Responses to NICE STA questions for vedolizumab for treating moderately to severely acute ulcerative colitis (ID691)

On behalf of Takeda UK, please find our response to the NICE clarification questions provided on the 20th August 2014 with regards to the NICE Single Technology Appraisal for vedolizumab for treating moderately to severely acute ulcerative colitis (ID691).

Please note that further information/ clarification has been provided for all questions with the exception of those in section C of the clarification questions (Section C: Textual clarifications and additional points). We will provide further clarification in the relevant section of this response document. Currently Takeda UK are assessing the further data request and working internally to deliver the required analyses. We hope to get back to NICE shortly with an appropriate response for these questions after clarification.

Section A: Clarification on effectiveness data

Network meta-analysis

Priority question
A1 Please clarify whether fixed effects or random effects models were used for network meta-analysis, and justify the model choice.

Both fixed effects and random effects models were used, although the random effects model couldn't be applied easily because of a lack of robust closed loops; consequently, most of the results are based on Bayesian fixed effects models. The use of random effects MTCs was restricted to instances when closed loops existed in the network. However, even when closed loops existed, in many cases the networks did not contain sufficient information for the random effect models to be estimated. The random effects MTCs did not have good convergence as observed through iteration plots and Gelman–Rubin diagnostic tests and in many cases appeared to have greatly inflated errors compared to the equivalent fixed effects and frequentist models.

Priority question
A2 Please explain what "sw" is in the model code for fitting a fixed effects mixed treatment comparison in OpenBUGS (Appendix 14 of the submission).

The "sw" refers to the study. It can be replaced with "s" to use the same notation as the NICE DSU documents.

Priority question

A3 Please explain how multi-arm trials were incorporated in the random effects model presented in Appendix 14 of the submission.

Where random effects models were run (see response to A1), only simple random effects models were conducted. Some were re-run using more complex models that incorporate correlations in multi-arm trials at a later date, although these results were not included in the submission. The results were within the range observed with different runs of the more simple random effects models. Given this, if multi-arm adjustments were made we would expect the results to be almost identical to the original MTC results.

Priority question

A4 Please provide all the R code used to conduct the network meta-analysis for each population and all the datasets which were read into R.

All of the data sets, which were read into R, for each of the MTCs are included here in Appendix 1. Time series MTCs were fitted using the MCMCglmm package in R, otherwise WinBUGS code was used to fit the fixed and random effect models. The same code was used for each of the MTCs. The R code used is as follows:

R code for frequentist fixed effects MTC

```
f.lm <- lm(formula, data=Pairwise.data, weight=1/vi)

s <- summary(f.lm)

br1 <- mvrnorm(n=2000, coef(f.lm), s$cov.unscaled)
```

formula = log-odds ratio ~ list of treatments (minus placebo); vi = variance associated with the log-odds ratio, Pairwise.data = data set up for all pairwise comparisons available for each study with log-odds and variance (adjusted for multiple comparisons) and dummy coded design matrix to describe all the treatment effects for each pairwise comparison).

R code for MTC model for frequentist random effects MTCs

```
m.lme <- lme(formula, method="REML", random=list(Study=~1),

 data=Pairwise.data, weights=varConstPower(form=~sqrt(vi),

 fixed=list(power=1)))

br2 <- mvrnorm(n=2000, fixed.effects(m.lme), vcov(m.lme))
```

formula = log-odds ratio ~ list of treatments (minus placebo); vi = variance associated with the log-odds ratio, Pairwise.data = data set up for all pairwise comparisons available for each study with log-odds and variance (adjusted for multiple comparisons) and dummy coded design matrix to describe all the treatment effects for each pairwise comparison).

R code for Bayesian MCMC meta-regression for dichotomous outcome: fixed-treatment and random study effect

```
prior=list(R=list(V=1, nu=0.0001), G=list(G1=list(V=1, nu=0.0001)))

MCMC1 <- MCMCglmm(cbind(r,n-r) ~ 0 + Treatment, random=~Study,

 data=stacked.data, thin=100, burnin=10000, nitt=210000,

 family = "multinomial2", prior=prior)
```

n = total number of patients in that study or treatment arm; r = number of patients with the endpoint.

R code for Bayesian INLA meta-regression for dichotomous outcome: fixed-treatment and random study effect

```
hyper <- list(theta=list(prior="loggamma",param=c(0.1, 0.1)))

formula.inla.2 <- formula(paste("r ~ f(Study, model = 'iid',

 hyper=hyper)", " + ", trt.formula, " -1", sep="") )

inla1 <- inla(formula.inla.2, family = "binomial", Ntrials = n,

 data = inla.data, quantiles = c(0.025, 0.5, 0.975))
```

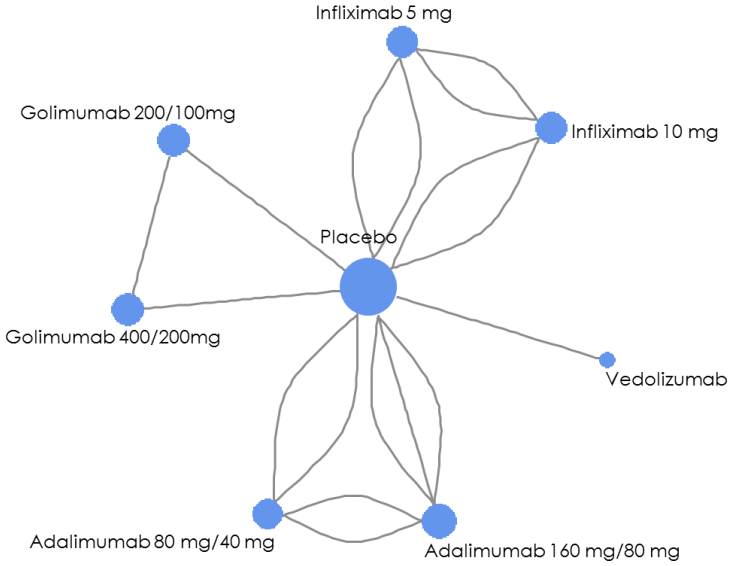
n = total number of patients in that study or treatment arm; r = number of patients with the endpoint.

Priority question

A5 Please provide the network diagram for each of the network meta-analyses, including details of which studies were included.

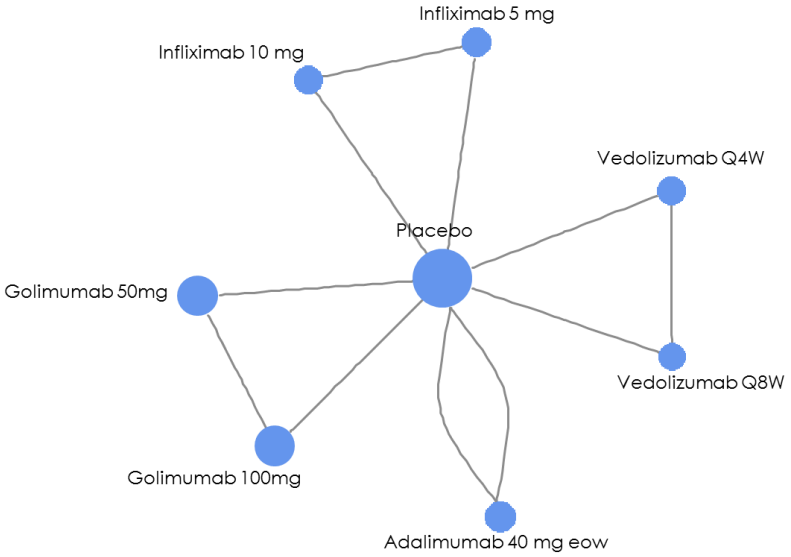
Network diagrams and trials included for the induction phase

Network of Evidence for Anti-TNF–Naïve Induction Clinical Response and Clinical Remission



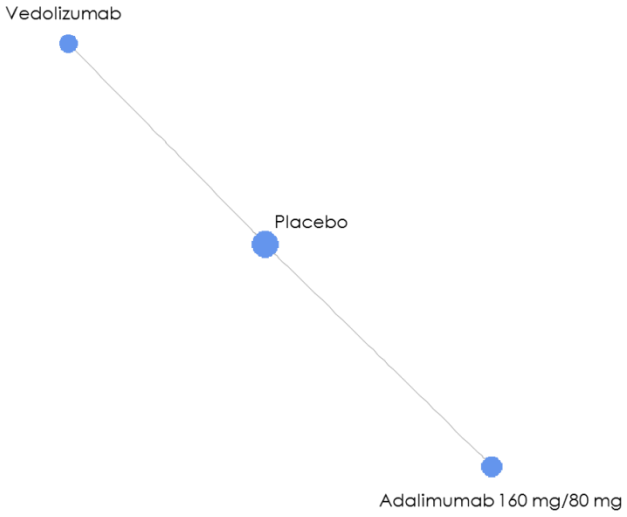
Trials included: GEMINI I; ULTRA-1; ULTRA-2; ACT-1; ACT-2; PURSUIT-SC; Suzuki (2014)

Network of Evidence for Anti-TNF–Naïve Maintenance Durable Clinical Response and Clinical Remission



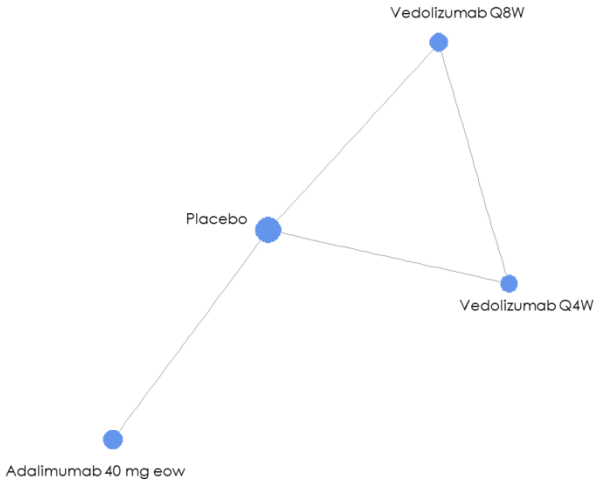
Trials included: GEMINI I; ULTRA-2; ACT-1; PURSUIT-SC; Suzuki (2014)

Network of Evidence Anti-TNF–Experienced/Failure Induction Clinical Response, Clinical Remission, and Mucosal Healing



Trials included: GEMINI I; ULTRA-1

Network of Evidence Anti-TNF–Experienced/Failure Maintenance Durable Clinical Response, Clinical Remission, and Mucosal Healing



Trials included: GEMINI I; Suzuki (2014)

Priority question

A6 Please provide the network meta-analysis results for all the contrasts for each population for both fixed effects and random effects. Please also provide the deviance information criterion (DIC) for both models and the estimated between-study standard deviation when random effects model were used.

Meta-analyses were conducted for the treatment-naïve patient subgroup using clinical response, clinical remission, discontinuation and mucosal healing as induction endpoints, and durable clinical response, clinical remission, discontinuation, mucosal healing and corticosteroid-free remission as maintenance endpoints. For treatment-experienced/failure patients, the induction endpoints were clinical response, clinical remission and mucosal healing, and the maintenance endpoints were durable clinical response, clinical remission, and mucosal healing. The figures for each analysis are shown below.

Please note that DIC and parameter estimates could not be estimated reliably for most of the random effect modes due to them not converging due to the very small networks (see also the answer to A1 above).

Meta-analysis contrasts: anti-TNF–naïve induction

All Pairwise Treatment Comparisons Anti-TNF–Naïve Induction Clinical Response

All pairwise comparisons: Bayesian MTC (BUGS)

	Placebo	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	Golimumab 200/100mg	Golimumab 400/200mg	Infliximab 5 mg	Infliximab 10 mg	Vedolizumab
Placebo	1	0.72 (0.5 , 1)	0.56 (0.44 , 0.7)	0.4 (0.28 , 0.6)	0.34 (0.24 , 0.5)	0.24 (0.17 , 0.4)	0.26 (0.18 , 0.4)	0.38 (0.24 , 0.6)
Adalimumab 80 mg/40 mg	1.39 (0.98 , 2)	1	0.79 (0.55 , 1.1)	0.55 (0.33 , 0.9)	0.48 (0.29 , 0.8)	0.34 (0.2 , 0.6)	0.37 (0.22 , 0.6)	0.53 (0.3 , 0.9)
Adalimumab 160 mg/80 mg	1.78 (1.36 , 2.3)	1.27 (0.88 , 1.8)	1	0.7 (0.45 , 1.1)	0.61 (0.39 , 1)	0.43 (0.28 , 0.7)	0.47 (0.29 , 0.7)	0.68 (0.4 , 1.1)
Golimumab 200/100mg	2.52 (1.75 , 3.6)	1.83 (1.1 , 3)	1.43 (0.93 , 2.2)	1	0.88 (0.62 , 1.2)	0.62 (0.37 , 1)	0.67 (0.39 , 1.1)	0.96 (0.54 , 1.7)
Golimumab 400/200mg	2.91 (2.02 , 4.2)	2.09 (1.26 , 3.4)	1.64 (1.05 , 2.6)	1.14 (0.8 , 1.6)	1	0.71 (0.43 , 1.2)	0.76 (0.45 , 1.3)	1.1 (0.61 , 2)
Infliximab 5 mg	4.11 (2.84 , 6)	2.96 (1.76 , 4.9)	2.32 (1.45 , 3.6)	1.61 (0.98 , 2.7)	1.42 (0.85 , 2.3)	1	1.08 (0.74 , 1.6)	1.56 (0.85 , 2.7)
Infliximab 10 mg	3.78 (2.6 , 5.6)	2.71 (1.63 , 4.5)	2.14 (1.38 , 3.5)	1.5 (0.91 , 2.6)	1.31 (0.78 , 2.2)	0.92 (0.64 , 1.3)	1	1.44 (0.78 , 2.6)
Vedolizumab	2.62 (1.69 , 4.2)	1.88 (1.09 , 3.4)	1.48 (0.9 , 2.5)	1.04 (0.58 , 1.8)	0.91 (0.51 , 1.6)	0.64 (0.36 , 1.2)	0.69 (0.39 , 1.3)	1

Percentile

50% Better than
37.5%
25%
12.5%
-12.5%
-25%
-37.5%
-50% Poorer than

All Pairwise Treatment Comparisons Anti-TNF–Naïve Induction Clinical Remission

All pairwise comparisons: Bayesian MTC (BUGS)

	Placebo	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	Golimumab 200/100mg	Golimumab 400/200mg	Infliximab 5 mg	Infliximab 10 mg	Vedolizumab
Placebo	1	0.81 (0.48 , 1.4)	0.57 (0.39 , 0.8)	0.29 (0.15 , 0.5)	0.3 (0.16 , 0.5)	0.2 (0.12 , 0.3)	0.26 (0.16 , 0.4)	0.27 (0.11 , 0.6)
Adalimumab 80 mg/40 mg	1.24 (0.72 , 2.1)	1	0.71 (0.42 , 1.2)	0.35 (0.16 , 0.8)	0.37 (0.17 , 0.8)	0.24 (0.11 , 0.5)	0.32 (0.16 , 0.7)	0.33 (0.12 , 0.9)
Adalimumab 160 mg/80 mg	1.75 (1.18 , 2.6)	1.42 (0.84 , 2.4)	1	0.5 (0.24 , 1)	0.53 (0.25 , 1.1)	0.34 (0.19 , 0.6)	0.46 (0.25 , 0.9)	0.48 (0.18 , 1.1)
Golimumab 200/100mg	3.51 (2.02 , 6.6)	2.83 (1.32 , 6.3)	2 (1.03 , 4.1)	1	1.06 (0.69 , 1.7)	0.68 (0.32 , 1.5)	0.93 (0.44 , 2.1)	0.95 (0.32 , 2.6)
Golimumab 400/200mg	3.3 (1.85 , 6.2)	2.68 (1.23 , 6)	1.89 (0.93 , 4)	0.94 (0.6 , 1.5)	1	0.64 (0.31 , 1.4)	0.87 (0.4 , 2)	0.9 (0.33 , 2.5)
Infliximab 5 mg	5.12 (3.2 , 8.4)	4.17 (2.01 , 8.9)	2.96 (1.56 , 5.3)	1.46 (0.68 , 3.1)	1.55 (0.71 , 3.3)	1	1.35 (0.91 , 2)	1.39 (0.51 , 3.5)
Infliximab 10 mg	3.81 (2.27 , 6.3)	3.09 (1.47 , 6.4)	2.15 (1.14 , 4)	1.07 (0.48 , 2.3)	1.15 (0.51 , 2.5)	0.74 (0.51 , 1.1)	1	1.04 (0.38 , 2.6)
Vedolizumab	3.67 (1.67 , 9.1)	3 (1.15 , 8.3)	2.09 (0.88 , 5.7)	1.05 (0.39 , 3.1)	1.11 (0.4 , 3.1)	0.72 (0.29 , 1.9)	0.97 (0.39 , 2.6)	1

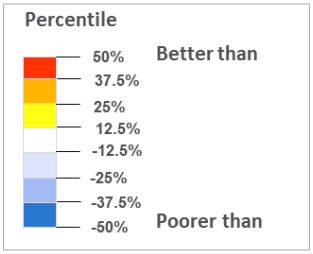
Percentile

50% Better than
37.5%
25%
12.5%
-12.5%
-25%
-37.5%
-50% Poorer than

All Pairwise Treatment Comparisons Anti-TNF–Naïve Induction Discontinuations Due to AEs

All pairwise comparisons: Bayesian MTC

	Placebo	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	Golimumab 200/100mg	Golimumab 400/200mg	Vedolizumab
Placebo	1	1.35 (0.59, 3.44)	0.88 (0.43, 1.73)	4.08 (0.42, 95.8)	3.77 (0.4, 115)	>1000 (5.67, >1000)
Adalimumab 80 mg/40 mg	0.74 (0.29, 1.69)	1	0.65 (0.26, 1.55)	2.95 (0.27, 79.1)	2.79 (0.24, 92)	>1000 (3.6, >1000)
Adalimumab 160 mg/80 mg	1.14 (0.58, 2.31)	1.54 (0.65, 3.82)	1	4.59 (0.42, 110.3)	4.42 (0.42, 137.4)	>1000 (6.17, >1000)
Golimumab 200/100mg	0.24 (0.01, 2.38)	0.34 (0.01, 3.67)	0.22 (0.01, 2.38)	1	0.98 (0.03, 43)	838.4 (0.66, >1000)
Golimumab 400/200mg	0.26 (0.01, 2.49)	0.36 (0.01, 4.2)	0.23 (0.01, 2.39)	1.02 (0.02, 33.2)	1	>1000 (0.61, >1000)
Vedolizumab	0 (0, 0.18)	0 (0, 0.28)	0 (0, 0.16)	0 (0, 1.51)	0 (0, 1.63)	1



All Pairwise Treatment Comparisons Anti-TNF–Naïve Induction Mucosal Healing

Odds ratios for all pairwise comparisons: Bayesian FE MTC

	Placebo	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	Golimumab 200/100mg	Golimumab 400/200mg	Infliximab 5 mg	Infliximab 10 mg	Vedolizumab
Placebo	1	0.89 (0.62, 1.29)	0.65 (0.48, 0.88)	0.52 (0.37, 0.75)	0.48 (0.33, 0.7)	0.29 (0.17, 0.5)	0.28 (0.16, 0.47)	0.34 (0.19, 0.63)
Adalimumab 80 mg/40 mg	1.13 (0.77, 1.62)	1	0.73 (0.51, 1.06)	0.59 (0.35, 1)	0.55 (0.33, 0.91)	0.33 (0.17, 0.63)	0.31 (0.16, 0.6)	0.38 (0.18, 0.77)
Adalimumab 160 mg/80 mg	1.53 (1.14, 2.07)	1.36 (0.94, 1.95)	1	0.81 (0.51, 1.26)	0.74 (0.46, 1.19)	0.45 (0.24, 0.82)	0.43 (0.23, 0.79)	0.52 (0.27, 1.03)
Golimumab 200/100mg	1.91 (1.33, 2.73)	1.69 (1, 2.9)	1.24 (0.79, 1.98)	1	0.92 (0.65, 1.31)	0.56 (0.29, 1.04)	0.54 (0.27, 1.01)	0.65 (0.32, 1.32)
Golimumab 400/200mg	2.08 (1.43, 2.99)	1.83 (1.1, 3.07)	1.36 (0.84, 2.16)	1.09 (0.77, 1.54)	1	0.61 (0.32, 1.16)	0.58 (0.3, 1.15)	0.71 (0.35, 1.42)
Infliximab 5 mg	3.42 (2, 5.94)	3.03 (1.58, 5.8)	2.23 (1.21, 4.14)	1.79 (0.96, 3.42)	1.65 (0.86, 3.17)	1	0.94 (0.57, 1.63)	1.17 (0.52, 2.63)
Infliximab 10 mg	3.63 (2.11, 6.14)	3.2 (1.66, 6.28)	2.34 (1.27, 4.36)	1.86 (0.99, 3.73)	1.73 (0.87, 3.37)	1.06 (0.61, 1.76)	1	1.22 (0.54, 2.8)
Vedolizumab	2.97 (1.59, 5.37)	2.61 (1.3, 5.44)	1.92 (0.97, 3.76)	1.54 (0.76, 3.09)	1.42 (0.7, 2.87)	0.86 (0.38, 1.91)	0.82 (0.36, 1.86)	1

Percentile

50% Better than
37.5%
25%
12.5%
-12.5%
-25%
-37.5%
-50% Poorer than

Meta-analysis contrasts: anti-TNF–naïve maintenance

All Pairwise Treatment Comparisons Anti-TNF–Naïve Maintenance Durable Clinical Response (no ACT-1 three-time-point information)

Odds ratios for all pairwise comparisons: Bayesian MTC

	Placebo	Adalimumab 40 mg eow	Golimumab 50mg	Golimumab 100mg	Infliximab 5 mg	Infliximab 10 mg	Vedolizumab Q4W	Vedolizumab Q8W
Placebo	1	0.8 (0.47, 1.4)	0.52 (0.32, 0.81)	0.44 (0.28, 0.7)	0.59 (0.29, 1.29)	0.43 (0.21, 0.95)	0.28 (0.14, 0.54)	0.19 (0.09, 0.37)
Adalimumab 40 mg eow	1.26 (0.72, 2.11)	1	0.64 (0.31, 1.31)	0.56 (0.27, 1.16)	0.74 (0.3, 1.82)	0.54 (0.22, 1.37)	0.35 (0.15, 0.82)	0.24 (0.1, 0.57)
Golimumab 50mg	1.94 (1.24, 3.09)	1.55 (0.76, 3.27)	1	0.87 (0.55, 1.33)	1.16 (0.49, 2.76)	0.84 (0.36, 2.06)	0.54 (0.24, 1.23)	0.37 (0.16, 0.85)
Golimumab 100mg	2.25 (1.42, 3.56)	1.79 (0.86, 3.71)	1.15 (0.75, 1.82)	1	1.35 (0.57, 3.15)	0.97 (0.42, 2.39)	0.63 (0.28, 1.42)	0.43 (0.19, 0.97)
Infliximab 5 mg	1.69 (0.78, 3.48)	1.35 (0.55, 3.3)	0.86 (0.36, 2.04)	0.74 (0.32, 1.76)	1	0.73 (0.38, 1.41)	0.47 (0.17, 1.21)	0.32 (0.12, 0.87)
Infliximab 10 mg	2.33 (1.06, 4.8)	1.84 (0.73, 4.63)	1.19 (0.49, 2.79)	1.03 (0.42, 2.39)	1.37 (0.71, 2.62)	1	0.65 (0.23, 1.73)	0.44 (0.15, 1.21)
Vedolizumab Q4W	3.55 (1.85, 7.22)	2.85 (1.23, 6.87)	1.84 (0.82, 4.15)	1.59 (0.71, 3.56)	2.13 (0.83, 5.88)	1.55 (0.58, 4.34)	1	0.68 (0.35, 1.27)
Vedolizumab Q8W	5.27 (2.7, 11)	4.21 (1.75, 10)	2.71 (1.18, 6.42)	2.33 (1.03, 5.37)	3.09 (1.15, 8.6)	2.28 (0.83, 6.52)	1.47 (0.79, 2.89)	1

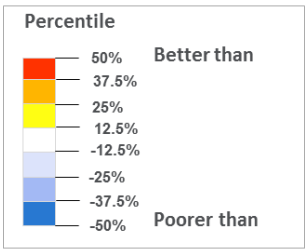
Percentile

50%	Better than
37.5%	
25%	
12.5%	
-12.5%	
-25%	
-37.5%	
-50%	Poorer than

All Pairwise Treatment Comparisons Anti-TNF–Naïve Maintenance Durable Clinical Response (ACT-1 three-time-point information)

