

Supplementary Appendix

Literature Search Strategies

PubMed Literature Search Strategy (November 9, 2016)

Table S-1. PubMed Literature Search Strategy (November 9, 2016)

Limits: Humans; Adults; No Comments or Case Reports

Search No.	Search Terms	No. of Articles
Disease		
1	"Crohn Disease"[Mesh] OR "Crohn's Disease"[Text Word] OR "Crohn Disease"[Text Word]	45,409
Population		
2	#1 AND (("Rectal Fistula"[Mesh] OR rectal fistula*[Text Word] OR anal fistula*[Text Word] OR perianal fistula*[Text Word]) AND (complex[Text Word] OR "high transsphincteric"[Text Word] OR suprasphincteric[Text Word] OR extrasphincteric[Text Word] OR horseshoe[Text Word] OR multiple track*[Text Word] OR "anteriorly lying track"[Text Word]))	211
Epidemiology		
3	#2 AND ("Crohn Disease/epidemiology"[Mesh] OR "Rectal Fistula/epidemiology"[Mesh] OR "Epidemiology"[Mesh] OR "Morbidity"[Mesh] OR "Incidence"[Mesh] OR "Prevalence"[Mesh] OR "Mortality"[Mesh] OR "Disease Progression"[Mesh] OR "Risk Factors"[Mesh] OR "Severity of Illness Index"[Mesh] OR "Population Characteristics"[Mesh] OR "Natural History"[Mesh] OR epidemiolog*[Text Word] OR morbidit*[Text Word] OR incidence*[Text Word] OR prevalence[Text Word] OR mortalit*[Text Word] OR "disease progression"[Text Word] OR "progression of disease"[Text Word] OR risk factor*[Text Word]	79

Search		No. of
No.	Search Terms	Articles
	OR severe[Text Word] OR severity[Text Word] OR "population characteristics"[Text Word] OR "populations at risk"[Text Word] OR "population statistics"[Text Word] OR "natural history"[Text Word])	
Humanistic burden		
4	#2 AND ("Quality of Life"[Mesh] OR "Surveys and Questionnaires"[Mesh] OR "Self Report"[Mesh] OR "Pain Measurement"[Mesh] OR "Activities of Daily Living"[Mesh] OR "Patient Satisfaction"[Mesh] OR "Patient Preference"[Mesh] OR "Quality-Adjusted Life Years"[Mesh] OR "Health Status"[Mesh] OR "Stress, Psychological"[Mesh] OR "Caregivers"[Mesh] OR "quality of life"[Text Word] OR burden[Text Word] OR "EuroQoL"[Text Word] OR "EQ5D"[Text Word] OR "EQ 5D"[Text Word] OR "quality of well being"[Text Word] OR "well being"[Text Word] OR "SF-6D"[Text Word] OR patient report*[Text Word] OR proxy report*[Text Word] OR self report*[Text Word] OR questionnaire*[Text Word] OR survey*[Text Word] OR "functional status"[Text Word] OR "activities of daily living"[Text Word] OR capabilit*[Text Word] OR function*[Text Word] OR "physical function"[Text Word] OR "patient satisfaction"[Text Word] OR patient preference*[Text Word] OR patient's preference*[Text Word] OR patients' preference*[Text Word] OR patient perspective*[Text Word] OR patient's perspective*[Text Word] OR patients' perspective*[Text Word] OR patient experience*[Text Word] OR patient's experience*[Text Word] OR patients' experience*[Text Word] OR "quality adjusted life year"[Text Word]	55

Search	No. of
No. Search Terms	Articles
<p>OR "quality adjusted life years"[Text Word] OR "QALY"[Text Word] OR "health status"[Text Word] OR "health state"[Text Word] OR stress[Text Word] OR "emotional strain"[Text Word] OR "standard gamble"[Text Word] OR "time trade off"[Text Word] OR "health utility index"[Text Word] OR "utility index"[Text Word] OR "disability adjusted life year"[Text Word] OR "disability adjusted life years"[Text Word] OR "DALY"[Text Word] OR caregiver*[Text Word])</p>	
Economic burden	
<p>5 #1 AND (("Crohn Disease/economics"[Majr] OR "Rectal Fistula/economics"[Majr] OR "Health Resources/utilization"[Majr] OR "Fees and Charges"[Majr] OR "Employment"[Majr] OR "Work"[Majr] OR "Unemployment"[Majr] OR "Health Care Costs"[Majr] OR "Absenteeism"[Majr] OR "Presenteeism"[Majr] OR "Costs and Cost Analysis"[Majr] OR "Economics, Hospital"[Majr] OR "Economics, Medical"[Majr] OR "Economics, Nursing"[Majr] OR "Economics, Pharmaceutical"[Majr] OR "Budgets"[Majr] OR "Efficiency"[Majr] OR "Insurance, Disability"[Majr] OR "Nursing Homes"[Majr] OR "Health Expenditures"[Majr] OR "Cost of Illness"[Majr] OR "Drug Utilization"[Majr] OR "Cost-Benefit Analysis"[Majr] OR "Insurance, Health, Reimbursement"[Majr]) AND (cost[Title] OR costs[Title] OR indirect cost*[Text Word] OR economic*[Title] OR fiscal[Title] OR fee[Title] OR fees[Title] OR expenditure*[Title] OR "resource use"[Text Word] OR "resource utilization"[Text Word] OR "resource utilisation"[Text Word] OR productiv*[Text Word] OR ((hospitalization*[Title] OR</p>	154

