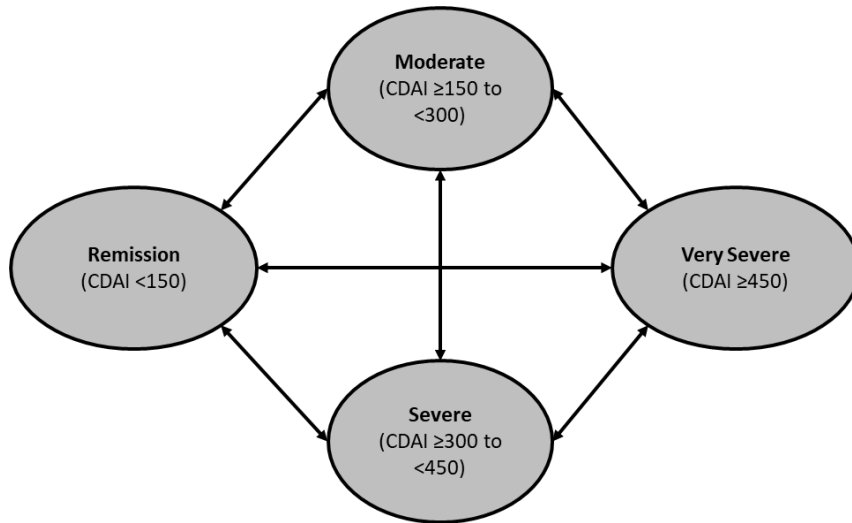


Supplemental Tables and Figures

Supplemental Figure 1. Model structure



Patients with Crohn's disease have different levels of disease activity, included as the following CDAI-based health states in the model: Remission (CDAI <150), Moderate (CDAI ≥ 150 to <300), Severe (CDAI ≥ 300 to <450), and Very severe (CDAI ≥ 450). Each model week, a patient was predicted to be in one of the health states. Transitions between health states were weekly and based on a regression model. Health states determined patients' costs, health utility and likelihood of hospitalisation. The model was programmed using STATA v.15 and Microsoft Excel.

Table S1. Baseline characteristics

Table S1: Comparison of baseline characteristics¹					
Characteristic	Tight Control (N = 122)		Clinical Management (N = 122)		p-value²
<i>Demographics</i>					
Age in years, mean (SD)	32.1	(12.0)	31.1	(11.4)	0.5364
Male, n (%)	50	(41.0%)	53	(43.4%)	0.6974
Disease duration in months, mean [median] (SD)	12.7 [2.5]	(27.3)	10.5 [2.7]	(20.5)	0.9609
CDAI					
Remission (CDAI < 150)	0	(0.0%)	0	(0.0%)	1.0000
Moderate (150 ≥ CDAI < 300)	89	(73.0%)	92	(75.4%)	0.6608
Severe (300 ≥ CDAI < 450)	33	(27.0%)	29	(23.8%)	0.5564
Very severe (CDAI ≥ 450)	0	(0.0%)	1	(0.8%)	0.3163
Previous CD-related drug use					
Aminosallylates	26	(21.3%)	20	(16.4%)	0.2290
Antibiotics	0	(0.0%)	3	(2.5%)	0.0607
Systemic corticosteroids	6	(4.9%)	7	(5.7%)	0.5944
<i>Employment characteristics</i>					
Percent of Work Hours Missed (Absenteeism), mean (SD)	35.8	(42.9)	30.0	(37.4)	0.9536
Notes:					
[1] Baseline characteristics assessed at the baseline visit in the CALM clinical trial.					
[2] Wilcoxon rank-sum tests and Chi-square tests used to compare continuous and categorical variables, respectively.					
Sources: CALM clinical trial data.					

