Supplementary Materials

Dose-escalation Patterns of Advanced Therapies in Crohn's Disease and Ulcerative Colitis: A Systematic Literature Review

Authors:

Remo Panaccione[1], Wan-Ju Lee[2], Ryan Clark[2], Kristina Kligys[2], Rhiannon I. Campden[3], Stacy Grieve[3], Tim Raine[4]

1. Division of Gastroenterology and Hepatology, Inflammatory Bowel Disease Unit, Cumming School of Medicine, University of Calgary, Calgary, Canada
2. AbbVie, Dept GMH1, Bldg ABV1-4NW 30802, 1 N Waukegan Road, North Chicago, IL, US
3. Cytel, Inc, Waltham, Massachusetts, US
4. Department of Gastroenterology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

Author contacts:

rpanacci@ucalgary.ca

wanju.lee@abbvie.com

ryan.clark@abbvie.com

kristina.kligys@abbvie.com

rhiannon.campden@cytel.com

stacy.grieve@cytel.com

tim.raine@addenbrookes.nhs.uk

Correspondence:

Remo Panaccione

rpanacci@ucalgary.ca

Division of Gastroenterology and Hepatology, Inflammatory Bowel Disease Unit, Cumming School of Medicine, University of Calgary, Calgary, Canada

Supplementary Appendix

Supplemental Table 1: Ovid Search Strategy CD

Search Strategy in CD				
Search conducted	26/Oct/2021			
Databases searched	EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 20, 2021> EBM Reviews - ACP Journal Club <1991 to September 2021> EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016> EBM Reviews - Cochrane Clinical Answers <October 2021> EBM Reviews - Cochrane Central Register of Controlled Trials <September 2021> EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> EBM Reviews - Health Technology Assessment <4th Quarter 2016> EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016> Econlit <1886 to October 14, 2021> Embase <1974 to 2021 October 25> Ovid MEDLINE(R) ALL <1946 to October 25, 2021>			
			Term	**Hits**
Population/Disease: Crohn's disease	Medline	1	Crohn Disease/	138,710
	Embase	2	Crohn disease/	138,710
	All	3	(Crohn disease$ or Crohns disease$ or Crohn's disease$ or cleron disease$ or Crohn Enteritis or Crohns Enteritis or Crohn's Enteritis or Crohn Colitis or Crohns Colitis or Crohn's Colitis or Regional Enteritis or Granulomatous Enteritis or Granulomatous Colitis or Ileocolitis or Terminal Ileitis or Regional Ileitides or Regional Ileitis or enteritis regionalis or morbus crohn or regional enterocolitis).ti,ab.	139,448
CD		**4**	**or/1-3**	**171,417**
Intervention	Medline	5	Ustekinumab/ or Adalimumab/ or Infliximab/ or Certolizumab Pegol/	91,827
	Embase	6	vedolizumab/ or ustekinumab/ or adalimumab/ or infliximab/ or certolizumab pegol/	93,875
	All	7	(vedolizumab or ustekinumab or adalimumab$ or infliximab$ or certolizumab pegol).ti,ab.	71,189
		8	(ENTYVIO$ or STELARA$ or HUMIRA$ or REMICADE$ or CIMZIA$).ti,ab.	3,151
		9	or/5-8	108,195
Treated patients with CD		**10**	**4 and 9**	**29,045**
Study Design-RWE		11	exp case-control studies/ or exp case control study/	1,451,460

