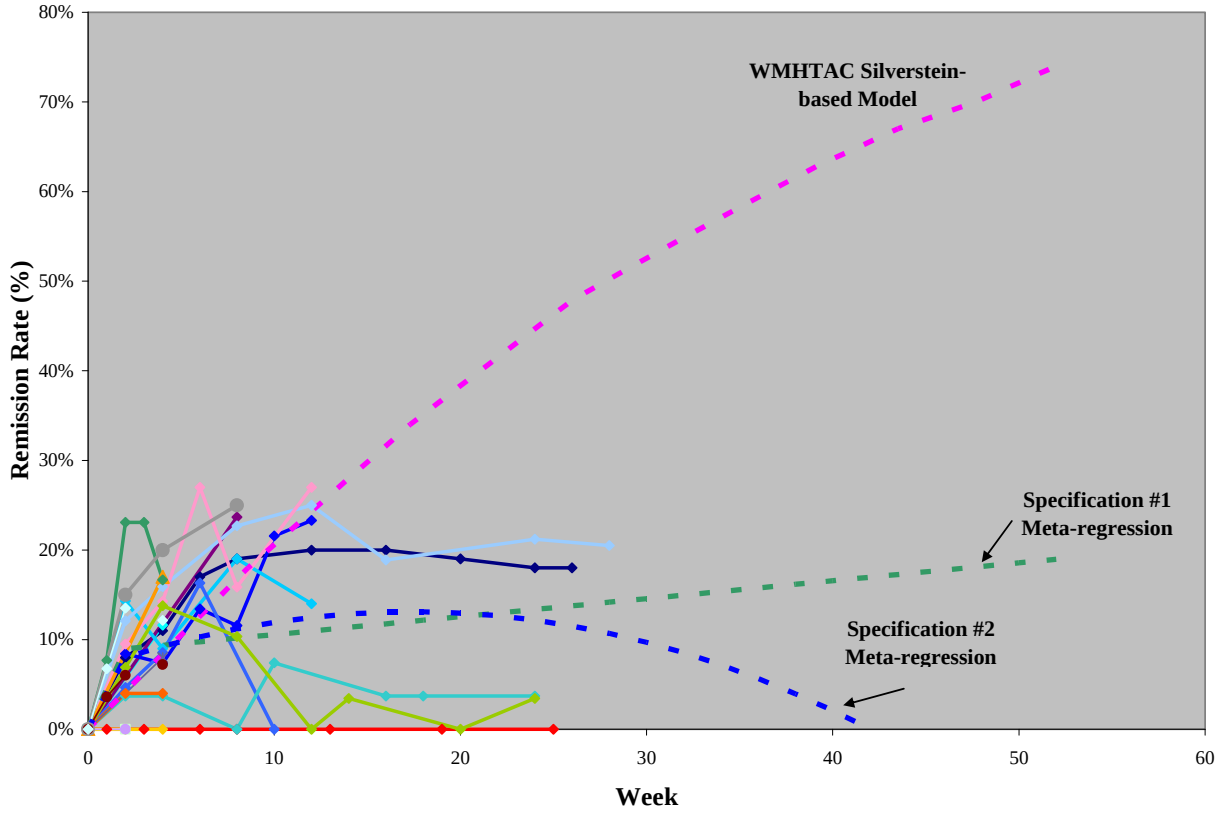
Data Source	Percentage of Time Spent in Remission
WMHTAC model	27.24%[†]
Systematic Literature Review of Placebo Arms in Biologic Trials Mean (N=1,257)	8.48%
Systematic Literature Review of Placebo Arms in Biologic Trials Mean Weighted by Sample Size (N=1,257)	11.61%
Systematic Literature Review of Placebo Arms in Biologic Trials Mean Weighted by Sample Size and Duration (N=1,257)	14.57%

[†] Estimated amount of time spent in remission over 26 weeks.

We also estimated two specifications of a meta-regression based on all of the biologic RCT arm observations. Meta-regressions are similar to meta-analyses and use the point estimates, variance, and sample size of each arm. The first specification included baseline CDAI, week, biologic arm, and week interacted with biologic arm. The second included the same covariates as per the first, but also incorporated a week-squared term, making it non-linear. We projected the predicted remission rates over time for both specifications.

Figure 2.2.2.3 presents the biologic RCT arm meta-regression predictions and the WMHTAC Model estimate, along with the reported remission outcomes for the 21 placebo arms from biologic trials. Regression lines represent the projected remission rate for a placebo-only cohort with the same baseline CDAI score as the CHARM patient population (mean = 313.1) [20]. Based on the two regression specifications, we projected Week-26 placebo remission rates of 11.5% to 13.8% for patients with moderate to severe CD. The differences between the WMHTAC Model and the observations in the literature review become more pronounced over time, as the WMHTAC Model predicts remission rates will monotonically increase over time.

Figure 2.2.2.3. Comparison of meta-analysis results with Abbott and WMHTAC Model remission rate by week - placebo arms of biologic trials only



Based on the systematic literature review of clinical trial data and meta-regression, we believe that the WMHTAC Model remission predictions for Standard Care are not valid for a sample of CD patients indicated for biologics.

- ***The probability of relapse from post-surgery remission under Standard Care (0.0011) is underestimated and not supported by the available clinical evidence. Conversely, the probability of remaining in post-surgery remission under Standard Care (0.9909) is overestimated and not supported by the available clinical evidence.***

One reason why the percentage of patients predicted to be in remission or post-surgery remission under Standard Care does not seem valid is the downwardly biased probability of transitioning out of the remission states. The WMHTAC Model uses probability values of 0.0059 for transitioning out of remission to relapse and 0.0011 for transitioning out of post-surgery remission to relapse. The second figure can be validated against the literature.

For patients with severe, active CD, recurrence after surgery is not infrequent. Lemann [21] presented a meta-analysis of clinical or endoscopic recurrence (CR or ER) rates for post-surgery CD patients. Taking clinical recurrence as a proxy for CD relapse, Lemann [21] found an average clinical recurrence rate of 33% over studies (5-ASA and placebo) ranging from 12 to 36 months in duration, which together include a sample of 1,223 patients. Among patients in placebo arms only, the average clinical recurrence rate was 28%; because patients indicated for biologics are refractory to 5-ASA, the placebo figure is probably more appropriate as a comparator.

We calculated the average monthly probability of CR or ER, assuming a constant hazard rate, to obtain a figure more comparable to that used by WMHTAC in their Markov matrix. The average for 5-ASA and placebo arms was 3.23% per month; for placebo arms alone it was 3.73%. The WMHTAC Model predicts

post-surgery clinical recurrence rates to be 0.11%, or about 1/29th and 1/34th of the 5-ASA and placebo arm probabilities, respectively, that we calculated from the independent meta-analysis. Even if transitions from the remitted state and the post-surgery remitted state (0.11% and 0.59%) were both included, the combined probability (0.7%) would still be only 19% and 22% of the 5-ASA and placebo arm probabilities, respectively. Note, however, that it could be argued that Lemann [21] estimates are biased downward as well, as the patients were prescribed 5-ASAs and not the types of medications that would be given to a patient indicated for biologics after a surgical hospitalisation.

Outside of this meta-analysis, other articles have found similar rates. Cottone et al. [22] estimated that 10-20% of patients will have a clinical recurrence within 1 year of surgery and 5% will have another surgery. Likewise, Williams and colleagues [23] estimated a 3-5 years median time to recurrence of CD after resection surgery. In summary, findings from the literature suggest that the WMHTAC Model dramatically overestimates the proportion of patients remaining in the remission state while on Standard Care.

Also, the post-surgery remission state acts as a practical terminal state for the Standard Care-treated but not for the adalimumab-treated patient; the probability of staying in post-surgery remission (the converse of the probability of relapse conditional on being in the post-surgery remission state) is 0.9909 per 4 weeks for an Standard Care-treated patient – for adalimumab it is 0.3305.