Search		No. of
No.	Search Terms	Articles
	hospitalisation*[Title]) AND ("length of stay"[Title] OR cost[Title] OR costs[Title])) OR societal cost*[Text Word] OR "budget impact"[Title] OR "economic impact"[Text Word] OR societal benefit*[Text Word] OR disability[Title] OR employ*[Title] OR unemploy*[Title] OR "health care cost"[Title] OR "health care costs"[Title] OR "healthcare cost"[Title] OR "healthcare costs"[Title] OR "cost of illness"[Title] OR "costs of illness"[Title]))	
Treatments		
6	#2 AND ("Crohn Disease/drug therapy"[Mesh] OR "Crohn Disease/therapy"[Mesh] OR "Crohn Disease/surgery"[Mesh] OR "Crohn Disease/complications"[Mesh] OR "Rectal Fistula/drug therapy"[Mesh] OR "Rectal Fistula/therapy"[Mesh] OR "Rectal Fistula/surgery"[Mesh] OR "Rectal Fistula/complications"[Mesh] OR "Therapeutics"[Mesh] OR "Surgical Procedures, Operative"[Mesh] OR "Treatment Failure"[Mesh] OR "Anti-Bacterial Agents"[Mesh] OR "Infliximab"[Mesh] OR "Adalimumab"[Mesh] OR therap*[Text Word] OR treat*[Text Word] OR complication*[Text Word] OR sequelae[Text Word] OR antibiotic*[Text Word] OR "anti-TNF"[Text Word] OR "non-biologic"[Text Word] OR failure*[Text Word] OR surgery[Text Word] OR surgeries[Text Word] OR surgical[Text Word] OR infliximab[Text Word] OR adalimumab[Text Word])	207
Guidelines and practice patterns		
7	#1 AND (("Practice Patterns, Physicians'"[Majr] AND (practice pattern*[Title] OR best practice*[Title])) OR (("Practice Guidelines as Topic"[Majr] OR "Practice Guideline"[Publication Type]) AND	85

Search		No. of
No.	Search Terms	Articles
	guideline*[Title]) OR (("Observational Studies as Topic"[Majr] OR "Observational Study"[Publication Type]) AND observational stud*[Title]))	
Exclusions		
8	"Animals"[Mesh] NOT "Humans"[Mesh]	4,269,791
9	"Comment"[Publication Type] OR "Case Reports"[Publication Type]	2,458,069
10	((("Infant"[Mesh] OR infant*[Title] OR "Child"[Mesh] OR child*[Title] OR "Adolescent"[Mesh] OR adolescen*[Title] OR teen*[Title] OR youth*[Title] OR "school age"[Title]) NOT ("Adult"[Mesh] OR "Aged"[Mesh] OR "Aged, 80 and Over"[Mesh] OR "Frail Elderly"[Mesh] OR "Middle Aged"[Mesh] OR adult*[Title] OR "old age"[Title] OR "senior citizen"[Title] OR elderly[Title]))	1,767,484
Total with non-US limit to be added		
11	(#3 OR #4 OR #5 OR #7) NOT (#8 OR #9 OR #10)	315
Geography		
12	#11 NOT ("United States"[Mesh] OR "United States"[Text Word] OR "USA"[Text Word] OR "U.S.A."[Text Word] OR "U.S."[Text Word])	193
Treatment with no geography limit		
13	#6 NOT (#8 OR #9 OR #10)	197
Combined total		
14	(#12 OR #13)	301

Inclusion and Exclusion Criteria

Inclusion and Exclusion Criteria for Level 1 (Titles and Abstracts) and Level 2 (Full-Text) Screening

Criteria	Included	Excluded
Population	Studies in adults (aged ≥ 18 years) with CD and/or complex perianal fistulas†	Studies in which most patients (> 50%) have a condition other than CD Studies of patients with CD, but no separate results in the population with complex perianal fistulas
Interventions	No specific drug interventions are the focus of this review; therefore, all interventions, including surgery and drug therapies, are of interest	Studies examining interventions other than drug therapies or surgery
Comparators	All drug comparators and surgery are of interest	None
Outcomes	Burden of complex perianal fistulas in CD Epidemiology of complex perianal fistulas in CD Costs of complex perianal fistulas in CD Treatments and treatment patterns for complex perianal fistulas in CD	Outcomes not related to the burden, epidemiology, costs, or treatments/treatment patterns of complex perianal fistulas in CD

Criteria	Included	Excluded
Study design	Clinical trials Epidemiology studies Economic analyses Utility studies (including studies where utility weights were mapped from other instruments [e.g., disease-specific patient-reported outcome measures]) Prospective studies reporting costs or resource utilisation (e.g., observational studies, clinical trials) Retrospective studies reporting costs or resource utilisation (e.g., cost-of-illness, cross-sectional studies) Health-related quality of life studies	Prognostic studies Genetic studies Diagnostic studies Commentaries Case studies Studies published prior to 2000† Review articles

CD = Crohn's disease; CPF = complex perianal fistula.

† Complex perianal fistulas were generally defined as fistulas with intersphincteric, transsphincteric, suprasphincteric, extrasphincteric, or horseshoe tracts. Rectovaginal fistulas were included as part of definition of CPF in some studies; however, if study was reporting results separately for CPF and rectovaginal fistulas, we focused on results reported for CPF.

Categorisation of Surgical Procedures

Categorisation of Surgical Procedures in Reviewed Studies†,‡

Major surgical procedures	Minor surgical procedures
Myocutaneous flaps and proctocolectomy – a single-stage	Abscess drainage Permanent (indwelling) drainage seton

procedure	Non-cutting seton
Gracilis muscle transposition	Fistula plug and fibrin glue
Over-the-scope-clip proctology	Fistulotomy
Mucosal advancement flap	Partial fistulotomy
Advancement flap closure and seton drain insertion	
Advancement flap repair/Transanal advancement flap	
Ligation of the intersphincteric fistula tract	
Fistula tract transposition	

† Studies were considered to focus on major surgeries if at least one of the treatment arms included a major surgery or if outcomes were reported together for different surgical procedures, at least one of which was a major surgery.

‡ Two studies did not report details of the surgical procedure studies and were thus categorised as "unclear" procedure.