		12	exp cross-sectional studies/ or exp cross-sectional study/	839,170
		13	exp cohort studies/ or exp cohort analysis/	3,154,999
		14	longitudinal studies/ or longitudinal study/	320,188
		15	prospective studies/ or prospective study/	1,418,355
		16	retrospective studies/ or retrospective study/	2,115,037
		17	observational study/	361,656
		18	follow-up studies/	2,028,323
		19	clinical study/	160,689
		20	(case control or case-control).ti,ab.	326,263
		21	(cohort adj1 (study or studies or analysis or analyses)).ti,ab.	691,035
		22	((longitudinal or retrospective or prospective or cross sectional or cross-sectional) adj1 (study or studies or review or analysis or analyses or cohort$)).ti,ab.	2,506,654
		23	((follow up or follow-up or followup or observational or uncontrolled or non randomi#ed or nonrandomi#ed or non-randomi#ed or non-interventional or noninterventional or non interventional or pragmatic) adj1 (study or studies)).ti,ab.	511,915
		24	(registry or register or database or claims or single center or single-center or multicenter or multi-center or multi center or survey or record$ or chart review or real world or real-world).ti,ab.	6,242,757
		25	follow up/	1,753,775
		26	cohort$.ti,ab.	1961257
		27	25 and 26	266,949
		28	or/11-24,27	1.2E+07
RWE studies in Treated patients with CD		**29**	**10 and 28**	**11,921**
Dose escalation	Embase	30	drug dose/ or recommended drug dose/ or repeated drug dose/ or drug dose sequence/ or drug dose reduction/ or maintenance drug dose/ or drug dose escalation/ or drug dose increase/	190,035
	All	31	((dose or dosage or dosing or treatment$ or therap$) adj3 (escalat$ or adjust$ or increase$ or variation$ or pattern$ or frequenc$ or switch$ or change$ or interval$ or optimiz$ or optimis$ or intensif$ or schedule$)).mp,af,tw.	1,213,973
		32	30 or 31	1,321,212
RWE studies reporting dosing in Treated patients with CD		**33**	**29 and 32**	**3,190**

Irrelevant Study Design		34	(addresses or bibliography or biography or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lectures or letter or monograph or news or "newspaper article" or practice guideline or "review literature" or "review of reported cases" or review, academic or review, multicase or review, tutorial or twin study).pt.	4,390,030
		35	(animals/ not (humans/ and animals/)) or (animal/ not (human/ and animal/))	6,041,309
		36	case report/ or case reports/	4,887,225
		37	34 or 35 or 36	1.5E+07
		38	33 not 37	3,020
Limits		39	limit 38 to english language	2,973
		40	limit 39 to human	2,809
		41	limit 40 to yr="2011 -Current"	2,564
FINAL: RWE studies reporting dosing in Treated patients with CD		**42**	**remove duplicates from 41**	**2,140**

Supplemental Table 2: Ovid Search Strategy UC

Search Strategy in UC				
Search conducted	26/Oct/2021			
Databases searched	EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 20, 2021> EBM Reviews - ACP Journal Club <1991 to September 2021> EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016> EBM Reviews - Cochrane Clinical Answers <October 2021> EBM Reviews - Cochrane Central Register of Controlled Trials <September 2021> EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> EBM Reviews - Health Technology Assessment <4th Quarter 2016> EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016> Econlit <1886 to October 14, 2021> Embase <1974 to 2021 October 25> Ovid MEDLINE(R) ALL <1946 to October 25, 2021>			
			Term	**Hits**
Population/Disease: Ulcerative colitis (UC)	Medline	1	Colitis, Ulcerative/	73,491
	Embase	2	ulcerative colitis/	117,712