- ***The probability of relapse from remission/post-surgery remission under adalimumab (0.6615) is grossly overestimated compared to Standard Care, and not supported by the available clinical evidence.***

The transitional probabilities used by the WMHTAC model from remission to relapse are 0.0059 for Standard Care vs. 0.6615 for adalimumab EOW, and from post-surgery remission to relapse are 0.0011 for Standard Care vs. 0.6615 for adalimumab, as per a comparison of Tables 2.1.1a and 2.1.1b in this document. That is, adalimumab-treated patients are predicted to be over 100 times more likely to relapse from remission over 4 weeks compared to Standard Care-treated patients. Conversely, adalimumab-treated patients are predicted to be over 600 times less likely to achieve remission from relapse over 4 week compared to Standard Care-treated patients.

To test these assumptions, we used individual-level CHARM data to calculate 4-week transitional probabilities for beginning in the remission state and moving to a non-remission state. As per Table 2.2.2.4, the probability for a CHARM placebo arm patient who begins in remission to move to non-remission 4 weeks later is 0.4213 vs. 0.2650 for EOW patients, as calculated using all CHARM data from week 4 to week 56. That is, the probability of a relapse by the Standard Care-treated patient is 42% versus 26.5% by the adalimumab EOW patient. To lessen the concern that the placebo patient transitional probability from remission to non-remission could be biased by having received an adalimumab induction dose, we also made the calculation using data for the placebo arm from week 12 to week 56 in sensitivity analysis 1, assuming that an adalimumab-induction effect would have likely washed out at that time (though arguably the data would be more prone to other time dependent biases). The placebo transitional probability in this case was 0.3992 vs. 0.2650.

In both cases, placebo patients have higher probabilities of moving into a non-remitted (e.g., relapsed) state.

Table 2.2.2.4 CHARM Data Analysis (unpublished) Comparing 4-week Transitional Probabilities of Patients moving from a Remission State to a Non-remission State

Analysis	Treatment group	Probability of going from remission to non-remission over 4 weeks
Base Case: Observed values, using LVCF only for placebo patients who went to OL	PLACEBO	**0.4213**
	ADA 40 MG EOW	**0.2650**
	ADA 40 MG EW	0.2273
Sensitivity Analysis 1: Dropping all visits prior to	PLACEBO	**0.3992**

week 12 for placebo group only	ADA 40 MG EOW	**0.2650**
	ADA 40 MG EW	0.2273

Of note, this is the most egregious of the differences in the Standard Care and adalimumab transitional probability matrices in Tables 2.1.1a and 2.1.1b. For example, WMHTAC computes that the probability of staying in the remission state of a Standard Care-treated patient is about three times higher (0.9837) than for an adalimumab-treated patient (0.3281). Also, the post-surgery remission state acts as a practical terminal state for the Standard Care-treated but not for the adalimumab-treated patient; the probability of staying in post-surgery remission is 0.9909 per 4 weeks for a Standard Care-treated patient, while for an adalimumab-treated patient it is 0.3305. This leads to a large overestimation in the number of patients in remission or post surgical remission in Standard Care.

- ***The assumed lack of differentiation in outcomes for moderate versus severe CD is invalid and not supported by the available clinical evidence.***

The WMHTAC Model makes no differentiation in the CD clinical course of patients with moderate or severe disease. Indeed, the WMHTAC stated in their report on pages 198-199,

> *"This is because the clinical course framework described above [i.e., their Markov states and transitions] did not differentiate between these two states [i.e., moderate or severe patients at baseline] and it is not clear how a mild/moderate division could be placed upon the active disease patients reported in Silverstein et al. The implicit assumption is that the treatments are equally likely to achieve remission in moderate and severe disease."*

Again, the Markov methods employed by WMHTAC require that this assumption be made. Abbott considers that, based on available clinical evidence, patients with moderate and severe CD do not face the same transition probabilities between disease states, but rather, severe patients on average fare worse than moderate patients. Indeed, as per Table 2.3.1.4 in the Abbott submission dossier, 14% and 9% of placebo week-4 responders who were severe at baseline were in remission at weeks 26 and 52, respectively. Comparably, as per Colombel et al. [20], 17% and 12% of placebo week-4 responders who were moderate and severe at baseline were in remission at weeks 26 and 52, respectively. Therefore, the inclusion of placebo week-4 responders who were moderate at baseline to those who were severe at baseline increased the percentage in remission at both weeks 26 and 52 by approximately 3% - an increase assumed to be zero by the WMHTAC.

- ***The number of surgical hospitalisations predicted for adalimumab-treated CD patients is overestimated and not supported by the available clinical evidence.***

The WMHTAC Model includes a surgery state that is borrowed directly from Silverstein et al. [18] and defined therein as "*inpatient surgical procedures for Crohn's disease... included the entire hospital admission and 6 weeks of post-hospitalisation convalescence*". The direct usage of this state from Silverstein et al. [18] in the WMHTAC Model resulted in an overestimation versus clinical trial estimates of the number of surgeries for adalimumab-treated patients.

The WMHTAC Model did not explicitly model the number of surgeries. However, the model does affix a cost to the surgery state using the "*reference costs [from the NHS Reference cost database 2005/2006] for in-patient and out-patient major and intermediate interventions for Inflammatory Bowel Disease are used as estimates of the costs of … major surgery*" on page 195. To ascertain the implicit number of surgeries in one year for adalimumab- and Standard Care-treated patients predicted by their model, we used the WMHTAC Markov traces to calculate the total expected costs of being in the surgery state over one year, and divided by the expected cost of a surgery, as per the following Table 2.2.2.4 among severe patients.

Table 2.2.2.5: WMHTAC Model adalimumab maintenance and Standard Care surgery predictions

WMHTAC Adalimumab Surgery Predictions, Severe Patients			WMHTAC Standard Care Surgery Predictions, Severe Patients		
Stage (month)	**% Surgery**	**Cost of Surgery (% Surgery X 4,592*)**	**Stage (month)**	**% Surgery**	**Cost of Surgery (% Surgery X 4,592*)**
0	0.00%	£0	**0**	0.00%	£0
1	3.48%	£160	**1**	3.48%	£160
2	5.17%	£237	**2**	5.43%	£249
3	5.81%	£267	**3**	6.42%	£295
4	6.02%	£276	**4**	6.80%	£312
5	5.96%	£274	**5**	6.81%	£313
6	5.75%	£264	**6**	6.60%	£303
7	5.46%	£251	**7**	6.28%	£288
8	5.14%	£236	**8**	5.91%	£271
9	4.81%	£221	**9**	5.52%	£253
10	4.49%	£206	**10**	5.13%	£236
11	4.18%	£192	**11**	4.77%	£219
12	3.90%	£179	**12**	4.43%	£203
13	3.65%	£84	**13**	4.13%	£95
Total Expected Surgery State Costs		£2,847	Total Expected Surgery State Costs		£3,198
Expected Number of Surgeries per Patient per Year (£2,847/4,592*)		**0.62**	**Expected Number of Surgeries per Patient per Year (£3,198/4,592*)**		**0.70**

* £4,592 is the cost of the surgery state, as per page 195 in the WMHTAC report.

Thus, the WMHTAC Model predicts that Standard Care-treated patients will incur 0.70 surgical procedures per patient per year, and adalimumab-treated patients will incur 0.62 surgical procedures per patient per year, resulting in a cost offset of £351 (£3,198-£2,847). To validate the 0.62 expected surgical procedures per patient per year for adalimumab, we looked to estimates from relevant clinical trials. In the CHARM trial, for example, 10 (3.8%) of the 260 patients intended for the adalimumab every other week (EOW) group experienced major surgery during the 54-week trial (Table 2.2.2.5 based on unpublished trial data). The WMHTAC Model would have predicted 0.62*260 = 161.2 instead of the 10 surgeries that actually were recorded in the trial.