Odds ratios for all pairwise comparisons: Bayesian MTC

	Placebo	Adalimumab 40 mg eow	Golimumab 50mg	Golimumab 100mg	Infliximab 5 mg	Infliximab 10 mg	Vedolizumab Q4W	Vedolizumab Q8W
Placebo	1	0.76 (0.45, 1.27)	0.51 (0.32, 0.83)	0.45 (0.28, 0.72)	0.47 (0.22, 1.01)	0.39 (0.18, 0.83)	0.28 (0.14, 0.56)	0.19 (0.09, 0.38)
Adalimumab 40 mg eow	1.31 (0.79, 2.22)	1	0.68 (0.34, 1.37)	0.58 (0.3, 1.16)	0.62 (0.25, 1.55)	0.52 (0.21, 1.33)	0.36 (0.15, 0.89)	0.25 (0.1, 0.59)
Golimumab 50mg	1.94 (1.21, 3.08)	1.48 (0.73, 2.97)	1	0.86 (0.55, 1.37)	0.91 (0.38, 2.22)	0.77 (0.3, 1.86)	0.54 (0.23, 1.22)	0.36 (0.16, 0.83)
Golimumab 100mg	2.24 (1.39, 3.6)	1.72 (0.86, 3.36)	1.16 (0.73, 1.82)	1	1.05 (0.45, 2.6)	0.88 (0.36, 2.2)	0.62 (0.27, 1.44)	0.42 (0.19, 0.99)
Infliximab 5 mg	2.12 (0.99, 4.47)	1.62 (0.64, 3.98)	1.1 (0.45, 2.62)	0.95 (0.38, 2.22)	1	0.85 (0.44, 1.56)	0.59 (0.21, 1.57)	0.4 (0.14, 1.08)
Infliximab 10 mg	2.54 (1.2, 5.41)	1.91 (0.75, 4.8)	1.3 (0.54, 3.32)	1.13 (0.45, 2.78)	1.18 (0.64, 2.29)	1	0.7 (0.25, 1.89)	0.47 (0.17, 1.32)
Vedolizumab Q4W	3.59 (1.8, 7.08)	2.75 (1.13, 6.48)	1.87 (0.82, 4.26)	1.61 (0.69, 3.75)	1.68 (0.64, 4.68)	1.42 (0.53, 3.94)	1	0.67 (0.35, 1.3)
Vedolizumab Q8W	5.3 (2.63, 11)	4.08 (1.68, 9.58)	2.76 (1.21, 6.43)	2.39 (1.01, 5.36)	2.49 (0.92, 6.92)	2.13 (0.76, 5.9)	1.48 (0.77, 2.82)	1



All Pairwise Treatment Comparisons Anti-TNF–Naïve Maintenance Clinical Remission

Odds ratios for all pairwise comparisons: Bayesian MTC

	Placebo	Adalimumab 40 mg eow	Golimumab 50mg	Golimumab 100mg	Infliximab 5 mg	Infliximab 10 mg	Vedolizumab Q4W	Vedolizumab Q8W
Placebo	1	0.58 (0.31, 1.08)	0.58 (0.35, 0.99)	0.55 (0.33, 0.89)	0.79 (0.37, 1.64)	0.63 (0.29, 1.29)	0.25 (0.12, 0.52)	0.27 (0.13, 0.54)
Adalimumab 40 mg eow	1.73 (0.93, 3.2)	1	1 (0.44, 2.2)	0.95 (0.43, 2.11)	1.38 (0.53, 3.61)	1.07 (0.41, 2.8)	0.44 (0.16, 1.14)	0.47 (0.17, 1.24)
Golimumab 50mg	1.73 (1.02, 2.87)	1 (0.45, 2.29)	1	0.95 (0.59, 1.51)	1.37 (0.57, 3.29)	1.08 (0.44, 2.82)	0.44 (0.18, 1.04)	0.48 (0.19, 1.12)
Golimumab 100mg	1.83 (1.13, 3.02)	1.05 (0.47, 2.34)	1.05 (0.66, 1.68)	1	1.44 (0.58, 3.44)	1.13 (0.45, 2.85)	0.46 (0.19, 1.08)	0.5 (0.2, 1.22)
Infliximab 5 mg	1.26 (0.61, 2.69)	0.72 (0.28, 1.88)	0.73 (0.3, 1.77)	0.69 (0.29, 1.73)	1	0.8 (0.41, 1.49)	0.32 (0.11, 0.96)	0.34 (0.12, 0.97)
Infliximab 10 mg	1.6 (0.78, 3.47)	0.93 (0.36, 2.47)	0.92 (0.35, 2.29)	0.88 (0.35, 2.21)	1.26 (0.67, 2.47)	1	0.41 (0.14, 1.16)	0.44 (0.15, 1.28)
Vedolizumab Q4W	3.93 (1.94, 8.48)	2.28 (0.88, 6.18)	2.26 (0.96, 5.71)	2.16 (0.92, 5.38)	3.16 (1.05, 8.88)	2.46 (0.86, 7.15)	1	1.08 (0.56, 2.1)
Vedolizumab Q8W	3.67 (1.85, 7.88)	2.14 (0.81, 5.82)	2.1 (0.9, 5.32)	2.01 (0.82, 4.97)	2.93 (1.03, 8.46)	2.3 (0.78, 6.66)	0.93 (0.48, 1.79)	1

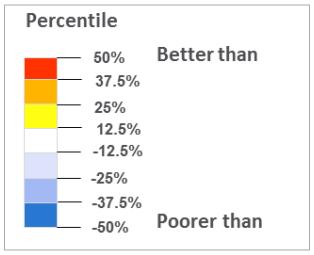
Percentile

50% Better than
37.5%
25%
12.5%
-12.5%
-25%
-37.5%
-50% Poorer than

All Pairwise Treatment Comparisons Anti-TNF–Naïve Maintenance Discontinuation Due to AEs

All pairwise comparisons: Bayesian MTC

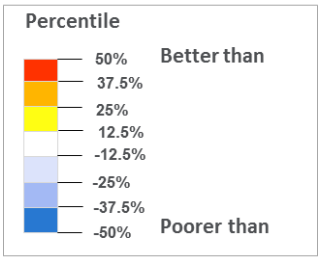
	Placebo	Adalimumab 40 mg eow	Golimumab 50mg	Golimumab 100mg	Infliximab 5 mg	Infliximab 10 mg	Vedolizumab Q4W	Vedolizumab Q8W
Placebo	1	-0.8 (0.16, 1.12)	0.23 (0.48, 3.37)	-0.39 (0.28, 1.57)	0.11 (0.47, 2.73)	0.01 (0.43, 2.69)	2.54 (1.86, 298)	1.17 (0.89, 16)
Adalimumab 40 mg eow	0.8 (0.89, 6.36)	1	1.03 (0.73, 12)	0.42 (0.42, 5.5)	0.92 (0.65, 9.65)	0.82 (0.63, 9.32)	3.36 (3.31, 828)	1.97 (1.48, 49)
Golimumab 50mg	-0.23 (0.3, 2.07)	-1.03 (0.08, 1.36)	1	-0.62 (0.22, 1.34)	-0.11 (0.23, 3.37)	-0.21 (0.21, 3.09)	2.34 (1.15, 257)	0.96 (0.51, 17)
Golimumab 100mg	0.39 (0.64, 3.59)	-0.42 (0.18, 2.36)	0.62 (0.75, 4.64)	1	0.51 (0.49, 5.86)	0.42 (0.45, 5.5)	2.94 (2.32, 446)	1.55 (1.01, 30)
Infliximab 5 mg	-0.11 (0.37, 2.15)	-0.92 (0.1, 1.53)	0.11 (0.3, 4.35)	-0.51 (0.17, 2.05)	1	-0.08 (0.36, 2.14)	2.44 (1.29, 299)	1.07 (0.59, 18)
Infliximab 10 mg	-0.01 (0.37, 2.34)	-0.82 (0.11, 1.59)	0.21 (0.32, 4.66)	-0.42 (0.18, 2.21)	0.08 (0.47, 2.75)	1	2.54 (1.46, 345)	1.14 (0.68, 19)
Vedolizumab Q4W	-2.54 (0, 0.54)	-3.36 (0, 0.3)	-2.34 (0, 0.87)	-2.94 (0, 0.43)	-2.44 (0, 0.78)	-2.54 (0, 0.68)	1	-1.37 (0.01, 2.49)
Vedolizumab Q8W	-1.17 (0.06, 1.13)	-1.97 (0.02, 0.67)	-0.96 (0.06, 1.97)	-1.55 (0.03, 0.99)	-1.07 (0.05, 1.69)	-1.14 (0.05, 1.48)	1.37 (0.4, 95)	1



All Pairwise Treatment Comparisons Anti-TNF–Naïve Maintenance Mucosal Healing

Odds ratios for all pairwise comparisons: Bayesian FE MTC

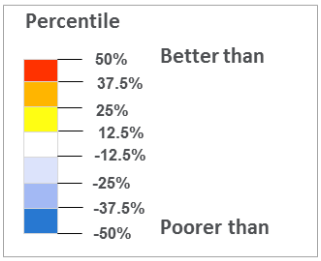
	Placebo	Adalimumab 40 mg eow	Infliximab 5 mg	Infliximab 10 mg	Vedolizumab Q4W	Vedolizumab Q8W
Placebo	1	0.67 (0.42, 1.06)	0.5 (0.25, 1.05)	0.3 (0.13, 0.64)	0.2 (0.1, 0.42)	0.21 (0.1, 0.43)
Adalimumab 40 mg eow	1.49 (0.95, 2.39)	1	0.77 (0.32, 1.75)	0.45 (0.17, 1.12)	0.31 (0.13, 0.71)	0.31 (0.14, 0.75)
Infliximab 5 mg	1.98 (0.96, 4.04)	1.31 (0.57, 3.12)	1	0.6 (0.28, 1.16)	0.4 (0.14, 1.07)	0.41 (0.15, 1.14)
Infliximab 10 mg	3.33 (1.57, 7.69)	2.21 (0.89, 5.89)	1.68 (0.86, 3.55)	1	0.69 (0.24, 1.97)	0.7 (0.25, 2)
Vedolizumab Q4W	4.88 (2.39, 9.94)	3.27 (1.41, 7.46)	2.48 (0.93, 7.02)	1.45 (0.51, 4.18)	1	1.02 (0.53, 1.97)
Vedolizumab Q8W	4.79 (2.33, 9.93)	3.21 (1.33, 7.35)	2.43 (0.87, 6.66)	1.43 (0.5, 3.97)	0.98 (0.51, 1.89)	1



All Pairwise Treatment Comparisons Anti-TNF–Naïve Maintenance CSF Remission

Odds ratios for all pairwise comparisons: Bayesian MTC

	Placebo	Adalimumab 40 mg eow	Infliximab 5 mg	Infliximab 10 mg	Vedolizumab Q4W	Vedolizumab Q8W
Placebo	1	0.48 (0.11, 1.47)	0.66 (0.23, 1.69)	0.97 (0.32, 2.66)	0.2 (0.07, 0.52)	0.39 (0.13, 1.09)
Adalimumab 40 mg eow	2.06 (0.68, 8.7)	1	1.36 (0.3, 7.41)	1.97 (0.41, 11)	0.41 (0.09, 2.11)	0.83 (0.17, 4.4)
Infliximab 5 mg	1.51 (0.59, 4.31)	0.74 (0.13, 3.31)	1	1.45 (0.64, 3.41)	0.31 (0.07, 1.22)	0.6 (0.14, 2.57)
Infliximab 10 mg	1.04 (0.38, 3.08)	0.51 (0.09, 2.41)	0.69 (0.29, 1.56)	1	0.2 (0.05, 0.87)	0.41 (0.09, 1.94)
Vedolizumab Q4W	4.91 (1.94, 15)	2.42 (0.47, 11)	3.26 (0.82, 14)	4.9 (1.15, 20)	1	1.98 (0.84, 4.99)
Vedolizumab Q8W	2.57 (0.92, 7.57)	1.2 (0.23, 5.97)	1.66 (0.39, 6.99)	2.46 (0.52, 11)	0.51 (0.2, 1.2)	1

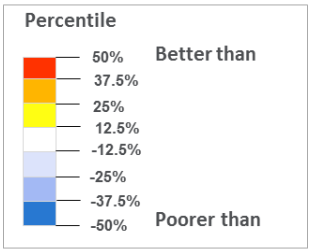


Meta-analysis contrasts: anti-TNF-experienced/failure induction

All Pairwise Treatment Comparisons Anti-TNF–Experienced/Failure Induction Clinical Response

Odds ratios for all pairwise comparisons: Bayesian MTC

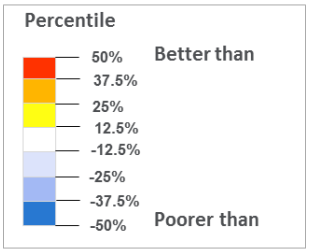
	Placebo	Adalimumab 160 mg/80 mg	Vedolizumab
Placebo	1	0.7 (0.4, 1.3)	0.4 (0.2, 0.8)
Adalimumab 160 mg/80 mg	1.4 (0.8, 2.6)	1	0.6 (0.2, 1.5)
Vedolizumab	2.5 (1.2, 5.5)	1.7 (0.7, 4.4)	1



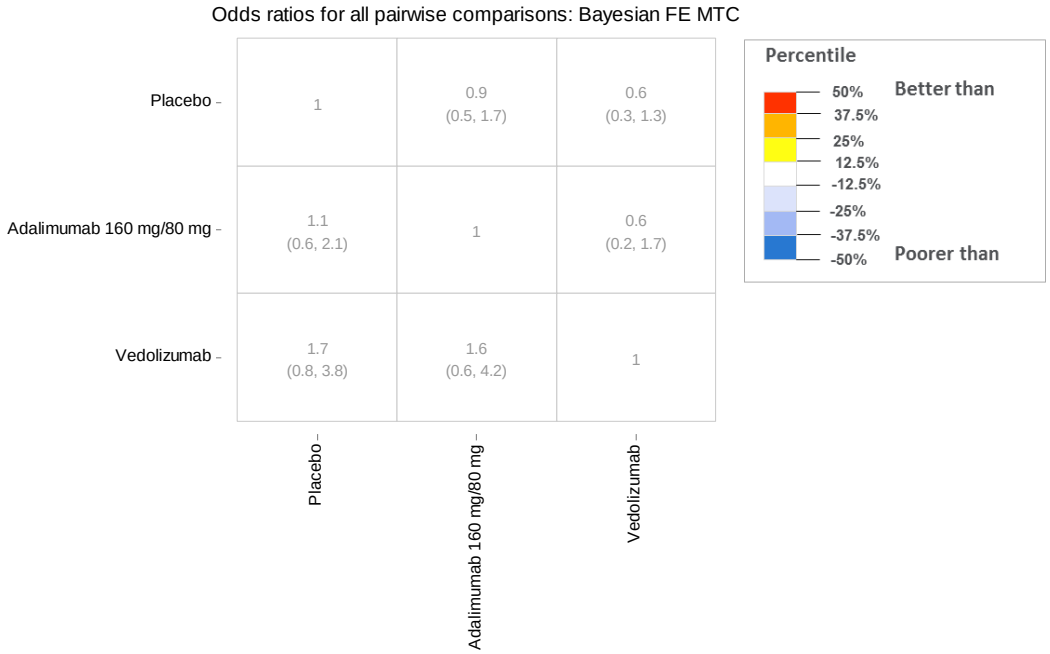
All Pairwise Treatment Comparisons Anti-TNF–Experienced/Failure Induction Clinical Remission

Odds ratios for all pairwise comparisons: Bayesian MTC

	Placebo	Adalimumab 160 mg/80 mg	Vedolizumab
Placebo	1	0.7 (0.2, 2.1)	0.3 (0, 1.2)
Adalimumab 160 mg/80 mg	1.4 (0.5, 4)	1	0.4 (0, 2.3)
Vedolizumab	3.7 (0.9, 28)	2.7 (0.4, 24)	1

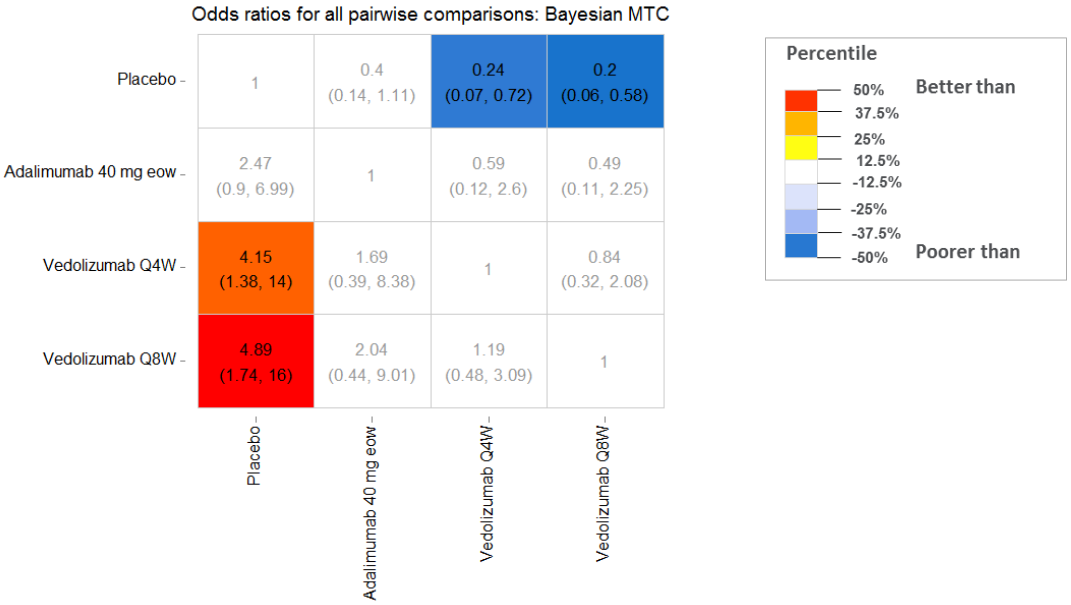


All Pairwise Treatment Comparisons Anti-TNF–Experienced/Failure Induction Mucosal Healing

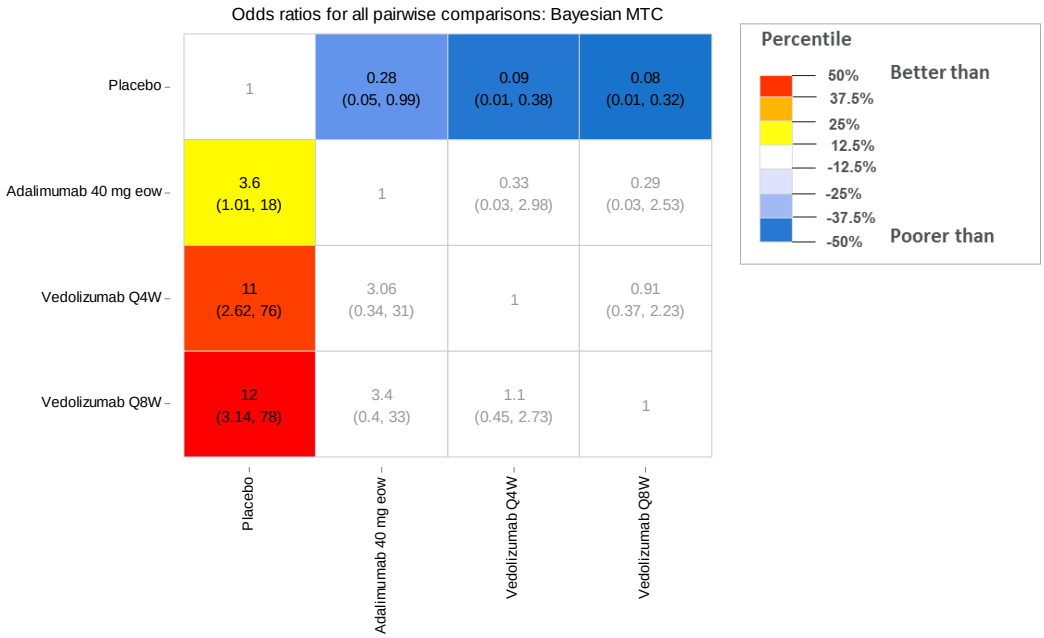


Meta-analysis contrasts: anti-TNF-experienced/failure maintenance

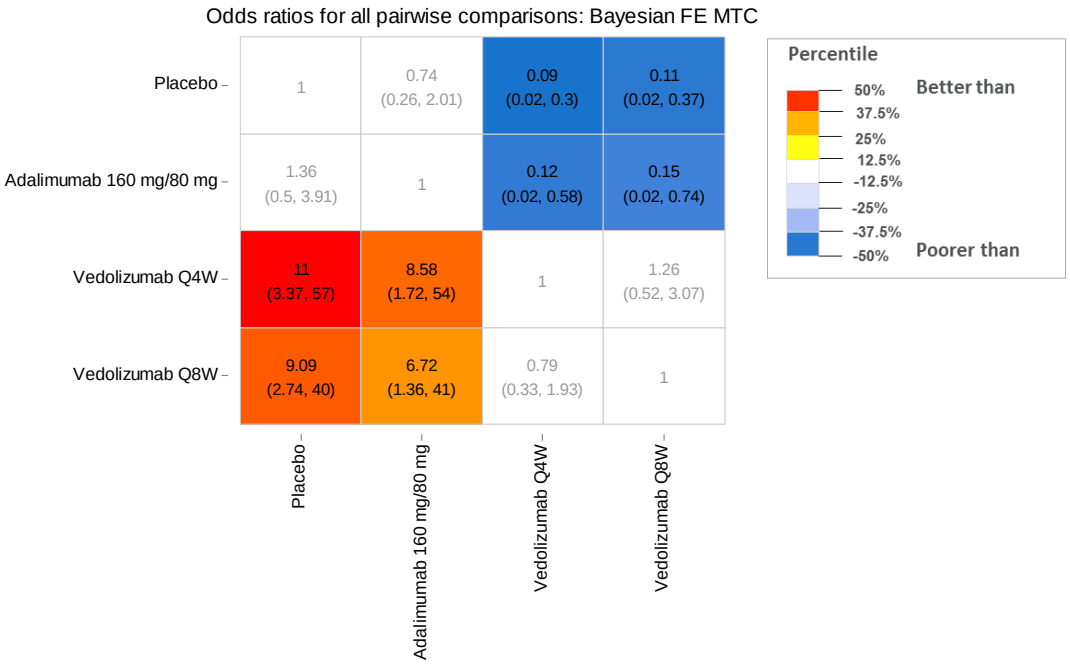
All Pairwise Treatment Comparisons Anti-TNF–Experienced/Failure Maintenance Durable Clinical Response



All Pairwise Treatment Comparisons Anti-TNF–Experienced/Failure Maintenance Clinical Remission



All Pairwise Treatment Comparisons Anti-TNF–Experienced/Failure Maintenance Mucosal Healing



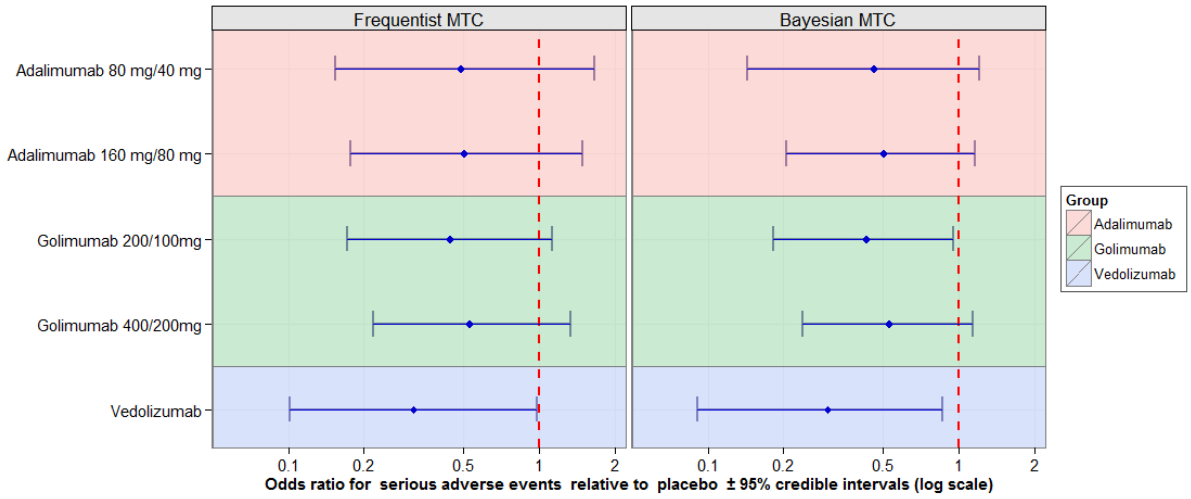
Priority question

A7 Please provide the results with interpretations when the complementary log-log model was used.