	All	3	(ulcerative colitis or Idiopathic Proctocolitis or Colitis Gravis or colitis ulcerosa or colitis ulcerativa or mucosal colitis or ulcerative colorectitis or ulcerative proctocolitis or ulcerous colitis).ti,ab.	113,897
UC		**4**	**or/1-3**	**143,592**
Intervention	Medline	5	Ustekinumab/ or Adalimumab/ or Infliximab/	89,860
	Embase	6	vedolizumab/ or ustekinumab/ or adalimumab/ or infliximab/ or tofacitinib/ or ozanimod/ or golimumab/	97,560
	All	7	(vedolizumab or ustekinumab or adalimumab$ or infliximab$ or tofacitinib or tasocitinib or ozanimod or golimumab).ti,ab.	77,000
		8	(ENTYVIO$ or STELARA$ or HUMIRA$ or REMICADE$ or XELJANZ$ or ZEPOSIA$ or SIMPONI$).ti,ab.	3,197
		9	or/5-8	114,821
Treated patients with UC		**10**	**4 and 9**	**18,434**
Study Design-RWE		11	exp case-control studies/ or exp case control study/	1,451,460
		12	exp cross-sectional studies/ or exp cross-sectional study/	839,170
		13	exp cohort studies/ or exp cohort analysis/	3,154,999
		14	longitudinal studies/ or longitudinal study/	320,188
		15	prospective studies/ or prospective study/	1,418,355
		16	retrospective studies/ or retrospective study/	2,115,037
		17	observational study/	361,656
		18	follow-up studies/	2,028,323
		19	clinical study/	160,689
		20	(case control or case-control).ti,ab.	326,263
		21	(cohort adj1 (study or studies or analysis or analyses)).ti,ab.	691,035
		22	((longitudinal or retrospective or prospective or cross sectional or cross-sectional) adj1 (study or studies or review or analysis or analyses or cohort$)).ti,ab.	2,506,654
		23	((follow up or follow-up or followup or observational or uncontrolled or non randomi#ed or nonrandomi#ed or non-randomi#ed or non-interventional or noninterventional or non interventional or pragmatic) adj1 (study or studies)).ti,ab.	511,915
		24	(registry or register or database or claims or single center or single-center or multicenter or multi-center or multi center or survey or record$ or chart review or real world or real-world).ti,ab.	6,242,757
		25	follow up/	1,753,775
		26	cohort$.ti,ab.	1,961,257

		27	25 and 26	266,949
		28	or/11-24,27	1.2E+07
RWE studies in Treated patients with UC		**29**	**10 and 28**	**8,233**
Dosing	Embase	30	drug dose/ or recommended drug dose/ or repeated drug dose/ or drug dose sequence/ or drug dose reduction/ or maintenance drug dose/ or drug dose escalation/ or drug dose increase/	190,035
	All	31	((dose or dosage or dosing or treatment$ or therap$) adj3 (escalat$ or adjust$ or increase$ or variation$ or pattern$ or frequenc$ or switch$ or change$ or interval$ or optimiz$ or optimis$ or intensif$ or schedule$)).mp,af,tw.	1,213,973
		32	30 or 31	1,321,212
RWE studies reporting dosing in Treated patients with UC		**33**	**29 and 32**	**2,116**
Irrelevant Study Design		34	(addresses or bibliography or biography or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lectures or letter or monograph or news or "newspaper article" or practice guideline or "review literature" or "review of reported cases" or review, academic or review, multicase or review, tutorial or twin study).pt.	4,390,030
		35	(animals/ not (humans/ and animals/)) or (animal/ not (human/ and animal/))	6,041,309
		36	case report/ or case reports/	4,887,225
		37	34 or 35 or 36	1.5E+07
		38	33 not 37	2,003
Limits		39	limit 38 to english language	1,964
		40	limit 39 to human	1,883
		41	limit 40 to yr="2011 -Current"	1,793
FINAL: RWE studies reporting dosing in Treated patients with UC		**42**	**remove duplicates from 41**	**1,522**

Supplemental Table 3: Reported reasons for dose escalation in CD publications

Intervention	N of studies reporting	Reason for dose escalation
Ustekinumab	13	Partial response, no response, loss of response [28-41]
	1	Low UST trough levels [39]
	1	Maintain clinical remission/response [102]
	1	Decision was reached jointly by patient and clinician based on patient's prior history and management preferences [91]
Vedolizumab	6	Partial response, no response, loss of response [42-52]
	2	No response at week 6 [113, 115]
	1	Non-remitters; discretion of the treating provider [114]
Certolizumab pegol	1	Partial response, no response, loss of response [89, 90]
Adalimumab	16	Partial response, no response, loss of response [53-75]
	1	Endoscopic and morphological recurrence [121]
	1	Deterioration in clinical symptoms [125]
	1	Maintenance of clinical response, loss of response, CRP re-elevation [126]
	1	Based on clinical and biochemical responses [128]
Infliximab	18	Partial response, no response, loss of response [53, 54, 64, 65, 67, 69, 73-88]
	1	Decided by discussion by physicians and patients [226]
	1	Serum IFX levels [136]
	1	Treating physician's clinical judgment on whether the patient's current therapy failed to provide adequate therapeutic response [212, 213]
	1	Lack of effectiveness, adverse events [132]
	1	Based on clinical and biochemical responses [128]