Table 2.2.2.6. Major Surgery Rate By Treatment Groups in the CHARM Trial (unpublished)

	Adalimumab EOW (n=260)	**Adalimumab EW (n=257)**	**Adalimumab Combined (n=517)**	**Placebo (n=261)**
Major Surgery % (# of surgeries)	3.8 (10)	3.50 (9)	3.7(19)	7.7 (20)

Note: based on ITT analysis, surgery under open label treatment has been included. All placebo patients received induction doses in CHARM.

Since trial-based surgery data for adalimumab are yet to be published, for a published proxy we look to the surgery data for infliximab from Rutgeerts et al. [24]. As shown in Figure 2.2.2.4 below, the proportion of patients with CD-related intra-abdominal surgeries in the 5 mg/kg scheduled infliximab treatment group is 5 (2.6%) out of 193. Again, assuming that patients experienced no more than one surgery each, the WMHTAC Model would have predicted 0.62*193 = 119.7 instead of 5 patients.

Therefore, the number of surgeries predicted by the WMHTAC Model for adalimumab-treated patients is considerably greater than the number observed from relevant clinical trials. It might be a reflection of change in in-patient management over years since the development of Silverstein's model, which was published more than 10 years ago, and based on data going back to the 1960's. Furthermore, the

benefits of anti-TNF therapy in reducing surgery observed in CHARM and ACCENT I have not been factored into the WMHTAC model.

- ***The number of medical hospitalisations is not modelled at all.***

As it is derived from the Silverstein et al. [18] model, the WMHTAC Model considers only surgical hospitalisations and not medical hospitalisations. The added benefit of adalimumab in preventing medical hospitalisations, which is a major documented advantage of adalimumab and anti-TNFs in general, is thus ignored by the model, further leading to biased results. Nonetheless, even assuming that the WMHTAC Model predicts both surgical and medical hospitalisations via its surgery state – such that 0.62 hospitalisations per patient per year is predicted for adalimumab – the prediction is still much higher than observed in clinical trials. In the CHARM trial, for example, 18 and 14 per 100-patient-years experienced all-cause and CD-related hospitalisations, respectively, among all patients randomised to the EOW treatment group (Table 2.2.2.6). Assuming that patients experienced no more than one surgery each, the WMHTAC Model would have predicted 0.62*100 = 62.0 instead of 18 and 14 patients who experienced all-cause and CD-related hospitalisations, respectively, in one year.

Table 2.2.2.7: All-Comers analysis of CHARM data: Risk of all-cause and CD-related hospitalisation - All randomised patients; Presented at the American College of Gastroenterology in 2007

Table 4. Risk of All-Cause and CD-Related Hospitalization: All Randomized Patients

Treatment Group	All-cause hospitalization (/100-patient-years)	Relative Risk (95% CI)	CD-related hospitalization (/100-patient-years)	Relative Risk (95% CI)
IO/R	33	1	22	1
EOW	18	0.55 (0.38–0.80)**	14	0.62 (0.40–0.97)*
EW	18	0.55 (0.38–0.80)**	12	0.52 (0.33–0.82)**

*p<0.05 and **p<0.01 vs. IO/R group.

Along with the All-Comers analysis of CHARM data, we look to published hospitalisation data for infliximab from Rutgeerts et al. [24] for a published proxy. As shown in Figure 2.2.2.5 below, the number of CD-related hospitalisations per 100 patients in the 5 mg/kg scheduled infliximab treatment group was 23.0. In contrast, the WMHTAC Model would have predicted 0.62*100 = 62.0 hospitalisations. More importantly, the benefits of anti-TNF therapy in reducing hospitalizations observed in CHARM and ACCENT I have not been factored into the WMHTAC model which biases the ICER estimates for anti-TNF therapy upward.

Of note, the Markov surgery state traces are also used to calculate the surgery state utilities, which factor into the overall ICER estimate. As such, the resulting WMHTAC Model calculation likewise understates the incremental utility difference between adalimumab and Standard Care.

2.2.3 Internal Validity:

- ***Imprecise surgery and relapse cost estimates used.***

We consider that the estimates that the WMHTAC Model use for surgery and relapse state costs, £4,592 and £1,489 in the maintenance severe model respectively, are biased downwards because they are not CD-specific but rather, are general for inflammatory bowel diseases (IBDs), which also include the less

expensive disease ulcerative colitis (UC). Indeed, the WMHTAC report on page 195, "The reference costs [from the NHS Reference cost database 2005/2006] for in-patient and out-patient major and intermediate interventions for Inflammatory Bowel Disease are used as estimates of the costs of severe, moderate relapses and major surgery." Evidence for the lower cost of UC versus CD is given by Bassi et al. [25], where they calculated the 6-month costs per patient of UC (£1,256) to be approximately 24% lower than the cost per patient of CD (£1,652). Considering that the £4,592 cost of surgery is from a non-CD-specific source (i.e., the NHS Costs for IBD) and that a CD-specific estimate for cost of surgery is available from Bassi et al. [25] – a NHS hospital-based, peer-reviewed micro-costing study – it appears inappropriate to not use the Bassi et al. [25] cost figures.

Conversely, the relapse state costs are also taken from IBD estimates, and are thus non-specific to CD and likely biased downwards.

- ***Errors in the construction of the model.***

Upon a closer inspection of the electronic (TreeAge) version of the WMHTAC Model, we identified some errors in the construction of the model. Below are the details of the errors we have identified focusing on the model for adalimumab maintenance therapy in severe CD patients which suggests that Standard Care dominates adalimumab (i.e., more costly and less effective).

  - ***Switch to Standard Care after two cycles in relapse with adalimumab:***
    In the WMHTAC Model, when patients switch to Standard Care after two cycles (i.e., 8 weeks) in relapse with adalimumab, they do so by first going into a "Relapse 2" state for one cycle and then to a "Standard Care Relapse" state (Table 2.1.1b). While in the "Standard Care Relapse" state, patients face the same probabilities of transitioning to "remission", "surgery", and "post-surgery remission" as the relapse state in the Standard Care Markov node. However, the states they enter are actually adalimumab-treated states, such that upon entering these states, they once again reinitiate adalimumab and incur its costs, despite having already failed adalimumab. Therefore, the 2-month stopping rule was implemented incorrectly in the WMHTAC Model. To implement the stopping rule correctly, three additional states would have to be created, to which patients in the "Standard Care Relapse" state would transition to instead: "Standard Care Remission", "Standard Care Post-Surgery Remission", and "Standard Care Surgery". Abbott considers that modelling these patients as remaining in Standard Care would reduce the ICER estimates.

    Note that the WMHTAC stated in their report "For the maintenance model, non-responders to two cycles of treatment as assumed transit to Standard Care relapse. Those who subsequently enter remission do not transit to remission with maintenance treatment. Rather they transit to Standard Care remission, with no possibility of restarting maintenance therapy." (pg. 198) However, we find this not to be true based on how the Markov model was constructed in TreeAge.

  - ***Adalimumab drug cost during EOW maintenance:***
    According to the WMHTAC Model for maintenance therapy, for each cycle (i.e., 4 weeks) of adalimumab maintenance treatment, patients incur £1,072.50 in drug cost. At £357.50 per dose, this is equivalent to three 40-mg doses of adalimumab, which is not correct because "every other week" maintenance therapy should only incur two 40-mg doses per month or £715.00. To account for the extra 40-mg induction dose, however, a £357.50 should be added as a one-time cost. After the monthly drug cost is corrected, the resulting ICER would be considerably lower.

  - ***Use of half-cycle correction:***
    The administration of adalimumab induction and maintenance therapy at specific weeks renders the use of the half-cycle correction invalid. Therefore, the half-cycle correction should be removed.