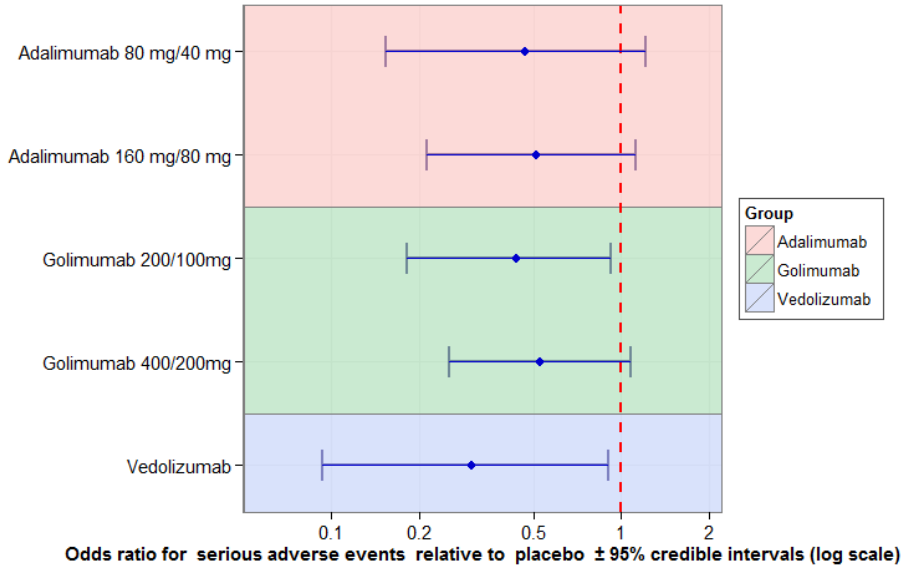
Results of the complementary log-log model are provided below. This analysis was conducted for discontinuation due to adverse events only and the results were identical to a standard MTC. It should be noted that the treatment regimens have time points for induction in their label. Therefore the whole regimen was being studied e.g. vedolizumab with a week 6 induction versus adalimumab 160 mg/80 mg with a 4 week induction. It may therefore not be appropriate to try and account for the length of induction since there is likely to be a reason for the length of induction such as higher risk of side effects etc.

The forest plots for standard frequentist and Bayesian binomial models and for the Bayesian complementary log-log model are shown below. Pairwise odds ratios for the simple Bayesian model and the odds ratios for the complementary log-log model are shown subsequently.

Forest Plot for Simple Fixed-Effects Binomial Models



Forest Plot for Complementary Log-Log Binomial Model With Underlying Poisson Distribution



Visually, there appears to be a greater difference between the standard fixed-effects frequentist and Bayesian MTCs, which have the same underlying assumptions, compared to the standard Bayesian fixed-effects MTC versus the Bayesian complementary log-log binomial model, with underlying Poisson process. The charts showing all the pairwise odds-ratios also confirm that there is very little difference between the standard binomial model and the complementary log-log model.

All Pairwise Odds Ratios From Bayesian Simple Fixed-Effects Binomial MTC

Odds ratios for all pairwise comparisons: Bayesian FE MTC

	Placebo	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	Golimumab 200/100mg	Golimumab 400/200mg	Vedolizumab
Placebo	1	2.18 (0.82, 7)	1.99 (0.86, 4.86)	2.34 (1.05, 5.48)	1.89 (0.88, 4.19)	3.32 (1.16, 11.1)
Adalimumab 80 mg/40 mg	0.46 (0.14, 1.21)	1	0.92 (0.27, 2.75)	1.07 (0.28, 4.09)	0.85 (0.22, 3.07)	1.49 (0.32, 7.36)
Adalimumab 160 mg/80 mg	0.5 (0.21, 1.16)	1.09 (0.36, 3.68)	1	1.18 (0.37, 3.76)	0.95 (0.31, 3.04)	1.63 (0.44, 7.27)
Golimumab 200/100mg	0.43 (0.18, 0.95)	0.93 (0.24, 3.58)	0.85 (0.27, 2.7)	1	0.82 (0.31, 2.04)	1.4 (0.38, 6.11)
Golimumab 400/200mg	0.53 (0.24, 1.13)	1.17 (0.33, 4.56)	1.06 (0.33, 3.23)	1.22 (0.49, 3.23)	1	1.74 (0.47, 7.22)
Vedolizumab	0.3 (0.09, 0.86)	0.67 (0.14, 3.09)	0.61 (0.14, 2.28)	0.72 (0.16, 2.66)	0.57 (0.14, 2.12)	1

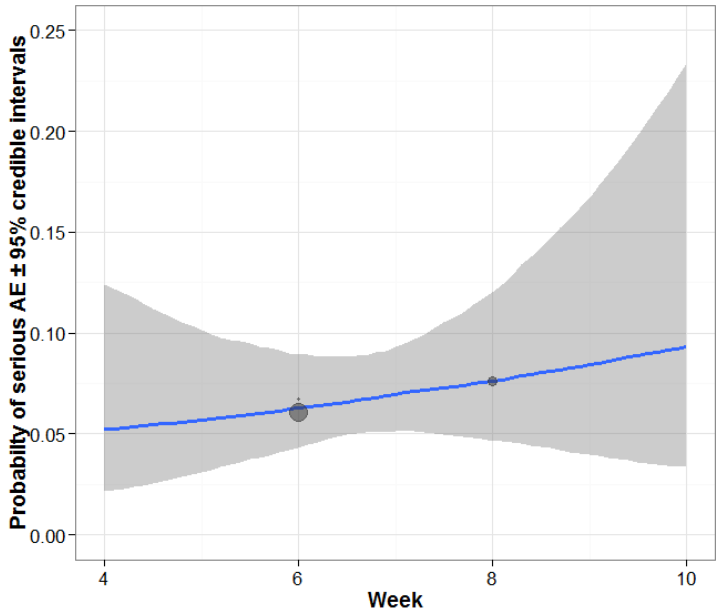
All Pairwise Odds Ratios From Bayesian Complementary Log-Log Binomial Model With Underlying Poisson Distribution

Odds ratios for all pairwise comparisons: Bayesian FE MTC

	Placebo	Adalimumab 80 mg/40 mg	Adalimumab 160 mg/80 mg	Golimumab 200/100mg	Golimumab 400/200mg	Vedolizumab
Placebo	1	2.14 (0.82, 6.53)	1.96 (0.89, 4.69)	2.31 (1.09, 5.49)	1.9 (0.92, 3.93)	3.28 (1.1, 10.7)
Adalimumab 80 mg/40 mg	0.47 (0.15, 1.22)	1	0.93 (0.26, 2.68)	1.07 (0.27, 3.95)	0.88 (0.23, 3.04)	1.5 (0.32, 7.17)
Adalimumab 160 mg/80 mg	0.51 (0.21, 1.12)	1.08 (0.37, 3.78)	1	1.18 (0.37, 3.78)	0.96 (0.33, 2.92)	1.65 (0.45, 6.79)
Golimumab 200/100mg	0.43 (0.18, 0.92)	0.93 (0.25, 3.71)	0.85 (0.26, 2.73)	1	0.81 (0.31, 2.02)	1.42 (0.36, 5.55)
Golimumab 400/200mg	0.53 (0.25, 1.08)	1.13 (0.33, 4.39)	1.05 (0.34, 3.02)	1.23 (0.49, 3.21)	1	1.73 (0.44, 6.83)
Vedolizumab	0.3 (0.09, 0.91)	0.67 (0.14, 3.14)	0.61 (0.15, 2.24)	0.7 (0.18, 2.81)	0.58 (0.15, 2.25)	1

In conclusion, the choice of model, i.e., standard binomial or complementary log-log model, appears to make negligible difference to the results obtained. A closer look at the relationship with serious adverse events for the control arm is shown in the figure below.

Occurrence of Serious Adverse Events With Time for the Control Arm



A weak trend with time was observed. Only 2 time points show an increase for serious adverse events, from 6% to 7%. This does not appear to be sufficient data to have an influence on the results.

Priority question

A8 Please clarify if the results presented in Tables 31 to 42 of the submission were the treatment effects of the treatments listed in the tables vs. VEDO, or VEDO vs. these treatments.

The MTC results are presented as odds ratios (ORs) for each treatment included in the MTC **relative to placebo**. We acknowledge that there was an error in the submission, with the ORs stated to be versus vedolizumab. The latest MTC bears the correct designation.
Placebo was the most common comparator across the network of evidence and therefore acts as the hub of the network. Consequently, odd ratios versus placebo for each comparator are included in submission Tables 31 to 42.

A9 Please provide the summary of studies found from the original review and update review for surgery/ciclosporin (see page 115 of the submission, Section 6.7.2 surgery/ciclosporin, currently cited as "Takeda, data on file 2014").

The studies found via the surgery/ciclosporin searches are as follows.

Original review:

- Full-Text Articles (n = 10)
    - Brazier F, Finet L, Duchmann JC, Dupas JL. Cyclosporin A treatment in inflammatory bowel diseases. Gastroenterologie Clinique et Biologique. 1995;19(5):494-504.
    - D'Haens G, Lemmens L, Geboes K, et al. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. Gastroenterology. 2001;120(6):1323-9.
    - Johnston D, Williamson MER, Lewis WG, Miller AS, Sagar PM, Holdsworth PJ. Prospective controlled trial of duplicated (J) versus quadruplicated, (W) pelvic ileal reservoirs in restorative proctocolectomy for ulcerative colitis. Gut. 1996;39(2):242-7.
    - Kusunoki M, Shoji Y, Yanagi H, Yamamura T. Usefulness of bipolar scissors for total colectomy. Dis Colon Rectum. 1998;41(9):1197-200.
    - Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med. 1994;330(26):1841-5.
    - McCormick PH, Guest GD, Clark AJ, et al. The ideal ileal-pouch design: a long-term randomized control trial of J- vs W-pouch construction. Dis Colon Rectum. 2012;55(12):1251-7.

- Oresland T, Fasth S, Nordgren S, Hallgren T, Hulten L. A prospective randomized comparison of two different pelvic pouch designs. Scand J Gastroenterol. 1990;25(10):986-96.
- Reilly WT, Pemberton JH, Wolff BG, et al. Randomized prospective trial comparing ileal pouch-anal anastomosis performed by excising the anal mucosa to ileal pouch-anal anastomosis performed by preserving the anal mucosa. Ann Surg. 1997;225(6):666-77.
- Selvaggi F, Giuliani A, Gallo C, Signoriello G, Riegler G, Canonico S. Randomized, controlled trial to compare the J-pouch and W-pouch configurations for ulcerative colitis in the maturation period. Diseases of the Colon and Rectum. 2000;43(5):615-20.
- Van AG, D'Haens G, Noman M, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology. 2003;125(4):1025-31.

- Conference Abstracts (n = 1)
  - Piche T. A randomized, double-blind comparative study of intravenous perfusion of cyclosporin at a dose of 4 mg/kg versus 2 mg/kg in severe attack of ulcerative colitis. Hepato-Gastro. 2004;11(2):153-4.

Review update

- Conference Abstracts (n = 1)
  - Hicks CW, Hodin RA, Savitt LR, Bordeianou L. Does intramesorectal proctectomy affect overall complication rates compared to standard total mesorectal excision in patients with ulcerative colitis? Gastroenterology 2013;144(5):S1053-S1054.

A10 Within the network meta-analysis, please clarify the methods used to determine the: burn-in period; numbers of simulations to keep; and numbers to thin.

The burn-in number of iterations and total number of iterations were chosen to give adequate time for models to converge. A conservative thin rate was chosen to avoid correlations between chains. The iteration plots produced by the R2WinBUGS package were used to guide this process although the actual numbers used were far more conservative than those indicated by these plots.

A11 Table 28 of the submission shows that clinical response at weeks 52 or 54 was one of the key outcome measures for each of the trials included in the maintenance phase network meta-analysis. Please explain why clinical response was not analysed for maintenance phase in the network meta-analyses? (see page 126 of the submission, Table 30).

Durable clinical response was not included in the results that were presented in the submission because it did not inform the economic model. Within the economic model, response is used as a clinical outcome / health state for the induction period only. Primarily, the endpoint is used in the

model to determine the proportion of patients that remain on a biologic therapy or switch to conventional therapy. Thereafter, the Markov model, like the model of Tsai et al., is based upon absolute Mayo scores: remission (Mayo 0–2), mild disease (Mayo 3–5), and moderate to severe disease (Mayo 6–12).

It was preferable to model the absolute Mayo score rather than durable clinical response. For example, a patient that responds from a Mayo score of 6 to 2 is likely to have a different quality of life and incur different costs compared with a patient that responds from a Mayo score of 12 to 8. Using response as a modelled health state would mean that these hypothetical patients would inform transitions to the same response health state. Essentially, the model would assume that these patients have the same costs and utility scores. By contrast, in the model for vedolizumab, these hypothetical patients would inform estimates for the remission and moderate to severe health states.

Although the results were not presented in the submission (for brevity), the analysis of durable clinical response was performed for the mixed treatment comparison and odds ratios are presented here, in answer to question A6.

A12 Please conduct an additional meta-regression analysis including type of population (anti-TNF naïve, and mixture of anti-TNF naïve and experienced patients) as a potential treatment effect modifier for each outcome measure for both induction and maintenance phase to assess if the treatment effects depend on the type of patient population.

We are unable to perform the additional analysis as requested. There are insufficient data available to fit a robust model with covariates. An independent advisor (Redwood Outcomes) advised on the methods during the analyses and he did not consider this to be a worthwhile exercise due to the low power of such an analysis. He argued that when such a model is fitted to a small network, the model may pick up on variation which could be caused by any number of study differences (known or unknown) causing the result to be spuriously significant or not significant, e.g. due to a lack of data. To perform the analysis requested by the ERG, at least 20 studies would be needed in the network to be able to fit MTCs that include treatment effect modifiers. The maximum number of studies in any of the networks we analysed was 7, which is clearly far below the number recommended to fit such a model. Since study designs differed considerably in the proportion of ant-TNF naïve and experienced patients, i.e. tended to focus on either population or report both groups separately, and we did not have sufficient data to include this as a covariate, separate MTCs were conducted for each patient population. In fact, the independent advisor did not consider it necessary for us to report the whole patient population results for the reasons mentioned above.

Background section

A13 Please clarify if vedolizumab is intended to be used as an alternative to tacrolimus or whether it would be used before/after tacrolimus (see Figure 3 of the submission, page 43)?

Vedolizumab would be used after tacrolimus as this may be considered a conventional therapy. However, it must be noted that tacrolimus is currently unlicensed for the treatment of ulcerative colitis at any stage of the disease and there is a lack of high quality data to support its use. The use of

unlicensed immunosuppressive agents as part of the care pathway highlights the significant unmet need relative to conventional and anti-TNFα therapies currently available on the NHS.

A14 Please justify the exclusion of calcineurin inhibitor as a comparator (see page 63/64 of the submission).

Ciclosporin was not included as a comparator because it is considered a hospital-only product used in emergency settings for severely acute ulcerative colitis. This is not the same patient population as in that in GEMINI I. No patient was hospitalised at the start of vedolizumab treatment and there was an exclusion criteria for any patient requiring surgery within 30 days of start of the trial. Therefore, ciclosporin cannot be considered a relevant comparator. In this context, NICE did not include ciclosporin in its list of requested comparators.

Searches / data extraction / quality assessment

A15 Please provide justification (including limitations) for not undertaking adverse event searches for vedolizumab (see page 140 of the submission). Please clarify whether evidence on the adverse events of vedolizumab could be missed as a consequence of not undertaking these searches? Please also explain how the safety studies considered within the submission were identified.

In the experience of Takeda, the approach taken regarding systematic searches for adverse events (AEs) are not dissimilar to other technology assessments by NICE. GEMINI I was designed to include standard safety assessments, as well as assessments to evaluate potential immunogenicity, such as human–anti-human antibody (HAHA) status and the occurrence of infusion-related reactions. Takeda has also presented results from all the phase III studies in UC and Crohn's disease: a pooled safety analysis of 6 studies on vedolizumab together with the interim results from a long-term safety study. The studies were identified through internal Takeda databases and the evidence presented in the submission is in line with information provided to the regulators. The pooled analysis includes over 2700 IBD patients (including 1107 UC patients) have confirmed the safety profile of vedolizumab to be similar that observed in GEMINI 1 study and no new safety issues have been identified with long-term use. The ongoing long-term safety study will assess AEs for up to 4 years. In conclusion, Takeda is confident that the safety data provided is as complete as possible and does not miss any relevant drug-related AEs. Takeda also acknowledges that no clinical trial programme can detect rare adverse events, hence the ongoing safety study.

A16 Please clarify whether literature before 2013 was considered for surgery and ciclosporin as the search strategy suggests that a date limit from 2013 was applied (Appendix 10, Table Medline Literature Search Strategy: UC).

Takeda confirms that literature published pre-2013 was considered in the original search strategy, which stated: "For the original review, no time limits were applied to the searches. The amended search for surgery and cyclosporine was conducted independently of the original search for biologics and was conducted to include publications **up until 9 April 2013**, the date of the original biologic

searches. For the update of the review, the searches were limited to articles published after April 1, 2013 in order to identify studies published since the previous searches."

A17 Please provide justification (including limitations) for not undertaking cost-effectiveness searches for surgery and ciclosporin

A search was not conducted for ciclosporin because it is considered a hospital-only product used in emergency settings for severely acute ulcerative colitis. This is not the same patient population as in the scope of assessment for vedolizumab. In this context, NICE did not include ciclosporin in its list of requested comparators.

A search for surgery was undertaken, separately from the other searches for cost-effectiveness analyses. In error, details of the search were left out of the submission. The full details of methods and results are presented here. The search was conducted for both ulcerative colitis and Crohn's disease. Therefore, the methods and some of the results include both indications, but the papers fully reviewed and presented here are just for ulcerative colitis. The aims, methodology and results are given here in Appendix 2.

A18 Please explain why (including limitations) the 'comparator terms' are different between the original and updated cost-effectiveness searches. For example, in the original cost-effectiveness search, evidence before 2013 was only considered for vedolizumab and the TNF inhibitors but not for the conventional treatments (ASAs, corticosteroids and immunomodulators); however, in the updated searches conventional treatments were also considered (see section 10.10.4 of the submission).

Takeda updated the literature searches to address NICE requirement that searches should not be older than 1 year. Regarding the comparator searches, the update was in response to the NICE scoping advice given to Takeda.

A19 Please confirm if data extraction and quality assessment was undertaken independently by a minimum of two reviewers. If not, why?

Takeda can confirm that two reviewers were involved in the systematic review.

A20 Please provide a full breakdown of all full text articles (i.e. full reason for exclusion and reference) which were excluded from the clinical effectiveness review, including those that were excluded from the meta-analysis.

The extracted studies were examined for outcomes and completeness of data presentation. Of the 13 studies in 28 records included in the original systematic review, 6 studies in 7 records were excluded from consideration in the MTC. Of the 4 newly identified studies included in the update of

the systematic review, 3 were excluded from consideration in the MTC. These 10 excluded records together with the reasons for exclusion are described in the table below.

Studies meeting the level 2 inclusion criteria and reasons for exclusion from the meta-analysis

Study Acronym	Citation	Reason for Exclusion
ICURE	Sjoberg D, Larsson M, Nielsen AL, Holmqvist L, Ronnblom A. Conservative approach results in lower colectomy rates in patients with severe ulcerative colitis data from 70 patients with S3 in the ICURE study. Journal of Crohn's and Colitis. 2013. 7(Suppl 1):S233	Not randomized trial
Jarnerot (2005)	Gustavsson A, Jarnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlen P, Granno C, Vilien M, Strom M, Verbaan H, Hellstrom PM, Magnuson A, Halfvarson J, Tysk C. Clinical trial: colectomy after rescue therapy in ulcerative colitis - 3-year follow-up of the Swedish-Danish controlled infliximab study. Aliment Pharmacol Ther. 2010 Oct. 32(8):984-989.	Secondary source for primary source that was excluded, Jarnerot et al., 2005; Gustavsson presents nonrandomized long-term follow-up outcomes
Jarnerot (2005)	Jarnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlen P, Granno C, Vilien M, Strom M, Danielsson A, Verbaan H, Hellstrom PM, Magnuson A, Curman B. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology. 2005 Jun. 128(7):1805-1811.	The only efficacy outcome was surgery required, which was not an endpoint analyzed in the MTC; no safety endpoints of interest
NCT00542152	Laharie D, Bourreille A, Branche J, Allez M, Bouhnik Y, Filippi J, Zerbib F, Savoye G, Nachury M, Moreau J, Delchier JC, Cosnes J, Ricart E, Dewit O, Lopez-Sanroman A, Dupas JL, Carbonnel F, Bommelaer G, Coffin B, Roblin X, Van AG, Esteve M, Farkkila M, Gisbert JP, Marteau P, Nahon S, de VM, Franchimont D, Mary JY, Colombel JF, Lemann M. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet. 2012 Dec 1. 380(9857):1909-1915.	Comparator was cyclosporine - no placebo arm
Parikh (2012)	Parikh A, Leach T, Wyant T, Scholz C, Sankoh S, Mould DR, Ponich T, Fox I, Feagan BG. Vedolizumab for the treatment of active ulcerative colitis: a randomized controlled phase 2 dose-ranging study. Inflamm Bowel Dis. 2012 Aug. 18(8):1470-1479.	The outcome reported was partial MAYO score, which was not one of the endpoints for the MTC

Study Acronym	Citation	Reason for Exclusion
Probert (2003)	Probert et al., 2003 [[p. 998]]	Glucocorticoid resistant ulcerative colitis, a small sub-population. Only remission was recorded and it had only 23 and 20 patients per study arm. The maintenance phase was open label so also can't be used
UC Success	Probert CS, Hearing SD, Schreiber S, Kuhbacher T, Ghosh S, Arnott ID, Forbes A. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. Gut. 2003 Jul. 52(7):998-1002.	Azathioprine as comparator; study did not link to other studies in the network
Gao et al., 2013	Gao J, Jiang XL. Low-dose infliximab for corticosteroid-refractory ulcerative colitis: Impact of number of infusions on efficacy and safety. World Chinese Journal of Digestology 2013;21(15):1453-7.	All patients received infliximab; no placebo arm.
Reinisch et al., 2013	Reinisch W, Sandborn WJ, Panaccione R, Huang B, Pollack PF, Lazar A, et al. 52-week efficacy of adalimumab in patients with moderately to severely active ulcerative colitis who failed corticosteroids and/or immunosuppressants. Inflamm Bowel Dis 2013 Jul;19(8):1700-9.	Open-label long-term follow up of induction study (ULTRA 1)
Reinisch et al., 2012	Reinisch W, Sandborn WJ, Rutgeerts P, et al. Long-term infliximab maintenance therapy for ulcerative colitis: the ACT- 1 and -2 extension studies. Inflamm Bowel Dis 2012;18: 201-11.	Extension of ACT-1 and -2, time points not suitable for analysis

MTC = mixed treatment comparison.

Data synthesis/analysis

A21 Please provide a breakdown of the GEMINI 1 clinical outcome data (clinical remission, clinical response, adverse events) for the anti-TNF failure group split by those that used vedolizumab after failure of the 1st biologic and after failure of the 2nd biologic, if data are available.

Takeda cannot perform the analysis requested. At the time GEMINI I was initiated (2008), infliximab was only approved biologic for UC. Therefore, patients could only have failed on infliximab before enrolling in GEMINI I. In the absence of other approved anti-TNFα agents, "anti-TNFα cycling" was not feasible.

A22 Page 103 of the submission states that "Time to disease worsening and time to treatment failure were not estimable among the study groups because of the large percentage of patients for whom events were censored at week 52." Is any further information available on these outcomes? What is the percentage of patients censored/experiencing these events in each treatment group?

