Cost-effectiveness analysis of Crohn's disease treatment with vedolizumab and ustekinumab after failure of tumor necrosis factor-α antagonist

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Supplementary File

1 Systematic review of cost-effectiveness studies of Crohn's disease treatment with ustekinumab or vedolizumab

Supplementary Table 1. Methods and results.

A. The selection criteria

	Criterion
Population	Patients with Crohn's disease
Intervention	Ustekinumab or vedolizumab
Comparator	No limit
Outcomes	No limit
Studies	1) Full cost-effectiveness analysis, i.e. study reporting all information on methods and results 2) Publication date ≥2015

B. Literature search strategy (24.02.2018)

		Records (PubMed)	Records (Embase)
#1	Intervention *ustekinumab OR stelara OR cnto1275 OR 'cnto 1275' OR vedolizumab OR entyvio OR 'ldp 02' OR 'ldp02'*	1,629	5,614
#2	Population PubMed: *"crohn disease"[MeSH Terms] OR crohn's[tiab] OR crohn[tiab]* EMBASE: *'Crohn disease'/exp/mj OR Crohn:ab,ti*	49,485	71,596
#3	Study/outcome [a] PubMed: *((((((((((((((budget*[tiab]) OR value for money[tiab]) OR ((expenditure*[tiab] NOT energy[tiab]))) OR (((economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab])))) OR "Economics, Pharmaceutical"[Mesh]) OR "Economics, Nursing"[Mesh]) OR "Economics, Medical"[Mesh:NoExp]) OR "Economics, Hospital"[Mesh]) OR "Economics, Dental"[Mesh:NoExp]) OR (("Costs and Cost Analysis"[Mesh])) OR "Economics"[Mesh:NoExp])) NOT (((((energy cost[tiab] OR oxygen cost[tiab])) OR metabolic cost[tiab]) OR ((energy expenditure[tiab] OR oxygen expenditure[tiab])))) NOT (((historical article[pt]) OR editorial[pt]) OR letter[pt])) NOT ((animals[mesh:noexp]) NOT ((humans[mesh]) AND animals[mesh:noexp]))*	710,088	974,156

	Embase: *'health economics'/de OR 'cost'/de OR 'cost'/exp/mj OR 'pharmacoeconomics'/exp OR 'economic evaluation':de OR 'economic evaluation'/exp/mj OR economic$:ab,ti OR cost:ab,ti OR costs:ab,ti OR costly:ab,ti OR costing:ab,ti OR price:ab,ti OR prices:ab,ti OR pricing:ab,ti OR pharmacoeconomic$:ab,ti OR (expenditure$:ab,ti NOT energy:ab,ti) OR 'value for money':ab,ti OR budget$:ab,ti NOT ((energy OR oxygen) NEAR/1 cost):ab,ti NOT (metabolic NEAR/1 cost):ab,ti NOT ((energy OR oxygen) NEAR/1 expenditure):ab,ti NOT letter:it NOT editorial:it NOT ('historical article':it) NOT ('animal'/de NOT ('animal'/de AND 'human'))*		
#4	Summary with limits PubMed: *#1 AND #2 AND #3 AND 2015:2019[dp]* EMBASE: *#1 AND #2 AND #3 AND [embase]/lim NOT [medline]/lim AND [2015-2018]/py*	16	57
Total records		73	
Number of unique records:		67	
Number of records screened:		67	
Additional records [b]:		11 (ERG reports, CADTH reports, SMC Advises, TLV report, NCPE report, NICE guidelines, Baji et al., 2017)	
Number of records (studies) evaluated for full-text papers (incl. additional records):		24 (18)	
Number of studies included		3	

[a] Neyt M and Chalon PX. Pharmacoeconomics. 2013;31:1087-90 and Holko P. DOI: 10.13140/RG.2.2.36545.66407

[b] hand searches; additional databases and portals (HTA Agencies, Cochrane Library, ISPOR Scientific Presentation Database, journals homepages; Google Scholar)

C. Assessment of full-text papers

Record	**Comment**	**Study selection**
Hodgson et al. Pharmacoeconomics. DOI: 10.1007/s40273-017-0593-2.	Appraisal of manufacture's submission to National Institute for Health and Care Excellence (NICE).	Excluded: incomplete reporting of the methods (confidential information regarding treatment cost and input data derived from unpublished analysis of clinical trials data was removed)
Hodgson et al. NICE Evidence Review Group (ERG) Report [a]	Appraisal of manufacture's submission to NICE. ERG report.	
NICE. Technology appraisal guidance [TA456]; www.nice.org.uk	NICE guidance based on the appraisal of manufacture's submission.	

Record	Comment	Study selection
Canadian Agency for Drugs and Technologies in Health (CADTH). Common Drug Review: Pharmacoeconomic Report [b]	Appraisal of manufacture's submission to CADTH.	Excluded: incomplete reporting of the methods and results (summary of the model presented; confidential information removed)
Scottish Medicines Consortium (SMC) Advise [c]	Appraisal of manufacture's submission to SMC. Summary.	Excluded: incomplete reporting of the methods and results (summary of the model presented; confidential information removed)
Rafia et al. Pharmacoeconomics. 2016;34(12):1241-1253.	Appraisal of manufacture's submission to NICE	Excluded: incomplete reporting of the methods (confidential information was removed)
NICE. TA352; www.nice.org.uk	NICE guidance based on the appraisal of manufacture's submission.	
Rafia et al. NICE ERG Report [d]	Appraisal of manufacture's submission to NICE. ERG report.	
CADTH. Common Drug Review: Pharmacoeconomic Report [e]	Appraisal of manufacture's submission to CADTH.	Excluded: incomplete reporting of the methods and results (summary of the model presented; confidential information removed)
SMC Advise [g]	Appraisal of manufacture's submission to SMC. Summary.	Excluded: incomplete reporting of the methods and results (summary of the model presented; confidential information removed)
Rencz et al. Expert Rev Pharmacoecon Outcomes Res. 2017;17(6):597-606.	Full cost-effectiveness analysis	**Full-text included**
Baji et al. United European Gastroenterol J. 2016 4:5 Supplement 1 (A60)	Conference abstract	
Erim et al. J Crohns Colitis. 2015;9(8):669-75.	Full cost-effectiveness analysis	**Included**
Baji et al. United European Gastroenterol J. 2017. DOI: 10.1177/2050640617708952	Full cost-effectiveness analysis	**Full-text (in press) included**
Baji et al. United European Gastroenterol J. 2016 4:5 Supplement 1 (A631)	Conference abstract	
Hansson-Hedblom A. et al. Value in Health 2017 20:9 (A634)	Conference abstract	Excluded: incomplete reporting of the methods and results
Schneider et al. Am J Gastroenterol 2016; 111 Supplement 1 (S335-S336)	Conference abstract	Excluded: incomplete reporting of the methods and results

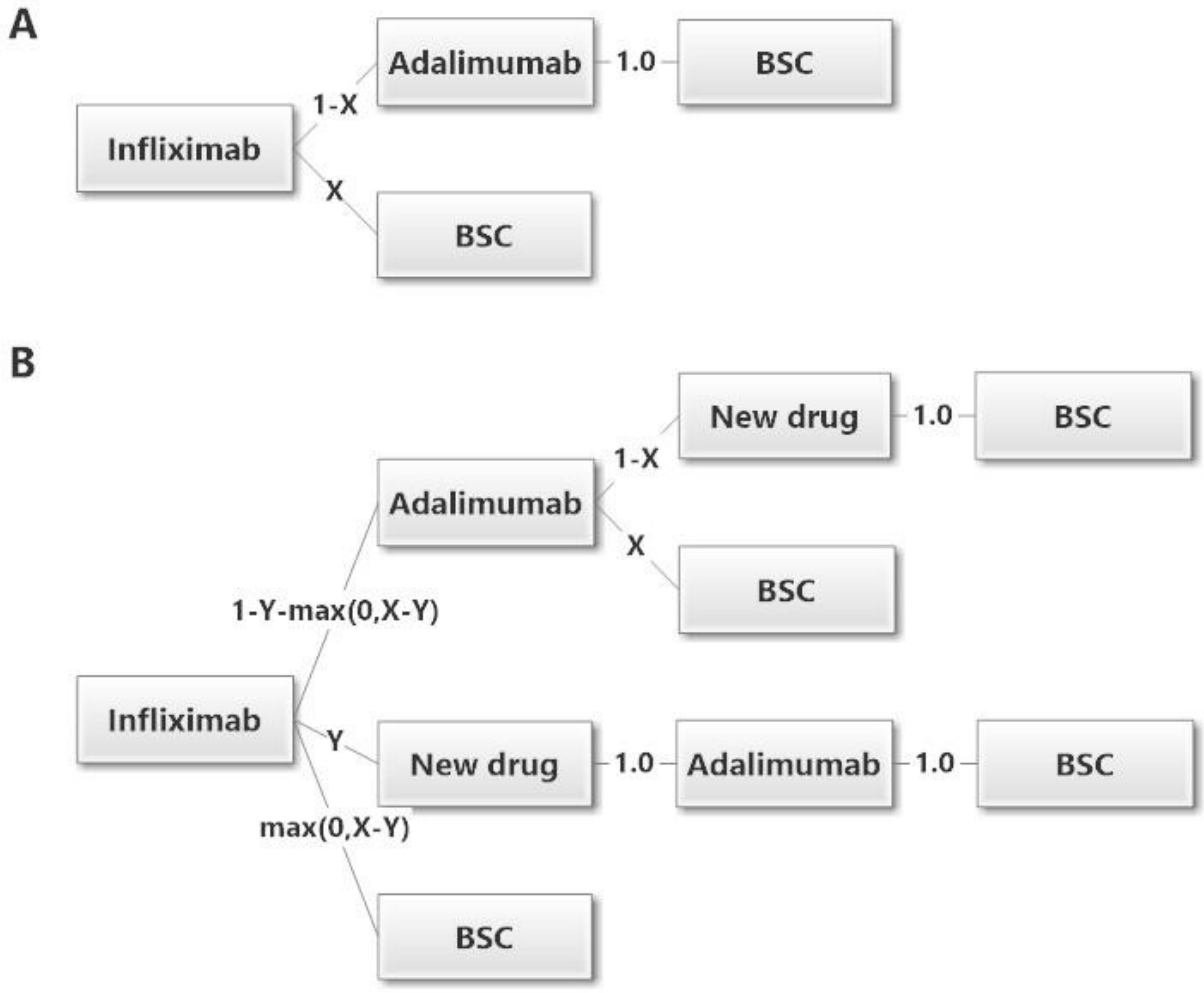
Record	Comment	Study selection
Bounthavong et al. Value Health. 2015;18(3):A224-A225	Conference abstract	Excluded: incomplete reporting of the methods and results
Liu et al. Gastroenterology. 2015;149(4):S862-S863.	Conference abstract	Excluded: incomplete reporting of the methods and results
Kanters et al. Front Pharmacol. 2017;8:322.	Full-text publication	Excluded: study type (budget-impact analysis)
Azzabi Zouraq I. et al. Value in Health 2017 20:5 (A183)	Conference abstract	Excluded: incomplete reporting of the methods and results
Schneider Y. et al. Gastroenterology 2017; 152:5 Supplement 1 (S589)	Conference abstract	Excluded: incomplete reporting of the methods and results
The Dental and Pharmaceutical Benefits Agency, TLV [h]	Appraisal of manufacture's submission to TLV. Summary.	Excluded: incomplete reporting of the methods and results (summary of the model presented; confidential information removed)
Pharmaceutical Benefits Advisory Committee (PBAC). Public Summary Document [i]	Appraisal of manufacture's submission to PBAC. Summary.	Excluded: incomplete reporting of the methods and results (summary of the model presented; confidential information removed)
National Centre for Pharmacoeconomics (NCPE) Summary [j]	Appraisal of manufacture's submission to NCPE. Summary.	Excluded: incomplete reporting of the methods and results (summary of the model presented; confidential information removed)