  - ***Number of cycles:***
    In their report, the WMHTAC said that their model is set to run for thirteen 4-week cycles, or 52 weeks (1 year) total. In the TreeAge model, however, the termination criterion was actually 14 cycles (i.e.,

the model runs until cycle >13). This is a key inconsistency between the WMHTAC report and actual TreeAge model.

Of note, Abbott considers that fixing all of the flaws in the TreeAge model will not result in a model capable of making valid predictions. As per the first section in the critique, the model uses data and methods that systematically overestimate the effectiveness of Standard Care, and as such is fundamentally incapable of measuring the value of anti-TNFs versus STANDARD CARE therapy.

2.2.4 Summary:

Summary of Abbott's critique of the WMHTAC Model is outlined in Table 2.2.4.1 below.

Table 2.2.4.1: Summary of critique of WMHTAC Model

Description of Bias	Effect of Bias	Expected Size of Bias Against Adalimumab
(1) Biased characterisation of clinical course for patients indicated for biologics due to use of Markov methods on a population-based sample of CD patients; use of antiquated and arbitrary Markov states	Data include healthier patients; Markov matrix estimated on these data assumes homogeneity and zero memory and is biased; Silverstein states based on practice patterns over 1960-1996 and responsiveness to conventional therapy and are inapplicable to valuing anti-TNF therapies	Very large (Invalidates study results)
(2) Overestimated Standard Care effectiveness	Biased Markov matrix causes WMHTAC model to predict remission rates of 76% at one year, compared to values of 0% to 19% predicted in meta-regressions of placebo arms in biologic trials. WMHTAC remission constantly increasing over time, contrary to systematic literature review results.	Very large
(3) Underestimated probability of relapse from post-surgery remission and overestimated probability of remaining in post-surgery remission under Standard Care	Markov transitional probabilities over-emphasize transitions into remission and under-emphasize transitions out of remission. WMHTAC transitional probability from post-surgery remission to relapse is 3.4% the size of that observed in a meta-analysis.	Large
(4) Overestimated probability of relapse from remission/post-surgery remission under adalimumab	WMHTAC transitional probabilities grossly overestimate the probability of relapse from remission/post-surgery remission under adalimumab compared to Standard Care, contrary to empirical evidence from CHARM trial.	Large
(5) Invalid assumption for lack of differentiation in outcomes, moderate versus severe CD	WMHTAC model assumes state distributions the same for moderate disease model and severe model, contrary to findings in CHARM trial.	Medium
(6) Overestimated number of surgeries under adalimumab	WMHTAC model predicts number of adalimumab surgeries per patient year is 0.62. Observed percent of surgeries in anti-TNF trials is below 0.05 over one-year maintenance trials.	Large
(7) WMHTAC did not model medical hospitalisations at all	WMHTAC model excluded any modeling of medical hospitalisations, the reduction of which is a key benefit of adalimumab therapy versus Standard Care.	Large
(8) Imprecise surgery and relapse cost inputs used in WMHTAC model	WMHTAC model uses an IBD cost for the cost of a surgery. This cost includes UC patients, who are less expensive than CD patients.	Medium
(9) Errors in the construction of the model	Inconsistencies between WMHTAC report and TreeAge software	Large

Section 3: Response to WMHTAC critique of Abbott submitted pharmacoeconomic model ("Abbott Model")

In their appraisal of the pharmacoeconomic model submitted by Abbott ("Abbott Model"), the WMHTAC implemented two major changes:

1) Incorporating the resource impact of the induction regimen for the 76 non-randomised patients in the CHARM trial

2) Use of the "Simulated Placebo" method of imputing missing values rather than last value carried forward (LVCF)

These two changes caused the incremental cost-effectiveness ratio (ICER) in the severe, active CD patient subgroup to increase from £10,959 to £32,185 for maintenance therapy, which was nonetheless marginally cost-effective. Besides these changes, the WMHTAC also had other critiques of the Abbott Model, which we summarise and respond to in the following.

3.1 Drug cost consumed by 76 non-randomised patients in CHARM

The WMHTAC argued that the 76 patients who dropped out of CHARM between weeks 0 and 4, and therefore were not randomised to adalimumab maintenance therapy, should not be omitted from the model because an ITT perspective should be taken from the start of therapy. We agree with this point to the degree that we should add the adalimumab dosages consumed by these patients into the drug costs of the adalimumab arm in our model.

We incorporate the additional drug costs of the 76 patients who dropped out into our model as follows. We use the observed total dosage (mg) of adalimumab used in the CHARM induction phase by the sample of 76 patients, which equals 8,280 mg or 207 40-mg dosages. We then use the price of £357.50 per 40-mg adalimumab dose to calculate per patient cost of this amount, which is £74,002.50 divided by 76 patients or £974 per patient in the moderate to severe group. We assume that one-third (25.33) of these patients would have been randomised to the EOW group. We also assume that aside from consuming £974 per patient worth of adalimumab, these patients experienced no therapeutic effect, such that their hospitalisation and disease state costs, as well as QALYs are the same as Standard Care-treated patients. These patients are then combined with the 260 EOW patients to calculate new ICERs for severe and moderate to severe patients. As per Table 3.1.1, the new weighted medication (i.e., anti-TNF) cost would be £974*(25.33/285.33) + £7,075*(260/285.33) = £6,533. While average anti-TNF costs decline on average for the new sample, the hospitalisation and disease state costs increase and QALYs decrease.

Table 3.1.1: Costs and QALYs for the Adalimumab Sample Weighted by the 260 EOW patients and the 76 Patients Who Dropped Out

	ADA: 76- patient analysis	ADA: 260 EOW analysis	Weighted ADA Analysis (76 and 260 EOW analysis)
N	25.33	260	285.33
Costs			
Medication cost	£974	£7,075	£6,533
Hospitalisation cost	£5,265*	£1,713	£2,028
Disease state cost	£2,049*	£1,171	£1,249
QALYs	0.7743*	0.865	0.857

* Assumed to be the same as the Standard Care arm, because these patients derive no benefit from adalimumab.

These values were incorporated into the ICER calculations. The Standard Care arm is assumed not to change. The new analysis renders the cost-effectiveness results presented in Tables 3.1.2 and 3.1.3 for moderate to severe and severe patients, respectively.

Table 3.1.2: Revised cost-effectiveness results including the drug cost of 76 non-randomised patients in the CHARM trial – moderate to severe patients

Costs	Adalimumab	Placebo	Incremental	
Randomised patients Anti-TNF Drugs (N=260)	£6,533	£0	£6,533	
CDAI States	£2,028	£5,265	-£3,237	Incremental cost-effectiveness ratio (ICER)
Hospitalisations	£1,249	£2,049	-£800	
Total	**£9,810**	**£7,315**	**£2,496**	
Quality-adjusted life-years (QALYs)	**0.8566**	**0.7743**	**0.0823**	**£30,319**

Table 3.1.3: Revised cost-effectiveness results including the drug cost of 76 non-randomised patients in the CHARM trial – severe patients

Costs	Adalimumab	Placebo	Incremental	
Randomised patients Anti-TNF Drugs (N=260)	£7,119	£0	£7,119	
CDAI States	£2,598	£7,485	-£4,886	Incremental cost-effectiveness ratio (ICER)
Hospitalisations	£1,429	£2,407	-£979	
Total	**£11,146**	**£9,892**	**£1,254**	
Quality-adjusted life-years (QALYs)	**0.8384**	**0.7339**	**0.1045**	**£11,998**

After adding in the additional dosages consumed by a third of the non-randomised patients to the overall sample, the cost-effectiveness of adalimumab among severe patients at baseline is £11,998 per QALY (Table 3.1.3). Considering that some of the 76 patients were excluded before randomisation at week 4 because of protocol violations, withdrawal of consent, and/or administrative reasons (N=16), these patients' biologic costs may not be realistic to include in a real world analysis, but we do so to be conservative.