Key Clinical Outcomes for Patients with Complex Perianal Fistulas in Crohn's Disease, by Treatment Type

Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Com plete Resp onse	Partia l Respo nse	Recurr ence/ Reopen ing	Mainte nance of Healin g/ Relaps e/ Respon se (% of Initial Popula tion)	Other Endpoi nts
compression"									
Ardizz one al. (2004)[31] 2004 Italy Prospe ctive	IFX (infusion; mg/kg over 2 hours at weeks 0, 2, and 6) Absence of drainage for 1 month, classific despite gentle finger pressure	6 with CPF (22 s at total) (CPF: accordi ng to Cardiff classific ation of anal CD)	10 week	50%					Tempor ary ileosto my: 1 patient (16.6%)
Alessa ndroni et al. (2011)[32]	IFX, local injections (20-25 repeated every	12 with CPF (refract ory)	12 mos EFU: med, 35	87.5%	62.5%				

								Maintenance of Healing/Response of Other Endpoints	
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definiton)	Time Point	Healing	Response	Partial Response	Reopening	(% of Population)	Other Endpoints
2011 Italy Prospective cohort	weeks until fistula healing) Complete closure of all fistula c tracts, as verified by probe exploration	(CPF: High/c omplex transsp of hincteri c and intrasp hincteri c periana l fistulas)	mos						
Duff et al. (2012)[30]	IFX (initial infusions at 0, 2, and 6 weeks; then NR) CR: complete	(initial 52 with [5 mg/kg] CPF: EFU, with multipl e	CD End of InTr §		42.3%	44.2%			
2012 UK Retrospectiv	weeks; then fistulas CR: complete	EFU, med, over all:				CR: 41% PR: 47.8%	CR: 25% PR: 23%		23 patients with PR:

Maintenance of Healing/Response of Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definitive)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	(% of Population)	Other Endpoints
e (prospectively maintained database)	closure of the fistula with further drainage of gentle finger pressure PR: reduction in half the number, size, drainage of fistulas Relapse: Definition NR included both relapse of	of opening 36.5 or those CR: a 40 mos; on track lying above more than anal sphincter mechanism)	36.5					(calculated)	Defunctioning ileostomy: 3 (5.8%); ileocecal resection: 1 (1.9%); colostomy: 1 (1.9%); subtotal colectomy: 1 (1.9%)

Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Resp onse	Partia l Respo nse	Recurr ence/ Reopen ing	Relaps e/ Respon se	Mainte nance of Healin g/ Respon se of Initial Popula tion)	Other Endpoi nts
---	--	--	---------------	-------------	--------------	--------------------------	----------------------------------	------------------------------	--	------------------------

and

perianal

disease

Treatment outcomes with adalimumab

Echarr i et al. (2010)[74] 2010 Spain Obser vation al study (multi centre, prospe ctive)	ADA (160+80 mg with induction; 40 mg maintenanc e every other week [weekly case of loss of response]) anal sphinct er, has 2 multipl consecutive visits	9 CD 4 week CPF (16 s 24 week s 48 week s the anal opening	44%							
--	--	--	-----	--	--	--	--	--	--	--

Refere	Count	Treatment	Number of Patients (CPF	Time Point	Healing	Response	Complete	Partial	Recurrent	Relapse	Response	Maintenance of Healing
Study	Endpoint	Definition	Definitive	Point	Healing	Response	Complete	Partial	Recurrent	Relapse	Response	Maintenance of Healing
Type	Definition	Definition	Definitive	Point	Healing	Response	Complete	Partial	Recurrent	Relapse	Response	Maintenance of Healing

PR: closure is of > 50% in association with the number of externally draining perianal fistulas or abscess, reduction in and/or drainage of connective tissue fistulas to an abscess, together, adjacent sustained for ≥ 2 visits structure of e) efficacy was defined as the development of abscesses or

Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)		Time Heal Point ing	Com plete Resp onse	Partia l Respo nse	Recurr ence/ Reopen ing	Relaps e/ Respon se	
		(% of Initial Popula tion)	Other Endpoi nts						
	relapse of discharge through existing or new fistula orifices								
Castan o-Mill a et al. (2015)[33] 2015 Spain Retros pectiv e multic entre	ADA (160+80 [93.5% patients] 80+40 [6.5% patients]	38 mg with CPF (46 or total) mg (CPF: Fistulas that are high mg [high maintenanc every hinc week c, high in intrasp loss hinc	6 mos 12 mos		41% 28%	21% 10%			

Refere	Count	Treatment	Number of Patients (CPF	Time Point	Healing	Response	Complete	Partial	Recurrent	Relapse	Maintenance of Healing/Response
Study	Endpoint	Definition	Definiton)	Point	ing	onse	nse	ing	tion)	nts	

of c,
 response]) suprasp
 Healing: hincteri
 absence of c, or
 high-signal extrasp
 tracks on fat hincteri
 saturated T2 c]
 sequences and/or
 PR: have
 reduction in several
 the number external
 of fistula opening
 tracts s
 and/or and/or
 draining are
 cavities associat
 and/or ed with
 reduction in periana
 volume of l
 inflammatio abscess,

								Maintenance of Healing/Response of Other Endpoints	
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	(% of Population)	Other Endpoints
	n of ≥ 10%	rectal stenosis, or macroscopic proctitis)							
Wiese et al. (2015)[28]	ADA 40 mg induction; maintenance every week	20 mg with CPF: rectovaginal fistula, in > 1 of fistula, or abscess present at	CD 24 weeks		EUS: 78%* Ctrl: 27%				
US Rando mised prospective	other [weekly lack/loss of response]) Complete cessation	every week fistula, in > 1 of fistula, or abscess present at	48 weeks		EUS: 88%† Ctrl: 73%				EUS evidence of activity: EUS: 25% ctrl: 27% Ileosto

Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Com plete Resp onse	Partia l Respo nse	Recurr ence/ Reopen ing	Mainte nance of Healin g/ Relaps e/ Respon se (% of Initial Popula tion)	Other Endpoi nts
	drainage	baseline						my: 1	patient
Treatment outcomes with anti-TNF- α (agent not specified)									
Erzin et (2013)[24] 2013 Turke y Retros pectiv e	anti-TNF- α al. Cessation of discharge, and closure of external orifice	39 with CPF (CPF definiti on not provide d)	CD EFU: n, 31 mos		54%			Radiolo gic closure: 10% Ileosto my: 7 patients (18%)	
Erzin et (2014)[25] 2014 Turke	anti-TNF- α al. Complete cessation of discharge or additional closure	51 with CPF (CPF definiti on not	CD EFU: n, 42 mos		53%			Radiolo gic closure: 14% Ileosto my: 14	

Maintenance of Healing/Response of Initial and Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Response	Partial Response	Relapse/Reopening	Percentage of Population	Other Endpoints
Retrospective analysis of the tract assessed by MRI	external orifice and, ultimately, radiological disappearance of the tract	provided, d)							patients (28%)

Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Heal Point ing	Com plete Resp onse	Partia l Respo nse	Relaps e/ Recurr ence/ Reopen ing	Mainte nance of Healin g/ Respon se (% of Initial Popula tion)	Other Endpoi nts
Erzin et (2016)[26] 2016 Turke y Retros pectiv e assess ment of prospe ctively gather ed data (long-t erm follow -up cohort)	anti-TNF- α al. Complete cessation of discharge or additional closure of external orifice and, d) ultimately, radiological disappearan ce of the tract assessed by MRI Relapse: reopening after complete closure	66 with of CPF (CPF definiti on not provide)	CD EFU: n, 48.50 mos	40%		27%		Radiolo gic closure: 24% Stoma: 16 patients (24%)

Maintenance of Healing/Response of Initial Other									
Refere		Numbe			Relaps	Respon			
nce,		r of			e/	se			
Count	Treatment	Patients		Com	Partia	Recurr	(% of		
ry,	and	(CPF		plete	l	ence/	Initial	Other	
Study	Endpoint	Definiti	Time	Heal	Resp	Respo	Reopen	Popula	Endpoi
Type	Definition	on)	Point	ing	onse	nse	ing	tion)	nts
Major surgical interventions in at least one arm									
Schade	Myocutaneo	5	CD	3	100				
n et al.	us flaps and with		mos	%					
(2007)[proctocolect	CPF	Mea			20%	80%		
35]	omy with	(refract	n,				(calcul		
2007	permanent	ory)	20				ated)		
Austri	ileostomy	(CPF	mos						
a	NR	definiti							
Retros		on not							
pectiv		provide							
e case		d)							
cohort									
study									
Maeda	Gracilis	14	CD	Medi	64%				
et al.	muscle	with	an,	(9 of					
(2011)[transpositio	CPF	10	14					
48]	n	(plus	4 mos	pati					
2011	Clinical	with		ents)					
Denm	examination	non-hea	Medi			11%	(1	57%	(8

Maintenance of Healing/Response of Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definiton)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	(% of Population)	Other Endpoints
Mark Retrospectiv e study + teleph one follow -up	by wound inspection, palpation, and absence of collection and/or abscess; Recurrence: NR	ling perineal sinus) (refractory) (CPF definiti on not provide d)	an, 64 mos				of patient s, calcula ted)	9 of 14 patient s, plus 1 additio nal patient from non-he aled group; overall healing rate at media n, 64 mos: 64%)	
Menni gen	OTSC et proctology	6 with	CD Medi an, %	83.3					Inconti nence:

Maintenance of Healing/Response of Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	(% of Population)	Other Endpoints
al. (2015)[49] 2015 Germa ny Retros pectiv e single centre	Complete closure of the external opening, after previous complete closure of the internal opening on single rectoscopy transperineal	CPF of (plus CrGl) after previous fistulas)	231 (5 of 4 days 6 pati ents)					0%	
Gottgens al. (2015)[53] 2015 Nether	Seton + flap injection with platelet-rich plasma no more symptoms,	10 CD Mea n, CPF: 23 mos Fistula involvi ng the		80%			12.5%	70% (calcul ated)	Median postope rative Vaizey score: 8.0, indicati

Maintenance of Healing/Response of Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definitive)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	(% of Initial Population)	Other Endpoints
lands	a	middle							ng
Prospective pilot feasibility study	macroscopically closed upper external fistula opening and drainage during manual compression;	and/or upper one-third of the anal sphincter complex)							moderate-severe e continue nce impair ment (range 0-21) Colostomy: 1 patient (10%)
Recurrence: A new fistula occurring after a symptom-free period									
Chung A.	Fistula 40	CD 12	A: 3						Continue

Maintenance of Healing/Response of Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	(% of Population)	Other Endpoints
et al. (2010)[34]	al. plug glue	with Fibrin CPF (plus 11)	week of 4	75%					ence was not affected in any of the treatment groups
2010 Canad a Retros pectiv e	C. Seton D. Advanceme nt flaps Closure external fistula opening with drainage infection, at 12 weeks postoperati vely (for the seton drain group, as a persistent	with UC) (CPF: High of transsp hincter c fistulas) no or at	B: 0 of 1 (0%) C: 10 of 32 (31.3%) D: 1 of 3 (33.3%)						

								Maintenance of Healing/Response of	
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definitive)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	(% of Initial Population)	Other Endpoints
fistula opening at the seton site but absence of drainage or infection)									
Michelassi et al. (2000)[66]	Surgery (various) Complete healing of anorectal septic complication or successful dilatation of anal stenosis, after	Transanal advancement flaps: 2 CD with CPF; Seton: 21 CD with CPF; (CPF:	Not reported	Transanal advancement men t flaps : 2 of 2 (100 %)					Rectal sparing with seton placement: 20 of 21 (95.2%)