[a] www.journalslibrary.nihr.ac.uk/programmes/hta/161012
[b] www.cadth.ca/ustekinumab-15
[c] www.scottishmedicines.org.uk/SMC_Advice/Advice/1250_17_ustekinumab_Stelara/ustekinumab_Stelara
[d] www.journalslibrary.nihr.ac.uk/programmes/hta/1312801
[e] www.cadth.ca/vedolizumab-0
[g] www.scottishmedicines.org.uk/SMC_Advice/Advice/1064_15_vedolizumab_Entyvio/vedolizumab_Entyvio
[h] www.tlv.se/download/18.467926b615d084471ac33514/1510316391704/bes141128-entyvio.pdf
i www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-03/Files/vedolizumab-1-psd-march-2015.pdf
[j] www.ncpe.ie/wp-content/uploads/2014/10/Summary-Crohns-disease.pdf

2 Additional methods and results

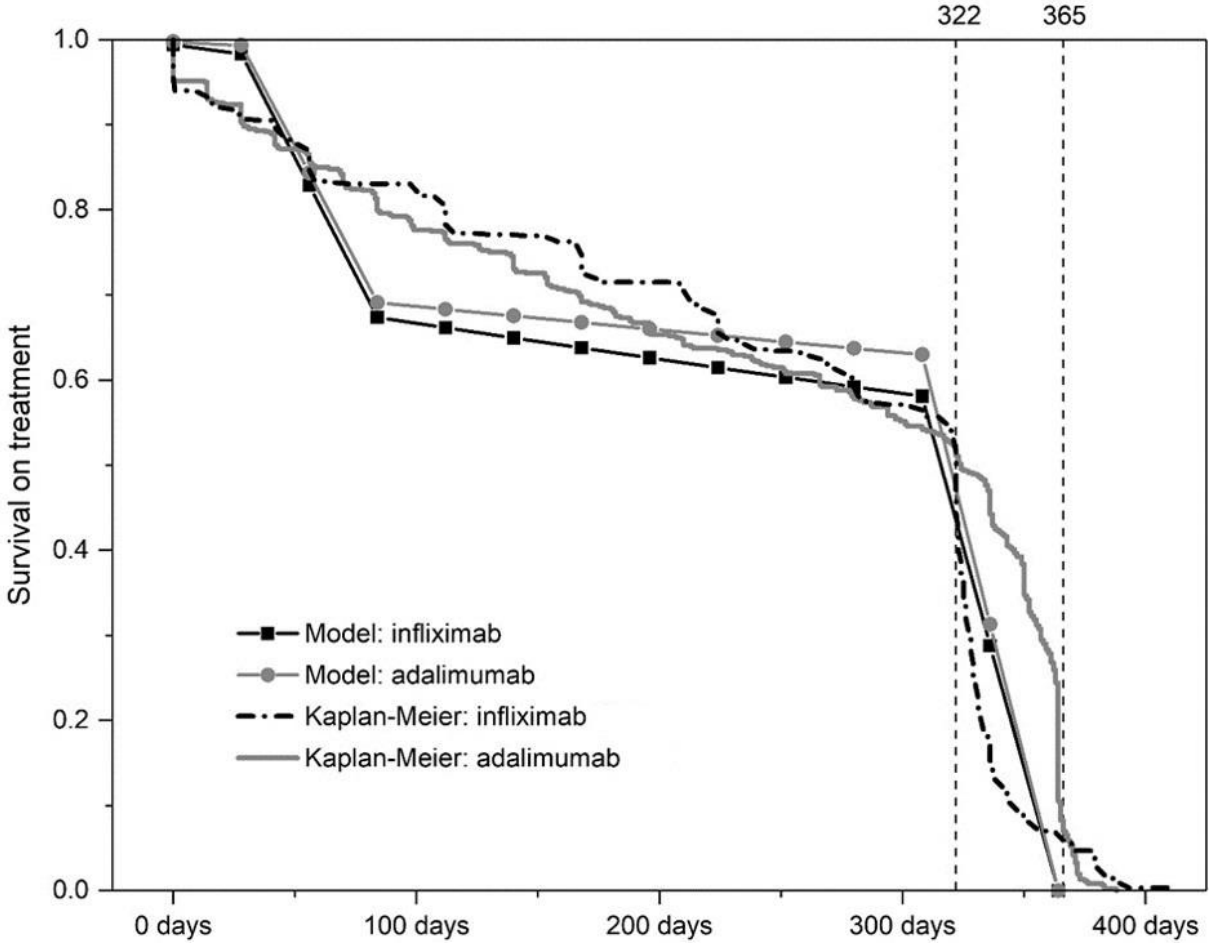
Supplementary Figure 1. Treatment strategies.

Treatment strategies in the analysis: (A) status quo and (B) the new strategy with the "new drug" (vedolizumab or ustekinumab). The X specifies the share of the best supportive care (BSC) in the last line (0.333 in the base-case analysis; source: retrospective analysis of 1393 adults with CD who used biologics in Poland); the Y specifies the share of the "new drug" in the second line (0.667 in the base-case analysis). The structure and the rules (e.g., no BSC after new drug; the share of adalimumab in the second line of new strategy could not be higher than that of status quo; in the second line of new strategy: the new drug replaced BSC first, and if Y>X then it replaced adalimumab) ensured that the cumulative length of anti-TNF treatment for the new strategy was not shorter than the one for status quo.



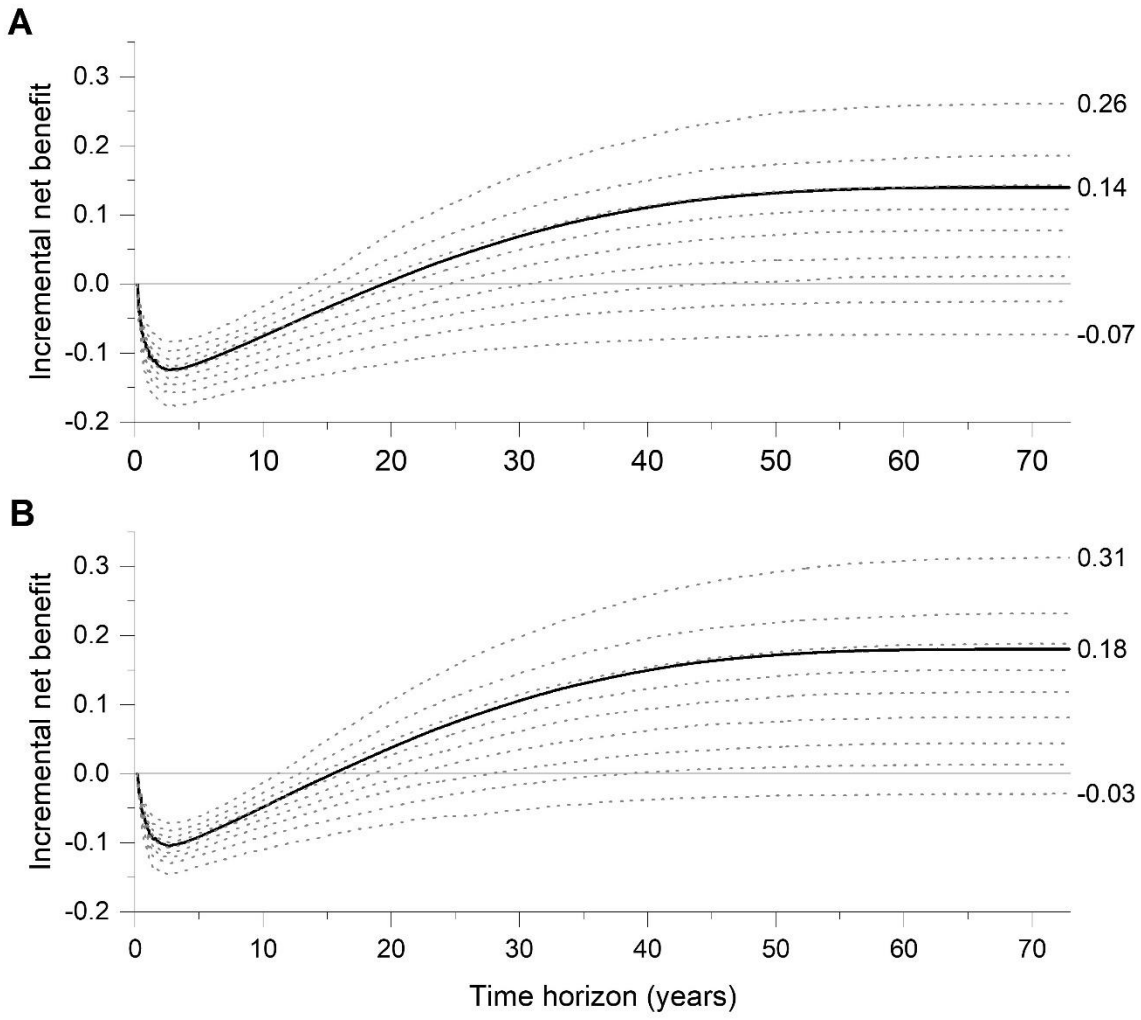
Supplementary Figure 2. Model validation.