3.2 Excess adverse events or hospitalisations for 76 non-randomised patients in CHARM

However, we disagree that the 76 patients who dropped out prior to week 4 would have incurred any incremental increase in costs (e.g., from additional hospitalisations) or disutility compared to a similar set of Standard Care-treated patients. To validate this assertion, we consider Figure 2.5.1 below, which is Table 3 from Colombel *et al*.[26]. This was a review of the safety records from all adalimumab CD clinical trials and open-label extensions, including CHARM, CLASSIC I, CLASSIC II, GAIN, and the 690 open-label extension study. Table 3 in this study includes all safety events in the induction trials (CLASSIC I and GAIN) as well as the induction part of the CHARM trial by dose (Figure 3.2.1).

Figure 3.2.1: Adalimumab Safety in CD Clinical Trials as of 14th February 2006

Table 3. Adverse Events of Interest: Induction Period

Adverse events (AE), n (%)	Placebo N=240	Adalimumab 80/40 mg DB N=75	Adalimumab 80/40 mg OL N=854	Adalimumab 160/80 mg DB N=235
Any AE	176 (73)	51 (68)	508 (60)	148 (63)*
Any serious AE	11 (5)	1 (1)	45 (5)	5 (2)
Any AE leading to discontinuation	6 (3)	1 (1)	54 (6)	2 (1)
Infectious AE	51 (21)	12 (16)	130 (15)	38 (16)
Serious infections	4 (2)	0	10 (1)	2 (1)
Injection-site related AE	29 (12)	16 (21)	109 (13)	41 (17)
Opportunistic infections	0	0	1 (0.1)	1 (0.4)
Demyelinating disease	0	0	1 (0.1)	0
Any fatal AE	0	0	1 (0.1)	0

*Statistically significant difference vs. placebo ($p \leq 0.05$) using Fisher's Exact test.
Statistical testing was only performed for the pooled adalimumab 160/80 mg and placebo groups.
No malignant neoplasm or congestive heart failure (CHF) occurred.

The CHARM adverse events in the induction period are listed in the column marked in blue entitled, "Adalimumab 80/40 mg OL, N=854" of Figure 2.5.1. To make a fair comparison for a true incremental analysis, there would have been a placebo arm in CHARM that received placebo induction, but there was not. There is a column marked in red, entitled "Placebo N=240," which corresponds to the placebo arms in CLASSIC I and GAIN for which we have adverse event information. However, this is not a fair comparison, owing to the less stringent inclusion criteria and healthier patient selection of these studies. Nevertheless, we use these patients for comparison versus the more severe CHARM column. As can be observed in comparing the numbers in parentheses of the two columns, the placebo adverse events are higher for any adverse event (AE), are the same for any serious AE, and are higher for infectious AE and serious infections. Any AE leading to discontinuation (which is a subset of the others) and injection-site related AEs are higher in CHARM. However, the serious AE row would be most appropriate for assuming incremental costs or disutilities. Because these rates are equivalent, there is no reason to model costs or disutilities related to them. It should be noted that the placebo column, which includes less severe patients than are in CHARM but patients of equal severity to those in CLASSIC I and GAIN, has higher rates of adverse event rates compared to the CLASSIC I and GAIN columns in almost every category of AE. Furthermore, modeling of the cost effectiveness of anti-TNF therapy in ankylosing spondylitis indicated that the inclusion of adverse events had minimal impact in changing the estimated ICERs.

Of note, more data has been released as to the positive risk profile of adalimumab. For instance, see Colombel et al. [27] and Lichtiger et al. [28].

3.3 Remission with adalimumab

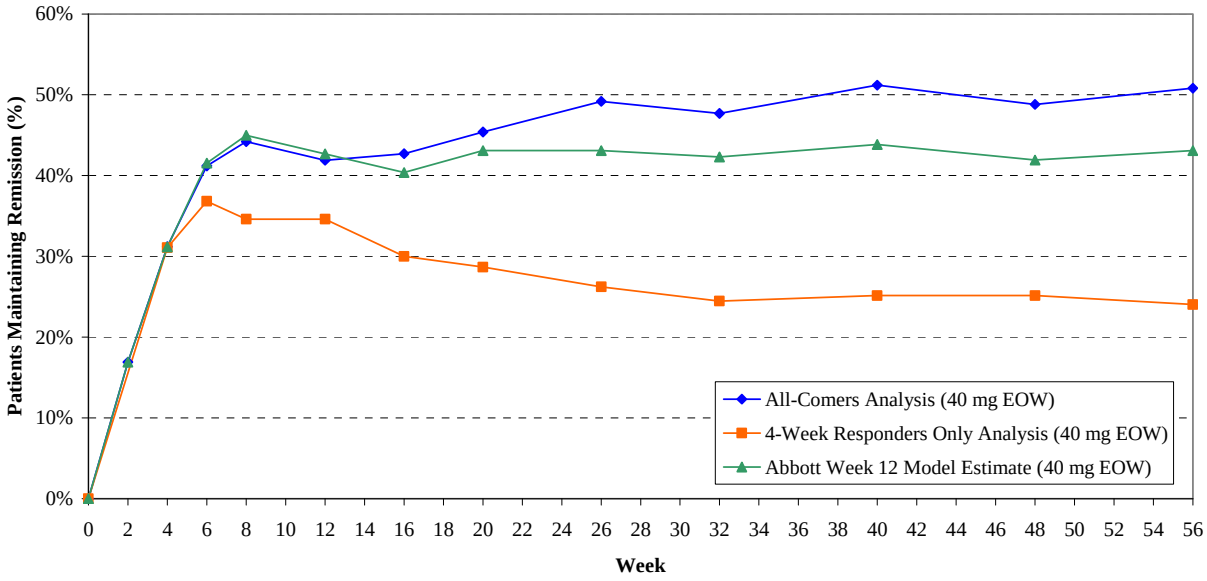
The WMHTAC argued in its report that the Abbott Model was not interpretable because it was unclear how the remission rates were derived:

> *"The clinical endpoints of the CHARM trial related to Week 4 responders (a reduction in CDAI of 70 points from baseline) and all published data referred to this group. This causes difficulties in interpreting the data, since terms are duplicated with few caveats. Where published data and the industry clinical submission referred to responders and non-responders, they did so based on a comparison of baseline and four week data (randomisation); the economic submission appeared to define this split using baseline versus Week 12 data."* Page 176 WMHTAC report

The WHMTAC considered only the Colombel et al. [20] analysis on week-4 responders in its report. However, the SmPC indicates that adalimumab should be used for the treatment of responders and non-responders to week 12, and for responders afterwards. In designing its pharmacoeconomic model, Abbott modelling was conducted in line with the licensed indication. As such, the 12-week responder stopping rule was used in the Abbott pharmacoeconomic model, as was an ITT perspective. Comparing outcomes of Colombel et al. [20] versus the Abbott Model implies a misconception of the data. The All-Comers Analysis should clarify the differences.

We compare the Abbott Model outcomes versus CHARM remission curves as presented in two publications. In the first publication, Colombel et al. [20] presented an analysis of only the 177 EOW patients in the CHARM trial who responded at week 4 and not of the full 260 patients randomised to the EOW arm (i.e., Week-4 Responder-Only analysis). As shown in Figure 2.6.1, the "Week-4 Responder-Only analysis" line diverges from the other CHARM remission curves at week 4. It also assumes that any patient who switched from the EOW dosing arm to open-label, including those who dose-escalated to every week (EW) dosing, is a treatment failure and therefore not in remission. Finally, for missing patients, the Week-4 Responders-Only analysis does not use LVCF but instead uses the most conservative method for handling patients who drop out of the trial - that is, these patients were assumed to not be in remission upon going missing. This is true even if a patient dropped out when in remission.