								Maintenance of Healing/Response of Relapse/Response of Recurrence/Reopening/Population/Initial/Other Endpoints	
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Response	Partial Response	Recurrence/Reopening	(% of Population)	Other Endpoints
patient surgical s	intervention	High, suprasphincteric, or rectovaginal fistulas)							
Jarrar and Churc h (2011)[54] 2011 US Retros	Advanceme nt flap NR	19 with CPF and follow-up data (plus 12 CD with	CD Mea n 7 years r	68% 7 (afte first proc edur e); 89% (afte					Ileosto my: 2 patients (10.5%) Inconti nence (before /after surgery

Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Com plete Resp onse	Partia l Respo nse	Recurr ence/ Reopen ing	Relaps e/ Respon se (%) of Initial Popula tion)	Other Endpoi nts	Mainte nance of Healin g/ of
pectiv e, descri ptive study of a consec utive series of patient s		AV and 44 CrGl fistulas) (CPF: Deep transsp hincteri c fistulas, fistulas with extensi ons of the primary track or associat ed abscess, fistulas	r 1-3 proc edur es)); inconti nent gas, 1/0 patients (5.3%/0 %); seeps, 9/6 patients (47.4%/ 31.2%); inconti nent solid, 3/0 patients (15.8%/ 0%)

		Maintenance of Healing/Response of Other Endpoints			Relapse/Reopening			Response of Initial Population	
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Complete Response	Partial Response	Reopening	(% of Initial Population)	Other Endpoints
	without anal pain	Wexner Perianal CD Activity Index and McMaster PCDAI scores)							
Baldin (2016)[36] 2016 Brazil Retrospective	Fistula tract transposition NR	5 with CPF (CPF: extrasphincteric)	CD 5	Median 100% (assumed from continence)			20%	80% (calculated)	Faecal incontinence: 0%
Loffler et al.	Any surgical	79 with	CD 60 mos					54.4%	Proctectomy/

Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Resp onse	Partia l Respo nse	Recurr ence/ Reopen ing	Mainte nance of Healin g/ Respon se (% of Initial Popula tion)	Other Endpoi nts
(2009)[42] 2009 Germa ny Prospe ctive cohort	intervention for CPF minor procedures, 52 major procedures) Patients were	CPF (plus 45 CD with rectova ginal fistulas and 22 CD with simple fistulas) (CPF: the accordi ng to Parks classific ation)						perineal resectio n: 18/79 (22.8%)	
Minor surgical interventions									
Galis-	Permanent	17	CD Medi						Signific

								Maintenance of Healing/
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Complete Response	Partial Response	Relapse/Reopening	Response (% of Initial Population)
Rozen et al. (2010)[52] 2010 Israel Retrospective review of clinical records	seton NR	with CPF (plus 60 months without CD) (CPF: High transsphincteric or suprasphincteric fistula)	an, 24					ant clinical improvement: 59% Incontinence (some degree): 1 patient (5.9%)
Surgical interventions: procedure not specified								
Alessandro et al. (2013)[11]	Surgery (procedure not specified); 58%	210 patients with perianal	72 months					Defunctioning stoma or proctectomy

Maintenance of Healing/Response of Initial Other									
Refere	Count	Treatment	Number of Patients (CPF	Complete	Relapse/	Response	Reopen	Population	Endpoints
nce,	ry,	and	Definiti	Time Heal	Resp	Respo	ing	tion)	nts
Study	Type	Endpoint	on)	Point	ing	nse			
2013	Italy	patients underwent two or more procedures) with Risk of CPF) negative outcome was defined on not as provide defunctioni d) ng stoma or proctectomy	fistulas (181 [86%]						omy: 30%
Combined medical and major surgical interventions in at least one arm									
Roum	IFX	(5 34	CD 14	85%	(CR:				
eguere	mg/kg	with	week	74%)					
et al.	infusions	at CPF	s						
(2011)[weeks	0, 2,	(CPF: 18	84%					Diverti
37]	and	6)	+ accordi	mos					ng
2011	surgery	ng	to						stoma:
France	(reconstruct	criteria							2

Maintenance of Healing/Response of Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definiton)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	(% of Population)	Other Endpoints
Prospective	ive/fibrin glue, fistulotomy, setons) CR: closure of all draining fistulas PR: reduction of $\geq 50\%$ of draining fistulas	by Sandborn et al. (2003)[65])							patients (5.9%)
van der Hagen et al. (2005)[51]	IFX 5 mg/kg; three doses over 6-8 weeks) non-IFX medical	(517 with CPF: Transphincteric,	CD Median, 19 mos	IFX: 100% Non-IFX: 100%			IFX: 10% Non-IFX: 29%	IFX: 90% Non-IFX: 71% (calculated)	Soiling IFX: 10% Non-IFX: 29% Incontinence:

Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Resp onse	Partia l Respo nse	Recurr ence/ Reopen ing	Main tenance of Healin g/ Respon se	
								(% Initial Popula tion)	Other Endpoi nts
Nether lands Prospe ctive	treatment surgery (mucosal advanceme nt flap fistulotomy, with without stoma) NR	+ suprasp hincteri c, intersp or hincteri c, and or extrasp hincteri c fistulas with tracts traversi ng the middle third or upper part of the anal sphinct							0%

									Mainte
									nance
									of
									Healin
									g/
Refere		Numbe						Relaps	Respon
nce,		r of						e/	se
Count	Treatment	Patients		Com	Partia	Recurr	(% of		
ry,	and	(CPF		plete	l	ence/	Initial	Other	
Study	Endpoint	Definiti	Time Heal	Resp	Respo	Reopen	Popula	Endpoi	
Type	Definition	on)	Point ing	onse	nse	ing	tion)	nts	

Complete closure of the fistula track with no further discharge from the opening(s) on the gentle application of finger pressure;
 Recurrence: reopening of a former track or the presence of a new fistula after