Model validation with real-world survival on biologic treatment among 1393 patients. The last allowed dose of biologics is given between 322 and 365 days of treatment, depending on the dosing frequency.



Supplementary Figure 3. Net benefit probability maps: (A) new strategy with ustekinumab versus status quo; (B) new strategy with vedolizumab versus status quo

Incremental net benefit (INB; celling ratio of €31,500) is presented as the function of time horizon. INB higher than 0 indicates that the strategy is cost-effective compared with status quo. Solid black lines indicate mean INBs, and dotted lines – deciles of INBs obtained via probabilistic sensitivity analysis.



Supplementary Table 2. Baseline matrixes of transition probabilities.

Baseline matrix of transition probabilities between states derived from the study by Silverstein et al., 1999 (A); adjusted matrix after discontinuation of biologics (B); adjusted matrix during induction treatment with a biologic agent (C); and adjusted matrix during maintenance treatment with a biologic agent (D).

A. Baseline matrix.

	"CR"	***"R"***	***"NR"***	***"S"***
"CR"	$1-\Sigma = 0.9378$	$a_2 = 0.0491$	$a_3 = 0.0067$	$a_4 = 0.0064$
"R"	$b_1 = 0.0683$	$1-\Sigma = 0.9079$	$b_3 = 0.0165$	$b_4 = 0.0073$
"NR"	$c_1 = 0.0715$	$c_2 = 0.0459$	$1-\Sigma = 0.8535$	$c_4 = 0.0292$
"S"	$d_1 = 0.5272$	$d_2 = 0.0771$	$d_3 = 0.0582$	$1-\Sigma = 0.3374$

B. The adjusted matrix after discontinuation of biologic treatment: relapse rate increased by odds ratio (OR).

	"CR"	***"R"***	***"NR"***	***"S"***
"CR"	$1-\Sigma$	$\frac{a_2}{(1-a_3)} \cdot (1-a_{3r})$	$a_{3r} = \frac{a_3 \cdot OR}{1-a_3+a_3 \cdot OR}$	$\frac{a_4}{(1-a_3)} \cdot (1-a_{3r})$
"R"	$\frac{b_1}{(1-b_3)} \cdot (1-b_{3r})$	$1-\Sigma$	$b_{3r} = \frac{b_3 \cdot OR}{1-b_3+b_3 \cdot OR}$	$\frac{b_4}{(1-b_3)} \cdot (1-b_{3r})$
"NR"	c_1	c_2	$1-\Sigma$	c_4
"S"	d_1	d_2	d_3	$1-\Sigma$

C. The adjusted matrix during induction treatment: the effect of maintenance treatment with biologics (using odds ratio, OR) was included; the "S" state was excluded.

	"CR"	***"R"***	***"NR"***
"CR"	$1-\Sigma$	$a_{2i} = \frac{\frac{a_2}{(1-a_4)}}{OR-OR \cdot \frac{a_2}{(1-a_4)}+\frac{a_2}{(1-a_4)}}$	$a_{3i} = \frac{\frac{a_3}{(1-a_4)}}{OR-OR \cdot \frac{a_3}{(1-a_4)}+\frac{a_3}{(1-a_4)}}$
"R"	$b_{1i} = \frac{b_1}{(1-b_4)}$	$1-\Sigma$	$b_{3i} = \frac{\frac{b_3}{(1-b_4)}}{OR-OR \cdot \frac{b_3}{(1-b_4)}+\frac{b_3}{(1-b_4)}}$
"NR"	$\frac{c_1}{(1-c_4)}$	$\frac{c_2}{(1-c_4)}$	$1-\Sigma$

D. The adjusted matrix during maintenance treatment: maintenance of remission and reduction of surgery rate during biologic treatment (using incidence rate ratio, IRR) were included.

	"CR"	***"R"***	***"NR"***	***"S"***
"CR"	$1-\Sigma$	$a_{2i} \cdot (1-a_{4b})$	$a_{3i} \cdot (1-a_{4b})$	$a_{4b} = 1 - e^{Ln(1-a_4) \cdot IRR}$
"R"	$b_{1i} \cdot (1-b_{4b})$	$1-\Sigma$	$b_{3i} \cdot (1-b_{4b})$	$b_{4b} = 1 - e^{Ln(1-b_4) \cdot IRR}$
"NR"	c_1	c_2	$1-\Sigma$	c_4
"S"	d_1	d_2	d_3	$1-\Sigma$

Supplementary Table 3. Meta-analyses and indirect comparisons.

A. Probability of response induction (anti-TNF naive patient population)

	Infliximab
ACCENT I, n/N	335/573
Targan et al., n/N	22/27
Meta-analysis	0.684 (95% CI: 0.454 – 0.874)
Method	variance-stabilization (arcsin-square root transformation) random-effect model; Q test p = 0.013

B. Probability of response induction (anti-TNF failure patient population)

	Placebo (BSC)
GEMINI 3 (10th week, anti-TNF failure group), n/N	39/157
UNITI-1, n/N	50/247
Sandborn et al., 2012 (8th week, 6 mg per kg group), n/N	23/132
Meta-analysis	0.210 (95% CI: 0.177 – 0.245)
Method	variance-stabilization (arcsin-square root transformation) fixed-effect model; Q test p = 0.295

C. Odds ratio (OR) of response induction, ustekinumab vs. placebo (anti-TNF failure patient population)

	Ustekinumab	Placebo
UNITI-1, n/N	94/249	50/247
Sandborn et al., 2012 (8th week, 6 mg per kg group), n/N	57/131	23/132
Meta-analysis	OR = 2.75 (95% CI: 1.98 – 3.82)	
Method	fixed-effect model; Q test p = 0.232	

D. OR of remission maintenance, ustekinumab vs. placebo (anti-TNF failure patient population)

	Ustekinumab	Placebo
UNITI-1 (44 week), n/N	22/57	16/61
UNITI-2 (anti-TNF failure patient population; 44 week), n/N	11/19	6/19
Sandborn et al., 2012 (8th week, 6 mg per kg group; 22 week), n/N	30/72	20/73
Meta-analysis	OR = 1.96 (95% CI: 1.21 – 3.18)	
Method	fixed-effect model; Q test p = 0.795	

E. Cumulative rate of discontinuation due to adverse events

	Infliximab
ACCENT I, n/N	45/385
ACCENT II, n/N	5/138
Meta-analysis	0.076 (95% CI: 0.017 – 0.171)
Method	variance-stabilization (arcsin-square root transformation) random-effect model; Q test p = 0.002

F. OR of rate of discontinuation due to adverse events, infliximab vs. ustekinumab

Study	Infliximab	Placebo	**Study**	Ustekinumab	Placebo
ACCENT I, n/N	45/385	5/188	IM-UNITI, n/N [a]	18/264	9/133

ACCENT II, n/N	5/138	12/144	Sandborn et al., 2012, n/N [a]	7/394	5/132
Rutgeerts et al., 1999, n/N	6/37	1/36	-	-	-
Present et al., 1999, n/N	1/63	0/26	-	-	-
Meta-analysis	OR = 1.99 (95% CI: 0.40 – 9.98)		Meta-analysis	OR = 0.79 (95% CI: 0.40 – 1.55)	
Method	random-effect model; Q test p = 0.004		Method	fixed-effect model; Q test p = 0.281	
Indirect comparison	OR = 2.51 (95% CI: 0.44 – 14.45)				
Method	Adjusted indirect comparison – Bucher model				

[a] Sources: https://clinicaltrials.gov/ct2/show/results/NCT01369355, https://clinicaltrials.gov/ct2/show/results/NCT00771667?term=NCT00771667&rank=1

G. Share of CD in remission among responders – infliximab (anti-TNF naive patient population)

	Infliximab
ACCENT I, n/N	63/113
Targan et al., n/N	8/22
Meta-analysis	0.485 (95% CI: 0.310 – 0.662)
Method	variance-stabilization (arcsin-square root transformation) random-effect model; Q test p = 0.098

H. Share of CD in remission among responders – adalimumab (anti-TNF naive patient population)

	Adalimumab
CLASSIC-I, n/N	27/38
GAIN, n/N	34/61
Meta-analysis	0.615 (95% CI: 0.519 – 0.707)
Method	variance-stabilization (arcsin-square root transformation) fixed-effect model; Q test p = 0.130

I. Share of CD in remission among responders – ustekinumab (anti-TNF failure patient population)

	Ustekinumab
UNITI-1, n/N	52/94
Sandborn et al., 2012 (8th week, 6 mg per kg group), n/N	24/57
Meta-analysis	0.503 (95% CI: 0.424 – 0.582)
Method	variance-stabilization (arcsin-square root transformation) fixed-effect model; Q test p = 0.117

J. Share of CD in remission among responders – placebo / BSC (anti-TNF failure patient population)

	Placebo (BSC)
UNITI-1, n/N	18/50
Sandborn et al., 2012 (8th week), n/N	14/23
GEMINI 3 (10th week, anti-TNF failure patient population), n/N	19/39
Meta-analysis	0.456 (95% CI: 0.366 – 0.547)
Method	variance-stabilization (arcsin-square root transformation) fixed-effect model; Q test p = 0.127

Supplementary Table 4. Sources of health-related quality of life utility weights.