Figure 3.3.1: Remission Rates for Moderate and Severe CD Patients Reported in the All-Comers Analysis of CHARM (presented at ACG 2007), the Week Four Responders-Only Analysis of CHARM [20]



Notes:
1) All-comers analysis focused on the intention-to-treat population, which included both responders and non-responders at week 4. The LOCF method was used to deal with missing data. Observed data for patients who switched to open label were included in the analysis.
2) Colombel et al.'s modified intention-to-treat analysis focused only on responders at week 4. Non-responders at week 4 were considered treatment failures, as were patients who switched to open label, and patients who dropped out, including when in remission.
3) The Abbott week 12 model employed a "stopping rule" which assumed that non-responders at week 12 discontinued treatment and set their clinical measures to missing at that point. Data for missing, dropped-out, and non-responsive patients were imputed using the LOCF method.

In the second publication, the All-Comers analysis [29] is different from the Week Four Responders-Only analysis. It used all CDAI observations as recorded in CHARM, including those of patients who did not respond by week 4 and those who went open-label, including dose-escalation. It also used LVCF for missing patients.

The Abbott Model uses all CDAI observations as recorded in CHARM until week 12, at which point only responders are treated, as per the SmPC label. It uses LVCF for missing patients and for non-responders after week 12 in its base case analysis. The Abbott Model also uses the direct observations of patients who went on to open-label adalimumab. It should be noted that all patients switching to

adalimumab EOW or EW open-label were included in the cost modelling, contrary to an assertion by WMHTAC. The main differences and similarities between the aforementioned publications and the Abbott Model are summarised in Table 3.3.1 below.

Table 3.3.1: Differences in CHARM Remission Calculations

	REPORTING DIFFERENCES IN CHARM DATA			
PUBLICATION/ MODEL	**Open-label Patients Are Assumed to Not Be in Remission** (Even if after dose-escalating to every week dosing, patients had CDAI < 150)	**Drop-out Patients Assumed to be Not in Remission** (Even if final CDAI observation was < 150 for a patient at drop-out)	**4-Week Responders-only Analysis** (Non-responders at week 4 assumed to be not in remission, even if CDAI < 150 after week 4)	**12-week Stopping Rule as per SMPC Label** (LVCF for non-responders at week 12; assumed to be not in remission, even if CDAI < 150 after week 12)
4-Week Responders Only Analysis [20]	YES	YES	YES	NO
All-Comers Analysis [29]	NO – OBSERVED CDAI USED	NO – LVCF USED	NO – ALL CDAI OBSERVATIONS USED	NO – ALL CDAI OBSERVATIONS USED
Abbott Model	NO – OBSERVED CDAI USED	NO – LVCF USED	NO – WEEK 12 STOPPING RULE USED	YES

Figure 3.3.1 presents remission curves from the sources reporting remission rates for moderate and severe CD patients of the EOW arm in the CHARM trial. As can be seen, the 12-week model submitted to NICE uses observations for remission, which are above the 4-week Responder-only outcomes (orange line) published in Colombel et al. [20] and below the All-Comers Analysis outcomes (blue line) presented at ACG 2007. Thus, Figure 3.3.1 demonstrates that the modelling of remission in the adalimumab arm is not overestimating the effectiveness of adalimumab. Due to the week-12 stopping rule, the Abbott Model remission outcomes are about eight percentage points lower than those of the All-Comers Analysis.

3.4 Dosing, open-label patients, and CDAI

The WMHTAC considers that the values used for the number of Abbott doses and the number of doses specifically used for patients who dose-escalated were incorrect:

> *"It appeared that the economic model is based on data considering only the blinded portion of the CHARM trial…"* Page 177 WMHTAC report
> Also: *"The total usage figures did not increase to the levels that would otherwise be expected because of a significant number of patients within CHARM who did not receive their indicated treatment."* Page 182 WMHTAC report

The Abbott Model used the observed mg of adalimumab doses consumed in the CHARM trial, including those consumed by patients who went into an open-label state or dose-escalated to EW dosing. The only adjustments to dose were for patients who had not responded by week 12. For these Week 12 non-responders, the Abbott Model calculated adalimumab doses using the observed dose reported in the clinical trial from Week 0 to Week 12, and then set their doses to zero thereafter (under the premise that they discontinued adalimumab treatment and switched to standard of care). In contrast, for patients who are Week 12 responders, doses were calculated using the observed dose as reported in the clinical trial from Week 0 to the last dose date. If a week-12 responder switched to open-label EW, the true observed dose was captured in the calculation as well.

Of note, WMHTAC is incorrect in their statement in the revised version of their report (June 2008) that, *"The revised model estimated resource use for Week 12 responders and non-responders up to Week 12, and non-responders after Week 12 (until missing or Week 56) for blinded EOW treatment only"* (Page 177). The Abbott model applies a stopping rule, under the premise that non-responders would not continue to receive therapy after week 12.

In conclusion, the Abbott Model used observed rather than predicted values for doses in its analysis. Please refer to Appendix 2, which presents the percentage of patients and average dose on each type of adalimumab dosing for each week by CDAI interval (remission, moderate, severe, very severe). Doses for blinded and open label patients are also listed. Of note, the 19.5 doses in Appendix 2 differs from the 19.8 used in the Abbott Model because of a rounding error.

3.5 Last observation carried forward (LVCF) for dropouts in CHARM

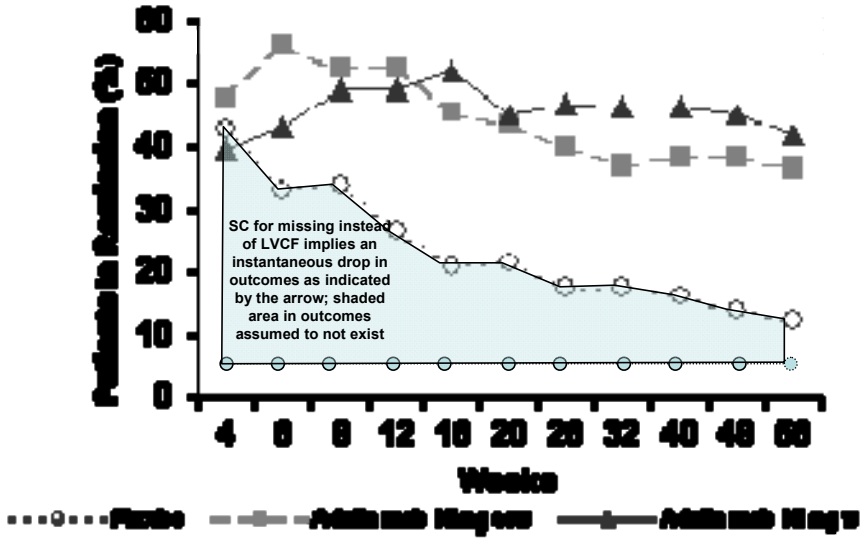
For dropouts in CHARM, the WMHTAC believes that assuming their last CDAI value carries forward indefinitely (i.e., LVCF) is not appropriate, but prefer that they immediately take on the CDAI state predicted for them by the Standard Care model (i.e., Simulated Placebo):

> *"The [WMHTAC] revised model used the "Simulated Placebo" method of imputing missing values. Those leaving the CHARM trial did so because of disease flare or other issues requiring protocol-violating treatments, and so their health may have been poorer than an "equivalent" simulated Standard Care outcome (which represented expected health at four weeks). The "simulated placebo" assumption is more neutral with respect to the prognosis of those leaving blinded CHARM treatment than the LVCF used in the industry model."* Page 176 WMHTAC report

While there is no agreed upon optimal method of handling missing observations, LVCF is a commonly accepted method because it is considered neutral in terms of bias. Both the FDA and EMEA accept submissions of trials that use LVCF to handle missing observations. Furthermore, LVCF was used to handle missing observations by Rutgeerts et al. [24] in their analysis of the ACCENT I trial, as well by Hanauer et al. 2006; Sandborn et al. 2001; Gordon et al. 2001; Hommes et al. 2006; Ghosh et al. 2003; Korzenik et al. 2005; and Sands et al. 2002 in the placebo arms of the biologic trials previously outlined in Table 2.2.2.1.