The percentage of patients for whom events were censored at week 52 was: 67% for placebo, 83% for vedolizumab Q8W and 85% for vedolizumab Q4W. The median days to disease worsening were not estimable for any of the treatment groups. As this was the end of the GEMINI I study, patients would not be receiving the same treatment subsequently: patients in the ITT placebo and ITT Q8W groups entering the C13008 study would be restarting or increasing vedolizumab, whereas those not entering C13008 would be discontinuing vedolizumab.

A23 Please clarify why glucocorticoid-free remission was not analysed (see Table 30, page 126 of the submission).

Glucocorticoid-free remission was analysed for the anti-TNF-naive subpopulation. The data were excluded from the submission as they were not used in the final model. The table on the next page summarises the odds ratios and 95% confidence intervals versus placebo for each comparator.

Summary of mixed treatment comparisons for glucocorticoid-free remission in the maintenance phase among the anti-TNF-naive subpopulation: odds ratio vs. placebo (95% CI)

Comparator						
Vedolizumab		Adalimumab	Golimumab		Infliximab	
Q4W	Q8W	40 mg eow	50 mg	100 mg	5 mg/kg	10 mg/kg
4.91* (1.94, 15.0)	2.57 (0.92, 7.57)	2.06 (0.68, 8.7)	NA	NA	1.51 (0.59, 4.31)	1.04 (0.38, 3.08)

* = significant vs. placebo. eow: every other week

A24 Page 74 of the submission states that “Permitted immunosuppressants were maintained at stable doses throughout the induction and maintenance periods, except for US study sites, where these agents were discontinued after induction” Please clarify why this was the case. Please also clarify if the US study sites’ immunosuppressants (e.g. azathioprine or 6-mercaptopurine) were balanced across treatment arms.

The rationale for this US-specific protocol amendment is based on interactions with the US Food and Drug Administration (FDA). Specifically, the FDA requested that the historical medical therapy failure inclusion criteria be modified for US patients to include only those patients who had previously demonstrated an inadequate response to, loss of response to, or intolerance of immunomodulators or TNFα antagonists. This is in contrast to the global protocols that included patients who had previously demonstrated an inadequate response to, loss of response to, or intolerance of corticosteroids, immunomodulators or TNFα antagonists. The US enrolled population was therefore a subset of the overall population being studied, as opposed to a distinct population.

The FDA also requested that the duration of concomitant immunomodulator therapy (azathioprine or 6-mercaptopurine) be limited to the 6-week induction phase for US patients in cohort 1. Therefore, they were required to discontinue immunomodulators at the beginning of the maintenance phase. Concomitant immunomodulators are not permitted for US patients enrolled in Cohort 2, in contrast to the global protocols in which patients entering GEMINI I on immunomodulators continue them throughout the maintenance phase up to week 52. This, patients in cohort 1 randomized to placebo (and active treatment given that cohort 1 was blinded) to continue immunomodulator treatment in the induction phase. This did not apply to cohort 2 as all patients received active MLN0002 treatment in the induction phase.

Discontinuation of concomitant immunomodulators at week 6 for US patients in cohort 1 would not affect the results of the induction phase. Any potential effect of these FDA requirements on the maintenance phase results was minimized by the modest anticipated relative contribution of US patients on concomitant immunomodulators in the induction phase, and by the stratification by cohort 1 and 2 among the 3 maintenance phase treatment groups.

A25 Please provide evidence (efficacy and safety including subgroup analyses) to support the following statement, “The efficacy of VEDO maintenance treatment was not substantively affected by concomitant use of glucocorticoids or immunosuppressants” (see submission page 102).

The efficacy of vedolizumab in the maintenance ITT population according to concomitant use of glucocorticoids or immunosuppressants is described in the tables over the page.

Patients administered vedolizumab with baseline concomitant corticosteroids and/or immunomodulators did not have increased rates of serious adverse events compared to patients who were not on these medications. Patients administered vedolizumab with baseline concomitant corticosteroids and/or immunomodulators did not have increased rates of infection compared to patients who were not on these medications. Overall, the incidence of infusion-related reactions was similar across treatment groups, independent of concomitant immunomodulator use (vedolizumab Q8Wwith concomitant immunomodulator: 2/43 (5%) with at least one adverse event; vedolizumab Q8Wwithout concomitant immunomodulator: 3/79 (4%) with at least one adverse event).

Maintenance efficacy endpoints in patients by baseline concomitant immunomodulator use.

	Patients with concomitant immunomodulator use			Patients without concomitant immunomodulator use		
	PLA	VDZ Q8W	VDZ Q4W	PLA	VDZ Q8W	VDZ Q4W
Endpoint	n = 51	n = 43	n = 45	n = 75	n = 79	n = 80
Clinical remission at Week 52[a]						
Number (%) achieving clinical remission	10 (19.6)	19 (44.2)	21 (46.7)	10 (13.3)	32 (40.5)	35 (43.8)
95% CI	(8.7, 30.5)	(29.3, 59.0)	(32.1, 61.2)	(5.6, 21.0)	(29.7, 51.3)	(32.9, 54.6)
Difference from placebo	-	24.6	27.1	-	27.2	30.4
95% CI for difference from placebo	-	(6.2, 43.0)	(8.9, 45.3)	-	(13.9, 40.5)	(17.1, 43.7)
Durable clinical response at Week 52[b]						
Number (%) achieving durable clinical response	14 (27.5)	29 (67.4)	23 (51.1)	16 (21.3)	40 (50.6)	42 (52.5)
95% CI	(15.2, 39.7)	(53.4, 81.4)	(36.5, 65.7)	(12.1, 30.6)	(39.6, 61.7)	(41.6, 63.4)
Difference from placebo	-	40.0	23.7	-	29.3	31.2
95% CI for difference from placebo	-	(21.4, 58.6)	(4.6, 42.7)	-	(14.9, 43.7)	(16.8, 45.5)
Mucosal healing at Week 52[c]						
Number (%) achieving mucosal healing	12 (23.5)	23 (53.5)	27 (60.0)	13 (17.3)	40 (50.6)	43 (53.8)
95% CI	(11.9, 35.2)	(38.6, 68.4)	(45.7, 74.3)	(8.8, 25.9)	(39.6, 61.7)	(42.8, 64.7)
Difference from placebo	-	30.0	36.5	-	33.3	36.4
95% CI for difference from placebo	-	(11.0, 48.9)	(18.0, 54.9)	-	(19.3, 47.3)	(22.5, 50.3)
Durable clinical remission at Week 52[d]						
Number (%) achieving durable clinical remission	7 (13.7)	10 (23.3)	10 (22.2)	4 (5.3)	15 (19.0)	20 (25.0)
95% CI	(4.3, 23.2)	(10.6, 35.9)	(10.1, 34.4)	(1.5, 13.1)	(11.0, 29.4)	(16.0, 35.9)
Difference from placebo	-	9.5	8.5	-	13.7	19.7
95% CI for difference from placebo	-	(-6.2, 25.3)	(-6.9, 23.9)	-	(-2.3, 29.1)	(3.7, 34.7)
Corticosteroid-free clinical remission at Week 52[e]						
Patients with concomitant immunomodulator use and using corticosteroids at baseline, n	24	22	25	48	48	48
Number (%) achieving corticosteroid-free clinical remission	4 (16.7)	7 (31.8)	13 (52.0)	6 (12.5)	15 (31.3)	20 (41.7)
95% CI	(4.7, 37.4)	(13.9, 54.9)	(31.3, 72.2)	(3.1, 21.9)	(18.1, 44.4)	(27.7, 55.6)
Difference from placebo	-	15.2	35.3	-	18.8	29.2
95% CI for difference from placebo	-	(-13.9, 42.4)	(8.7, 60.1)	-	(2.6, 34.9)	(12.4, 46.0)

a Clinical remission is defined as a complete Mayo score of ≤ 2 points and no individual subscore > 1 point at Week 52.
b Durable clinical response is defined as a reduction in complete Mayo score of ≥ 3 points and ≥ 30% from baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point at both Weeks 6 and 52.
c Mucosal healing is defined as a Mayo endoscopic subscore of ≤ 1.
d Durable clinical remission is defined as a complete Mayo score of ≤ 2 points and no individual subscore > 1 point at both Weeks 6 and 52.
e Corticosteroid-free clinical remission is defined as patients using oral corticosteroids at baseline (Week 0) who discontinued corticosteroids and were in clinical remission at Week 52.

Maintenance efficacy endpoints in patients by baseline concomitant corticosteroid use.

	Patients with concomitant corticosteroid use			Patients without concomitant corticosteroid use		
Endpoint	**PLA n = 72**	**VDZ Q8W n = 70**	**VDZ Q4W n = 73**	**PLA n = 54**	**VDZ Q8W n = 52**	**VDZ Q4W n = 52**
Clinical remission at Week 52[a]						
Number (%) achieving clinical remission	11 (15.3)	25 (35.7)	37 (50.7)	9 (16.7)	26 (50.0)	19 (36.5)
95% CI	(7.0, 23.6)	(24.5, 46.9)	(39.2, 62.2)	(6.7, 26.6)	(36.4, 63.6)	(23.5, 49.6)
Difference from placebo	-	20.4	35.4	-	33.3	19.9
95% CI for difference from placebo	-	(6.5, 34.4)	(21.2, 49.6)	-	(16.5, 50.2)	(3.4, 36.3)
Durable clinical response at Week 52[b]						
Number (%) achieving durable clinical response	14 (19.4)	36 (51.4)	37 (50.7)	16 (29.6)	33 (63.5)	28 (53.8)
95% CI	(10.3, 28.6)	(39.7, 63.1)	(39.2, 62.2)	(17.5, 41.8)	(50.4, 76.5)	(40.3, 67.4)
Difference from placebo	-	32.0	31.2	-	33.8	24.2
95% CI for difference from placebo	-	(17.1, 46.8)	(16.6, 45.9)	-	(16.0, 51.7)	(6.0, 42.4)
Mucosal healing at Week 52[c]						
Number (%) achieving mucosal healing	14 (19.4)	32 (45.7)	42 (57.5)	11 (20.4)	31 (59.6)	28 (53.8)
95% CI	(10.3, 28.6)	(34.0, 57.4)	(46.2, 68.9)	(9.6, 31.1)	(46.3, 73.0)	(40.3, 67.4)
Difference from placebo	-	26.3	38.1	-	39.2	33.5
95% CI for difference from placebo	-	(11.4, 41.1)	(23.5, 52.7)	-	(22.1, 56.4)	(16.2, 50.8)
Durable clinical remission at Week 52[d]						
Number (%) achieving durable clinical remission	5 (6.9)	11 (15.7)	20 (27.4)	6 (11.1)	14 (26.9)	10 (19.2)
95% CI	(2.3, 15.5)	(8.1, 26.4)	(17.6, 39.1)	(2.7, 19.5)	(14.9, 39.0)	(8.5, 29.9)
Difference from placebo	-	8.8	20.5	-	15.8	8.1
95% CI for difference from placebo	-	(-7.4, 25.2)	(4.5, 36.1)	-	(1.1, 30.5)	(-5.5, 21.7)

a Clinical remission is defined as complete Mayo score of ≤ 2 points and no individual subscore > 1 point at Week 52.
b Durable clinical response is defined as reduction in complete Mayo score of ≥ 3 points and ≥ 30% from baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point at both Weeks 6 and 52.
c Mucosal healing is defined as Mayo endoscopic subscore of ≤ 1.
d Durable clinical remission is defined as complete Mayo score of ≤ 2 points and no individual subscore > 1 point at both Weeks 6 and 52.
e Corticosteroid-free clinical remission is defined as patients using oral corticosteroids at baseline (Week 0) who discontinued corticosteroids and were in clinical remission at Week 52

A26 Please provide data on compliance and adherence to study treatment in GEMINI 1 trial.

Percent compliance/adherence in GEMINI I was defined as the number of complete infusions (at least 75% of the infusion by volume) administered between the start and end dates of study therapy, where the start date of study therapy was the date of the first dose of vedolizumab or placebo, and the end date of study therapy was the date of the last known dose of vedolizumab or placebo treatment during the maintenance phase.

In the induction phase, compliance/adherence was 100% in all groups. In the maintenance phase, compliance/adherence was greater than 99%, with just one incomplete infusion (a patient in the non-ITT vedolizumab group who experienced an infusion-related reaction).

A27 Please provide data on discontinuation of treatment in maintenance phase in GEMINI 1 trial.

In the maintenance ITT population, more patients discontinued do to drug-related adverse events in the placebo group than in either vedolizumab group.

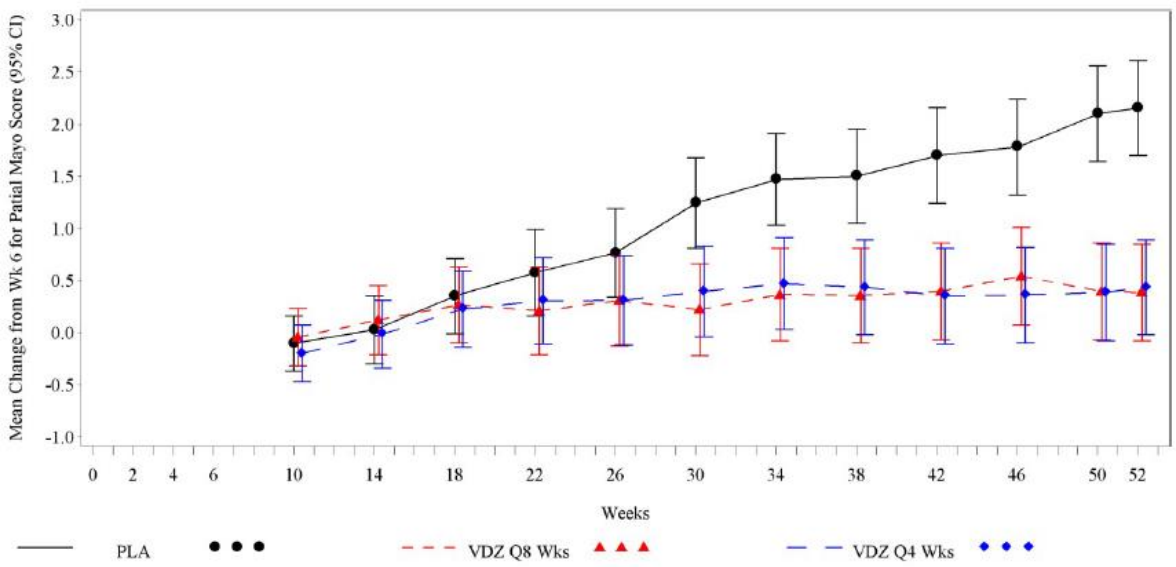
- Placebo: 5/126 (4%, 95% CI: 1.3, 9.0)
- Vedolizumab (Q8W): 1/122 (<1%, 95% CI: 0.0, 4.5)
- Vedolizumab (Q4W): 2/125 (2%, 95% CI: 0.2, 5.7)

In the same population, discontinuation due to any adverse event was twice as common in the placebo group (12%) than in the vedolizumab groups (5% to 6%).

A28 Please clarify whether there are any data available concerning maintenance of response following discontinuation of vedolizumab?

The ITT placebo arm shows maintenance of response in subjects that responded to 2 doses of VDZ. As shown in the figure, the adjusted mean partial Mayo score (LOCF with 95% CI) changes from week 6 (maintenance study ITT population) were similar for responders in the placebo and treatment arms between weeks 10 and 30.

Change in adjusted partial Mayo score over the course of the maintenance phase of GEMINI I

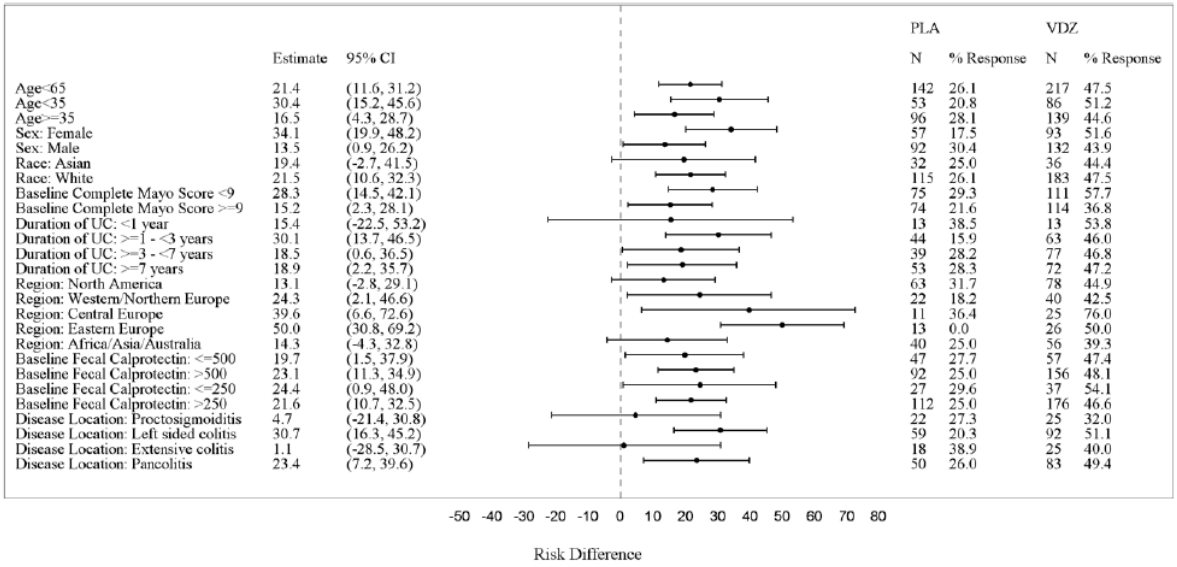


Subjects that discontinued after maintenance therapy and did not enter C13008 had safety follow up only, so no response data are available for this group of patients.

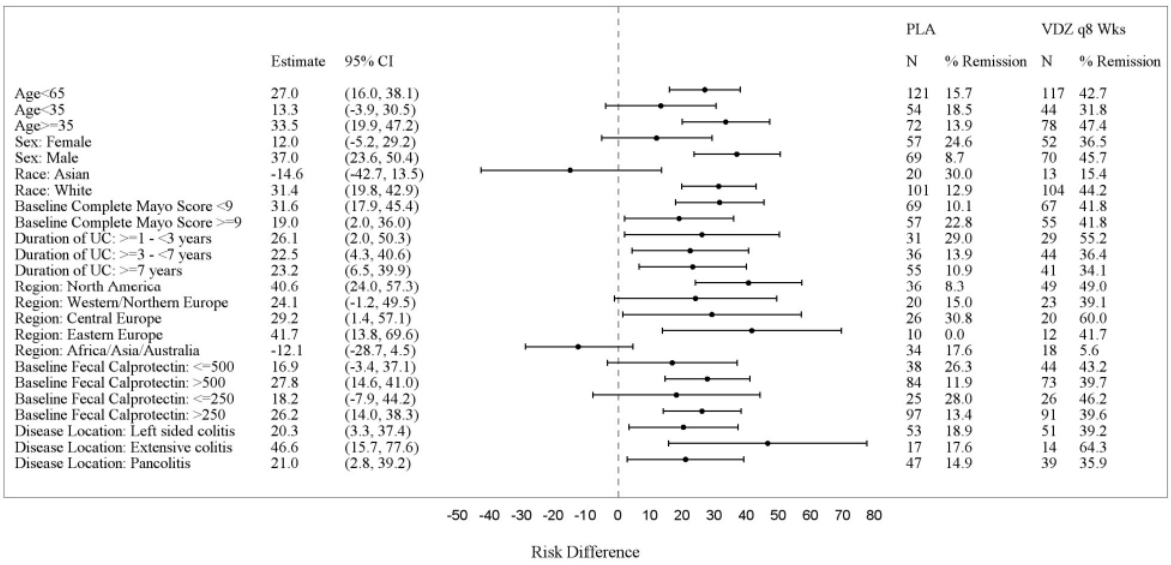
A29 Page 100 of the submission states that "Efficacy was generally similar between subgroups based on patient demographics and disease severity." Please provide evidence to substantiate this finding.

Subgroup analyses for clinical remission week 6 (induction ITT population) and at week 52 (maintenance ITT population) show no significant effects of age, gender, race, duration from UC diagnosis to first dose, geographical region, baseline disease activity, baseline fecal calprotectin and disease localization. The treatment benefit of vedolizumab was observed in all subgroups and for both dosing regimen groups in the maintenance phase.

Risk difference (95% confidence interval) for subgroup analyses of clinical response at week 6 versus placebo (induction study ITT population)

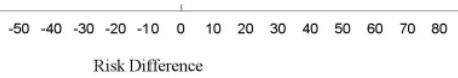


Risk difference (95% confidence interval) for subgroup analyses of clinical remission at week 52 for vedolizumab Q8W versus placebo



Risk difference (95% confidence interval) for subgroup analyses of clinical remission at week 52 for vedolizumab Q4W versus placebo

	Estimate	95% CI	PLA N	PLA % Remission	VDZ q4 Wks N	VDZ q4 Wks % Remission
Age<65	29.7	(18.6, 40.7)	121	15.7	119	45.4
Age<35	16.6	(0.4, 32.7)	54	18.5	57	35.1
Age>=35	39.1	(24.8, 53.4)	72	13.9	68	52.9
Sex: Female	31.6	(14.5, 48.6)	57	24.6	57	56.1
Sex: Male	26.6	(13.4, 39.8)	69	8.7	68	35.3
Race: Asian	8.1	(-20.8, 37.0)	20	30.0	21	38.1
Race: White	34.7	(22.9, 46.4)	101	12.9	101	47.5
Baseline Complete Mayo Score <9	40.5	(27.0, 54.0)	69	10.1	73	50.7
Baseline Complete Mayo Score >=9	13.7	(-3.3, 30.8)	57	22.8	52	36.5
Duration of UC: >=1 - <3 years	1.4	(-23.3, 26.1)	31	29.0	23	30.4
Duration of UC: >=3 - <7 years	27.6	(8.7, 46.4)	36	13.9	41	41.5
Duration of UC: >=7 years	46.0	(30.1, 61.8)	55	10.9	51	56.9
Region: North America	34.9	(16.6, 53.2)	36	8.3	37	43.2
Region: Western/Northern Europe	41.0	(16.0, 66.0)	20	15.0	25	56.0
Region: Central Europe	13.2	(-13.1, 39.6)	26	30.8	25	44.0
Region: Eastern Europe	45.5	(16.0, 74.9)	10	0.0	11	45.5
Region: Africa/Asia/Australia	19.4	(-2.9, 41.7)	34	17.6	27	37.0
Baseline Fecal Calprotectin: <=500	23.7	(2.8, 44.6)	38	26.3	40	50.0
Baseline Fecal Calprotectin: >500	32.3	(19.2, 45.3)	84	11.9	77	44.2
Baseline Fecal Calprotectin: <=250	29.1	(1.6, 56.7)	25	28.0	21	57.1
Baseline Fecal Calprotectin: >250	30.3	(18.3, 42.4)	97	13.4	96	43.8
Disease Location: Left sided colitis	38.9	(21.0, 56.8)	53	18.9	45	57.8
Disease Location: Extensive colitis	25.2	(-6.4, 56.8)	17	17.6	14	42.9
Disease Location: Pancolitis	21.6	(5.1, 38.2)	47	14.9	52	36.5



A30 Please provide data on how many patients in GEMINI 1 study progressed to colectomy (if available).

Colectomies in the maintenance study, ITT population were uncommon in all groups and the time to colectomy did not differ between groups.