										Mainte nance of Healin g/
Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Resp onse	Com plete	Partia l Respo nse	Recurr ence/ Reopen ing	Relaps e/ Respon se (% of Initial Popula tion)	Other Endpoi nts
a primary response										
Guidi et al. (2008)[67] 2008 Italy Prospe ctive case cohort	IFX al. mg/kg weeks and maintenanc e every weeks in the responders) + surgery (partial fistulectomy , abscess drainage, seton) CR: further discharge from	(5 9 at with 0, 2, CPF 6, (CPF: deep 8 involve ment of the anal sphinct ers or extensi of the fistula no above the dentate the line)	CD Mea n, 28 mos		88.9%	11.1%	12.5%	78%	Retreat ment success rate: 100%	

									Mainte nance of Healin g/ Relaps e/ Respon se
Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Resp onse	Partia l Respo nse	Recurr ence/ Reopen ing	(% of Initial Popula tion)	Other Endpoi nts

fistula on

firm finger

pressure

PR:

reduction in

number of

fistulas,

amount of

drainage,

size of

fistulas, or

PDAI score

Recurrence:

NR

Sciaud one al. (2010)[38] 2010	A: IFX et mg/kg weeks and 6, then approximat	(5 35 at with 0, 2, CPF and 6, and High [high	CD Medi an, 19 mos B:	A: 36.4 %† B: 40.0 %†	A: 63.6% † B: 70.0% †	A: 27.3% † B: 20.0% †	A: 42.9%† B: 42.9%† C: 18.2%†	A: 36.4%† B: 40.0%† C: 64.3%†	Proctect omy with a termina l colosto
--	---	--	-----------------------------------	--------------------------------	--------------------------------	--------------------------------	-------------------------------------	-------------------------------------	--

								Mainte
								nance
								of
								Healin
								g/
Refere	Numbe			Relaps			Respon	
nce,	r of			e/			se	
Count	Treatment	Patients		Com	Partia	Recurr	(% of	
ry,	and	(CPF		plete	l	ence/	Initial	
Study	Endpoint	Definiti	Time	Heal	Resp	Respo	Reopen	
Type	Definition	on)	Point	ing	onse	nse	ing	
Italy	ely every 8 intersp			C:	C:	C:		
Prospe	weeks in the hincteri			64.3	78.6%	14.3%		
ctive	responders c, high			%†	†	†		
	[at least transsp			(calc				
	partial hincteri			ulat				
	response]) c,			ed)				
	(n = 11 suprasp							
	patients) hincteri							
	B: Surgery c, or							
	(draining extrasp							
	seton) (n = hincteri							
	10 patients) c] with							
	C: IFX + either							
	surgery (n = multipl							
	14 patients) e							
	CR: closure external							
	of all opening							
	external s							
	openings associat							
	and ed with							

Maintenance of Healing/Response of Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definiton)	Time Point	Healing	Response	Partial Response	Recurrence/Reopening	(% of Population)	Other Endpoints
et al. (2016)[68]	(induction dosing maintenance 40 mg every other week) surgery (loose seton) Fistula Drainage Assessment Index	with mos NR; CPF (CPF definiti on + provide d)							4 patients (6.9%)
Solina et al. (2011)[69]	Medical treatment (including IFX ADA; dosing + Surgery	31 CD Mea n, 22 CPF (40 mos or total) (CPF: NR) Inter-sp hincteri		After seton remo val: 14 of 16 (87.5		2 of 14 12 responders (14.3%)		16 (75%) (calculated)	of Ileosto my: 2 patients (6.5%)

Maintenance of Healing/Response of Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	(% of Initial Population)	Other Endpoints
Active	(partial fistulectomy / fistulotomy and loose seton drainage) NR	c fistulas, transsp hincteri c fistulas, or periana l abscesses)		%); the other s under went ileostomy					
Antaki et al. (2013)[39]	IFX 5 mg/kg at 0, 2, and 6 weeks; maintenanc	48 at 0, with 6 CPF (CPF: Multip	CD Medi an, 20 mos		29%	42%	25%	45.8% (calcul ated)	Proctect omy: 6.3%
UK Retrospectiv e	e not e mentioned) + seton Fistula	not e external opening s or had							

								Maintenance of Healing/Response of Other Endpoints	
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Response	Partial Response	Reopening	(% of Population)	Other Endpoints
analyses of consecutive operative series of patient series of	Drainage Assessment endpoints CR, PR, or no response	tracts extending proximally beyond the lower half of the anal sphincter mechanism)							
Talbot et al. (2005)[40]	IFX 5 mg/kg at 0, 2, and 6 weeks; maintenance	21 CPF (CPF: not with	CD Median, 20 mos		47%	53%		CR: 0% PR: not clear	

Maintenance of Healing/Response of Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	(% of Initial Population)	Other Endpoints
2005 US Retrospective	week and (seton, incision, and drainage) (treatment choice guided by EUS) Fistula Drainage Assessment criteria	Fistula that + involve s more of the anal sphincters [i.e., high h by transsp hincteri c, extrasp hincteri c), has multipl		vaginal: 66.7% Horse shoe: 42.9%					Transsp hincteri c: 75% Rectovaginal: 33.3% Horses hoe: 14.3%

								Maintenance of Healing/Response	
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Response	Partial Response	Reopening	(% of Initial Population)	Other Endpoints
connect s to an adjacent structure e such as the vagina or bladder)									
Schwartz et al. (2015) [70]	A: certolizumab pegol (400 mg at weeks 0, 2, and 4 (CPF and then 400 mg every 4 wks)	18 CD 52 with CPF (21 s	week	Any fistula:	A: 50%				
2015 US Multicenter					B: 55%†				

Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Resp onse	Partia l Respo nse	Recurr ence/ Reopen ing	Mainte nance of Healin g/ Respon se (% of Initial Popula tion)	Other Endpoi nts
---	--	--	---------------	-------------	--------------	--------------------------	----------------------------------	--	------------------------

prospe seton

ctive B:

rando certolizuma

mised b pegol only

study (as above)