Nonetheless, we did perform a sensitivity analysis that very conservatively assumed that patients take on their Standard Care-predicted CDAI state *instantaneously* upon dropping out. To illustrate how this "Simulated Placebo" method is very conservative, we refer to a figure from Colombel et al. [20] that is reproduced below as Figure 3.5.1, which shows that for patients who discontinued adalimumab after week 4 (i.e., randomised to placebo after induction), the treatment effect diminished *gradually* over time rather than *instantaneously* (i.e., the downward slope of the placebo remission curve is gradual). Note also that Colombel et al. [20] aggressively assumed non-remission whenever patients drop out or switch to open-label, such that the actual placebo remission curve is likely to decrease even more gradually than in Figure 3.5.1. In contrast, the "Simulated Placebo" method would imply that the remission rates of patients discontinuing adalimumab at week 4 would fall from 42% to below 10% *instantaneously* upon treatment discontinuation. The light blue-shaded area of Figure 3.5.1 demonstrates the large difference in remission rate benefits between the observed remission curve for patients discontinuing adalimumab at week 4 and the remission curve that the "Simulated Placebo" method would impute for this same group of patients.

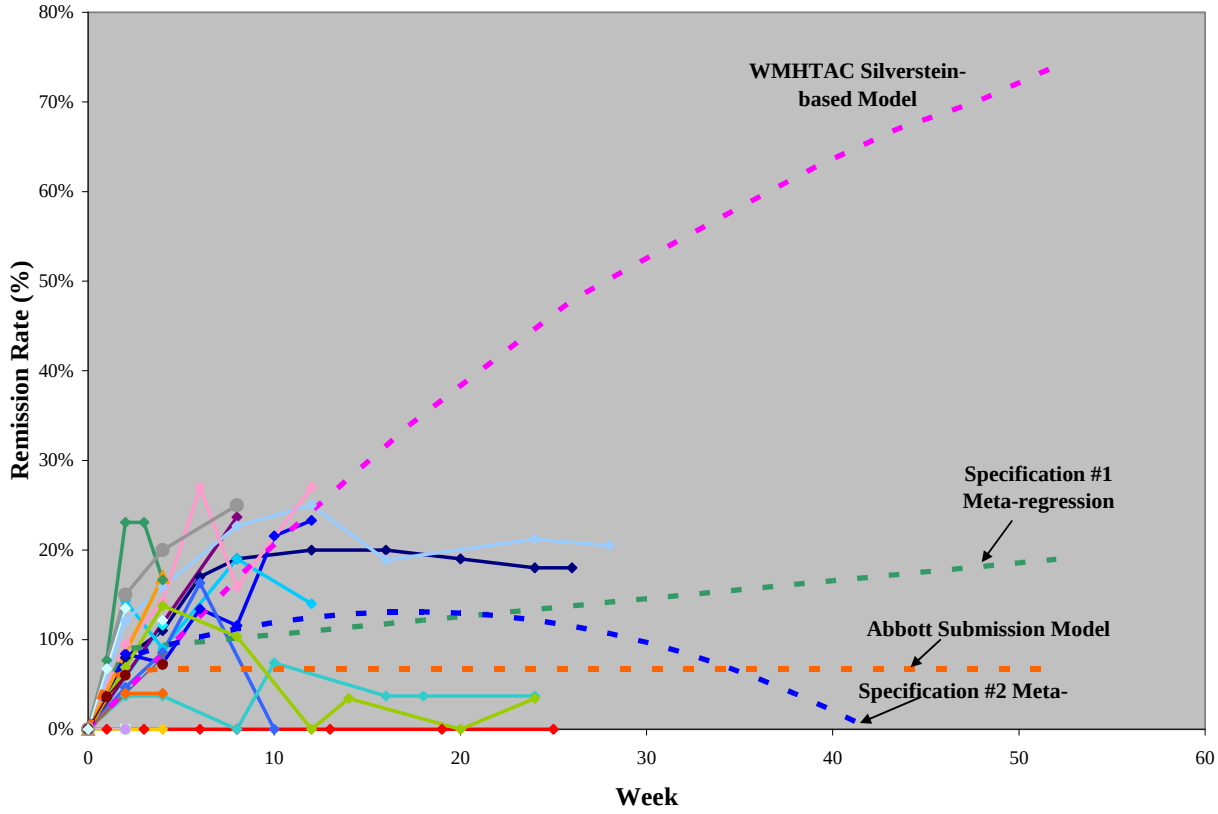
Figure 3.5.1: Remission Rates from CHARM for Week Four Responder Patients Randomised to Placebo, EOW, and EW dosing



3.6 Validating the Abbott submission Standard Care-prediction model remission rates versus the systematic literature review

The systematic literature review of placebo arms from randomised controlled trials evaluating biologics, described in detail previously, was also used to test the external validity of the Abbott Model. The remission rate over 56 weeks for the Abbott Model appears in Figure 3.6.1, along with the systematic literature review observations, meta-regressions, and remission rate predicted by the WMHTAC Model.

Figure 3.6.1: Comparison of meta-analysis results with Abbott and WMHTAC prediction models remission rate by week- placebo arms of biologic trials only



The remission estimates of the Abbott Model for moderate to severe CD patients are somewhat lower than those predicted by the meta-regressions by week 26. The Abbott Model reaches a steady state at 6.8%, while the linear meta-regression predicts a value of 13.8% and the week-squared model predicts a value of 11.5% in remission at week 26. By week 42, the week-squared meta-regression predicts 0% remission. By week 52, the linear meta-regression predicts a 19.0% remission rate.

The mean remission percentage over 26 weeks for the Abbott Model appears in Table 3.6.1 below, along with the percentages from the systematic literature review and WMHTAC Model.

Table 3.6.1: Comparison of biologic RCT weighted averages with Abbott and WMHTAC Model estimates over 26 weeks

Model	Time Spent in Remission
Abbott Model	6.75%
WMHTAC Model	27.24%
Systematic Literature Review Biologic Placebo Arm Mean (N=1,257)	8.48%
Systematic Literature Review Biologic Placebo Arm Mean Weighted by Sample Size of the Trial (N=1,257)	11.61%
Systematic Literature Review Biologic Placebo Arm Mean Weighted by Sample Size and Duration of the Trial (N=1,257)	14.57%

The Abbott Model prediction is closer to the systematic literature review results than the WMHTAC Model, but lower than the systematic literature review. We believe that the lower remission percentage of the Abbott Model is caused by three factors. First, the CHARM sample was severe even for a biologic-

evaluation trial. CHARM CDAI average was 313 versus 296 in the systematic review and 51% of CHARM patients had prior infliximab exposure at baseline versus 28% in the review, among other factors. Secondly, drop-out from the trials in the systematic literature review is substantial, averaging 30%, and it is particularly acute in the longer term trials (47% dropout from Sandborn et al., 2007). It is likely that this placebo arm drop-out is correlated with lack of therapeutic effect (see analysis of Sutherland et al., in Appendix 1). As such, the systematic literature review and the meta-regression based upon it reflect an upper-bound of remission rates. The systematic literature review demonstrates the validity of the Abbott submission Standard Care-prediction model.