- Placebo: 2/126 (1.6%, 95% CI: 0.2, 5.6) underwent colectomy
- Vedolizumab (Q8W): 1/122 (0.8, 95% CI: 0.0, 4.5) underwent colectomy
- Vedolizumab (Q4W): 0/125 (0.0%, 95% CI: 0.0, 2.9) underwent colectomy

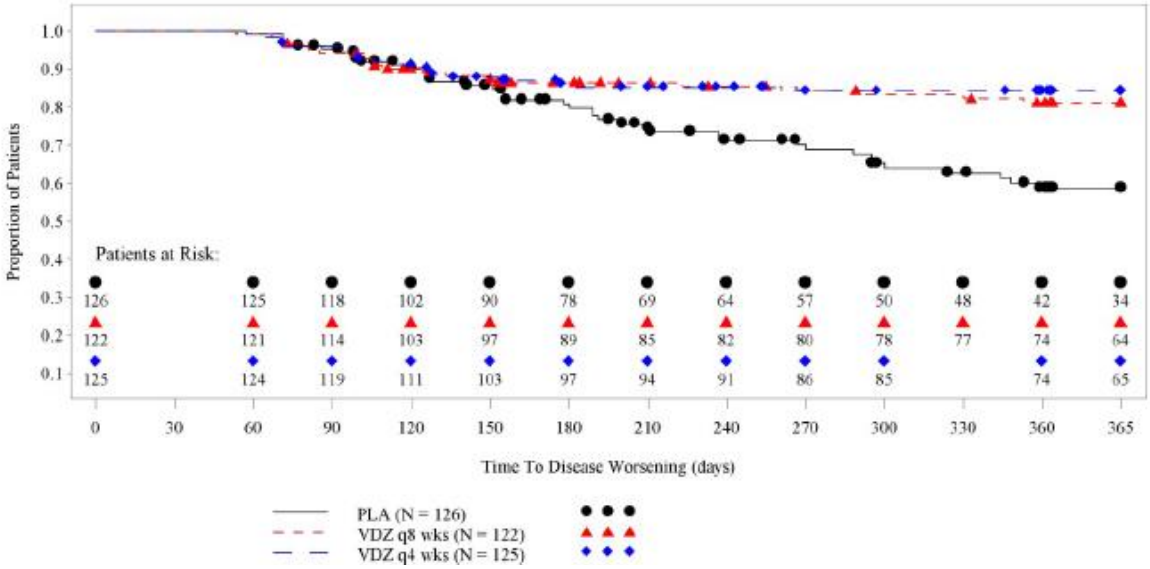
A31 Please provide the following outcome data by phase (induction and maintenance) and treatment group: i) measures of disease activity; ii) rates of hospitalisation; iii) rates of surgical intervention; and iv) time to surgical intervention (as per NICE scope and page 63 of the submission).

We have provided the requested data where available. Please note that not all data have been reported by phase, but in cases where they were, they are reported as such

i) Measures of disease activity

We identified several markers of disease activity: disease worsening based on Mayo score change over time, faecal calprotectin level, prednisone dosing and partial Mayo score change over time. These data are provided below, all showing that vedoluzmab reduces disease activity over the course of the maintenance phase.

Kaplan-Meier Curve of Time to Disease Worsening*

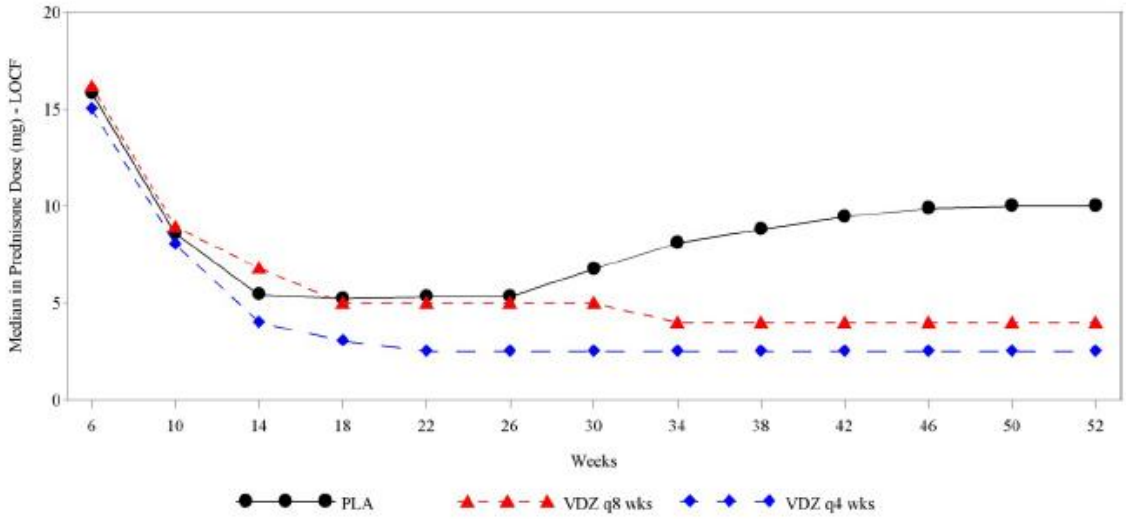


*Defined as an increase in partial Mayo score of ≥ 3 points from the week 6 value on 2 consecutive visits (or an increase to 9 points on 2 consecutive visits if the week 6 value > 6) and a partial Mayo score ≥ 5 points.

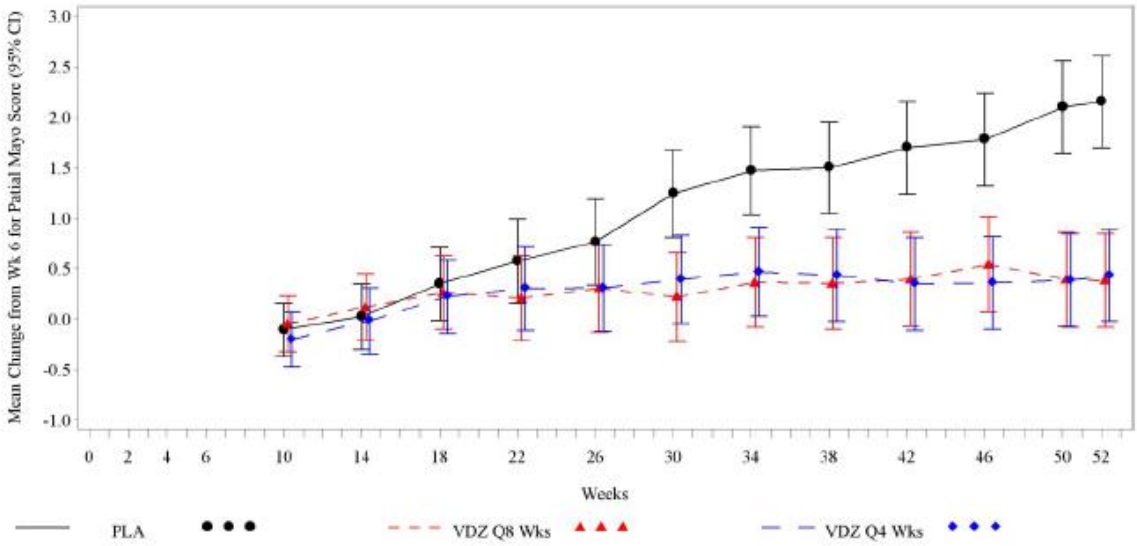
Faecal Calprotectin by Study Visit – Maintenance Study ITT Population

Faecal Calprotectin	***PLA N = 126***	***VDZ Q8W N = 122***	***VDZ Q4W N = 125***
Baseline			
n	122	117	117
≤ 250 µg/g, n (%)	25 (20)	26 (22)	21 (18)
> 250 to ≤ 500 µg/g, n (%)	13 (11)	18 (15)	19 (16)
> 500 µg/g, n (%)	84 (69)	73 (62)	77 (66)
Missing	4	5	8
Week 6			
n	114	112	120
≤ 250 µg/g, n (%)	58 (51)	59 (53)	67 (56)
> 250 to ≤ 500 µg/g, n (%)	18 (16)	17 (15)	17 (14)
> 500 µg/g, n (%)	38 (33)	36 (32)	36 (30)
Missing	12	10	5
Week 30			
n	63	74	89
≤ 250 µg/g, n (%)	36 (57)	51 (69)	53 (60)
> 250 to ≤ 500 µg/g, n (%)	4 (6)	5 (7)	14 (16)
> 500 µg/g, n (%)	23 (37)	18 (24)	22 (25)
Missing	13	12	9
Week 52			
N	44	75	76
≤ 250 µg/g, n (%)	22 (50)	56 (75)	52 (68)
> 250 to ≤ 500 µg/g, n (%)	6 (14)	8 (11)	8 (11)
> 500 µg/g, n (%)	16 (36)	11 (15)	16 (21)
Missing	4	2	8

Median Prednisone Dose Use by Study Visit (LOCF)



Adjusted Mean Partial Mayo Score LOCF (95% CI) Change from Week 6 by Study Visit - Maintenance Study ITT Population



ii) Rates of hospitalisation (not reported by phase)

- Placebo: 10/126 (7.9%, 95% CI 3.9, 14.1) were hospitalised
- Vedolizumab (Q8W):3/122 (2.5, 95% CI: 0.5, 7.0) were hospitalised
- Vedolizumab (Q4W): 4/125 (3.2%, 95% CI: 0.9, 8.0) were hospitalised

iii) Rates of surgical intervention (not reported by phase)

- Placebo: 2/126 (1.6%, 95% CI: 0.2, 5.6) underwent colectomy
- Vedolizumab (Q8W): 1/122 (0.8, 95% CI: 0.0, 4.5) underwent colectomy
- Vedolizumab (Q4W): 0/125 (0.0%, 95% CI: 0.0, 2.9) underwent colectomy

iv) Time to surgical intervention (not reported by phase)

As stated above, colectomies were uncommon in all groups and the time to colectomy did not differ between groups.

Safety

A32 Please provide the protocol-defined criteria and remission and response data from the C13008 long-term safety study (see submission, page 92).

The protocol-defined criteria for inclusion and exclusion are available on Clinicaltrials.gov (identifier: NCT00790933).

- Inclusion criteria are: adults aged 18 years or older with previous treatment in Study C13004 (phase II long-term follow-up), Study C13006 (GEMINI I), Study C13007 (GEMINI II), or Study 13011 (GEMINI III) that, in the opinion of the investigator, was well tolerated OR moderate to severe Crohn's disease or ulcerative colitis that has not been previously treated with vedolizumab (MLN0002). Patients may be receiving a therapeutic dose of conventional therapies for Crohn's disease or ulcerative colitis as defined by the protocol.
- Exclusion Criteria: Development of any new, unstable, or uncontrolled disease

There are no induction or remission data analyses for patients in the C13008 study, which is a long-term safety study.

A33 Please provide any details on mortality in the GEMINI 1 trial, post-study follow-up and C13008 study.

One patient with UC died in GEMINI I:

- **Patient C13006-46007-608** (vedolizumab induction, arteriosclerosis coronary artery) was a 66-year-old male from the Russian Federation with a history of ischemic heart disease. The patient died 14 days after a single infusion of vedolizumab due to acute cardiac death. The patient reportedly experienced edema of the right leg and died suddenly the next day. The cause of death was reported as "diffuse multi-focal cardiosclerosis" on the basis of autopsy findings. The event was assessed by the investigator as not related to study medication.

In the uncontrolled, extension study C13008, 3 patients with UC died during the study period:

- **Patient C13006-50016-602** (PT: septic shock; cause of death: "respiratory failure") was a 49-year-old white female from South Africa with UC who received 2 doses of vedolizumab during induction and then placebo during maintenance in Study C13006. The patient withdrew after 8 months of treatment due to lack of efficacy in Study C13006 before enrolling in Study C13008. At entry into Study C13008 (13 September 2010), her ongoing standard UC treatment was prednisone (20 mg daily). On 18 October 2010, 5 days after her 2nd and final dose of vedolizumab in Study C13008, the patient was hospitalized for 4 days due to worsening of UC, presenting with continuous rectal bleeding and anemia. The patient was re-hospitalized on 04 November 2010, 22 days after her final dose of vedolizumab, and a proctocolectomy with

ileostomy was performed. On 13 November, she developed an acute abdomen and septic shock as a complication of surgery and required resuscitation. She underwent emergency laparotomy where it was found that the surgical anastomosis had leaked. She developed renal failure post-operatively and received intermittent dialysis with no improvement in urine output. On 24 November, a culture of the abdominal wall grew Enterococcus as well as fungus, and she was treated with antibiotics to which she initially responded. She developed lobar pneumonia systemic deterioration and became critically ill on 02 December 2010. On 03 December 2010 (51 days after her second and final dose of vedolizumab in C13008), she experienced respiratory failure, septic shock, and pneumonia, and died. The immediate cause of death was reported as respiratory failure, with renal failure as a secondary cause of death; an autopsy was not performed. The events of worsening UC, septic shock, pneumonia, and respiratory failure were considered by the investigator to be serious, severe in intensity, and not related to study drug.

- **Patient C13006-58023-603** (PTs: myocardial ischaemia and ventricular tachycardia; cause of death: "acute stroke") was a 71-year-old white female from the US with UC who received 4 doses of vedolizumab in Study C13006 before she enrolled in Study C13008 and received 1 dose of vedolizumab. On 30 December 2009 (23 days after her only dose of vedolizumab in C13008), the patient experienced a nonserious event of esophageal candidiasis. No action was taken regarding study drug, although no additional doses were administered following the event. On 12 January 2010, 36 days after her dose of vedolizumab, she was hospitalized and, 1 day later, underwent a cystopanendoscopy, bilateral ureteral catheterization, laparoscopic panproctocolectomy, and permanent ileostomy. Her postoperative course was complicated by dehydration and complaints of dizziness with some ECG changes, a drop in blood pressure, and tachycardia (details not provided). On 25 January 2010, 49 days after her only dose of vedolizumab in Study C13008, she was diagnosed with Grade 3 myocardial ischemia. She underwent placement of 4 cardiac stents. She continued to have tachycardia post-procedure. The event of myocardial ischemia was considered resolved as of 05 February 2010 upon discharge to a rehabilitation unit. On 04 March 2010, 87 days after her last dose of vedolizumab in Study C13008, the patient was hospitalized for pneumonia. Five days later, while still hospitalized for pneumonia, she experienced nonsustained episodes of ventricular tachycardia. A scheduled automatic implantable cardioverter/defibrillator insertion was postponed due to an acute hemiparetic stroke on 13 March 2010. On 21 March 2010 (104 days after her only dose of vedolizumab in C13008), the patient experienced a second cerebrovascular accident (acute stroke), was intubated, and sent to palliative care. The patient died 112 days after her single dose of vedolizumab in Study C13008. The events of myocardial ischemia and both episodes of cerebrovascular accident were all considered by the investigator to be serious, severe in intensity, and not related to study drug. The events of pneumonia and ventricular tachycardia were both considered by the investigator to be serious, moderate in intensity, and not related to study drug.

- **Patient C13008-46210-005** (PT: pulmonary embolism; cause of death: pulmonary embolism) was a 72-year-old white male from Russia with UC who received 4 doses of vedolizumab (10 mg/kg) in Study C13002 and 12 doses of vedolizumab (2 mg/kg) in Study C13004 before enrolling in Study C13008. On 03 January 2010, 14 days after his only dose of vedolizumab in Study C13008, the patient was hospitalized due to pulmonary embolism after presenting with severe dyspnea,

weakness, dizziness, and chest pain. He had a history of coronary heart disease, hypertension, bronchial asthma, and diabetes mellitus. On 06 January 2010, 16 days after the only dose in Study C13008, the patient's condition deteriorated and he died. Pulmonary embolism was the immediate cause of death per autopsy findings. The autopsy showed no evidence of acute myocardial infarction. The investigator considered the event to be serious, severe and not related to study drug.

A34 Please provide supporting evidence (efficacy and safety data) for the following statement, "The treatment interruption period in clinical trials extended to one year. Efficacy was regained with no evident increase in adverse events or infusion-related reactions during retreatment with vedolizumab" (see submission, page 24).

Subjects that responded to vedolizumab at week 6 in GEMINI I and who were then re-randomised to the placebo group in the maintenance phase could be enrolled in the C13008 if they completed the study. This equated to a treatment interruption of one year.

A35 Please clarify whether the July 2012 interim analysis for GEMINI LTS study is the most recent available? If so, please confirm when the next analysis is scheduled?

Takeda can confirm that the July 2012 interim analysis is the latest data set. Currently, the next analysis date is to be confirmed.

Section B: Clarification on cost-effectiveness data

Decision problem

Priority question

B1 Please clarify the intended primary target population? Is it patients who have failed a prior anti-TNF-α agent, patients who are anti-TNF-α naïve, or both of these populations? Would you expect vedolizumab to be used (a) before (b) after or (c) in place of other anti-TNF-α therapies?

The intended target patient population for treatment with vedolizumab corresponds exactly to marketing authorisation: adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Because clinical data are lacking for infliximab, adalimumab and golimumab in patients that have failed anti-TNF-α agents, the submission only presents the cost-effectiveness versus conventional therapy and surgery in the overall population. In the anti-TNF-α naïve and anti-TNF-α failure populations, we used the appropriate comparators.

In terms of place in therapy, based on the results of GEMINI I, vedolizumab can be used either before or after an anti-TNF- α therapy, i.e. options (a) and (b). Option (c), in place of ***other*** anti-TNF-α therapies, does not apply to vedolizumab. It has a different mechanism of action from the anti-TNF-α drugs: it binds to integrin $\alpha_4\beta_7$. Therefore, it represents an additional therapeutic option for patients failing current therapies, not an alternative. The only exception to this might be for patients who have failed on a prior anti-TNF-α agent: some patients undergo costly dose escalation or cycling, with the potential for diminished clinical response. In these cases, vedolizumab represents a valuable new option.

Priority question

B2 Please explain why all patients still on biologic treatment at 1-year are assumed to discontinue and subsequently receive only conventional non-biologic therapies. Please also comment on the practical feasibility of implementing such a stopping rule in clinical practice and the extent to which such a rule would reflect the licenses for vedolizumab, golimumab, adalimumab and infliximab. What evidence is there to support whether such discontinuation of biologic treatment actually happens in clinical practice?

In the absence of a stopping rule, it is uncertain what the average duration of treatment is with vedolizumab, golimumab, adalimumab and infliximab. A treatment duration of 1-year in responding patients was chosen to reflect the follow-up within clinical trials, particularly the GEMINI I trial upon which the model is mostly based. The impact on the ICER of patients receiving vedolizumab, golimumab, adalimumab or infliximab for 3 years was presented in the submission.

B3 Given that the population considered relates to patients with acute exacerbations of ulcerative colitis, please explain why the study by Punekar et al (2010) is included in the review of cost-effectiveness evidence?

The study was included as there were no exclusion criteria in the original search related to terms for chronic or acute ulcerative colitis. The patient population considered in that paper is different from the license for vedolizumab. Further, the model by Punekar et al. did not inform the structure of the model for vedolizumab.

B4 Please clarify how the impact of different doses, for patients with body mass <80kg and>80kg, on the costs and/or efficacy of golimumab is captured within the model?

The costs and efficacy of golimumab maintenance dosing for patients that weigh more or less than 80kg is not captured within the model. The average weight used in the model is 76.29kg and within the model, the dosing for golimumab is calculated on the basis of all patients weighing less than 80kg. This is a conservative assumption in terms of the cost-effectiveness analysis for vedolizumab, because including the higher dose of golimumab would increase the costs of treatment for the proportion of patients over 80kg.

In addition, there are non-significant differences in efficacy for the 50mg and 100mg maintenance doses for golimumab (PURSUIT-M). There are also non-significant differences in the 200/100 and 400/200 dosing regimens in induction (PURSUIT-SC). No differences in terms of efficacy at different doses were included for golimumab within the model.

Model structure

Priority question

B5 Please justify the inclusion of the moderate-to-severe (responders) state within the model. Please explain how the inclusion of separate states for moderate to severe responders and non-responders impacts upon costs and QALYs in each treatment group.

The GEMINI-1 clinical trial re-randomised patients that responded to treatment at the start of the maintenance period. However, the model health states are based upon absolute Mayo scores. Therefore, some patients responded to treatment (i.e. had a decrease in their Mayo score of 3 or more) but did not leave the moderate to severe health state in the model (i.e. did not have a Mayo score less than 6). The health state for moderate to severe responders is intended to capture this and to allow these responding patients to continue on treatment even though they remained in the moderate-severe health state.

Removing this health state would require strong assumptions about which treatments patients receive after the induction phase. However, it is unclear what those assumptions should be, as without this health state we would either have to assume all responders are in the mild disease or

remission states, or assume that any responders who remain in moderate to severe state would not continue on to maintenance therapy.

Priority question

B6 Please clarify why 5% of patients who undergo surgery are assumed to remain in the surgery state during each 8-week maintenance cycle? What evidence is there to support this assumption?

The 5% noted above is not patients remaining in the surgery state, but rather patients requiring a subsequent surgery 8 weeks later. The transition probability for surgery is taken from the study by Loftus et al., 2008, who present the probability of surgery within a 6-month period. The 6-month probability of surgery in that study was 0.153. This was converted to an 8-week probability using the formula 1 − (1 − 0.153)^(56/180). It was assumed that this probability applied for the duration of the model. Although it is possible that patients within the model receive many surgeries, the memory-less nature of a Markov model mean that it is not possible to say how many patients received multiple surgeries. However, it is possible to say that, within the model, over 10 years, patients treated with vedolizumab spend 0.138 years having surgery and that, on average, patients had 0.902 surgeries.

In the base-case model, for the mixed patient population, the ICER is £33,295 per QALY versus conventional therapy. If the transition probability is set to 0 and the transition probability to post-surgical remission is set to 0.5 (i.e. if it assumed that no patients have repeat surgery), then the ICER is £33,740 per QALY.

More sophisticated modelling approaches would include the use of tunnel states (possibly with a cap on the number of surgeries that a patient could receive), or a time-dependent transition probability. However, this would require additional data to inform the model and would substantially increase the complexity of the model programming. In the interests of simplicity, and given the rather small effect on the cost-effectiveness ratio, Takeda considered that collecting such data would be of very limited worth.

B7 Please explain why, when the parameter relating to the probability of a responding patient being moderate-to-severe is set to zero, (sheet SA Parameters cell H130), patients are still subsequently filtered between the moderate-to-severe (responders) and moderate-to-severe (non-responders) states in the conventional management groups of the Markov model (see Markov worksheets, columns V and W)?

When the model parameter for percentage of responders in moderate to severe disease is set to zero, any patients in column V (labelled “MS (Resp)”) are patients that initially responded to conventional therapy and then subsequently lost response. Patients in column W (labelled “No Resp”) did not respond to conventional therapy at all.

B8 Please explain why patients cannot move to surgery from the moderate-to-severe (non-responders) state whilst on biologic therapy?

Within the model, non-responders on biologic therapy, after the induction period, are assumed to switch to conventional therapy (compare columns K and S: these are the same patients). These patients can switch to surgery from column S (to column X).

B9 Please explain why the probability of a responding patient being moderate to severe (probability = 13.19% in the mixed ITT population) is applied to the overall probability of response (calculated in Markov sheets J49), rather than those patients who were specifically not in remission (as these patients by definition could not still be in moderate to severe)?

A total of 19 of 144 responders (both treated and placebo patients: 13.19%) had moderate to severe disease. This is applied to the overall probability of response within the model, as this matches the source of the data. An alternative would be to apply the data for non-remitters from the clinical trial to non-remitters in the model but this would provide the same proportions in each health state.

B10 Please clarify why the conventional management costs are assumed to be halved when used alongside biologics? Does this reflect conventional non-biologic drug use within the intervention and control arms of the GEMINI 1 trial?

A detailed assessment of the use of conventional therapy alongside vedolizumab would be complex. The use of conventional therapy within the GEMINI-1 trial was protocol driven and the trial was international and may not represent treatment patterns in England and Wales. A full analysis of the use of conventional therapy within the trial would involve assessment of frequency, dosing and duration and still would not replicate NHS treatment patterns. The model, as submitted, was intended to provide a reasonable assumption of the use of conventional therapy in real-world, NHS use.

In a scenario analysis (not in the submission but conducted for this clarification), an extreme value of 100% was used. In other words, it was assumed that patients receiving vedolizumab have the same costs of conventional therapy as patients receiving conventional therapy alone (i.e. £204.80 per cycle). In this scenario, the ICER would be £35,893 per QALY compared with conventional therapy for the mixed patient population, compared to an ICER of £33,295 per QALY in the base-case in the main submission.

B11 The cost of conventional non-biologic therapy during induction is reported to be £204 in the model (see Markov sheets cell N43) yet this value is multiplied by 6/8 during the induction stage of the model (see Markov sheets cell AO70). Please clarify which cost was intended, £204 or £204*(6/8)?

A cost of £204*(6/8) was used because the induction period, per GEMINI I, was 6 weeks and, thereafter in the model, the cycle length is 8 weeks.

B12 On page 204 of the submission (Table 53), it states that a half-cycle correction was not applied within the model, yet the model appears to employ such a correction. Please state which is true.

This was an error in the submission document. A half cycle correction was applied.

Efficacy transition parameters

Priority question

B13 Please provide a worked example showing how the odds ratios for response and remission during maintenance have been used to generate the transition matrices for infliximab, adalimumab and golimumab (these are currently hardcoded in the Data Store worksheet row 342 onwards).

The calculations for the transition matrices cannot be provided in a worked example as they depend on the algorithm used by SOLVER. The description of the methods used is provided in the submission, with additional details provided in Appendix 15.