	Holko 2016	Bodger 2009	Blackhouse 2012, Rench 2017	Dretzke 2011	Lindsay 2008	Ananthakrishnan 2011	Punekar 2010	Hodgson 2017	Rafia 2015
„CR" state	0.908	0.83	0.82	0.949	0.83	0.83	0,83	0.80	0.82
„R" state	0.822	0.69	0.73	0.949	0.55	0.55	0,55	0.68*72.4% + 0.55*27.6% = 0.644	0.73*72.4% + 0.57*27.6% = 0.686
„NR" state	0.727	0.42	0.54	0.806	0.40	0.55	0,55	0.55	0.57
„S" state	0.878	0.73	0.54	0.507	0.73	0.40	0,73	(2*0.55 + 6*0.80)/8 = 0.738	(2*0.57 + 6*0.82)/8 = 0.758
Description	EQ-5D, cross-sectional study, 200 patients	CDAI (905 patients from study Sandborn et al., 2005) mapped to EQ-5D	SG data from cross-sectional study of 180 patients from Canada (Gregor 1997) with assumptions	TTO data from cross-sectional study of 180 patients from Canada (Gregor 1997) with assumptions	EQ-5D data from cross-sectional study from Spain (Casellas 2005) with assumptions	EQ-5D data from cross-sectional study from Spain (Casellas 2005) with assumptions	EQ-5D data from cross-sectional study from Spain (Casellas 2005) with assumptions	IBDQ (patients from UNITI trials) mapped to EQ-5D	EQ-5D, patients from GEMINI II and GEMINI III studies
Limitations	Overall CD patient population; cross-sectional	Mapping procedure, patients from other countries;	Overall CD patient population; cross-sectional; SG; patients from Canada	Overall CD patient population; cross-sectional; TTO; patients from Canada	Overall CD patient population; cross-sectional; patients from Spain	Overall CD patient population; cross-sectional; patients from Spain	Overall CD patient population; cross-sectional; patients from Spain	Mapping procedure, patients from other countries;	Patients from other countries;
Strengths	Patients from Poland, EQ-5D, individual patient data available	CD patients eligible for biologic treatment	-	-	EQ-5D, study size (628 patients, Casellas 2005)	EQ-5D, study size (628 patients, Casellas 2005)	EQ-5D, study size (628 patients, Casellas 2005)	CD patients eligible for biologic treatment; based on individual patient data	CD patients eligible for biologic treatment; based on individual patient data, EQ-5D

Sources: Holko et al. PLoS One. 2016;11(12):e0168586; Bodger et al. Aliment Pharmacol Ther. 2009;30(3):265-74; Sandborn et al. N Engl J Med. 2005;353(18):1912-25; Blackhouse et al. J Crohns Colitis. 2012;6(1):77-85; Rench et al. Expert Rev Pharmacoecon Outcomes Res. 2017;17(6):597-606; Gregor et al. Inflamm Bowel Dis. 1997;3(4):265-76; Dretzke et al. Health Technol Assess 2011;15(6); Casellas et al. Inflamm Bowel Dis. 2005 May;11(5):488-96; Lindsay et al. Aliment Pharmacol Ther. 2008;28(1):76-87; Ananthakrishnan et al. Am J Gastroenterol. 2011 Nov;106(11):2009-17; Punekar et al. Value Health. 2010;13(2):188-95. Hodgson 2017, www.journalslibrary.nihr.ac.uk/programmes/hta/161012; Rafia 2015, www.journalslibrary.nihr.ac.uk/programmes/hta/1312801

Supplementary Table 5. The threshold price calculations.

Description	The method incorporates deterministic results of the model, assumed threshold and reference drug price and provide threshold prices via rearrangement of the formula for incremental net monetary benefit ($INMB$)
The results or input parameters of the model	$ICER$ – incremental cost-effectiveness ratio $INMB$ – incremental net monetary benefit ΔC – difference in total cost ΔE – difference in QALYs C_{comp} – total cost of the comparator C_{new} – total cost of the new strategy $Price$ – unit price of ustekinumab or vedolizumab Ref – unit price of the reference drug WTP – the threshold $C_{UST/VED}$ – total acquisition cost of the ustekinumab or vedolizumab (with $Price$) $C_{other} = C_{new} - C_{UST/VED}$ – other costs of the new strategy
Assumptions	The $ICER = WTP$. Hence, $INMB = 0$ The C_{other} and ΔE are not dependent on $C_{UST/VED}$, i.e. only $Price$ can be changed; other parameters fixed (standard assumption for the threshold analysis)
The unknowns	$\overline{C_{UST/VED}}$ – the maximal total acquisition cost at $ICER = WTP$ $\overline{Price}$– the threshold unit price of ustekinumab or vedolizumab
Calculations	*The threshold price as a function of the threshold* $INMB = \Delta E \cdot WTP - \Delta C$ $INMB = \Delta E \cdot WTP - (C_{new} - C_{comp})$ $INMB = \Delta E \cdot WTP - (C_{UST/VED} + C_{other} - C_{comp})$ $INMB = 0$ $\Delta E \cdot WTP = (\overline{C_{UST/VED}} + C_{other} - C_{comp})$ and by rearranging we get: $\overline{C_{UST/VED}} = \Delta E \cdot WTP - (C_{other} - C_{comp})$ and the unit threshold price is: $\overline{Price} = Price \cdot \overline{C_{UST/VED}} / C_{UST/VED}$ which is: $\overline{Price} = \frac{Price \cdot (\Delta E \cdot WTP - (C_{other} - C_{comp}))}{C_{UST/VED}} = \frac{Price \cdot (\Delta E \cdot WTP + (C_{comp} - C_{other}))}{C_{UST/VED}}$ and further: $$\overline{Price} = \frac{Price \cdot \Delta E}{C_{UST/VED}} \cdot WTP + \frac{Price \cdot (C_{comp} - C_{other})}{C_{UST/VED}}$$ by substituting $Price$ with the model's input and the ΔE, $C_{UST/VED}$, C_{other}, and C_{comp} with the model's output we get a function of the threshold unit price $\overline{Price}$ and the threshold WTP And the threshold price as a function of the threshold and the unit price of the reference drug is: $$\overline{Price} = a \cdot WTP \cdot Ref + b \cdot Ref = (a \cdot WTP + b) \cdot Ref$$ where: $a = \frac{Price \cdot \Delta E}{C_{UST/VED} \cdot Ref}$ and $b = \frac{Price \cdot (C_{comp} - C_{other})}{C_{UST/VED} \cdot Ref}$
Validation	The method was validated using standard hand imputation of the prices

Supplementary Table 6. Input parameters.

Parameter(s)		Category	Value	Bounds	Distribution in PSA	Source
Par1.	Threshold cost per QALY gained (WTP)		€31,500 (PLN134,514)	-	Fixed	HTA Guidelines (www.aotmit.gov.pl)
Par2.	Cycle length		28 days	-	Fixed	Assumption
Par3.	Annual discount rate	Health effects	0.035	0, 0.035	Fixed	HTA Guidelines (www.aotmit.gov.pl)
		Costs	0.05	0, 0.05	Fixed	HTA Guidelines (www.aotmit.gov.pl)
Par4.	Time horizon, in years		68.1 (up to age of 100 years)	0.08, 72.9	100-current age	Assumption (lifetime)
Par5.	Conversion rate (PLN per €1)	-	4.2704	-	-	Average rate in the first half of 2017 (www.nbp.pl)
Par6.	Dose of biologics (per administration)	Infliximab	5 mg/kg IV	-	Fixed	Summary Product Characteristics (www.ema.europa.eu) and description of the drug program B.32. for CD (www.mz.gov.pl)
		Adalimumab	160, 80, then 40 mg every time; SC	-	Fixed	
		Vedolizumab	300 mg IV	-	Fixed	
		Ustekinumab	130 mg/vial IV x 2, 3 or 4 vials, then 90 mg every time; SC	-	Fixed	
Par7.	Moment of administration, weeks	Infliximab	0, 2, 6, then every 8	-	Fixed	
		Adalimumab	0, 1, then every 2	-	Fixed	
		Vedolizumab	0, 2, 6, then every 8	-	Fixed	
		Ustekinumab	0, 8, then every 12	-	Fixed	
Par8.	The maximum treatment period, in months	Infliximab	12	-	Fixed	
		Adalimumab	12	-	Fixed	
		Vedolizumab	12	-	Fixed	
		Ustekinumab	12	-	Fixed	
Par9.	The maximum period of induction, in cycles	Infliximab	3	-	Fixed	
		Adalimumab	3	-	Fixed	
		Vedolizumab	3	-	Fixed	
		Ustekinumab	3	-	Fixed	
		Infliximab	4	-	Fixed	
		Adalimumab	2	-	Fixed	

Parameter(s)		Category	Value	Bounds	Distribution in PSA	Source
Par10.	No induction phase of retreatment when relapse occurs during (cycles):	Vedolizumab	4	-	Fixed	
		Ustekinumab	4	-	Fixed	
Par11.	Weight, in kg	Average	61.9	60.8, 63.1	Normal(61.9, 16.0)	Retrospective analysis of 1393 adults with CD who used biologics in Poland (data on patients treated with infliximab)
Par12.	Share of patients with a weight of:	≤55 kg	0.332	~Par17	~Par17	Based on cumulative distribution function of the weight
		>55 and ≤85 kg	0.593	~Par17	~Par17	
		>85 kg	0.075	~Par17	~Par17	
Par13.	Age at start of biologic treatment, in years	-	31.9	31.4, 32.4	Log-normal(3.46, 0.31)	Retrospective analysis of 1393 adults with CD who used biologics in Poland
Par14.	% of women	-	47.5%	44.8%, 50.1%	Beta(661,732)	Retrospective analysis of 1393 adults with CD who used biologics in Poland
Par15.	% of mild CD among responders without remission	-	72.4%	57.4%, 85.1%	Beta(27.7, 10.6)	Targan et al. 1997
Par16.	Health-related utility weights, by state:	"CR"	0.908	0.890, 0.924	Beta(991.6, 100.9)	Holko et al., 2016 (92 patients)
		"R"	0.822	0.754, 0.882	Beta(110.3, 23.8)	Holko et al., 2016 (mild CD: 39 pts; moderate or severe CD: 64 pts; uses Par15)
		"NR"	0.727	0.667, 0.782	Beta(168.5, 63.4)	Holko et al., 2016 (moderate or severe CD: 64 pts)
		"S"	0.878	0.796, 0.941	Beta(66.6, 9.2)	Holko et al., 2016 (CD with surgery during the previous month: 5 pts)