Abbreviations: CD, Crohn's disease; CRP, C reactive protein; IFX, infliximab; N, number within the overall population; UST, ustekinumab.

Supplemental Table 4: Ustekinumab Dose Escalation Patterns by Region, Crohn's disease

Maintenance pattern at the start of study*	Maintenance pattern at follow-up	Studies recording pattern (n)	Proportion of patients, median % (range)ł
Interval Shortening (n=24)			
US & Canada			
90 mg q8w [30, 31, 39, 91, 92, 95-97, 99]	90 mg q4w	7	27% (17 to 77%)
90 mg q8w [95, 96, 99]	90 mg q6w	1	23%
45 mg q12w [98]	90 mg q8w	1	100%
Outside of North America			
90 mg q12w$^{\epsilon}$	90 mg q8w	4	43% (21 to 50%)

[36, 37, 105, 106, 108, 209-211, 230]			
90 mg q8w$^{\epsilon}$ [29, 33, 35, 40, 101, 103-108]	90 mg q4w†	5	24% (11 to 33%)
90 mg q8w [35, 103-106]	90 mg q6w	3	4% (1 to 14%)
90 mg q12 [105, 106, 209, 210, 230]	90 mg q4w	1	11%
45 mg q12w [35]	45 mg q8w	1	25%
45 mg q8w [35]	45 mg q6w	1	11%
Dose strength increase (n=2)¤			
US & Canada			
Outside of North America (NSI)			

Note: Label indication 90 mg q8w (FDA) and 90 mg q12w (EMA).
Abbreviations: mg, milligram; n, number within the specified subpopulation; N, number within the overall population; NSI, no studies identified; q4w, every 4 weeks; q6w, every 6 weeks; q8w, every 8 weeks; q12w, every 12 weeks.
*Assumption of 90 mg per interval if not explicitly indicated; ŧDenominator of the proportion is based on the number of patients with a specific initial maintenance regimen; $^{\epsilon}$Includes Biemans et al. 2020 study[[108]] where the maintenance pattern proportions were calculated based on the number of individuals at 12 weeks instead of baseline; †Includes IV-reinduction plus 90 mg q4w dosing; ¤Dose strength increase values occurred along a continuum therefore succinct categorization wasn't possible. Value ranges are therefore described in text.

Supplemental Table 5: Vedolizumab Dose Escalation Patterns by Region, Crohn's disease

Maintenance pattern at the start of study	Maintenance pattern at follow-up	Studies recording pattern (n)	Proportion of patients, median % (range)ŧ
Interval Shortening (n=11)			
US & Canada			
300 mg q8w‡ [46, 47, 110, 111, 114, 116]	300 mg q4w	2	18% (8 to 27%)
300 mg q8w [46, 47, 114, 116]	300 mg q6w	1	10%
300 mg q8w [46, 47, 110, 114]	300 mg <q6w	2	18% (8 to 27%)
Outside of North America			
300 mg q8w‡ [44, 45, 48, 49, 51, 52, 107, 115]	300 mg q4w	6	33% (12 to 79%)
300 mg q8w [44, 45, 48, 49, 114, 116]	300 mg q6w	3	4% (4 to 13%)
300 mg q8w [44, 45]	300 mg q5w	1	2%
300 mg q8w [44, 45]	300 mg q7w	1	1%
300 mg q8w [42-45, 48, 49, 51, 52, 107, 112-116]	300 mg <q6w	6	24% (12 to 79%)
Dose Strength Increase (n=0)			

Note: Label indication 300 mg q8w (FDA, EMA).
Abbreviations: mg, milligram; n, number within the specified subpopulation; N, number within the overall population; q4w, every 4 weeks; q5w, every 5 weeks; q6w, every 6 weeks; q7w, every 7 weeks; q8w, every 8 weeks.
ŧDenominator of the proportion is based on the number of patients with a specific initial maintenance regimen; ‡Includes maintenance patterns where only the interval (eg, q8w) was reported.