Priority question

B14 Please provide details of the baseline model within the network meta-analyses of induction and maintenance therapy.

Following Takeda request for clarification, this was reworded by the ERG to: *Did you use a baseline model in the network meta-analyses of induction and maintenance therapy? If yes, please provide details.*

A model to predict the response to the reference treatment was used. The MCMCglmm package in R was first used to estimate the response to the reference treatment. However, due to the small networks i.e. trying to estimate a distribution with only a few values, this often ran into convergence problems. When this occurred, a Bayesian integrated Laplacian approximation was used using the inla package in R. This latter model assumes a normal distribution rather than trying to estimate the distribution exactly and didn't have any convergence problems. In fact, this model runs until convergence is achieved and only gives an answer when it has converged.

Regarding a baseline risk adjusted model, we did not use a baseline-adjusted MTC. This type of model is unlikely to give robust results for small networks.

Priority question

B15 Please explain what adjustments were made to account for the re-randomisation in the PURSUIT-Maintenance and GEMINI 1 trials?

No adjustment was made within the model to account for re-randomisation or no re-randomisation between the trials. It is unclear what adjustment should be made.

The trials formed two groups, with GEMINI I and PURSUIT-M containing re-randomized responders and ACT-1, ULTRA-2 and Suzuki et al. (2014) following the same patients through induction and maintenance phases. The network for re-randomized responders was analysed, but this only contained vedolizumab (Q8W and Q4W) and golimumab (50mg and 100mg). However, we also tried to make the comparison with infliximab (5 mg and 10mg) and adalimumab 40 mg. In order to do this we used the reported number of responders at end of induction for each study arm and number of responders at end of maintenance for each study arm. However, this assumes that only patients that responded at end of induction responded at end of maintenance.

Priority question

B16 The maintenance analysis calibrates the probability that patients are in the mild state or remission within the model against the probability of achieving response or remission within the GEMINI1 trial. Please explain why, within the model, patients achieving response who were still in the moderate to severe state were not also included in this comparison?

The model has a discontinuation rule: all patients in the moderate to severe health state after one year discontinue biologic therapy and switch to conventional therapy. Responders in the moderate to severe health state would immediately be discontinued. As such, it was assumed that all responders at week 54 were in either remission or had mild disease. Therefore, those responders who were still in the moderate to severe disease state were transitioned to mild disease.

The transition probabilities are calibrated to move patients gradually toward this outcome. To clarify, these patients are not suddenly switched at week 54; they are subsumed into the mild disease state prior to calibration of the transition probabilities. The transition probabilities are calibrated such that no responders at week 54 are actually in the moderate to severe disease state: anyone in the moderate to severe disease state at week 54 is considered to have lost response. These transition probabilities were derived irrespective of the one-year treatment rule.

Priority question

B17 Please provide evidence to justify the constraints used in the Solver optimisation (listed in the bullet points on page 338 of the submission). Please provide evidence to justify the initial values used in the Solver optimisation (detailed on page 339 of the submission).

In order to calibrate the model with SOLVER (linear programming), constraints and initial values are required. Therefore, reasonable assumptions were made: e.g. that patients would move only to the

next health state (i.e. that patients could not transition from remission to moderate-severe disease or vice versa). The initial values were chosen to be reasonable estimates.

The calibration provided estimates that produced very similar proportions of patients with remission and mild disease that were observed in the GEMINI I study.

B18 Please further explain how the multinomial transition probabilities are sampled within the probabilistic sensitivity analysis? The model states that Dirichlet distributions are used, please clarify where are these implemented within the model?

These are implemented on the "SA Parameters" sheet" using the Dirichlet distributional assumption and the sample sizes from the pooled trial data. The transition probabilities are jointly dependent on each other. As such, the Dirichlet assumption varies these probabilities jointly: when one value changes, the others change as well.

Other parameter values

Priority question

B19 In Table 69, the first row relates to the overall population of GEMINI 1. Please clarify whether these estimates are of EQ-5D at baseline, or some other time point?

These are estimates of the EQ-5D scores at all time points of the GEMINI I study, regardless of when patients were assessed. For example, a patient that had mild disease at baseline and at week 52, and was in remission at week 6, would contribute their Mayo score twice for the mild health state and once for the remission health state.

Priority question

B20 Please clarify why the utility for patients in the post-surgery state is lower than that for patients in the moderate to severe state.

The utility data are taken from different sources. The mean utility scores observed in GEMINI I were used for the remission, mild and moderate-severe health states. However, utility scores for surgery and post-surgery were not collected in GEMINI I so had to be taken from the literature.

The EQ-5D score for patients with moderate to severe disease in GEMINI I was higher than previously published estimates. For example, the study by Tsai et al. (2008) used a value of 0.42. The recently published assessment report for the on-going MTA of infliximab, adalimumab and golimumab for the treatment of moderate to severely active ulcerative colitis used a value of 0.41.[1]

[1] Archer R, Tappenden P, Ren S, et al. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy. Technology Assessment Report: Final report to the National Institute for Health and Care Excellence, 2014.

However, to be conservative, the value observed in the GEMINI I study (EQ-5D score of 0.68) was used in the model. This discrepancy could be explained by the frequent interactions between patients in a clinical trial and healthcare providers, and the consequent additional care received.

Scenario analyses are presented within the submission that use alternative sources of utilities. For this response to the clarification questions, a value of 0.42 was used for moderate to severe disease (i.e. equivalent to surgery and post-surgical complications described in the previous paragraph). All of the other utilities were unchanged from the base-case. In this scenario, the ICER was £17,954 per QALY for the comparison with conventional therapy in the mixed population (compared with £33,295 in the submitted base-case).

B21 Please clarify the source of the £308 infusion costs which is reportedly from the PbR tariff and which year was used?

The infusion cost of £308 is from the PbR tariff, year 2012/13. It is the combined day case/ordinary elective spell tariff for inflammatory bowel disorders with a length of stay of 1 day or less (code FZ37F).

B22 The submission states that NHS Reference Costs have been used to value the costs of resource use items listed in Table 80 (page 261 of the submission). However the model appears to use the values originally reported by Tsai et al (see worksheet "Data Store" cells D82:D86). Please clarify which source was intended.

Cells D82:D86 provide the unit costs using NHS reference costs. These are applied to estimates of resource use in cells F82:K86. The estimates of resource used are from the study by Tsai et al (2008).

B23 On page 216 of the submission it states "we derived these probabilities from a targeted review of the available published literature." Please provide details of this review (including the search strategy and the list of studies considered for inclusion in the model).

The targeted review of the literature was a simple search of Medline and was not a systematic search. Neither the search strategy nor the list of studies identified was recorded.

Section C: Textual clarifications and additional points

Priority question
C1 Please complete the following table relating to data from the intention-to-treat population of the GEMINI 1 trial. Please include only data relating to the vedolizumab arm at the recommended licensed dose (300mg q8w) and the placebo arm of the trial. Please note that we are only interested in those patients who were re-randomised following an induction response.

GEMINI 1 ITT population (baseline to 52 weeks)

Outcome	**Vedolizumab 300mg q8w**	**Placebo**
Number of patients who had neither response nor remission at baseline who lost response at 52 weeks		
Number of patients who had neither response nor remission at baseline who achieved response (without remission) at 52 weeks		
Number of patients who had neither response nor remission at baseline who achieved remission at 52 weeks		
Number of patients who had response (without remission) at baseline who lost response at 52 weeks		
Number of patients who had response (without remission) at baseline who maintained response (without remission) at 52 weeks		
Number of patients who had response (without remission) at baseline who achieved remission at 52 weeks		
Number of patients who had remission at baseline who lost response at 52 weeks		
Number of patients who had remission at baseline who maintained response (without remission) at 52 weeks		
Number of patients who had remission at baseline who achieved remission at 52 weeks		

Takeda does not have the data requested and cannot provide them in the time available. The utility of the analysis as requested is unclear, as is the use of ‘baseline’, ’remission’ and ‘response’. Does ‘baseline’ refer to the baseline for the induction phase or the maintenance phase? Do ‘remission’ and ‘response’ refer specifically to vedolizumab or to any treatment? If the ERG can provide an explanation for the data request, Takeda will further consider the question.

Priority question

C2 Please complete the following table relating to data from the prior anti-TNF-α failure population of the GEMINI 1 trial. Please include only data relating to the vedolizumab arm at the recommended licensed dose (300mg q8w) and the placebo arm of the trial. Please note that we are only interested in those patients who were re-randomised following an induction response.

GEMINI 1 failure population (baseline to 52 weeks)

Outcome	**Vedolizumab 300mg q8w**	**Placebo**
Number of patients who had neither response nor remission at baseline who lost response at 52 weeks		
Number of patients who had neither response nor remission at baseline who achieved response (without remission) at 52 weeks		
Number of patients who had neither response nor remission at baseline who achieved remission at 52 weeks		
Number of patients who had response (without remission) at baseline who lost response at 52 weeks		
Number of patients who had response (without remission) at baseline who maintained response (without remission) at 52 weeks		
Number of patients who had response (without remission) at baseline who achieved remission at 52 weeks		
Number of patients who had remission at baseline who lost response at 52 weeks		
Number of patients who had remission at baseline who maintained response (without remission) at 52 weeks		
Number of patients who had remission at baseline who achieved remission at 52 weeks		

Takeda does not have the data requested and cannot provide them in the time available. The utility of the analysis as requested is unclear, as is the use of 'baseline', 'remission' and 'response'. Does 'baseline' refer to the baseline for the induction phase or the maintenance phase? Do 'remission' and 'response' refer specifically to vedolizumab or to any treatment? If the ERG can provide an explanation for the data request, Takeda will further consider the question.

Appendix 1.Additonal tables for response to A4

Entire Population

Induction

Clinical Response

Study	Reference	Treatment	Week	N	n	%
GEMINI-1	CSR C13006	Placebo	6	149	38	26%
GEMINI-1	CSR C13006	Vedolizumab	6	225	106	47%
ULTRA-1	Reinisch et al., 2011	Placebo	8	130	58	45%
ULTRA-1	Reinisch et al., 2011	Adalimumab 160 mg/80 mg	8	130	71	55%
ULTRA-1	Reinisch et al., 2011	Adalimumab 80 mg/40 mg	8	130	67	52%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	8	246	85	35%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 160 mg/80 mg	8	248	125	50%
ACT-1	Rugeerts et al., 2005	Placebo	8	121	45	37%
ACT-1	Rugeerts et al., 2005	Infliximab 5 mg	8	121	84	69%
ACT-1	Rugeerts et al., 2005	Infliximab 10 mg	8	122	75	61%
ACT-2	Rugeerts et al., 2005	Placebo	8	123	36	29%
ACT-2	Rugeerts et al., 2005	Infliximab 5 mg	8	121	78	64%
ACT-2	Rugeerts et al., 2005	Infliximab 10 mg	8	120	83	69%
PURSUIT-SC	Sandborn et al., 2013	Placebo	6	256	76	30%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 200/100 mg	6	257	133	52%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 400/200 mg	6	258	142	55%

Study	Reference	Treatment	Week	N	n	%
NA	Suzuki et al., 2014	Placebo	8	96	34	35%
NA	Suzuki et al., 2014	Adalimumab 80 mg/40 mg	8	87	37	43%
NA	Suzuki et al., 2014	Adalimumab 160 mg/80 mg	8	90	45	50%

Clinical Remission

Study	Reference	Treatment	Week	N	n	%
GEMINI-1	CSR C13006	Placebo	6	149	8	5%
GEMINI-1	CSR C13006	Vedolizumab	6	225	38	17%
ULTRA-1	Reinisch et al., 2011	Placebo	8	130	12	9%
ULTRA-1	Reinisch et al., 2011	Adalimumab 160 mg/80 mg	8	130	24	18%
ULTRA-1	Reinisch et al., 2011	Adalimumab 80 mg/40 mg	8	130	13	10%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	8	246	23	9%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 160 mg/80 mg	8	248	41	17%
ACT-1	Rugeerts et al., 2005	Placebo	8	121	18	15%
ACT-1	Rugeerts et al., 2005	Infliximab 5 mg	8	121	47	39%
ACT-1	Rugeerts et al., 2005	Infliximab 10 mg	8	122	39	32%
ACT-2	Rugeerts et al., 2005	Placebo	8	123	7	6%
ACT-2	Rugeerts et al., 2005	Infliximab 5 mg	8	121	41	34%
ACT-2	Rugeerts et al., 2005	Infliximab 10 mg	8	120	33	28%
PURSUIT-SC	Sandborn et al., 2013	Placebo	6	256	16	6%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 200/100 mg	6	257	48	19%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 400/200 mg	6	258	46	18%
NA	Suzuki et al., 2014	Placebo	8	96	11	11%

Study	Reference	Treatment	Week	N	n	%
NA	Suzuki et al., 2014	Adalimumab 80 mg/40 mg	8	87	12	14%
NA	Suzuki et al., 2014	Adalimumab 160 mg/80 mg	8	90	9	10%

Discontinuation Due to AEs

Study	Reference	Treatment	Week	N	n	%
GEMINI-1	CSR C13006	Placebo	6	149	4	3%
GEMINI-1	CSR C13006	Vedolizumab	6	225	0	0%
ULTRA-1	Reinisch et al., 2011	Placebo	8	223	12	5%
ULTRA-1	Reinisch et al., 2011	Adalimumab 160 mg/80 mg	8	223	12	5%
ULTRA-1	Reinisch et al., 2011	Adalimumab 80 mg/40 mg	8	130	8	6%
PURSUIT-SC	Sandborn et al., 2013	Placebo	6	330	3	1%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 200/100 mg	6	331	1	0%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 400/200 mg	6	332	1	0%
NA	Suzuki et al., 2014	Placebo	8	96	4	4%
NA	Suzuki et al., 2014	Adalimumab 80 mg/40 mg	8	87	0	0%
NA	Suzuki et al., 2014	Adalimumab 160 mg/80 mg	8	90	6	7%

Mucosal Healing

Study	Reference	Treatment	Week	N	n	%
GEMINI-1	CSR C13006	Placebo	6	149	37	25%
GEMINI-1	CSR C13006	Vedolizumab	6	225	92	41%
ULTRA-1	Reinisch et al., 2011	Placebo	8	130	54	42%
ULTRA-1	Reinisch et al., 2011	Adalimumab 160 mg/80 mg	8	130	61	47%
ULTRA-1	Reinisch et al., 2011	Adalimumab 80 mg/40 mg	8	130	49	38%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	8	246	78	32%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 160 mg/80 mg	8	248	102	41%
ACT-2	Rugeerts et al., 2005	Placebo	8	123	38	31%
ACT-2	Rugeerts et al., 2005	Infliximab 5 mg	8	121	73	60%
ACT-2	Rugeerts et al., 2005	Infliximab 10 mg	8	120	74	62%
PURSUIT-SC	Sandborn et al., 2013	Placebo	6	256	73	29%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 200/100 mg	6	257	111	43%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 400/200 mg	6	258	117	45%
NA	Suzuki et al., 2014	Placebo	8	96	29	30%
NA	Suzuki et al., 2014	Adalimumab 80 mg/40 mg	8	87	34	39%
NA	Suzuki et al., 2014	Adalimumab 160 mg/80 mg	8	90	37	41%

Serious Adverse Events

Study	Reference	Treatment	Week	N	n	%
GEMINI-1	CSR C13006	Placebo	6	149	10	7%
GEMINI-1	CSR C13006	Vedolizumab	6	225	5	2%
ULTRA-1	Reinisch et al., 2011	Placebo	8	223	17	8%
ULTRA-1	Reinisch et al., 2011	Adalimumab 160 mg/80 mg	8	223	9	4%
ULTRA-1	Reinisch et al., 2011	Adalimumab 80 mg/40 mg	8	130	5	4%
PURSUIT-SC	Sandborn et al., 2013	Placebo	6	330	20	6%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 200/100 mg	6	331	9	3%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 400/200 mg	6	332	11	3%
NA	Suzuki et al., 2014	Placebo	8	96	7	7%
NA	Suzuki et al., 2014	Adalimumab 80 mg/40 mg	8	87	2	2%
NA	Suzuki et al., 2014	Adalimumab 160 mg/80 mg	8	90	4	4%

Maintenance

Durable Clinical Response

Study	Reference	Treatment	Week	N	n	%	Randomization
PURSUIT-M	Sandborn et al., 2013	Placebo	54	156	49	31%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 50 mg	54	153	72	47%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 100 mg	54	154	78	51%	Re-randomized
GEMINI-1	CSR C13006	Placebo	52	126	30	24%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	122	69	57%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	125	65	52%	Re-randomized
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	52	85	30	35%	Not re-randomized (N = number of responders at **end** of induction)
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 40 mg eow	52	125	76	61%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Placebo	54	45	24	53%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab.5 mg	54	84	55	65%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab.10 mg	54	75	54	72%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Placebo	52	34	6	18%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Adalimumab 40 mg eow	52	82	25	30%	Not re-randomized (N = number of responders at **end** of induction)

Clinical Remission

Study	Reference	Treatment	Week	N	n	%	Randomization
PURSUIT-M	Sandborn et al., 2013	Placebo	54	156	35	22%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 50 mg	54	153	51	33%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 100 mg	54	154	53	34%	Re-randomized
GEMINI-1	CSR C13006	Placebo	52	126	20	16%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	122	51	42%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	125	56	45%	Re-randomized
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	52	85	17	20%	Not re-randomized (N = number of responders at **end** of induction)
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 40 mg eow	52	125	44	35%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Placebo	54	45	20	44%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab.5 mg	54	84	42	50%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab.10 mg	54	75	42	56%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Placebo	52	34	2	7%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Adalimumab 40 mg eow	52	82	19	23%	Not re-randomized (N = number of responders at **end** of induction)

Discontinuation Due to AEs

Study	Reference	Treatment	Week	N	n	%	Randomization
PURSUIT-M	Sandborn et al., 2013	Placebo	54	156	10	6%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 50 mg	54	154	8	5%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 100 mg	54	154	14	9%	Re-randomized
GEMINI-1	CSR C13006	Placebo	52	126	15	12%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	122	7	6%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	125	6	5%	Re-randomized
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	52	260	34	13%	Not re-randomized
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 40 mg eow	52	257	23	9%	Not re-randomized
ACT-1	Rugeerts et al., 2005	Placebo	54	121	11	9%	Not re-randomized
ACT-1	Rugeerts et al., 2005	Infliximab.5 mg	54	121	10	8%	Not re-randomized
ACT-1	Rugeerts et al., 2005	Infliximab.10 mg	54	122	11	9%	Not re-randomized
NA	Suzuki et al., 2014	Placebo	52	96	6	6%	Not re-randomized
NA	Suzuki et al., 2014	Adalimumab 40 mg eow	52	177	22	12%	Not re-randomized

Mucosal Healing

Study	Reference	Treatment	Week	N	n	%	Randomization
GEMINI-1	CSR C13006	Placebo	52	126	25	20%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	122	63	52%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	125	70	56%	Re-randomized

Study	Reference	Treatment	Week	N	n	%	Randomization
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	52	85	37	44%	Not re-randomized (N = number of responders at **end** of induction)
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 40 mg eow	52	125	62	50%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Placebo	54	45	22	49%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab 5 mg	54	84	55	65%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab 10 mg	54	75	57	76%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Placebo	52	34	15	44%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Adalimumab 40 mg eow	52	82	51	62%	Not re-randomized (N = number of responders at **end** of induction)

CSF Remission

Study	Reference	Treatment	Week	N	n	%	Randomization
GEMINI-1	CSR C13006	Placebo	52	72	10	14%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	70	22	31%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	73	33	45%	Re-randomized
ACT-1	Rugeerts et al., 2005	Placebo	54	45	7	16%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab.5 mg	54	84	18	21%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab.10 mg	54	75	12	16%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Placebo	52	34	4	12%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Adalimumab 40 mg eow	52	82	17	21%	Not re-randomized (N = number of responders at **end** of induction)

Serious Adverse Events

Study	Reference	Treatment	Week	N	n	%	Randomization
PURSUIT-M	Sandborn et al., 2013	Placebo	54	156	12	8%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 50 mg	54	154	13	8%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 100 mg	54	154	22	14%	Re-randomized
GEMINI-1	CSR C13006	Placebo	52	126	20	16%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	122	10	8%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	125	11	9%	Re-randomized
ACT-1	Rugeerts et al., 2005	Placebo	54	121	31	26%	Not re-randomized
ACT-1	Rugeerts et al., 2005	Infliximab.5mg	54	121	26	21%	Not re-randomized
ACT-1	Rugeerts et al., 2005	Infliximab.10mg	54	122	29	24%	Not re-randomized
ULTRA-2	Sandborn et al., 2012	Placebo	52	260	32	12%	Not re-randomized
ULTRA-2	Sandborn et al., 2012	Adalimumab 40 mg eow	52	257	32	12%	Not re-randomized
NA	Suzuki et al., 2014	Placebo	52	96	14[a]	15%	Not re-randomized
NA	Suzuki et al., 2014	Adalimumab 40 mg eow	52	177	33[a]	19%	Not re-randomized

[a]In order to connect adalimumab in the network we have used data for the number of SAEs rather than the number of patients experiencing an SAE, assuming one SAE per patient.