Parameter(s)		Category	Value	Bounds	Distribution in PSA	Source
Par17.	Utility weights of general population, by age:	<25 years	0.968	0.962 0.974	Beta(3,330.7, 110.1)	Golicki et al., 2015. Was used to adjust utilities (Par16; among patients at an average age of 32 years) for aging of the cohort (utility multiplicator was calculated from the data).
		25-34 years	0.962	0.956 0.968	Beta(3,906.5, 154.3)	
		35-44 years	0.943	0.937 0.949	Beta(5,631.0, 340.4)	
		45-54 years	0.903	0.891 0.915	Beta(2,196.2, 235.9)	
		55-64 years	0.861	0.849 0.873	Beta(2,861.5, 462.0)	
		65-74 years	0.815	0.797 0.833	Beta(1,516.2, 344.2)	
		75+ years	0.730	0.703 0.757	Beta(733.4, 271.2)	
Par18.	Probability of induction of the response (anti-TNF naive)	Infliximab	0.684	0.580, 0.754	Sin^2[Normal(1.95, 0.24)/2]	Meta-analysis of ACCENT I and Targan et al. 1997
Par19.	OR for response at induction of adalimumab vs. infliximab (anti-TNF naive)	-	1.00	0.32, 2.40	Log-normal(0.00, 0.51)	Hazlewood et al. 2015
Par20.	OR for response at induction vs. BSC/placebo (anti-TNF failure)	Vedolizumab	2.67	1.65, 4.31	Log-normal(0.98, 0.06)	GEMINI 3 (10th week, anti-TNF failure group)
		Ustekinumab	2.75	1.98, 3.82	Log-normal(1.01, 0.17)	meta-analysis of UNITI-1 and Sandborn et al., 2012 (8th week, 6 mg/kg group)
Par21.	Probability of induction of the response (anti-TNF failure)	BSC / placebo	0.210	0.177, 0.245	Sin^2[Normal(0.95, 0.04)/2]	Meta-analysis of placebo group from GEMINI 3 (10th week, anti-TNF failure group), UNITI-1, Sandborn et al., 2012 (8th week, 6 mg per kg group)

Parameter(s)		Category	Value	Bounds	Distribution in PSA	Source
Par22.	HR of response induction failure for anti-TNF among anti-TNF failure vs naive patients	-	1.00	0.86, 2.38	Fixed	Assumption; Results of Billiet et al., 2016 and Gisbert et al., 2015b in DSA
Par23.	IRR of surgery: biologic treatment vs. post-treatment	-	0.26	0.18, 0.38	Log-normal(-1.35, 0.19)	Retrospective analysis of 1393 adults with CD who used biologics in Poland (generalized linear mixed model)
Par24.	OR for maintenance of remission vs. placebo (anti-TNF naive)	Infliximab	2.80	1.80, 4.50	Log-normal(1.03, 0.23)	Hazlewood et al. 2015
		Adalimumab	5.10	3.30, 8.10	Log-normal(1.63, 0.23)	
Par25.	OR for maintenance of remission vs. placebo (anti-TNF failure)	Vedolizumab	2.60	1.23, 5.53	Log-normal(0.96, 0.38)	Sands et al., 2017 (post hoc GEMINI-2 subgroup analysis)
		Ustekinumab	1.96	1.21, 3.18	Log-normal(0.67, 0.25)	Meta-analysis of IM-UNITI (2 groups: UNITI-1 and subgroup from UNITI-2) and Sandborn et al., 2012
Par26.	Cumulative discontinuation rate of infliximab (adverse event)	-	0.076	0.017, 0.171	Sin^2[Normal(0.56, 0.15)/2]	Meta-analysis of ACCENT I and ACCENT II; after 7 administrations (i.e. 38 weeks) of treatment, overall – exponential survival model assumed.
Par27.	OR of discontinuation (adverse event) for infliximab vs.	Adalimumab	5.56	2.94, 11.11	Log-normal(1.71, 0.34)	Hazlewood et al. 2015
		Vedolizumab	4.17	1.96, 8.33	Log-normal(1.43, 0.37)	
		Ustekinumab	2.51	0.44, 14.45	Log-normal(1.63, 0.23)	Indirect comparison: meta-analysis of IM-UNITI and Sandborn et al., 2012 vs. meta-

Parameter(s)		Category	Value	Bounds	Distribution in PSA	Source
						analyses of ACCENT I, ACCENT II, Rutgeerts et al., 1999, Present et al., 1999
Par28.	Probability matrix of the natural course of the disease	-	***"CR"*** 0.9378 0.0491 0.0067 0.0064 ***"R"*** 0.0683 0.9079 0.0165 0.0073 ***"NR"*** 0.0715 0.0459 0.8535 0.0292 ***"S"*** 0.5272 0.0771 0.0582 0.3374	-	Dirichlet distributions (n=174)	Silverstein et al. (median follow up = 10 years), reduced using the methods described by Dretzke et al., 2011
Par29.	Time to effect of biologics	All biologics	1 cycle of treatment	-	Fixed	Assumption
Par30.	CD severity in "NR"	All biologics	100% moderate or severe CD	-	Fixed	No or minimal change from baseline
Par31.	Share of remission among responders	Infliximab	0.485	0.454, 0.678	Sin^2[Normal(1.54, 0.18)/2]	Meta-analysis of ACCENT I and Targan et al. 1997
		Adalimumab	0.615	0.519, 0.707	Sin^2[Normal(1.80, 0.10)/2]	Meta-analysis of clinical trials for adalimumab (CLASSIC-I and GAIN)
		Vedolizumab	0.568	0.454, 0.678	Beta(42, 32)	GEMINI 3 (10th week, anti-TNFα failure group)
		Ustekinumab	0.503	0.424, 0.582	Sin^2[Normal(1.58, 0.08)/2]	Meta-analysis of UNITI-1, Sandborn et al., 2012 (8th week, 6 mg per kg group)
		BSC	0.456	0.366, 0.547	Sin^2[Normal(1.48, 0.09)/2]	Meta-analysis of placebo group from GEMINI 3 (10th week, anti-TNF failure group), UNITI-1, Sandborn et al., 2012 (8th week, 6 mg per kg group)

Parameter(s)		Category	Value	Bounds	Distribution in PSA	Source
Par32.	Share of surgeries leading to discontinuation of biologic treatment	All biologics	0.407	0.330, 0.486	Beta(61, 89)	Retrospective analysis of 1393 adults with CD who used biologics in Poland
Par33.	Cumulative probability of relapse after elective discontinuation of biologics	All biologics	0.380	0.345, 0.416	Beta(273.6, 446.4)	Gisbert et al., 2015, Gisbert et al., 2016; used for adjustment of probability matrix of the natural course of disease (OR calculation and then adjustment)
Par34.	HR of relapse: discontinuation due to failure vs. elective discontinuation	All biologics	1.23	1.00, 1.50	Log-normal(0.20, 0.10)	Casanova et al., 2017; used for adjustment of probability matrix of the natural course of disease along with Par33
Par35.	Period of higher relapse rate occurrence	Standard of care	6 months	-	Fixed	Gisbert et al., 2015, Gisbert et al., 2016, and assumption
		BSC	Infinitely	-	Fixed	
Par36.	Probability of early elective discontinuation (therapeutic success)	All biologics	0.0105 per cycle after induction	0, 0.0221	Fixed	Retrospective analysis of 1393 adults with CD who used biologics in Poland
Par37.	Probability of the success of retreatment	All biologics	0.92	0.84, 1.00	Beta(39.72, 3.45)	Gisbert et al., 2016 (without outlier studies), confirmed by Kennedy et al., 2016
Cost inputs						
Par38.	Ex-factory price (without VAT and margins)	Ustekinumab	€2,362.80 per vial (130 mg IV or 90 mg SC)	-	Fixed	Maximum reimbursement price in Slovakia (www.liekinfo.sk), without margins (21%); to obtain cost in Poland, the price was multiplied by 1.134 (wholesale margin and VAT)
		Vedolizumab	€1,872.37 per 300 mg	-	Fixed	
Par39.	Unit cost of anti-TNF	Infliximab	€2.64 per 1 mg	-	Fixed	Average cost in Poland in the 1st half of 2017 (www.nfz.gov.pl)
		Adalimumab	€9.73 per 1 mg	-	Fixed	