Table S2. Regressions for CDAI-based health states, CD-related hospitalisation, and change in absenteeism using simple specification

	CDAI-based health state ¹ (N=244)		CD-related Hospitalisation ² (N=244)		Change in absenteeism from Baseline due to CD ³ (N=129)	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
Treatment Effect						
Clinical Management	Ref.		Ref.		Ref.	
Tight Control	-0.293	0.012	-0.247	0.037	-5.606	0.346
Intercept/Cut 1			-2.548	0.000	-12.174	0.000
Cut 1	-0.095	0.000	N/A	N/A	N/A	N/A
Cut 2	1.063	0.000	N/A	N/A	N/A	N/A
Cut 3	2.422	0.000	N/A	N/A	N/A	N/A
Notes:						
[1] CDAI is a categorical variable taking on values of 1 through 4, where 1 is remission and 4 is very severe. An ordered probit is used to determine the effect of tight control relative to clinical management.						
[2] CD-related hospitalisations were captured at a weekly level and there was never more than one hospitalisation per individual at this time unit of measurement. The effect of tight control relative to clinical management was modeled using a probit model.						
[3] Absenteeism, or the percent of work hours missed from baseline, is calculated as the number of hours missed divided by the sum of the hours missed and the hours worked in the past seven days. The effect of tight control relative to clinical management was determined using an OLS model.						
[4] All regressions used robust standard errors clustered at the patient level.						
Sources: CALM clinical trial data.						

Table S3: Multivariate regressions for CDAI-based health states, CD-related hospitalisation, and change in absenteeism using cost-effectiveness model specification

	CDAI-based health state ¹ (N=244)		CD-related Hospitalisation ² (N=244)		Change in absenteeism from Baseline due to CD ³ (N=129)	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
Interaction Treatment x Lagged CDAI-based health state						
CM x Remission	Ref.		Ref.		Ref.	
CM x Moderate	2.285	0.000	0.420	0.022	4.518	0.331
CM x Severe	4.354	0.000	0.584	0.006	12.974	0.009
CM x Very Severe	6.151	0.000	0.998	0.031	N/A	
TC x Remission	-0.195	0.143	-0.305	0.176	-8.332	0.264
TC x Moderate	2.143	0.000	0.196	0.319	3.888	0.666
TC x Severe	4.005	0.000	0.483	0.051	25.794	0.002
TC x Very Severe	5.038	0.000	N/A		N/A	
Indicator for Visits after Week 23	0.305	0.000	0.191	0.094	-2.214	0.245
Time Since Last Health State	0.024	0.317	N/A		N/A	
Intercept			-2.938	0.000	-14.147	0.003
Cut 1	1.715	0.000	N/A	N/A	N/A	N/A
Cut 2	3.955	0.000	N/A	N/A	N/A	N/A
Cut 3	6.311	0.000	N/A	N/A	N/A	N/A
Notes:						
[1] CDAI-based health state is a categorical variable taking on values of 1 through 4, where 1 is remission and 4 is very severe. An ordered probit is used to determine the effect of tight control relative to clinical management.						
[2] CD-related hospitalisations were captured at a weekly level and there was never more than one hospitalisation per individual at this time unit of measurement. The effect of tight control relative to clinical management was modeled using a probit model.						
[3] Absenteeism, or the percent of work hours missed, is calculated as the number of hours missed divided by the sum of the hours missed and the hours worked in the past seven days. The effect of tight control relative to clinical management was determined using an OLS model.						
[4] All regressions used robust standard errors clustered at the patient level.						
Sources: CALM clinical trial data.						

Table S4. Markov matrices derived from CE model ordered probit specification

Transition probabilities up to and including model week 23				
CM				
	Remission	Moderate	Severe	Very Severe
Remission	0.947	0.053	0.000	0.000
Moderate	0.253	0.689	0.057	0.000
Severe	0.003	0.308	0.658	0.031
Very Severe	0.000	0.011	0.515	0.474
TC				
	Remission	Moderate	Severe	Very Severe
Remission	0.965	0.035	0.000	0.000
Moderate	0.300	0.657	0.043	0.000
Severe	0.009	0.434	0.544	0.014
Very Severe	0.000	0.119	0.761	0.119
Transition probabilities after model week 23				
CM				
	Remission	Moderate	Severe	Very Severe
Remission	0.906	0.094	0.000	0.000
Moderate	0.166	0.732	0.102	0.000
Severe	0.001	0.211	0.728	0.060
Very Severe	0.000	0.005	0.400	0.595
TC				
	Remission	Moderate	Severe	Very Severe
Remission	0.934	0.065	0.000	0.000
Moderate	0.204	0.717	0.079	0.000
Severe	0.004	0.323	0.645	0.028
Very Severe	0.000	0.069	0.739	0.191

Supplemental Appendix: Sensitivity analysis using model structure with Mild and Non-mild sub-states

A sensitivity analysis was conducted, where the moderate state (CDAI 150 to <300) was divided into two sub-states, “Mild” based on patients who at a given observation had CDAI from 150 to <220, and “Non-mild Moderate” based on patients who at a given observation had CDAI 220 to <300. Model inputs were estimated based on the weight of “Mild” and “Non-mild Moderate” sub-state.