Anti-TNF–Naïve Population

Induction

Clinical Response

Study	Reference	Treatment	Week	N	n	%
GEMINI-1	CSR C13006	Placebo	6	76	20	26%
GEMINI-1	CSR C13006	Vedolizumab	6	130	69	53%
ULTRA-1	Reinisch et al., 2011	Placebo	8	130	58	45%
ULTRA-1	Reinisch et al., 2011	Adalimumab 160 mg/80 mg	8	130	71	55%
ULTRA-1	Reinisch et al., 2011	Adalimumab 80 mg/40 mg	8	130	67	52%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 160 mg/80 mg	8	150	89	59%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	8	145	56	39%
ACT-1	Rugeerts et al., 2005	Placebo	8	121	45	37%
ACT-1	Rugeerts et al., 2005	Infliximab 5 mg	8	121	84	69%
ACT-1	Rugeerts et al., 2005	Infliximab 10 mg	8	122	75	61%
ACT-2	Rugeerts et al., 2005	Placebo	8	123	36	29%
ACT-2	Rugeerts et al., 2005	Infliximab 5 mg	8	121	78	64%
ACT-2	Rugeerts et al., 2005	Infliximab 10 mg	8	120	83	69%
PURSUIT-SC	Sandborn et al., 2013	Placebo	6	256	76	30%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 200/100 mg	6	257	133	52%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 400/200 mg	6	258	142	55%
NA	Suzuki et al., 2014	Placebo	8	96	34	35%

Study	Reference	Treatment	Week	N	n	%
NA	Suzuki et al., 2014	Adalimumab 80 mg/40 mg	8	87	37	43%
NA	Suzuki et al., 2014	Adalimumab 160 mg/80 mg	8	90	45	50%

Clinical Remission

Study	Reference	Treatment	Week	N	n	%
GEMINI-1	CSR C13006	Placebo	6	76	5	7%
GEMINI-1	CSR C13006	Vedolizumab	6	130	30	23%
ULTRA-1	Reinisch et al., 2011	Placebo	8	130	12	9%
ULTRA-1	Reinisch et al., 2011	Adalimumab 160 mg/80 mg	8	130	24	18%
ULTRA-1	Reinisch et al., 2011	Adalimumab 80 mg/40 mg	8	130	13	10%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 160 mg/80 mg	8	150	32	21%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	8	145	16	11%
ACT-1	Rugeerts et al., 2005	Placebo	8	121	18	15%
ACT-1	Rugeerts et al., 2005	Infliximab 5 mg	8	121	47	39%
ACT-1	Rugeerts et al., 2005	Infliximab 10 mg	8	122	39	32%
ACT-2	Rugeerts et al., 2005	Placebo	8	123	7	6%
ACT-2	Rugeerts et al., 2005	Infliximab 5 mg	8	121	41	34%
ACT-2	Rugeerts et al., 2005	Infliximab 10 mg	8	120	33	28%
PURSUIT-SC	Sandborn et al., 2013	Placebo	6	256	16	6%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 200/100 mg	6	257	48	19%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 400/200 mg	6	258	46	18%
NA	Suzuki et al., 2014	Placebo	8	96	11	11%

Study	Reference	Treatment	Week	N	n	%
NA	Suzuki et al., 2014	Adalimumab 80 mg/40 mg	8	87	12	14%
NA	Suzuki et al., 2014	Adalimumab 160 mg/80 mg	8	90	9	10%

Discontinuation Due to AEs

Study	Reference	Treatment	Week	N	n	%
GEMINI-1	CSR C13006	Placebo	6	76	3	4%
GEMINI-1	CSR C13006	Vedolizumab	6	130	0	0%
ULTRA-1	Reinisch et al., 2011	Placebo	8	130	5	4%
ULTRA-1	Reinisch et al., 2011	Adalimumab 160 mg/80 mg	8	130	5	4%
ULTRA-1	Reinisch et al., 2011	Adalimumab 80 mg/40 mg	8	130	5	4%
PURSUIT-SC	Sandborn et al., 2013	Placebo	6	330	3	1%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 200/100 mg	6	331	1	0%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 400/200 mg	6	332	1	0%
NA	Suzuki et al., 2014	Placebo	8	96	4	4%
NA	Suzuki et al., 2014	Adalimumab 80 mg/40 mg	8	87	0	0%
NA	Suzuki et al., 2014	Adalimumab 160 mg/80 mg	8	90	6	7%

Mucosal Healing

Study	Reference	Treatment	Week	N	n	%
GEMINI-1	CSR C13006	Placebo	6	76	19	25%
GEMINI-1	CSR C13006	Vedolizumab	6	130	64	49%
ULTRA-1	Reinisch et al., 2011	Placebo	8	130	54	42%
ULTRA-1	Reinisch et al., 2011	Adalimumab 160 mg/80 mg	8	130	61	47%
ULTRA-1	Reinisch et al., 2011	Adalimumab 80 mg/40 mg	8	130	49	38%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 160 mg/80 mg	8	150	74	49%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	8	145	51	35%
ACT-2	Rugeerts et al., 2005	Placebo	8	123	38	31%
ACT-2	Rugeerts et al., 2005	Infliximab 5 mg	8	121	73	60%
ACT-2	Rugeerts et al., 2005	Infliximab 10 mg	8	120	74	62%
PURSUIT-SC	Sandborn et al., 2013	Placebo	6	256	73	29%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 200/100 mg	6	257	111	43%
PURSUIT-SC	Sandborn et al., 2013	Golimumab 400/200 mg	6	258	117	45%
NA	Suzuki et al., 2014	Placebo	8	96	29	30%
NA	Suzuki et al., 2014	Adalimumab 80 mg/40 mg	8	87	34	39%
NA	Suzuki et al., 2014	Adalimumab 160 mg/80 mg	8	90	37	41%

Maintenance

Durable Clinical Response

Study	Reference	Treatment	Week	N	n	%	Randomization
GEMINI-1	CSR C13006	Placebo	52	79	21	27%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	72	47	65%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	73	41	56%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Placebo	54	156	49	31%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 50 mg	54	153	72	47%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 100 mg	54	154	78	51%	Re-randomized
ACT-1	Rugeerts et al., 2005	Placebo	54	45	24	53%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab 5 mg	54	84	55	65%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab 10 mg	54	75	54	72%	Not re-randomized (N = number of responders at **end** of induction)
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	52	56	35	63%	Not re-randomized (N = number of responders at **end** of induction)
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 40 mg eow	52	89	55	62%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Placebo	52	34	6	18%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Adalimumab 40 mg eow	52	82	25	30%	Not re-randomized (N = number of responders at **end** of induction)

Clinical Remission

Study	Reference	Treatment	Week	N	n	%	Randomization
GEMINI-1	CSR C13006	Placebo	52	79	15	19%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	72	33	46%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	73	35	48%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Placebo	54	156	35	22%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 50 mg	54	153	51	33%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 100 mg	54	154	53	34%	Re-randomized
ACT-1	Rugeerts et al., 2005	Placebo	54	45	20	44%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab 5 mg	54	84	42	50%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab 10 mg	54	75	42	56%	Not re-randomized (N = number of responders at **end** of induction)
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	52	56	18	32%	Not re-randomized (N = number of responders at **end** of induction)
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 40 mg eow	52	89	33	37%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Placebo	52	34	2	6%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Adalimumab 40 mg eow	52	82	19	23%	Not re-randomized (N = number of responders at **end** of induction)

Discontinuation Due to AEs

Study	Reference	Treatment	Week	N	n	%	Randomization
GEMINI-1	CSR C13006	Placebo	52	88	9	10%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	79	3	4%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	85	3	4%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Placebo	54	156	10	6%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 50 mg	54	154	8	5%	Re-randomized
PURSUIT-M	Sandborn et al., 2013	Golimumab 100 mg	54	154	14	9%	Re-randomized
ACT-1	Rugeerts et al., 2005	Placebo	54	121	11	9%	Not re-randomized
ACT-1	Rugeerts et al., 2005	Infliximab 5 mg	54	121	10	8%	Not re-randomized
ACT-1	Rugeerts et al., 2005	Infliximab 10 mg	54	122	11	9%	Not re-randomized
NA	Suzuki et al., 2014	Placebo	52	96	6	6%	Not re-randomized
NA	Suzuki et al., 2014	Adalimumab 40 mg eow	52	177	22	12%	Not re-randomized

Mucosal Healing

Study	Reference	Treatment	Week	N	n	%	Randomization
GEMINI-1	CSR C13006	Placebo	52	79	19	24%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	72	43	60%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	73	44	60%	Re-randomized
ACT-1	Rugeerts et al., 2005	Placebo	54	45	22	49%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab 5 mg	54	84	55	65%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab 10 mg	54	75	57	76%	Not re-randomized (N = number of responders at **end** of induction)
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	52	56	28	50%	Not re-randomized (N = number of responders at **end** of induction)
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 40 mg eow	52	89	47	53%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Placebo	52	34	15	44%	Not re-randomized (N = number of responders at **end** of induction)
NA	Suzuki et al., 2014	Adalimumab 40 mg eow	52	82	51	62%	Not re-randomized (N = number of responders at **end** of induction)

CSF Remission

Study	Reference	Treatment	Week	N	n	%	Randomization
GEMINI-1	CSR C13006	Placebo	52	43	8	19%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	39	14	36%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	44	23	52%	Re-randomized
ACT-1	Rugeerts et al., 2005	Placebo	54	45	7	16%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab 5 mg	54	84	18	21%	Not re-randomized (N = number of responders at **end** of induction)
ACT-1	Rugeerts et al., 2005	Infliximab 10 mg	54	75	12	16%	Not re-randomized (N = number of responders at **end** of induction)

Anti-TNF Experienced/Failure Population

Induction

Clinical Response

Study	Reference	Treatment	Week	N	n	%
GEMINI-1	CSR C13006	Placebo	6	63	13	21%
GEMINI-1	CSR C13006	Vedolizumab	6	82	32	39%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 160 mg/80 mg	8	98	36	37%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	8	101	29	29%

Clinical Remission

Study	Reference	Treatment	Week	N	n	%
GEMINI-1	CSR C13006	Placebo	6	63	2	3%
GEMINI-1	CSR C13006	Vedolizumab	6	82	8	10%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 160 mg/80 mg	8	98	9	9%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	8	101	7	7%

Mucosal Healing

Study	Reference	Treatment	Week	N	n	%
GEMINI-1	CSR C13006	Placebo	6	63	13	21%
GEMINI-1	CSR C13006	Vedolizumab	6	82	25	30%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 160 mg/80 mg	8	98	28	29%
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	8	101	27	27%

Maintenance

Clinical Response

Study	Reference	Treatment	Week	N	n	%	Randomization
GEMINI-1	CSR C13006	Placebo	52	38	6	16%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	43	20	47%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	40	17	43%	Re-randomized
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	52	36	10	28%	Not re-randomized (N = number of responders at **end** of induction)
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 40 mg eow	52	29	20	69%	Not re-randomized (N = number of responders at **end** of induction)

Clinical Remission

Study	Reference	Treatment	Week	N	n	%	Randomization
GEMINI-1	CSR C13006	Placebo	52	38	2	5%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	43	16	37%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	40	14	35%	Re-randomized
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	52	36	3	8%	Not re-randomized (N = number of responders at **end** of induction)
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 40 mg eow	52	29	10	34%	Not re-randomized (N = number of responders at **end** of induction)

Mucosal Healing

Study	Reference	Treatment	Week	N	n	%	Randomization
GEMINI-1	CSR C13006	Placebo	52	38	3	8%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q8W	52	43	18	42%	Re-randomized
GEMINI-1	CSR C13006	Vedolizumab Q4W	52	40	19	48%	Re-randomized
ULTRA-2	Sandborn et al., 2012 (Gastro)	Placebo	52	36	10	28%	Not re-randomized (N = number of responders at **end** of induction)
ULTRA-2	Sandborn et al., 2012 (Gastro)	Adalimumab 160 mg/80 mg	52	29	15	52%	Not re-randomized (N = number of responders at **end** of induction)

Appendix 2: Systematic literature search for surgery and cost-effectiveness

Aims

The aims of the systematic review were to answer the following research questions:

- What is the humanistic burden associated with surgery, and its complications, for the treatment of Crohn's disease and ulcerative colitis?
- What are the direct and indirect costs, economic evaluations and resource utilisation associated with surgery, and its complications, to treat Crohn's disease and ulcerative colitis?

Methods

The search strategy was based on the following PICOS elements:

- Participants: adult patients with ulcerative colitis or Crohn's Disease
- Intervention: all surgery types
- Comparators: not applicable
- Outcomes: humanistic burden (utilities and PROs) and economic burden (direct and indirect costs, economic evaluations, resource utilisation)
- Study design: all, excluding case studies and non-systematic reviews.

Inclusion criteria

- All studies reporting costs associated with surgery, and its complications, including any of the following:
    - Cost-effectiveness analysis for the treatments of interest
    - Cost-utility analysis
    - Cost-minimization analysis
    - Cost-benefit analysis
    - Budget impact analysis
    - Cost studies.

- Studies reporting (dis)utilities of surgery and its complications (this includes time spent without complications, post-surgery) including any of the following:
    - Standard Gamble (SG)
    - Short Form - 36 questionnaire.
    - Euroqol 5 dimensions (EQ-5D)
    - Health Utilities Index (HUI).

- Studies that report both direct and indirect costs of surgery and its complications to treat ulcerative colitis and Crohn's disease.

- Studies that report the resource use associated with surgery, and its complications, to treat ulcerative colitis and Crohn's disease.

- Studies conducted in any country.

- Studies in human subjects.
- Studies reported in English.

Exclusion criteria

- Non-UK resource use and cost studies will be excluded. However, studies reporting productivity losses will be included irrespective of country of analysis.
- Studies on modelling development for economic evaluations, i.e. studies that only discuss model structure and do not present results.
- Articles not related to costs of interest.
- Publications that are editorials, letters, case reports, commentaries, interview-based research, legal cases, newspaper article, or patient education handouts (excluded electronically if indexed correctly).
- Studies that are non-systematic reviews of other studies.
- Studies published before 2003.

Electronic Searches

The key characteristics of the searches undertaken are listed below:

- **Language**: English or translated where appropriate.
- **Scope countries**: There was no country limit for humanistic burden or indirect costs. Non-UK resource use and cost studies were excluded. However, studies reporting productivity losses were included irrespective of country of analysis.
- **Time frame**: The search strategy did not consider studies preceding 2003, as before this date biologic drugs for Crohn's disease and ulcerative colitis had not yet been developed. In addition, resource use and cost studies published over 10 years ago would be out of date. For example, resource use might not apply to current practice or be measured at current prices.
- **Publication type/status:** Publications were excluded electronically if they are indexed as editorials, letters, case reports, commentaries, interview-based research, legal cases, newspaper articles or patient education hand outs.

The databases searched for the literature review included:

- MEDLINE (Ovid SP) (searched 13/03/14)
- MEDLINE (R) In-Process Citations and Daily Updates (Ovid SP) (searched 13/03/14)

- EMBASE (Ovid SP) (searched 13/03/14)
- EconLit (searched 18/03/14)
- The Cochrane Library (searched 18/03/14)
- Disease-specific websites such as European Crohn's and Colitis Organisation (ECCO). (searched 20/04/14)

The search strategies specific to each database were designed to focus retrieval on the published articles most likely to be relevant to the review questions. The search strategies and the searches were designed and performed by an experienced medical librarian.

Searching Other Resources

The electronic search was supplemented by hand searching in order to identify other published or unpublished material (grey literature). Additional internet searches included a general internet search, and searches of the following websites for abstracts, slide presentations, and posters from relevant conferences:

- NICE Website
- Cost effectiveness analysis registry
- International Society for Pharmacoeconomics and Outcomes Research: Research Digest, at http://www.ispor.org/research_study_digest/research_index.asp
- Digestive Disease Week
- United European Gastroenterology Week
- American College of Gastroenterology.

Selection of Studies

Selected studies fulfilled all inclusion criteria and none of the exclusion criteria. Two reviewers independently screened the titles, abstracts and key words of all citations retrieved and marked every citation for inclusion or exclusion. The full manuscript of studies judged to be relevant by either reviewer were obtained and assessed for inclusion or exclusion. If excluded, the reason for exclusion was recorded. Any disagreements were resolved through discussion.

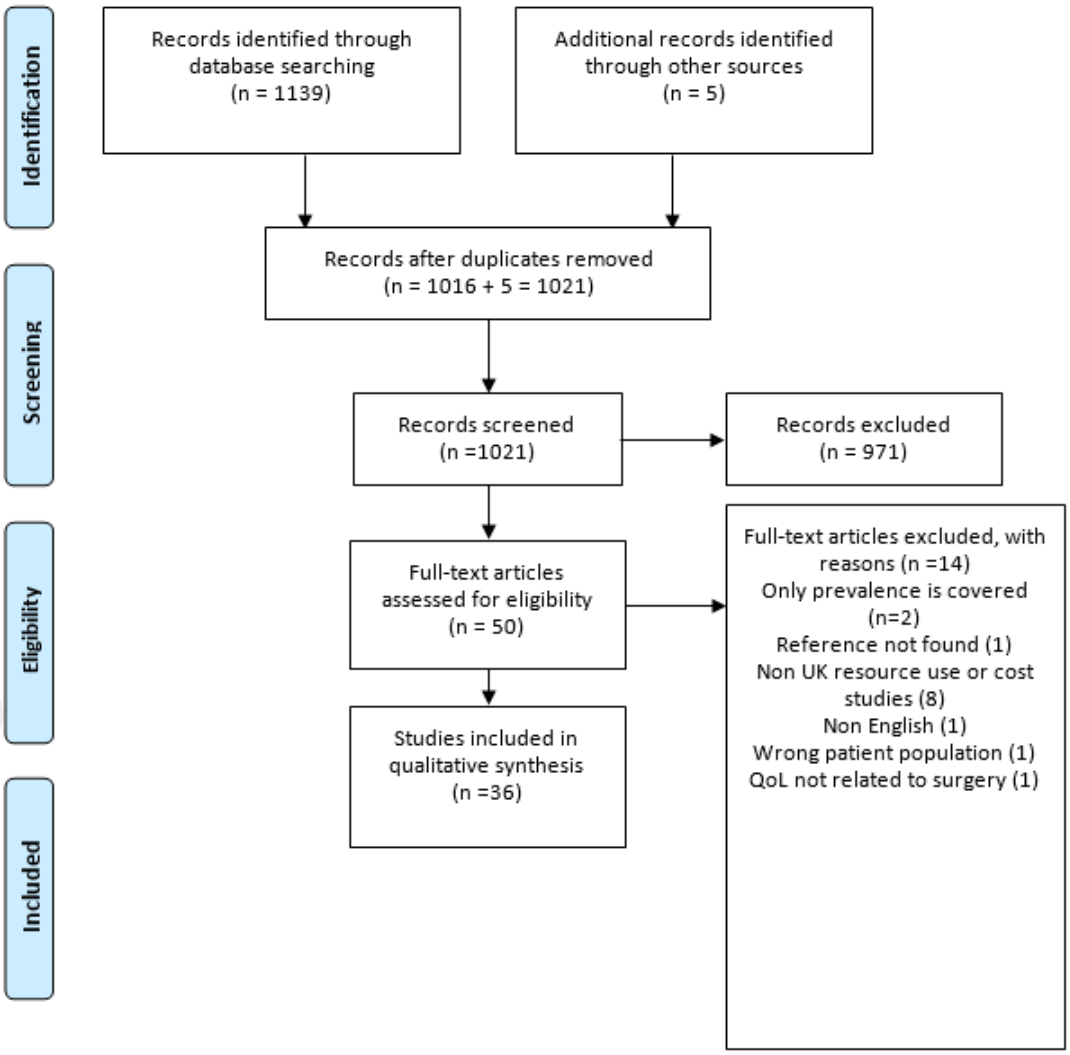
Data were extracted where possible from the selected papers. Data was extracted from the included studies by one of the reviewers and recorded in predefined data extraction sheets.

Results

A total of 1139 records (titles and abstracts) were identified through the search strategy; of these records, 123 duplicates were identified[2]. A hand search was undertaken, covering relevant disease-specific resources outlined in the search strategy, as a result five additional items were identified as meeting the inclusion criteria and none of the exclusion criteria.

The titles and abstracts of 1021 articles were then manually screened, of which 971 records were excluded according to the agreed criteria. The remaining 50 articles underwent a full text review, of which 14 were excluded for the reasons outlined in the PRISMA diagram (below) leaving 36 records for inclusion in the qualitative analysis.

PRISMA diagram for Study Inclusion and Exclusion (16)



[2] Jones et al (2012); Tsai et al (2008), Woehl et al 2008a, Woehl 2008b and Lindsay 2008.

Included economic analyses

Disease Area	Author (Year)	Publication Type, Country, Cost Year	Methods	Patient Population	Results			
UC	Park et al (2012) (19)	Full article, US, 2009	Markov model with the following 7 health states; Mesalamine 2g per day; Azathioprine 125 mg per day; Infliximab; 5mg/kg/dose 8 weeks; Tacrolimus 1.5mg twice daily; Colectomy + IPAA; Stable "Cured"; Acute or Chronic pouchitis. Study/model horizon covered 79 years (as model follows patients from 21 until 100 years. Costs were discounted at 3%. One way deterministic and probabilistic sensitivity analysis were undertaken.	Model simulating 2 cohorts of 21-year-old patients with severe UC, following them until 100 years of age or death.	Interventions	Cost (US Dollars)	Outcome QALY	ICER ($ per QALY)
					Early colectomy with IPAA	147,763	20.72	----
					Standard medical therapy	236,370	20.78	1,476,783

Disease Area	Author (Year)	Publication Type, Country, Cost Year	Methods	Patient Population	Results			
UC	Arebi et al (2011) (20)	Poster presentation, UK,	30 patients underwent surgery and 8 received Infliximab (N= 38). The time frame of analysis was between April 2010 and March 2011 using patient level data. Clinical outcomes were based on last recorded clinical state, quality of life (EQ5D) and length of hospital stay (days).	Patients with refractory UC.	Interventions	Cost (£)	Outcome QALY	ICER per good surgical outcome/ per day in hospital.
					Surgery	£22,920	--	--
					Infliximab	£12,723	--	£784

Disease Area	Author (Year)	Publication Type, Country, Cost Year	Methods	Patient Population	Results			
UC	Holubar et al (2012) (21)	Abstract; US;	Markov decision model to determine the most cost-effective management strategy for chronic ulcerative Colitis taking into account both benefits and risks of therapeutic options. 5 major health states were used (remission on IFX, ileostomy with rectal stump, ileal pouch-anal anastomosis, permanent ileostomy, and death). The model time horizon covered 70 years and standard discount rate of 3% was used. Deterministic sensitivity analysis was undertaken.	Ulcerative colitis patients undergoing surgery or treatment with infliximab.	Interventions	Cost (£) (Lifetime)	Outcome QALY	ICER
					Infliximab	$270,477.74	18.34	NR
					Surgery	$305,705.34	16.59	NR

Disease Area	Author (Year)	Publication Type, Country, Cost Year	Methods	Patient Population	Results			
UC	Jones et al (2009) (22)	Abstract, Canada.	Cost-effectiveness of Infliximab compared to restorative proctocolectomy (RPC) in patients with moderate to severe, medically refractory UC (from a Canadian public payer perspective). A Markov model was used where cycles were one year in duration and cycled over 20 stages. HRQL data derived from clinical trials and observational data were utilized to derive utility estimates	Patients with moderate to severe, medically refractory UC.	Interventions	Cost (Canadian $) (average)	Outcome QALY	ICER
					Infliximab	$326,000	9.41	NR
					RPC	$320,000	9.32	NR

Disease Area	Author (Year)	Publication Type, Country, Cost Year	Methods	Patient Population	Results			
UC	Punekar (2010) (23)	CEA	A decision analysis model was constructed to simulate the progression of acute UC patients treated within infliximab induction regimen over 1 year. Infliximab treatment was compared with standard care, ciclosporin and surgery using transitions derived from infliximab and ciclosporin randomised trials. Costs and outcomes were discounted at 3.5%. Intermediate outcomes of colectomy and post-surgery complications were translated into the primary effectiveness measurement, which was quality adjusted life years (QALYs) estimated using EQ-5D.	Patients with 'moderate-to-severe' UC	Treatment	Total costs	Total QALYs	ICER
					Surgery	£17,067	0.58	-
					Ciclosporin	£18,122	0.70	£9,032
					Standard care	£18,524	0.68	Dominated
					Infliximab	£19,847	0.80	£18 388

Included utility studies

Disease Area	Author (Year)	Study type/description	Methods of elicitation and valuation	Health states	Estimate
UC	Waljee et al (2009) (26)	Utility study (TTO)	A cross-sectional study of 450 patients (150 responses) in a tertiary referral centre. The enrolment of UC patients was stratified to collect equal numbers of mildly, moderately, and severely active UC patients.	Post-colectomy patients[3]	0.87

Disease Area	Author (Year)	Study type/description	Methods of Elicitation and Valuation.	Health states	Time in Health State	Estimate	SD
UC	Van der Valk (2012) (27)	Utility study	Data were obtained from the 'Cost of Inflammatory bowel disease in the Netherlands (COIN)' study, a prospective web-based 3 monthly questionnaire. We included all UC patients with a self-reported pouch or ileostomy at 3 months after initial questionnaire.	Ileostomy	3 Months	0.85	0.17
				Pouch	3 Months	0.85	0.19

[3] Whether this health state included complications was not specified.

Disease Area	Author (Year)	Study type/description	Methods of Elicitation and Valuation.	Health states	Time in Health State	Estimate	SA analysis
UC	Waljee et al (2011) (28)	Utility study (TTO)	Time-Trade-Off (TTO) utilities of subjects for standardized scenarios, describing moderate UC and a post-colectomy state. (Responses were obtained from 150 patients per group).	All post-colectomy for UC	NA		0.92
				Chronic activity, n=113	NA		0.92
				Exacerbation of disease, n=25	NA		0.98
				Dysplasia / cancer, n=10	NA		0.95
				Unknown, n=2	NA		0.86

Disease	Author	Study	Methods of Elicitation and Valuation.	Health states	Time in Health	Estimate	SD
	(29)	health states)	life years (QALYs) estimated using EQ-5D. Sensitivity analyses explored the uncertainty around the results. Utilities are based on Woehl (2007) (30) and Arseneau (2006).	Postsurgery remission	NR	0.61	0.60
				Postsurgery complications	NR	0.55	0.49

Disease Area	Author (Year)	Study type/description	Methods of Elicitation and Valuation.	Health states	Time in Health State	Estimate	SD
UC	Woehl (2008) (31)	Utility study	The survey research was conducted in Cardiff, UK. Patients with an active hospital profile and diagnosed with UC were included in the study. The survey covered QoL, measured by SIBDQ, demographics, surgery status, disease activity, medical treatment and resource use. To assess the health utility for patients related to different UC disease stages/severity, the SCAI was used. Health utility was measured by EQ5D.	UC Patients who have undergone IPAA	NA	0.71	0.29
				UC Patients with an ileostomy	NA	0.72	0.35

Area	(Year)	type/description		State			
UC	Punekar et al (2010) (23)	Cost effective analysis (inclusion of relevant utilities)	The preferences for the health states used in this analysis were obtained from a patient survey carried out in Cardiff Hospital, using the EQ-5D and valued using UK tariffs, which reflect valuations of the UK population (Woehl et al., 2007). The utilities derived from these health-state preferences were further classified into individual presurgery health states by indexing them with a SCAI. The utilities obtained for postsurgery complications were adopted from a study conducted by Arseneau et al. (2006).	Surgical Remission	NA	0.6	0.38
				Surgical complications	NA	0.42	0.32

Disease Area	Author (Year)	Study Type/Description	Study Population	Methods of elicitation and Valuation	Results
UC	Andersson et al (2011) (35)	Short Form 36 questionnaire (SF36).	One hundred and ten (71%) patients answered the questionnaires, 60 (55%) of whom were men. All except five patients had ulcerative colitis.	SF-36 results for IPAA patients compared with the general population, adjusted for age and gender by ANCOVA. SF-36 results for patients with pouchitis compared with patients without pouchitis.	Full results are reported in Data extraction table.