Parameter(s)		Category	Value	Bounds	Distribution in PSA	Source
Par40.	The unit cost of outpatient procedure during drug program	All biologics	€25.33	-	Fixed	Current unit cost of biologic treatment in Poland (services no: 5.08.07.0000004, 5.08.07.0000003 or 5.08.07.0000002, 5.08.08.0000040 or 5.08.08.0000041); source: www.nfz.gov.pl
Par41.	The unit cost of inpatient procedure during drug program	All biologics	€113.98 per day	-	Fixed	
Par42.	Flat rate of diagnostic procedures during biologic treatment	All biologics	€52.42 per cycle	-	Fixed	
Par43.	The frequency of visit to the clinic due to administration of biologics	Infliximab	At each administration	-	Fixed	Retrospective analysis of 1393 adults with CD who used biologics in Poland and assumptions
		Adalimumab	Every 4 weeks	Every time, every 8 weeks	Fixed	
		Ustekinumab	At each administration	-	Fixed	
		Vedolizumab	At each administration	-	Fixed	
Par44.	Share of outpatient procedure during administration	Infliximab	0.030	0.026, 0.034	Beta(200, 6475)	Retrospective analysis of 1393 adults with CD who used biologics in Poland and assumptions
		Adalimumab	0.487	0.477, 0.497	Beta(4433, 4673)	
		Ustekinumab	As for adalimumab	-	-	
		Vedolizumab	As for infliximab	-	-	
Par45.	Length of stay during inpatient procedure, days	Infliximab	1.41	1.31, 1.50	Normal(1.41, 0.05)	Retrospective analysis of 1393 adults with CD who used biologics in Poland and assumptions
		Adalimumab	1.83	1.60, 2.06	Normal(1.83, 0.12)	
		Ustekinumab	As for adalimumab	-	-	
		Vedolizumab	As for infliximab	-	-	
Par46.	Healthcare cost during biologic treatment, per cycle	NFZ	€79.49	72.20, 87.13	Gamma(435.742, 0.182)	Retrospective analysis of 1393 adults with CD who used biologics in Poland; BSC calculated among patients with cumulative exposure to biologics ≤100 days (similar costs as
		Patients	€7.31	6.84, 7.79	Gamma(910.798, 0.008)	
		NFZ	€113.61	102.67, 125.10	Gamma(394.039, 0.288)	

Parameter(s)		Category	Value	Bounds	Distribution in PSA	Source
Par47.	Healthcare cost after effective biologic treatment, per cycle	Patients	€7.93	7.29, 8.59	Gamma(570.538, 0.014)	among all participants before biologic treatment) During treatment: 119 pts, 12,508.2 patient-years; Post-treatment (> 100 days): 862 pts, 11,771 patient-years; Post-treatment (≤100 days): 179 pts, 3,843.425 patient-years Surgery: 1043 non-overlapping procedures among 678 pts.
Par48.	BSC, per cycle	NFZ	€144.70	100.17, 197.29	Gamma(33.930, 4.265)	
		Patients	€8.03	6.82, 9.34	Gamma(156.209, 0.051)	
Par49.	Surgery and healthcare post-surgery costs, per cycle	NFZ	€1,170.06	1,086.60, 1,256.57	Gamma(727.956, 1.607)	
		Patients	€10.07	8.89, 11.31	Gamma(265.485, 0.038)	
Par50.	Non-medical cost from the patients' perspective per cycle	"CR"	€12.62	8.05, 18.20	Gamma(23.627, 0.534)	Holko et al., 2016 – minimal valuation technique (remission: 89 pts, mild CD: 40 pts; moderate or severe CD: 63 pts; surgery in the previous month: 5 pts; uses Par15 to obtain cost for "R" state)
		Mild CD ("R")	€20.87	13.77, 29.41	Gamma(27.199, 0.767)	
		Moderate or severe CD ("R" and "NR")	€29.59	20.16, 40.81	Gamma(31.389, 0.943)	
		"S"	€22.00	7.15, 45.04	Gamma(5.005, 4.395)	
Par51.	Cost of absenteeism	"CR"	€55.44	22.95, 102.01	Gamma(7.383, 7.509)	Holko et al., 2016 (remission: 92 pts, mild CD: 40 pts; moderate or severe CD: 58 pts; surgery in a previous month: 5 pts; uses Par15 to obtain cost for "R" state). Set to 0 among ≥65 year olds.
		Mild CD ("R")	€148.49	63.57, 268.82	Gamma(7.869, 18.871)	
		Moderate or severe CD ("R" and "NR")	€149.99	81.26, 239.44	Gamma(13.642, 10.995)	
		"S"	€499.83	205.03, 923.72	Gamma(7.259, 68.859)	

Parameter(s)		Category	Value	Bounds	Distribution in PSA	Source
Par52.	Cost of presenteism	"CR"	€94.96	63.34, 132.88	Gamma(28.476, 3.335)	Holko et al., 2016 (remission: 92 pts, mild CD: 40 pts; moderate or severe CD: 58 pts; surgery in the previous month: 5 pts; uses Par15 to obtain cost for "R" state). Set to 0 among ≥65 years old.
		Mild CD ("R")	€125.64	77.53, 185.18	Gamma(20.758, 6.053)	
		Moderate or severe CD ("R" and "NR")	€184.42	122.80, 258.37	Gamma(28.262, 6.525)	
		"S"	€153.36	33.52, 362.57	Gamma(3.169, 48.401)	
Par53.	Cost of informal care	"CR"	€17.56	7.49, 31.84	Gamma(7.821, 2.245)	Holko et al., 2016 (remission: 91 pts, mild CD: 40 pts; moderate or severe CD: 58 pts; surgery in the previous month: 5 pts; uses Par15 to obtain cost for "R" state).
		Mild CD ("R")	€44.07	17.28, 83.19	Gamma(6.695, 6.582)	
		Moderate or severe CD ("R" and "NR")	€84.86	53.47, 123.39	Gamma(22.459, 3.779)	
		"S"	€98.02	6.04, 314.45	Gamma(1.396, 70.224)	
Par54.	Cost of productivity loss at unpaid work	"CR"	€17.56	7.49, 31.84	Gamma(7.821, 2.245)	Holko et al., 2016 (remission: 91 pts, mild CD: 40 pts; moderate or severe CD: 58 pts; surgery in the previous month: 5 pts; uses Par15 to obtain cost for "R" state; when Par53 is included the part of the loss compensated by caregivers is excluded
		Mild CD ("R")	€47.92	18.64, 90.79	Gamma(6.605, 7.256)	
		Moderate or severe CD ("R" and "NR")	€87.52	55.20, 127.17	Gamma(22.550, 3.881)	
		"S"	€98.02	6.04, 314.45	Gamma(1.396, 70.224)	

Parameter(s)		Category	Value	Bounds	Distribution in PSA	Source
Par55.	The baseline probability of death	All biologics	Age and sex dependent among general population of Poland	-	Fixed	Life table, 2016 (stat.gov.pl)
Par56.	State-dependent probability of death due to CD, per cycle	"CR"	0.00088	0.00072, 0.00106	Beta(99.911, 113,566.232)	Silverstein et al. (median follow up = 10 years); in DSA other sources and other assumption were tested (e.g., data from Odes et al., 2010, no state-dependent mortality, i.e., the same for each state using data from Jess et al., 2013, i.e., overall SMR of 1.73)
		"R"	0.00258	0.00210, 0.00311	Beta(99.740, 38,609.694)	
		"NR"	0.00315	0.00257, 0.00380	Beta(99.681, 31,495.453)	
		"S"	0.00041	0.00031, 0.00049	Beta(99.959, 243,651.470)	

Additional references: *Billiet et al., 2016:* Billiet T, Cleynen I, Ballet V, Ferrante M, Van Assche G, Gils A, Vermeire S. Prognostic factors for long-term infliximab treatment in Crohn's disease patients: a 20-year single centre experience. Aliment Pharmacol Ther. 2016 Oct;44(7):673-83. doi: 10.1111/apt.13754. *Gisbert et al., 2015:* Gisbert JP, Marín AC, Chaparro M. Systematic review: factors associated with relapse of inflammatory bowel disease after discontinuation of anti-TNF therapy. Aliment Pharmacol Ther. 2015 Aug;42(4):391-405. *Gisbert et al., 2015b:* Gisbert JP, Marín AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Aliment Pharmacol Ther. 2015;41(7):613-23. *Jess et al., 2013:* Jess T, Frisch M, Simonsen J. Trends in overall and cause-specific mortality among patients with inflammatory bowel disease from 1982 to 2010. Clin Gastroenterol Hepatol. 2013;11:43–48. *Kennedy et al., 2016:* Kennedy NA, Warner B, Johnston EL, et al. Relapse after withdrawal from anti-TNF therapy for inflammatory bowel disease: an observational study, plus systematic review and meta-analysis. Aliment Pharmacol Ther. 2016. 43(8):910-923.

Supplementary Table 7. Model validation.

Parameter	Model	Source(s) data
12-months remission rate (overall, including induction phase)		
Infliximab (anti-TNFα naïve)	37.3%	38.9% (ACCENT I)
Adalimumab (anti-TNFα naïve)	47.5%	39.5% to 84.2%, average of 56.3% (CLASSIC II, CHARM)
Ustekinumab (anti-TNFα failure)	25.4%	38.6% (IM-UNITI [UNITI-1 subpopulation])
Vedolizumab (anti-TNFα failure)	27.7%	27.7% (Sands et al., 2017)
12-months response rate (overall, including induction phase)		
Infliximab (anti-TNFα naïve)	60.5%	40%-50% (ACCENT I), ~60% (ACCENT II)
Adalimumab (anti-TNFα naïve)	66.5%	51.7% - 84.2%; average of 65.2% (CLASSIC II, CHARM)
Ustekinumab (anti-TNFα failure)	41.5%	50-60% (IM-UNITI: non-randomized patients)
Vedolizumab (anti-TNFα failure)	41.9%	33.3% (Sands et al., 2017)
12-months rate in placebo arm (maintenance of remission or response among 100% responders at induction)		
Remission (anti-TNFα failure)	22.97%	26.2% (IM-UNITI [UNITI-1 subpopulation]), 12.8% (Sands et al., 2017)
Response (anti-TNFα failure)	35.07%	20.5% (Sands et al., 2017)
2-year rates of starting biologic treatment (retreatment, subsequent lines of treatment)		
Infliximab	47.6%	IFX 48.1%; 43.9% overall (retrospective analysis of 1393 adults with CD who used biologics in Poland)
Adalimumab	44.3%	ADA 39.5%; 43.9% overall (retrospective analysis of 1393 adults with CD who used biologics in Poland)
Average number of infliximab administrations (12-month)	6.2	5.5 (retrospective analysis of 1393 adults with CD who used biologics in Poland)
Average consumption of adalimumab (12-month)	967 mg	778 mg (retrospective analysis of 1393 adults with CD who used biologics in Poland)
322-day survival on treatment		
Infliximab	43.5%	42.8% (retrospective analysis of 1393 adults with CD who used biologics in Poland)
Adalimumab	47.2%	51.0% (retrospective analysis of 1393 adults with CD who used biologics in Poland)
150-day survival on treatment		
Infliximab	65.0%	76.8% (retrospective analysis of 1393 adults with CD who used biologics in Poland)
Adalimumab	67.6%	72.1% (retrospective analysis of 1393 adults with CD who used biologics in Poland)

CLASSIC II: Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007; 56:1232–9.