Supplemental Table 6: Certolizumab pegol Dose Escalation Patterns by Region, Crohn's disease

Maintenance pattern at the start of study	Maintenance pattern at follow-up	Studies recording pattern (n)	Proportion of patients, median % (range)
Interval shortening (n=1)			
US & Canada			
400 mg q4w [89, 90]	400 mg q2w	1	17%
400 mg q4w [89, 90]	200 mg q2w	1	37%
Outside of North America (NR)			
Dose Strength increase (n=1)			
US & Canada			
200 mg q2w [89, 90]	400 mg q2w	1	18%
Outside of North America (NR)			

Note: Label indication 400 mg q4w (FDA).
Abbreviations: mg, milligram; n, number within the specified subpopulation; N, number within the overall population; NR, not reported; q2w, every 2 weeks; q4w, every 4 weeks.

Supplemental Table 7: Adalimumab Dose Escalation Patterns by Region, Crohn's disease

Maintenance pattern at the start of study*	Maintenance pattern at follow-up	Studies recording pattern (n)	Proportion of patients, median % (range)ŧ
Interval shortening (n=18)			
US & Canada			
40 mg EOW [70, 117, 118]	40 mg EW	2	43% (40 to 45%)
Outside of North America			
40 mg EOW [53, 54, 59-69, 71, 72, 118, 120-128]	40 mg EW	17‡	29% (14 to 77%)
Dose strength increase (n=4)			
US & Canada			
40 mg [54, 71, 72, 117]	80 mg	1	5%
Outside of North America			
40 mg [54, 71, 72]	80 mg	1	12%

Note: Label indication 40 mg q2w (FDA, EMA).
Abbreviations: EOW, every other week; EW, every week; mg, milligram; n, number within the specified subpopulation; N, number within the overall population; NR, not reported.

*40 mg EOW assumed if dosage not reported; ŧDenominator of the proportion is based on the number of patients with a specific initial maintenance regimen; ‡Including Barberio et al. 2020[128] which reported "NR" for the proportion of patients dose escalated.

Supplemental Table 8: Infliximab Dose Escalation Patterns by Region, Crohn's disease

Maintenance pattern at the start of study	Maintenance pattern at follow-up	Studies recording pattern (n)	Proportion of patients, median % (range)ŧ
Interval shortenings (n=17)			
US & Canada (NR)			
Outside of North America			
q8w [53, 64, 65, 67, 69, 75, 76, 79, 80, 82, 83, 85-87, 211]	q4-7w	7	20% (3 to 87%)
q8w [53, 69, 73, 84, 86, 87, 128]	q4w	4	8% (3 to 20%)
q8w [53, 69, 73, 75, 83, 86, 87, 128]	q6w	5	20% (3 to 87%)
q8w [73, 74, 86, 87, 138]	q7w	1	9%
Dose strength increase (n=19)			
US & Canada			
5 mg/kg [81, 129-133]	>5 mg/kg	1	11%
5 mg/kg [81, 129-131, 133]	10 mg/kg	1	8%
5 mg/kg [139, 140]	7.5 mg/kg	1	4%
Outside of North America			
5 mg/kg [53, 54, 64, 65, 67, 69, 73-75, 77-80, 82, 83, 85-88, 128, 134-139]	>5 mg/kg	15	14% (3 to 67%)
5 mg/kg [53, 54, 64, 65, 67, 69, 73-75, 77-80, 82-88, 128, 134-140]	10 mg/kg	15	14% (3 to 67%)

Note: Label indication 5 mg/kg q8w (FDA, EMA).
Abbreviations: kg, kilogram; mg, milligram; n, number within the specified subpopulation; N, number within the overall population; NR, not reported; q4w, every 4 weeks; q4-7w, every 4-7 weeks; q6w, every 6 weeks; q7w, every 7 weeks; q8w, every 8 weeks.
ŧDenominator of the proportion is based on number of patients with a specific initial maintenance regimen.