Disease Area	Author (Year)	Study Type/Description	Study Population	Methods of elicitation and Valuation	Results
UC	Bengtsson et al (2011) (36)	SF36 Questionnaire	36 patients with pouch failure were compared with 72 age and sex-matched controls with ulcerative colitis and functioning pouches.	SF 36 questionnaire covering the various health domains.	Relevant results were presented in graph form and were extracted based on interpretation of figure. See data extraction table

Disease Area	Author (Year)	Study Type/Description	Study Population	Methods of elicitation and Valuation	Results
UC	Berndtsson et al (2007) (37)	SF36 Questionnaire	286 patients with ileal pouch-anal anastomosis for ulcerative colitis.	Health-related quality of life, short Form-36 (SF-36) scores with associated normal scores for an age and gender matched	Relevant results were presented in graph form and were extracted based on interpretation of figure. See data extraction

Included PRO studies

population. table.

Disease Area	Author (Year)	Study Type/Description	Study Population	Methods of elicitation and Valuation	Results
UC	Bours et al (2013) (38)	SF36 Questionnaire	Fifty-six patients (53 UC, 3 FAP) participated in this study (response rate 78.9%).	QoL was scored using the Short-Form 36 (SF-36) health survey. Eight subscales of SF-36 (physical functioning, role limitations due to physical health (role-physical), role limitations due to emotional health (role-emotional), vitality, mental health, social functioning, pain, general health) were used to aggregate the Physical (PCS) and Mental (MCS) Component Summary scores.	Full results are presented in data extraction table.

Disease Area	Author (Year)	Study Type/Description	Study Population	Methods of elicitation and Valuation	Results

UC	Camilleri-Brennan et al (2003) (39)	SF36 and the inflammatory bowel disease questionnaire (IBDQ).	Nineteen patients (12 males and 7 females, median age 41 years) who had undergone total colectomy and ileoanal pouch formation for ulcerative colitis were individually matched with patients who had had a panproctocolectomy and ileostomy; patients were matched for disease process, sex, age, socioeconomic status, and time since surgery.	Quality of life was assessed using the Short-Form 36 version 2 questionnaire, the inflammatory bowel disease questionnaire, and a few additional questions on perception of body image. The scores were compared using the nonparametric Wilcoxon signed-rank test for paired samples.	Full results are presented in data extraction table.SF36 results were presented in graph form extraction data is based on interpretation of figure.

Disease Area	Author (Year)	Study Type/Description	Study Population	Methods of elicitation and Valuation	Results
UC	Carmon et al (2003) (40)	SF36 Questionnaire and Global assessment function.	All patients with UC who had undergone IPAA during the period 1990–2001 were included. Data were obtained in 77 of 99 patients (78%).	QOL and functional outcome were evaluated by mailed questionnaires. QOL was scored using the Short Form 36 (SF-36). Global Assessment of Function Scale was used to evaluate functional outcome.	Full results are presented in data extraction table. SF36 results were presented graphically and extracted

Disease Area	Author (Year)	Study Type/Description	Study Population	Methods of elicitation and Valuation	Results

UC	Hauser et al (2004) (41)	Health-Related Quality of Life Measured by various questionnaires.	61 patients with UC (age 52.7 ± 13.9 years; 47% female) completed the questionnaire.	German version of the Inflammatory Bowel Disease Questionnaire (IBDQ-D), the Short Form Health Survey (SF – 36), the German version of the Hospital Anxiety and Depression Scale (HADS-D) and the Giessener Symptom List (GBB 24). Where possible, IPAA-patients were compared with the data for the German general population and with a clinical sample of patients with UC and no IPAA	Full results are presented in data extraction table.

Disease Area	Author (Year)	Study Type/Description	Study Population	Methods of elicitation and Valuation	Results
UC	Holubar et al (2011) (42)	Health-Related Quality of Life Measured by various questionnaires	An incident cohort of ulcerative-colitis patients from Olmsted County was identified using the Rochester Epidemiology Project. A total of 134 completed surveys were returned, 87 in the Medical group and 47 in the surgical group.	Subjects were stratified into Medical and Surgical groups and surveyed using the EuroQoL-5D, the Short Inflammatory Bowel Disease Questionnaire (SIBDQ), the Fecal Incontinence Quality of Life Scale (FIQL), and the Fecal Incontinence Severity Index (FISI).	Full results are presented in data extraction table.

Disease Area	Author (Year)	Study Type/Description	Study Population	Methods of elicitation and Valuation	Results

UC	Swinburn et al (2012) (43)	Health-Related Quality of Life Measured by various questionnaires	230 UC patients (including 30 post-surgery patients) were recruited along with 100 age and gender matched controls	Participants completed an online survey which comprised the Simple Clinical Colitis Activity Index, EuroQol EQ-5D and the IBD-Q. Basic sociodemographic and clinical data were also collected. Disease severity was categorised using established cut-off values for the IBD-Q. EQ-5D utility scores were compared across disease severity, among post-surgery patients vs non-surgery patients, and among post-surgery patient vs controls.	Relevant results were presented in graph form and were extracted based on interpretation of figure. See data extraction table.

Disease Area	Author (Year)	Study Type/Description	Study Population	Methods of elicitation and Valuation	Results
UC	Wuthrich et al (2009) (45)	SF36 Questionnaire	107 patients (median age 38 [range 17–69] years) underwent reconstructive proctocolectomy with IPAA between 1981 and 2002.Median duration of follow-up was 83 (range 4– 230) months. 66 patients (61%) answered both questionnaires.	1) Medical Outcome 36 item Health Survey (SF-36); and 2) a specific questionnaire evaluating various aspects of anorectal and urogenital function.	Relevant results were presented in graph form and were extracted based on interpretation of figure. See data extraction table

Disease Area	Author (Year)	Study Type/Description	Study Population	Methods of elicitation and Valuation	Results
UC and CD	Das et al (2007) (51)	SF36 and Cleveland Clinic Foundation (CCF) questionnaires.	Fifty-three patients (17 men) responded; comprising 31 patients after pouch excision and 22 patients with indefinite diversion in a case–control study.	SF-36 general health survey and the Cleveland Clinic Foundation (CCF) functional outcomes questionnaire.	Full results are presented in data extraction table.

Included resource use and cost studies

Disease Area	Author (Year)	Cost Type	Description of available data	Details of Methods	Results (surgery)	Infliximab
UC	Arebi et al (2013) (20)	Resource use	Hospital stays; Mean number of admissions and mean number of interventions of Infliximab compared with surgery.	Retrospective analysis of patients with refractory UC undergoing surgery or IFX between Apr 2010 and Mar 2011 was undertaken.	Mean hospital stay (days) =28.8 Mean no. of admissions= 2.5 Mean no. of interventions = 2.6 Patients with good outcome (%)= 50	Mean hospital stay (days) =15.8 Mean no. of admissions= 1.7 Mean no. of interventions =5.3 Patients with good outcome (%)= 63

Disease Area	Author (Year)	Cost Type	Description of available data	Details of Methods	Results (6/12 months)

UC	Jones et al (2012) (52)	Resource use and one-time cost.	Health-care costs of second line treatment of recurrent pouchitis.	Clinical experts estimated medical resource use for second-line treatments using structured interviews. The study perspective was the UK NHS.	Consultant visit 1/1 (£526) Endoscopy 1/1 (£526) Surgery/complications 1/1 (£12,058) Stoma supplies 1/2 (£1,379)

Disease Area	Author (Year)	Cost Type	Description of available data	Details of Methods	Results summary (Table 4 page 310)
UC	Tsai et al (2008) (29)	Resource use and costs; 2006/7 pounds sterling.	Resource use in postsurgery remission (PSR) and postsurgery complications (PSC) health state.	This resource use therefore was estimated by a panel of six UK gastroenterologists. Each panel member independently estimated the number of tests, assessments and consultant visits for a single patient in a particular health state over 1 year. The estimates used in the analysis were averages of resource use estimated by each panel member.	**Postsurgery remission**: **Total costs = £394.05** 1.5 consultant visits, 1.5 blood tests, 1.25 elective endoscopies, 0.5 emergency endoscopy. **Postsurgery complications:** **Total costs = £1672.78** 1.75 consultant visits, 3.25 hospitalisation episodes (SC and IFX), 3.25 blood tests, 0.65 elective endoscopy and 0.125 emergency endoscopy. (table 1 page 1234)

Disease Area	Author (Year)	Cost Type	Description of available data	Details of Methods	Results
UC	Punekar et al (2010) (23)	Direct costs and resource use.	Direct costs; surgical procedures, primarily ileostomy and IPAA. Resource use includes consultant visits, hospital days, surgical procedures and diagnostic endoscopy.	A Delphi panel of five experts estimated the resource use of UC patients during and after hospitalization. All patients were assumed to have 10 days of hospitalization during initial treatment period. Patients suffering post-surgery complications were assumed to have 10 days of hospital stay in addition to the stay due to their surgical procedure. The total cost of surgery was calculated using a weighted average based on the prevalence of 2 surgical techniques (29% IPAA, 71% ileostomy).	Sub-total for resource use **Surgery=£13,871.98** **Surgical Remission=£580.55** **Complications=£4,238.3** See data extraction table for full resource use and costs.

UC and CD	Buchanan (2011) (55)	Direct costs	Costs were extracted from UK sources. Cost were also reported at each model stage. All costs were discounted at a rate of 3.5%. 2008 pounds sterling.	Decision models were employed to simulate the natural disease history of UC, informed by UK and European clinical pathways. UK NHS perspective was used for UK costs; unit costs were extracted from NHS reference costs and the BNF. Definitions of disease stages and type of costs included at each disease stage were detailed in the study's supplementary appendix. European costs were reported in addition to UK costs.	for CD: **Surgery** = £7545.17 **Postsurgical remission**= £2748.13 **Postsurgical complication**= £2748.13 for UC: **Surgery** = £11,619.72 **Postsurgical remission**=£30.26 **Postsurgical complication**= £357.28

Appendix 2a: Search Strategy

Database: Embase <1974 to 2014 March 17> (via Ovid platform)

Search Re-run Date: 18/03/14

Search Strategy:

Line No.	Search Terms	Results
Cost-effectiveness studies		
1	exp "cost"/	250675
2	exp "cost benefit analysis"/	63659
3	exp statistical model/	99442
4	(Cost effective* or cost-effective* or cost utility or cost-utility or economic model or pharmacoeconomic* or pharmaco economic or modelling or modeling or cost-minimi?ation or economic evaluation).tw.	155662
5	((Cost* or costs) and (effective* or utilit* or benefit* or minimi*)).tw.	197918
6	or/1-5	574889
Economic analyses, resource use, and cost studies		
7	exp health economics/	605012
8	exp pharmacoeconomics/	164556
9	exp health care utilization/	39345
10	exp fee/	33330
11	exp "health care cost"/	200961
12	((Price*or pricing or cost* or costs) and (hospitali?ation* or productivity or employment or unemployment)).tw.	29897
13	(exp employment/ or exp work/) and (price* or pricing or cost*).tw.	17480
14	(Cost analysis or cost-analysis or "resource use" or resource utili?ation or health care cost* or health-care cost* or healthcare cost* or productivity cost* or societal cost* or economic benefit*).tw.	39872
15	or/7-14	655310
Utilities studies		

16	exp quality adjusted life year/	11626
17	((sf or short form or shortform) and "6").tw.	11052
18	(EuroQol or standard gamble or time trade off or time tradeoff or TTO or EQ5D or EQ-5D or health utilit$ index).tw.	8581
19	((Health and utilit* and index) or HUI* or SF-6D or sf6* or sf 6* or short form 6* or shortform 6* or sf six or sfsix or short form six or shortform six or QALY or quality adjusted life year* or quality-adjusted life year or quality adjusted life-year* or quality-adjusted life-year* or SF-36 or sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty-six or short form thirty six or short form health survey or willingness to pay).tw.	41895
20	((utilit* and score*) or (utilit* and weight*) or Rosser or (health and utilit*) or (utilit* and value) or disutility*).tw.	44161
21	or/16-20	93848
Disease area		
22	exp Crohn disease/	55834
23	crohn$.tw.	46135
24	exp ulcerative colitis/	47006
25	Ulcerative colitis.tw.	36025
26	or/22-25	90006
Competitor terms		
27	exp surgery/	3297090
28	exp colon resection/	26130
29	exp anastomosis/	119929
30	exp proctocolectomy/	3670
31	exp ileostomy/ or exp ileostomy bag/	8623
32	(proctocolectom* or procto-colectom*).mp.	4618
33	(Coloproctectom* or colo-proctectom*).mp.	109
34	(Colectom* or colon* pouch* or ileoanal pouch* or ileo-anal pouch* or ileo anal pouch* or ilealanal pouch* or ileal-anal pouch* or ileal anal pouch* or ileal pouch-anal or ileal-pouch-anal or ile* pouch-anal or ile* pouch anal or IPAA or	1587786

	proctectom* or anastomos* or surgic* or strictureplasty or resection or operation or stricturoplasty or Koch pouch or Kock pouch).mp.	
35	or/27-34	3765022
Exclusionary terms		
36	animal/ not (animal/ and human/)	1183445
37	(editorial or comment* or letter or note or case series or case study or case studies or case report).pt. or (editorial/ or letter/ or case study/ or case report/ or note/)	3580857
Subtotal		
Cost-effectiveness studies of biologics in CD&UC		
38	6 and 26 and 35	645
Resource use in CD&UC		
39	15 and 26 and 35	789
Utilities in CD&UC		
40	21 and 26 and 35	253
Total		
41	38 or 39 or 40	1125
42	41 not (36 or 37)	1050
43	limit 42 to yr="2003 -Current"	916

CD, crohn’s disease; UC, ulcerative colitis

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Re-run Date: 13/03/14

Search Strategy:

Line No.	Search Terms	Results
Cost-effectiveness studies		
1	"Costs and Cost Analysis"/	41383
2	Cost-Benefit Analysis/	58970
3	Models, Economic/	6091
4	(Cost effective* or cost-effective* or cost utility or cost-utility or economic model or pharmacoeconomic* or pharmaco economic or modelling or modeling or cost-minimi?ation or economic evaluation).tw.	120419
5	((Cost* or costs) and (effective* or utilit* or benefit* or minimi*)).tw.	151399
6	or/1-5	253963
Economic analyses, resource use, and cost studies		
7	Economics, Hospital/	9904
8	Economics, Medical/	8581
9	Economics, Nursing/	3887
10	Economics, Pharmaceutical/	2508
11	Health Resources/	8663
12	"Fees and Charges"/	8062
13	Health Care Costs/	26506
14	((Price*or pricing or cost* or costs) and (hospitali?ation* or productivity or employment or unemployment)).tw.	21013
15	(exp employment/ or exp work/) and (price* or pricing or cost*).tw.	3371
16	(Cost analysis or cost-analysis or "resource use" or resource utili?ation or health care cost* or health-care cost* or healthcare cost* or productivity cost* or societal cost* or economic benefit*).tw.	28630

17	or/7-16	104208
Utilities studies		
18	Quality-Adjusted Life Years/	6765
19	((sf or short form or shortform) and "6").tw.	7511
20	(EuroQol or standard gamble or time trade off or time tradeoff or TTO or EQ5D or EQ-5D or health utilit$ index).tw.	5708
21	((Health and utilit* and index) or HUI* or SF-6D or sf6* or sf 6* or short form 6* or shortform 6* or sf six or sfsix or short form six or shortform six or QALY or quality adjusted life year* or quality-adjusted life year or quality adjusted life-year* or quality-adjusted life-year* or SF-36 or sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty-six or short form thirty six or short form health survey or willingness to pay).tw.	30225
22	((utilit* and score*) or (utilit* and weight*) or Rosser or (health and utilit*) or (utilit* and value) or disutility*).tw.	31771
23	or/18-22	66513
Disease area		
24	exp Crohn Disease/	29932
25	crohn$.tw.	32469
26	exp Colitis, Ulcerative/	26894
27	Ulcerative colitis.tw.	26397
28	or/24-27	60077
Competitor terms		
29	exp General Surgery/	33327
30	exp Colectomy/	14698
31	exp Anastomosis, Surgical/	66417
32	exp Ileostomy/ or exp Proctocolectomy, Restorative/ or exp Colonic Pouches/	8177
33	(proctocolectom* or procto-colectom*).mp.	3800
34	(Coloproctectom* or colo-proctectom*).mp.	88
35	(Colectom* or colon* pouch* or ileoanal pouch* or ileo-anal pouch* or ileo anal	1255719

	pouch* or ilealanal pouch* or ileal-anal pouch* or ileal anal pouch* or ileal pouch-anal or ileal-pouch-anal or ile* pouch-anal or ile* pouch anal or IPAA or proctectom* or anastomos* or surgic* or strictureplasty or resection or operation or stricturoplasty or Koch pouch or Kock pouch).mp.	
36	or/29-35	1295783
Exclusionary terms		
37	animal/ not (animal/ and human/)	3810084
38	(editorial or comment* or letter or note or case series or case study or case studies or case report).pt. or (editorial/ or letter/ or case study/ or case report/ or note/)	2805605
Subtotals		
Cost-effectiveness studies of biologics in CD		
39	6 and 28 and 36	132
Resource use in CD		
40	17 and 28 and 36	66
Utilities in CD		
41	23 and 28 and 36	110
Total		
42	39 or 40 or 41	261
43	42 not (37 or 38)	257
44	limit 43 to yr="2003 -Current"	173

CD, crohn's disease; UC, ulcerative colitis

Econlit (via American Economic association Platform)

Search Re-run Date: 18/03/14

Search Strategy:

Line No.	Search Terms	Results
Disease area		

1	Crohn's disease	4
Subtotal		
2	Limit 1 to (year min:2003 yearmax:2014)	3

CD, crohn's disease

Line No.	Search Terms	Results
Disease area		
1	Ulcerative colitis	3
Subtotal		
2	Limit 1 to (year min:2003 yearmax:2014)	2
Total		
3	2 or 2	5

Database: Cochrane Library (via Wiley)

Search Re-run Date: 18/03/14

Search Strategy:

Line No.	Search Terms	Results
Cost-effectiveness studies		
1	MeSH descriptor: [Costs and Cost Analysis] explode all trees	21477
2	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	15299
3	MeSH descriptor: [Models, Economic] explode all trees	1878
4	cost* near/2 (effective* or utilit* or benefit* or minimi*) or cost next effective* or "cost utility" or "economic model" or pharmacoeconomic* or "pharmaco economic" or modeling or modelling or "economic model" or "cost minimization" or "cost minimisation" or "cost minimisation analysis" or "economic evaluation" or "cost effectiveness analysis"	83986
5	1 or 2 or 3 or 4	86288
Economic analyses, resource use, and cost studies		
6	MeSH descriptor: [Economics, Hospital] explode all trees	1590
7	MeSH descriptor: [Economics, Nursing] explode all trees	15
8	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	231
9	MeSH descriptor: [Health Resources] explode all trees	496
10	MeSH descriptor: [Fees and Charges] explode all trees	469
11	MeSH descriptor: [Health Care Costs] explode all trees	6462
12	(price* or pricing or cost*) near/2 (hospitalization* or hospitalisation* or productivity or employment or unemployment) or "cost analysis" or "resource use" or "resource utilization" or "resource utilisation" or "health care" next cost* or healthcare next cost* or productivity next cost* or societal next cost* or economic next benefit*	16588
13	MeSH descriptor: [Employment] explode all trees	1083
14	MeSH descriptor: [Work] explode all trees	282
15	(price* or pricing or cost) *:ti,ab,kw	53215

16	(13 or 14) and 15	313
17	6 or 7 or 8 or 9 or 10 or 11 or 12 or 16	18497
Utilities studies		
18	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	3524
19	Rosser:ti,ab,kw or EuroQol or "standard gamble" or "time trade off" or "time tradeoff" or TTO or EQ5D or "EQ 5D" or "health utility index" or "health utilities index" or (health and utilit* and index) or HUI? or "SF-6D" or sf6* or sf next 6* or "short form" next 6* or shortform next 6* or "sf six" or sfsix or "shortform six" or "short form six" or QALY or "Quality adjusted life" next year* or "SF 36" or sf36 or "sf 36" or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six" or "Short Form Health Survey" or willingness next/1 pay or utilit* near/2 score* or utilit* near/2 weight* or health near/2 utilit* or utilit* near/2 value or disutility	16733
20	18 or 19	16733
Disease area		
21	MeSH descriptor: [Crohn Disease] explode all trees	929
22	("crohn disease" or crohn* next/2 disease or "crohns disease"):ti,ab,kw	1414
23	MeSH descriptor: [Colitis, Ulcerative] explode all trees	887
24	("Ulcerative colitis" or ulcerative next/2 colitis):ti,ab,kw	1325
25	21 or 22 or 23 or 24	2578
Competitor terms		
26	MeSH descriptor: [General Surgery] explode all trees	289
27	MeSH descriptor: [Colectomy] explode all trees	638
28	MeSH descriptor: [Anastomosis, Surgical] explode all trees	1866
29	MeSH descriptor: [Ileostomy] explode all trees	164
30	MeSH descriptor: [Colonic Pouches] explode all trees	62
31	MeSH descriptor: [Proctocolectomy, Restorative] explode all trees	120
32	(proctocolectom* or procto-colectom*):ti,ab,kw	161

33	(Coloproctectom* or colo-proctectom*):ti,ab,kw	0
34	(Colectom* or colon* pouch* or ileoanal pouch* or ileo-anal pouch* or ileo anal pouch* or ilealanal pouch* or ileal-anal pouch* or ileal anal pouch* or ileal pouch-anal or ileal-pouch-anal or ile* pouch-anal or ile* pouch anal or IPAA or proctectom* or anastomos* or surgic* or strictureplasty or resection or operation or stricturoplasty or koch pouch or kock pouch):ti,ab,kw	57276
35	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	57947
Exclusionary terms		
36	MeSH descriptor: [Animals] explode all trees	6516
37	MeSH descriptor: [Humans] explode all trees	1125
38	36 not 37	5391
39	Comment or Editorial or Letter or "Clinical Trial Phase I" or "phase 1" or "Case Reports":pt or "case study" or "case studies"	35300
Subtotals		
Cost-effectiveness studies of biologics in CD&UC		
40	5 and 25 and 35	59
41	40 not (38 or 39) Publication Date from 2003 to 2014	40
Resource use in CD&UC		
42	17 and 25 and 35	13
43	42 not (38 or 39) Publication Date from 2003 to 2014	10
Utilities studies in CD&UC		
44	20 and 25 and 35	21
45	44 not (38 or 39) Publication Date from 2003 to 2014	16
Total		
46	41 or 43 or 45	45

CD, crohn's disease; UC, ulcerative colitis; MeSH, Medical Subject Heading

Appendix 2b: List of Included Articles

1. Park KT, Tsai R, Perez F, Cipriano LE, Bass D, Garber AM. Cost-effectiveness of early colectomy with ileal pouch-anal anastamosis versus standard medical therapy in severe ulcerative colitis. Ann Surg [Internet]. 2012 Jul [cited 2014 Apr 28];256(1):117–24.

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an Ileostomy? Gastroenterology [Internet]. AGA; 2011;142(5):S–263. Available from: http://dx.doi.org/10.1016/S0016-5085(12)60992-5

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11. Tsai HH, Punekar YS, Morris J, Fortun P. A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther [Internet]. 2008 Dec 15

12. Woehl A, Hawthorne A, McEwan P. The relation between disease activity, quality of life and health utility in patients with ulcerative colitis [402]. Inflamm Bowel Dis Pap. 2008;

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14. Woehl A, Hawthorne A, McEwan P. The relation between disease activity, quality of life and health utility in patients with crohn's disease [403]. Inflamm Bowel Dis Pap. 2008;

15. Andersson T, Lunde OC, Johnson E, Moum T, Nesbakken a. Long-term functional outcome and quality of life after restorative proctocolectomy with ileo-anal anastomosis for colitis. Colorectal Dis [Internet]. 2011 Apr;13(4):431–7.

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