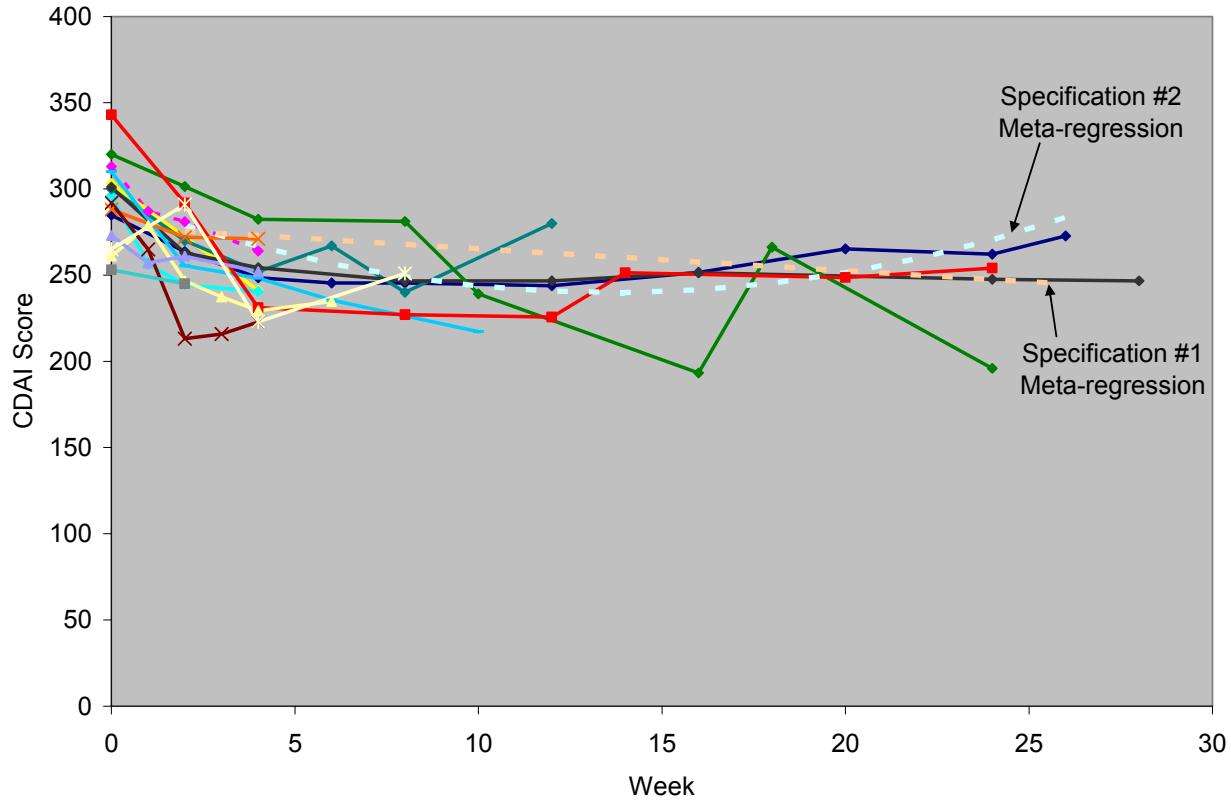
3.7 Validating the Abbott submission Standard Care-prediction model assumption of steady state distribution over time after week four versus the systematic literature review

The WMHTAC Model predicts a monotonically increasing remission rate, and low and decreasing proportions of patients in more severe states. The Abbott Model predicts for Standard Care an improvement over four weeks, and then a constant percentage of patients in each of the four CDAI intervals (remission, moderate, severe, and very severe) over time. We tested these two premises in the systematic literature review by examining data on CDAI.

As per Appendix 1, fewer studies reported CDAI. Therefore, meta-regression analysis on CDAI scores was performed using the 23 placebo and Standard Care intervention study arms with valid mean CDAI and variance data identified in the initial study selection. The Abbott and WMHTAC models did not directly estimate mean CDAI—so we cannot directly test versus model predictions. However, visual inspection of the CDAI values from the systematic literature review can present information about whether the overall severity distribution is increasing, decreasing (as per the WMHTAC Model) or remaining constant (as per the Abbott Model).

Again, we fitted meta-regression models with a linear (specification 1) and a non-linear specification (specification 2) using week plus week-squared in the non-linear specification. Please review Appendix 1 for details. Specification 1 and 2 predictions of CDAI values at week 26 were 244 and 283, respectively. Considering that the week-squared coefficient had a significant p value ($p = 0.001$) and that specification 2 has a better fit, the non-linear specification is the more valid projection of CDAI over time. This is strong evidence that CDAI is convex and worsening. Both meta-regressions for CDAI score appear in Figure 3.7.1.

Figure 3.7.1: CDAI Meta-regressions and Observations from the Systematic Literature Review - Placebo Arms



Because of the better fit of the non-linear specification 2, the overall trend in severity is worse over time. The meta-regression for CDAI suggests that CD patients not only do not have a monotonically increasing remission rate over time as per the WMHTAC Model, but that the Abbott Model steady state prediction may be conservative. This supports the evidence that the WMHTAC Model underestimates the severity of CD over time.

3.8 WMHTAC assumption that dropout is linear is incorrect: a lifetime model is warranted

The WMHTAC did not believe that a lifetime model was warranted because of a linear dropout effect. Specifically, the WMHTAC stated that the final patient on adalimumab would drop out of therapy during year four:

> *"With an approximately constant number of people leaving the trial's adalimumab arm from Week 7 onwards within CHARM, it can be predicted when the last individual would cease to receive adalimumab on this until-flare maintenance regimen. With the limited data made available from the economic model, it is predicted that the last dose of adalimumab corresponding to the blinded (and costed) treatment on CHARM would have occurred in Week 189. A lifetime model is not necessary here as - under the assumptions of the placebo method of imputing lost values – the Standard Care and adalimumab model arms would have been identical after four years and so a 4-year timeframe suffices." (*Page 177 WMHTAC report*)*

The WHMTAC argued that study dropout could be extrapolated using a linear function. Using this assumption, the last patient on adalimumab would have dropped out of the trial in week 189. Available long-term data indicate that this assumption is erroneous.

Figure 3.8.1: Non-linear dropout rate in CHARM study

Note: Several patients that completed CHARM until week 56 did not enrol in the OL extension trial. As a result, the lines in figure 3.8.1 do not intersect.

Figure 3.8.1 demonstrates that of the N=260 patients randomised to adalimumab EOW, [redacted] continue to receive adalimumab at the end of year 3. Of the patients randomised to adalimumab EOW who entered the open label extension at week 56, [redacted] remained on adalimumab up to week 164. Thus, a lifetime model is warranted.

3.9 Probabilistic sensitivity analysis (PSA) of Abbott model

Abbott has submitted an updated PSA with this response to address the WMHTAC's concerns on the lack of uncertainty regarding the clinical effectiveness of adalimumab. For both Standard Care and adalimumab arms, the probability of being in the remission, moderate, severe or very severe states over the 56-week period was varied with a Dirichlet distribution. The moments of the Dirichlet distribution (in the severe patient population) are detailed in the table below. This distribution has been incorporated into the revised July 2008 model (in the attached MS Excel file). Further, the Addendum of Results (Appendix 4) also includes the new PSA results that incorporate this distribution.

Table 3.9.1. Moments of Dirichlet distribution used to model stochastic variation of the probability of being in the remission, moderate, severe and very severe states for the adalimumab and Standard Care arms

Proportion (%) of Time Spent in CDAI States over 56 Weeks	Probability	Dirichlet alpha	Dirichlet beta
Adalimumab - Remission	39.9%	103.7	156.3
Adalimumab - Moderate	43.7%	113.6	146.4
Adalimumab - Severe	16.1%	41.9	218.1
Adalimumab - Very Severe	0.3%	0.86	259.1
Standard Care - Remission	6.6%	17.2	242.8
Standard Care - Moderate	39.2%	102.0	158.0
Standard Care - Severe	44.6%	115.9	144.1
Standard Care - Very Severe	9.6%	25.0	235.0

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