Supplemental Table 9: Reported reasons for dose escalation in UC publications

Intervention	N of studies reporting	Reason for dose escalation
Tofacitinib	1	Relapsed 52 weeks after achieving remission [157]
Ustekinumab	1	No/minimal response to induction, loss of response during maintenance, endoscopic inflammation, elevated CRP, or fecal calprotectin [159, 160]

Vedolizumab	1	Continued clinical activity or objective evidence of continued inflammation [154, 155]
	5	Partial response, no response, loss of response [44-47, 51, 52, 115, 141-143]
Golimumab	1	Weight >80 kg [167, 231]
	2	Partial response, no response, loss of response [151-153]
	1	Decision by physician based on the clinical symptoms [171]
Adalimumab	2	Partial response, no response, loss of response [128, 144, 145]
Infliximab	6	Partial response, no response, loss of response [128, 137, 146-150]

Abbreviations: CRP, C-reactive protein; kg, kilogram; N, number within the overall study population UC, ulcerative colitis.

Supplemental Table 10: Ustekinumab Dose Escalation Patterns by Region, Ulcerative Colitis

Maintenance pattern at the start of study	Maintenance pattern at follow-up	Studies recording pattern (n)	Proportion of patients, median % (range)ł
Interval shortening (n=3)			
US & Canada			
90 mg q8w [159, 160]	90 mg q6w	1	12%
90 mg q8w [158]	90 mg q4w	1	47%
q12w or q8w [158-160]	q6w or q4w	2	30% (12 to 47%)
Outside of North America			
q12w or q8w [161-163]	q6w or q4w	1	27%
Dose strength increase (n=0)			

Note: Label indication 90 mg q8w (FDA), 90 mg q12w (EMA).
Abbreviations: mg, milligram; n, number within the specified subpopulation; N, number within the overall population; q4w, every 4 weeks; q6w, every 6 weeks; q8w, every 8 weeks; q12w, every 12 weeks.
łDenominator of the proportion is based on number of patients with a specific initial maintenance regimen.

Supplemental Table 11: Vedolizumab Dose Escalation Patterns by Region, Ulcerative Colitis

Maintenance pattern at the start of study	Maintenance pattern at follow-up	Studies recording pattern (n)	Proportion of patients, median % (range)ł
Interval shortening (n=10)			
US & Canada			
300 mg q8w [46, 47, 111, 141-143, 154, 155, 164]	300 mg ≤q6w	6*	25% (6 to 44%)
300 mg q8w [164]	300 mg q6w	1	5%
300 mg q8w [44-47, 92, 111, 115, 141-143, 154, 155, 164]	300 mg q4w	6*	20% (6 to 44%)

Outside of North America			
300 mg q8w [42-45, 48, 49, 51, 52, 112, 115]	300 mg ≤q6w	4	25% (13 to 63%)
300 mg q8w [44, 45, 48, 49]	300 mg q6w	2	7% (6 to 7%)
300 mg q8w [48, 49, 51, 52, 115]	300 mg q4w	3	32% (12 to 56%)
Dose strength increase (n=1)			
US & Canada (NSI)			
Outside of North America			
300 mg q8w [7, 165]	1.8 times recommended daily dose	1	50%

Note: Label indication 300 mg q8w (FDA, EMA).
Abbreviations: mg, milligram; n, number within the specified subpopulation; N, number within the overall population; NSI, no studies identified; q4w, every 4 weeks; q6w, every 6 weeks; q8w, every 8 weeks.
ŧProportion calculated based on overall number of individuals who started on maintenance treatment; *Includes one study that did not report the number of individuals dose escalated[111].