CHARM: Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132: 52–65.

Supplementary Table 8. Additional scenarios of ustekinumab and vedolizumab prices.

	Base-case analysis [a]	List prices in UK [b]	Prices in UK [c]	Prices in Germany [d]	Prices in US [e]
The prices					
Vedolizumab 300 mg	2 123.27 EUR	2 329.55 EUR	2 329.55 EUR	2 532.01 EUR	5 424.41 EUR
Ustekinumab 90 mg	2 679.42 EUR	2 439.77 EUR	2 439.77 EUR	5 005.34 EUR	19 025.28 EUR
Ustekinumab 130 mg	2 679.42 EUR	2 439.77 EUR	190.54 EUR	5 005.34 EUR	1 485.81 EUR
The deterministic results (vedolizumab vs. ustekinumab)					
Difference in QALYs	0.015	0.015	0.015	0.015	0.015
Difference in costs	-€993.58	€372.25	€2,551.70	-€6,546.28	-€12,113.68
ICER	Vedolizumab dominates	€24,652	€168,988	Vedolizumab dominates	Vedolizumab dominates
Cost-effective treatment [f]	Vedolizumab	Vedolizumab	Ustekinumab	Vedolizumab	Vedolizumab

[a] The list price in Slovakia adjusted for difference in taxes and margins between Poland and Slovakia;

[b] The list price for UK converted to EUR (average rate in 2017). Source: ERG report for ustekinumab (https://www.journalslibrary.nihr.ac.uk/programmes/hta/161012/#/);

[c] The list price for UK with assumed cost reduction of ustekinumab 130 mg (relation of price of 130 mg to price of 90 mg as in the US);

[d] The lowest pharmacy price in Germany, without statutory discounts and prescription fee. Source: www.medizinfuchs.de (23.02.2018);

[e] The total price (without discounts) in US converted to EUR (average rate in 2017). Source: www.drugs.com (23.02.2018);

[f] Based on the point estimate of the ICER. In the base-case analysis we found that ustekinumab and vedolizumab resulted in similar outcomes (the difference was not significant).

Supplementary Table 9. Cross-validation with scenario presented by Hodgson et al. 2017.

	New strategy (ustekinumab) vs. status quo		New strategy (vedolizumab) vs. status quo		Ustekinumab vs vedolizumab
	ΔQALY	**ICER**	**ΔQALY**	**ICER**	**ΔQALY**
ERG preferred base-case scenario (Hodgson et al. 2017)	0.06	£110,967	0.03	£408,844	0.03
Current model (€1 = £0.88)					
Base-case analysis	0.35	£16,612	0.36	£13,525	-0.01
Base-case + utilities from Rafia et al. 2015	0.37	£15,750	0.38	£12,826	-0.01
Previous scenario + discount rates: 3.5% cost; 3.5% effects	0.37	£17,271	0.38	£14,172	-0.01
Previous scenario + public payer's perspective (healthcare cost only)	0.37	£21,479	0.38	£18,361	-0.01
Previous scenario + no increase in relapse rate after discontinuation of biologic treatment	0.06	£94,370	0.08	£71,455	-0.02
Previous scenario + rate of responders during induction phase from ERG report by Hodgson et al. 2017 (6-week data from clinical trial)	0.06	£104,089	0.07	£77,285	-0.01
Previous scenario + rate of remissions among responders during induction phase from ERG report by Hodgson et al. 2017 (6-week data from clinical trial)	0.06	£96,199	0.05	£102,713	0.01
Other differences: transition probabilities during maintenance treatment and after discontinuation of biologic treatment; cost data	These aspects could not be addressed without major restructuring of the economic model and/or data not available				

Sources: Hodgson et al. Pharmacoeconomics. 2017. DOI: 10.1007/s40273-017-0593-2; Hodgson et al. ERG report. 2017 (www.journalslibrary.nihr.ac.uk/programmes/hta/161012); Rafia et al. 2015 (www.journalslibrary.nihr.ac.uk/programmes/hta/1312801); Rafia et al. Pharmacoeconomics. 2016;34(12):1241-1253.

3 Retrospective analysis of 1393 adults with CD who used biologics in Poland

3.1 Methods

This was a retrospective analysis of medical resource utilization among patients with CD treated with infliximab or adalimumab in the years from 2012 to 2014 in Poland. The cohort was identified from the database of the National Health Fund (in Polish, Narodowy Fundusz Zdrowia), a public payer for all medical services in Poland.

The eligibility criteria for the study were at least one administration of biologics and age of 18 years or older during the first biologic treatment. Patients using infliximab or adalimumab in other indications and patients below 17 years of age at the first administration of biologics were excluded owing to different criteria for continuation of treatment.

The data on eligible patients were extracted from the database created for study by Holko et al., 2017. All medical resources used between the first and the last resource utilization in the years from 2012 to 2014 for each eligible patient were analyzed. The observation period for each patient was divided according to an index date of the first administration of a biologic drug (before the first administration [pre-index period] and after the first administration of a biologic drug [post-index period]). The post-index period was further divided into periods depending on whether the patient was on active treatment (during treatment [i.e., during drug administration]) or not (post-treatment [i.e., the periods in-between active treatments when the drug was discontinued and the period after the last administration of a biologic]) to check if the reduction of resources utilization occurs after treatment.

The costs of publicly funded medical resources were assessed via official remuneration schemes and reflected the real cost incurred by the public payer in Poland. The cost of biologic treatment (acquisition, administration and diagnostics) and the cost of other healthcare resources were analyzed separately. All costs presented here were converted to euros with the exchange rate of 4.19 PLN per €1 (the average rate in 2012 – 2014). The costs

were not corrected for inflation because the consumer price index for the health sector did not vary significantly during the study period. The bias-corrected and accelerated bootstrap standard error (SE) for monthly cost estimates was obtained (1000 replications).

All medical services with the main diagnosis code of CD or related intestinal or extraintestinal complications were considered as being directly related to CD. The medium, large or complex surgical or endoscopic procedures (according to a diagnosis-related group system) directly related to CD were considered as surgeries for CD. The group of potentially CD-related services included inflammation or infection of the gastrointestinal tract and possible complications with the exception of tumors other than malignant and non-malignant tumors of the lower gastrointestinal tract. Hospitalization was defined as a stay in a hospital for more than 1 day. Immunomodulatory drugs (azathioprine, cyclosporine, mercaptopurine, methotrexate), aminosalicylates and systemic glucocorticoids (e.g., budesonide, methylprednisolone, prednisolone, prednisone) were considered as CD-related medications. Antibiotics were analyzed separately. The group of medications potentially related to CD included the ones used in the treatment of extraintestinal complications among other indications (a specific indication for each prescription was not available).

The principal and secondary diagnosis ICD-10 codes, established for each patient over the first 6 months of the study was used to calculate the Charlson comorbidity index score. The Classification of Territorial Units for Statistics was used for grouping patients by the geographical regions of Poland.

The generalized linear mixed model with Poisson or negative binominal (when overdispersion was present) distribution, log link, robust errors, period duration as a quantification of exposure and random intercepts by patient was used to test relative frequency of surgeries during biologic treatment (i.e., during drug administration) and after treatment (i.e., the

periods in-between active treatments when the drug was discontinued and the period after the last administration of a biologic).

The model with "exposure" variable allowed us to determine the incidence rate ratio (IRR) for each predictor while considering the differences in period duration.

Data preparation and statistical analyses were done using Access 2016 (Microsoft Co., Redmond, WA) and STATA 14.2 (StataCorp, College Station, TX).

3.2 Results

Data on 1393 patients (age, 31.9 years; males, 52.6%; 1–4 treatments/patient) were analyzed over a median of 1064 days (range: 71, 1148). The median cumulative duration of biologic treatment was 314 days (IQR: 134, 365)

The study included 626 patients treated with infliximab, 587 patients treated with adalimumab and 180 patients treated with both biologics. A total of 1050, 285, 56 and 2 patients received 1, 2, 3 and 4 biologic treatments, respectively, during follow-up. Most of the patients (94.4%) had no life-threatening comorbidities (comorbidity score of 0), and 44.7% were from the eastern or central region of Poland. There were no differences in patients' characteristics between patients treated with adalimumab and infliximab. The rates of immunomodulatory drug and steroid use did not differ significantly between patients treated with adalimumab and those treated with infliximab at the index date and between patients during subsequent biologic treatments.

From the perspective of the NFZ, the average cost of biologic treatment was €618.72 per patient per month (infliximab at index: €597.94, SE €13.97; adalimumab: €639.73, SE €15.94). The average post-index monthly healthcare cost was €136.61 (SE 7.05) and €134.48 (SE 8.78) per patient treated with infliximab and adalimumab at index date, respectively. The healthcare cost in a month with surgery for CD was estimated at €1188.68 (SE €42.49).