After we divided Moderate patients in Mild and Non-mild Moderate sub-states, CM patients were slightly more likely to be Mild than Non-mild Moderate (simple average: 54.2%) compared to TC patients (46.8%) based on a simple average over the entire 48 weeks. The higher rate of Mild sub-state observed in the CM arm is probably due to the fact that TC had a higher remission rate (CDAI<150) compared to the CM.

Model input estimation based on “Mild” and “Non-mild Moderate” sub-states:

Health Utility

We modified health utilities in the sensitivity analysis using the Buxton et al.¹ health utility regression, as we had done for the other analyses in the manuscript. This changed the Mild patient annual health utility input to 0.6918 and the Non-mild Moderate annual health utility to 0.6024; both had been 0.647 when classified as Moderate in the base case analysis.

Other Direct Medical Costs

We modified other direct medical costs (excluding hospitalization and biologic costs) in the sensitivity analysis using the findings in Bodger et al²., applying £41.93 of other direct medical weekly cost to the Mild patients and £65.50 to the Non-mild Moderate sub-state; both had been £41.93 when classified as Moderate in the base case analysis. £41.93 and £65.50 are the weekly cost of other direct medical costs in patients with Moderate and Severe health state in Bodger et al. respectively.

Hospitalization Costs:

We modified the hospitalization regression in the sensitivity analysis, so that it would predict hospitalization for weeks persons spent in the Mild or Non-mild Moderate sub-states. As an example, for TC patients in the post-week 23 period, this changes the Mild weekly probability input to 0.0037 and the Non-mild Moderate weekly probability to 0.0070; both had been 0.0054 when classified as Moderate in the base case analysis.

Results and ICER from the sensitivity analysis incorporating “Mild” and “Non-mild Moderate” sub-states:

In the cost-effectiveness results based on this sensitivity analysis, the total costs were £606 higher in the TC than CM (total costs £13,449 for TC and £12,842 for CM) with incremental 0.029 QALY (total QALY 0.668 in TC and 0.639 in CM), resulting an ICER of £20,991/QALY, see Table S5 below. When including absenteeism effects, TC continues to dominate. The conclusion from the sensitivity analysis is consistent with the results of the base case model in the manuscript (ICER of £18,656/QALY), where TC

¹ Buxton MJ, Lacey LA, Feagan BG, Niecko T, Miller DW, Townsend RJ. Mapping from disease-specific measures to utility: an analysis of the relationships between the Inflammatory Bowel Disease Questionnaire and Crohn's Disease Activity Index in Crohn's disease and measures of utility. *Value in Health*. 2007 May;10(3):214-20.

² Bodger K, Kikuchi T, Hughes D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. *Alimentary pharmacology & therapeutics*. 2009 Aug;30(3):265-74.

remains cost effective (excluding absenteeism effect) based on the UK threshold, and TC is dominant when including the effect of absenteeism (i.e., the cost is less and the QALY is higher for TC vs CM).

Table S5. Cost-effectiveness results: Sensitivity Splitting Moderate into Mild and Non-mild Moderate Sub-states

Outcome	Sensitivity Model Splitting Moderate into Mild and Non-mild Moderate Sub-states		
	TC	CM	Incremental (TC - CM)
Hospitalisation events per patient	0.1239	0.298	-0.174
Direct medical costs			
Adalimumab costs	£10,770	£8,601	£2,170
CRP and FC testing costs	£109	£0	£109
Hospitalisation costs	£1,046	£2,509	-£1,463
Other direct medical costs	£1,524	£1,732	-£209
Total costs	£13,449	£12,842	£606
Total QALYs	0.668	0.639	0.029
ICER (excluding absenteeism)			£20,991
Change in absenteeism	-£3,962	-£2,748	-£1,214
ICER (including absenteeism)			TC dominant