Supplemental Table 12: Golimumab Dose Escalation Patterns by Region, Ulcerative Colitis

Maintenance pattern at the start of study	Maintenance pattern at follow-up	Studies recording pattern (n)	Proportion of patients, median % (range)ŧ
Interval shortening (n=1)			
US & Canada (NSI)			
Outside of North America			
100 mg q4w [152, 153, 171, 172]	100 mg q2w	1	NR*
Dose strength increase (n=6)			
US & Canada (NSI)			
Outside of North America			
50 mg [151-153, 168-172]	100 mg	4	76% (16 to 83%)

Note: Label indication 100 mg q4w (>80 kg), 50 mg q8w (<80 kg) (EMA).
Abbreviations: kg, kilogram; mg, milligram; n, number within the specified subpopulation; NR, not reported; NSI, no studies identified; q4w, every 4 weeks.
ŧDenominator of the proportion is based on the number of patients with a specific initial maintenance regimen; *Despite reports of interval shortening in 2% of patients, the number of individuals dose escalated from a known starting dose was not reported.

Supplemental Table 13: Adalimumab Dose Escalation Patterns by Region, Ulcerative Colitis

Maintenance pattern at the start of study	Maintenance pattern at follow-up	Studies recording pattern (n)	Proportion of patients, median % (range)ŧ
Interval shortening (n=7)			
US & Canada (NSI)			
Outside of North America			
40 mg EOW	40 mg EW	7	39% (30 to 56%)

[62, 128, 144, 145, 173-177, 179-183]			
40 mg EOW [144, 145]	40 mg q10d	1	1%
Dose strength increase (n=4)			
North America (NSI)			
Outside of North America			
40 mg EOW [144, 145]	80 mg EOW	1	2%
40 mg EOW [7, 144, 145, 165, 178, 179]	Avg. biweekly dose ≥50mg	4	22% (2 to 74%)

Note: Label indication 40 mg EOW (FDA, EMA).
Abbreviations: EW, every week; EOW, every other week; mg, milligram; n, number within the specified subpopulation; N, number within the overall population; NSI, no studies identified; q10d, every 10 days.
ŧDenominator of the proportion is based on the number of patients with a specific initial maintenance regimen.

Supplemental Table 14: Infliximab Dose Escalation Patterns by Region, Ulcerative Colitis

Maintenance pattern at the start of study	Maintenance pattern at follow-up	Studies recording pattern (n)	Proportion of patients, median % (range)ŧ
Interval shortening (n=8)			
US & Canada (NR)			
Outside of North America			
5 mg/kg q8w [128, 147-150, 188-190]	5 mg/kg <q8w	2	23% (21 to 25%)
5 mg/kg q8w [128, 147, 148, 150, 188, 189]	5 mg/kg q6w	2	20% (15 to 25%)
5 mg/kg q8w [128, 147, 148, 150]	5 mg/kg q4w	1	6%
Dose strength increase (n=7)			
US & Canada			
5 mg/kg q8w [129, 130, 132]	>5 mg/kg	1	27%
Outside of North America			
5 mg/kg q8w [137, 146-150, 186, 187, 189, 190]	10 mg/kg q8w	5	10% (5 to 38%)
5 mg/kg q8w [150, 189]	10 mg/kg q4-6w	2	14% (7 to 21%)
5 mg/kg q8w [7, 132, 137, 147-150, 165, 186, 187, 189, 190]	>5 mg/kg	6	33% (12 to 65%)

Note: Label indication 5 mg/kg q8w (FDA, EMA).
Abbreviations: kg, kilogram; mg, milligram; n, number within the specified subpopulation; N, number within the overall population; NR, not reported; q4w, every 4 weeks; q4-6w, every 4-6 weeks; q6w, every 6 weeks; q8w, every 8 weeks.
ŧDenominator of the proportion is based on number of patients with a specific initial maintenance regimen.