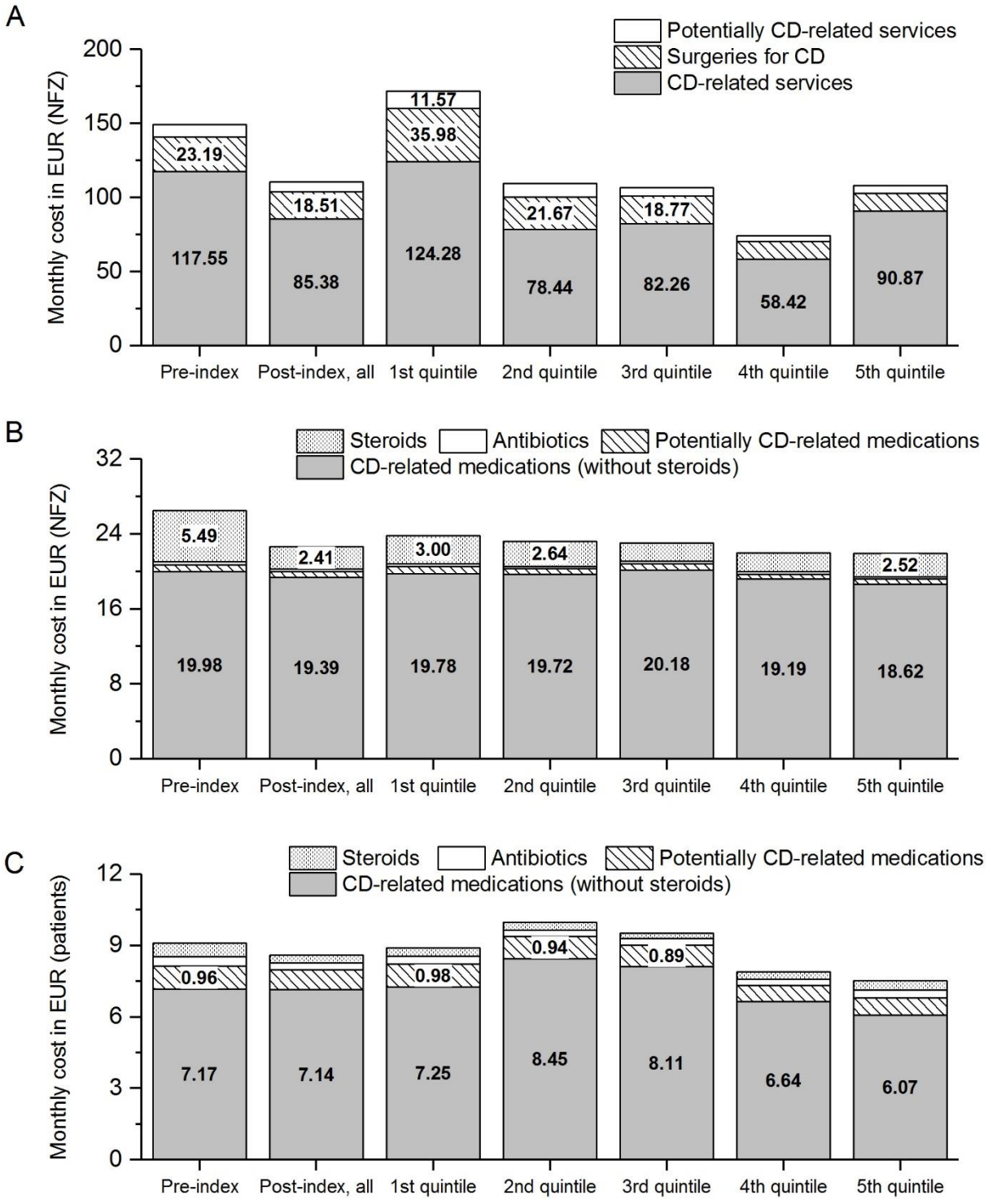
In comparison to the pre-index period, in the post-index period a reduction in the cost of surgeries, other medical services related to CD and steroid use was observed among patients with exposure to biologic treatment for more than 100 days (>1st quintile; **Supplementary Figure 4**). Further analysis suggested that it was mainly associated with the reduction of healthcare cost during biologic treatment (**Supplementary Figure 5**).

Among all patients, monthly healthcare cost from the perspective of NFZ was reduced by €41.05 (SE €7.98) after the first biologic administration. The difference increased to €62.27 (SE €8.23) among patients with exposure to biologic treatment for more than 100 days. There were no differences in the costs from patient's perspective in relation to index treatments, levels of exposure to biologic treatment or study periods.

Among the 678 patients, there were 1045 surgeries for CD, including 482 surgeries (346 patients) before, 150 surgeries (140 patients) during, and 413 surgeries (308 patients) after biologic treatment. Of 150 surgeries, 40.7% most probably resulted in discontinuation of biologic treatment, that is, they occurred during the estimated treatment period, between the last and the next expected administration of biologics according to the treatment schedule. The rate of surgeries differed between periods with or without biologic treatment, but not between the index treatments. Compared with the post-treatment period, patients during biologic treatment showed a lower rate of surgeries (adjusted difference of -0.27 events per year, $p < 0.001$; **Supplementary Table 10**). The difference was used to adjust the baseline matrix of transition probabilities during biologic treatment.

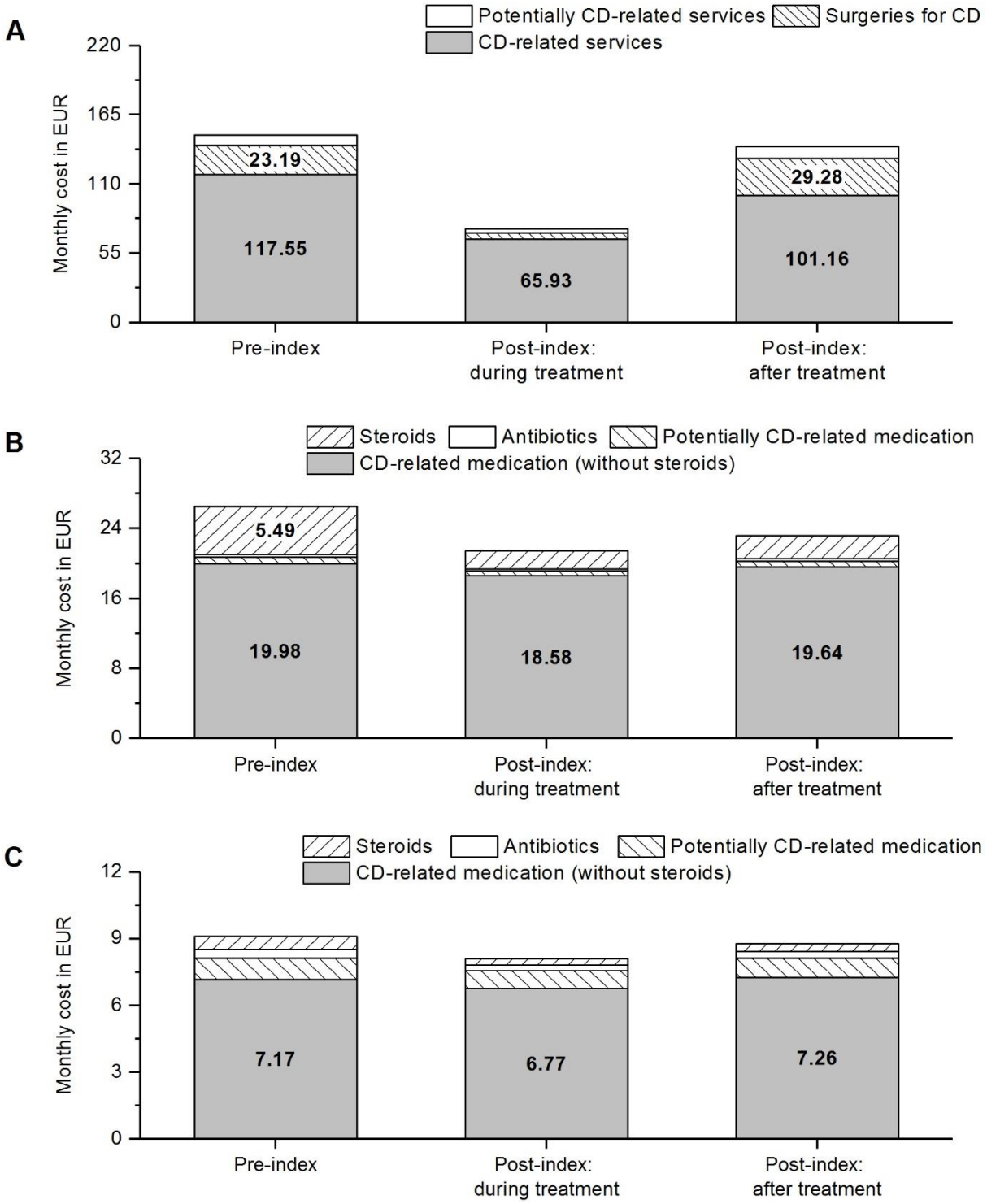
Supplementary Figure 4.

Average monthly cost of medical services (A) and medicines on prescription (B, C) from the perspective of the National Health Fund (in Polish, Narodowy Fundusz Zdrowia [NFZ]; A and B) and patients (C) by study period and quintiles of total exposure to biologic treatment.



Supplementary Figure 5.

Average monthly cost of medical services (A) and medication on prescription (B, C) from the economic perspective of the National Health Fund (A, B) and patients (C) before, during and after biologic treatment.



Supplementary Table 10.

The statistical model for the assessment of rate of surgeries after the first dose of biologics (post-index period).

	Surgeries
Fixed effects – IRR (95% CIs)	
Age (increase by 1 year)	0.99 (0.98, 1.01)
Sex (female vs. male)	0.95 (0.69, 1.32)
Comorbidity index (1+ vs. 0)	1.34 (0.65, 2.76)
North or north-western region (vs. eastern or central)	0.94 (0.65, 1.37)
South or south-western region (vs. eastern or central)	0.87 (0.59, 1.30)
Immunomodulatory drug user	0.93 (0.66, 1.32)
Treatment at index (ADA vs. IFX)	0.87 (0.63, 1.19)
During treatment (vs. post treatment)	**0.26 (0.18, 0.38)***
Other parameters and model performance	
Exp(intercept) (95% CIs)	0.45 (0.24, 0.85)*
Random effect (95% CIs)	0.40 (0.18, 0.88)
Akaike information criterion	2670.79
Root-mean-square error (events)	0.41

The model was based on 3067 observations for 1393 patients (1 to 7 observations per patient) and included exposure variable indicating the length of a period. * $p < 0.05$.

ADA, adalimumab; IFX, infliximab; IRR, incidence rate ratio.