Fistula

Drainage

Assessment

criteria

Reguei A: IFX (at 20 CD With

ro and least three with in 3

Mardi infusions; 5 CPF (32 mos

ni mg/kg at total) from

(2003)[weeks 0, 2, (CPF: 3rd

41] and 6) + Multipl IFX

2003 EUA with e infus

US seton (n = 6 external ion

Retros patients) opening 2

pectiv B: IFX only s, years

e (n = 14 involve

A:

100%

*

B:

71.5%

Diverti

ng

colosto

my: 1

patient

(5%)

Recurr

ence

rate:

								Maintenance of Healing/Response of Other Endpoints	
Referee	Count	Treatment and Endpoint Definition	Number of Patients (CPF Definitive)	Time Point	Healing Response	Complete Response	Partial Response	Recurrence/Reopening	Response (%) Initial Population)
		patients)	ment of					A: 50%	
		Complete closure and cessation of drainage from the fistula based on history and physical examination ;	the anal sphincter or extensi on of the track above the dentate line; a					B: 100% (P = 0.036)	
		Recurrence: simple reopening of external fistula with drainage noted	simple fistula the was single track and active in-ano)					Mean time to recurrence: A: 13 mos B: 2.1 mos (P = 0.001)	

Maintenance of Healing/Response of Initial and Other Endpoints									
Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Com plete Resp onse	Partia l Respo nse	Recurr ence/ Reopen ing	(% of Initial Popula tion)	Other Endpoi nts
history and examination									
Spradl in al. (2008) 71] 2008 US Prospe ctive rando mised study	IFX et mg/kg at 0, with 2, and 6 weeks, then every 8 weeks until week 54) + AGA surgery (seton, incision and drainage) (treatment guided or not by EUS) Fistula Drainage Assessment criteria	(5 10 CD 54 with CPF s (CPF: accordi ng to AGA classific ation)			EUS: 80%‡ Ctrl: 20%‡			Stoma: 0 patients	

Maintenance of Healing/Response of Initial and Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definiton)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	(% of Population)	Other Endpoints
Kim et al. (2011)[43] 2011 Repub lic Korea Retros pectiv e (prosp ective enroll ment), among single-centre study	Medical (no anti-TNF) +/- surgery (fistulotomy and/or seton of drainage) Fistula Drainage Assessment criteria; Recurrence: redevelopment of fistula (ment), among patients with initial response	85 with CPF (CPF definiton) not provide d)	CD 3 mos	Comb ined: 68% (34/50) Medi cal: 40.9% (9/22) Surge ry: 38.5% (5/13)					Any treatm ent: 45.7% (22/48)

Maintenance of Healing/Response of Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF)	Definitive Point	Time Healing	Complete Response	Partial Response	Relapse/Reopening	Response (%) Initial Population	Other Endpoints
Combined medical and surgical interventions (surgery type not specified)									
Lauret i et al. (2012)[72]	ADA (dosing mg every days) surgery	33 CD 40 with 15 CPF + (CPF definiti	Medi an, 9 inject ions		40%				Failure of the proced ure: 24%
Italy Prospe ctive	(type NR reported)	not on provide d)	not Medi an, 11 mos		40%		0%		
Stem cell therapies									
Panes et al. (2016)[3]	Darvadstrocel (Cx601) vs. placebo added to standard of care	212 CD 24 week s			Darvadstrocel: 53%†	Darvadstrocel: 66%†			Combin ed clinical and radiolo gical remissi on (ITT populat
Multin ational Phase 3	Combined remission: clinical	(CPF: 1 or more of the followi			bo: 41%	bo: 53%			

Study	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Complete Response	Partial Response	Reurrence/Reopening	Response (%) of Initial Population)	Other Endpoints
randomised, double-blind, control led trial	assessment of closure of all treated external openings that were draining at baseline and c, absence of extrasp collections > 2 cm of the c, or treated suprasp perianal hincteri fistulas in ≥ c origin; 2 of 3 at least dimensions, two confirmed external by masked opening central MRI s; or Clinical associat	ng:							ion, primary endpoi nt) Darvad stroccl: 50%* Placebo : 34%

Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Resp onse	Com plete	Partia l Respo nse	Recurr ence/ Reopen ing	Relaps e/ Respon se (% of Initial Popula tion)	Other Endpoi nts	Mainte nance of Healin g/ g/

remission: ed
closure of collecti
all treated ons.
external The
openings fistulas
that were had to
draining at have a
baseline maxim
despite um of
gentle two
finger internal
compressio and
n three
Response: external
closure of \geq opening
50% of all s and
treated had to
external have
openings been
that were drainin

Study	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Complete Response	Partial Response	Reurrence/Reopening	Response (%) of Initial Population)	Other Endpoints
de la Torre et al. (2013)	drainage at baseline, week 24	at least 6 weeks before inclusion)							
Portillo et al. (2013)	Combined assessment of fistula closure: absence of suppuration, complete re-epithelialisation, MRI absence of collections > 2 cm	24 weeks with CPF (persistent) (CPF definitively not provided)	CD 24 weeks	56.3%	Response rate (reduction in the number of draining fistulas): 69.2%				Combined ed fistula closure: 30%

Maintenance of Healing/Response of Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definiton)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	(% of Population)	Other Endpoints
Guadalupe et al. (2012)[27]	A: eASCs + fibrin glue B: eASCs + fibrin glue Long-term efficacy assessed using clinical MRI of the treated fistula of (recurrence or not) phase 2 study	+ 34 with CPF (CPF definiton not provide d) n, 42.6 mos	CD A: mean, 38.0 mos					A: 58.3% (7 of 12 patient s) B: 66.7% (2 of 3 patient s)	Incontinence:
Garcia-Olmo	A: eASCs + fibrin glue	+ 14 with	CD 8 week	A: 71%			NR separat		Incontinence:

Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Resp onse	Com plete	Partia l Respo nse	Relaps e/ Recurr ence/ Reopen ing	Mainte nance of Healin g/ Respon se (% of Initial Popula tion)	Other Endpoi nts
et al. (2009) 46] 2009 Spain Rando mised, multic entre, active- control led, open-l abel, add-o n phase 2 study	B: fibrin glue Proportion of patients whose CrGl fistula had origin at 8 weeks after least the last one of the treatment the control received followi ng conditio ns was fulfilled : (1) fistula tract under the	CPF (plus 35 after B: 16% of treat ment	s †					ely for CD	0%	

Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Resp onse	Partia l Respo nse	Recurr ence/ Reopen ing	Relaps e/ Respon se	Mainte nance of Healin g/ Respon se	Other Endpoi nts
---	--	--	---------------	-------------	--------------	-----------------------------	----------------------------------	------------------------------	---	------------------------

periana
l skin
unident
ifiable
in the
physica
l
examin
ation;
(2)
fistula
tract
parallel
to the
rectum
when
examin
ed with
a probe;
(3)

								Maintenance of Healing/Response of Other Endpoints	
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Response	Partial Response	Reopening	(% of Population)	Other Endpoints
<p>tomy or advancement flap); (5) suprasphincterian tracts; (6) presence of CD; or (7) rectovaginal fistula)</p>									
Usual care									
Bell et al. (2003)[15]	Usual care (medical [excluding anti-TNF- α]	approx. 79 CPF	Median, 2.3 years	70%		23%			Retreatment success rate:

								Mainte nance of Healin g/ Relaps e/ Respon se	
Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Resp onse	Partia l Respo nse	Recurr ence/ Reopen ing	(% of Initial Popula tion)	Other Endpoi nts
2003 UK Retros pectiv e analysi s of prospe ctively collect ed databa se	and surgery (calcula [including complex surgeries such as resection, a defunctioni ng stoma, periana lly proctectomy]) (CPF: Healing: no Transsp discharge hincteri on history c, or suprasp examination hincteri , with c, or healing of extrasp external hincteri opening; c) Relapse:	(total: 169, 80% comple x; 65% periana lly (CPF: no Transsp hincteri c, suprasp hincteri c, or extrasp hincteri c)						57%	

Maintenance of Healing/Response									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	(% of Initial Population)	Other Endpoints
recurrence after initial healing									
Molendijk et al. (2014)[13]	Usual care (medical [including anti-TNF-α and surgery]	181 with CPF (232 total)	CD Median, 10 years	64.6%	81.3%	41.9%	Remission: 37.0%		
2014 Netherlands Retrospective	[colectomy, fistulectomy, stoma, and rectum amputation]	(CPF: CPF defined according to criteria by Sandborn et al. (2003)[6])							
Response: decrease of discharge, pain, bleeding from the									

									Mainte nance of Healin g/ Relaps e/ Respon se (% of Initial Other Popula tion) Endpoi nts
Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Resp onse	Partia l Respo nse	Recurr ence/ Reopen ing		

fistula tract;
 Remission:
 absence of
 an external
 opening
 without
 discharge
 on history
 and
 physical
 examination
 ; Relapse:
 recurred
 discharge
 on history
 and
 physical
 examination
 with
 reopening

Maintenance of Healing/Response of Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Response	Complete Response	Partial Response	Reurrence/Reopening	Percentage of Initial Population
of the previous external opening and/or formation of new perianal fistulas after initial remission									
Lozynsky (2009)[47] 2009 Ukraine Design not	Usual (medical care [excluding anti-TNF- α] and surgery [transanal advancement flap and seton])	15 with CPF (total: 144 with perianal and 1 complic	CD NR	Transanal advancement with flap: 5 of					Incontinence Transanal advancement flap: 3 of 11 (27%)

Refere nce, Count ry, Study Type	Treatment and Endpoint Definition	Numbe r of Patients (CPF Definiti on)	Time Point	Heal ing	Com plete	Partia l	Recurr ence/ Reopen ing	Relaps e/ Respon se	Mainte nance of Healin g/ Respon se	Other Endpoi nts
report ed; appear s to be a retros pectiv e analysi s	NR	ations, 30 simple fistulas, 7 rectova ginal fistulas) (CPF: Supra-, trans-, and extrasp hincteri c comple x fistulas)	11 (45%) Seto n: 2 of 4 (50%)							Seton: 0% Proctect omy Transan al advanc ement flap: 2 (18%) Seton: 2 of 4 (50%)
Arbera	Usual	care ~250	NR		Antib	Antib	Any			

Maintenance of Healing/Response of Other Endpoints									
Reference, Count, Study Type	Treatment and Endpoint Definition	Number of Patients (CPF Definition)	Time Point	Healing	Complete Response	Partial Response	Recurrence/Reopening	Percentage of Initial Population	Other Endpoints
s-Diez et al. (2013)[18] 2013 Spain Retrospective	(medical anti-TNF- α and surgery [fistulotomy with , setons and other – detailed NR])	CD with CPF (313 CD)			iotics: 37% Thiopurine s: 32% Surge ry: 50% Any fistula a: anti-TNF- α : 63%	iotics: NR Thiopurine s: NR Surge ry: NR Any fistula a: anti-TNF- α : 29%	fistula: Antibiotics: 66% Thiopurines: 46% Surger y: 51% anti-TNF- α : 36% TNF- α :		

ADA = adalimumab; AV = anovaginal; CD = Crohn's disease; CPD = complex perianal disease; CPF = complex perianal fistula; CR = complete response; CrGl = cryptoglandular; eASC = expanded allogeneic adipose-derived stem cells; EFU = end of follow-up; EUA = examination under anaesthesia; EUS =

endoscopic ultrasound; IFX = infliximab; ITT = intention-to-treat; LIFT = ligation of the intersphincteric fistula tract; mos = months; MRI = magnetic resonance imaging; NR = not reported; OTSC = over-the-scope clip; PCDAI = Pediatric Crohn's Disease Activity Index; PDAI = Perianal Disease Activity Index; PR = partial response; TNF- α = tumour necrosis factor alpha; UC = ulcerative colitis; UK = United Kingdom; US = United States.

* $P < 0.05$.

† Not statistically different.

‡ The need for additional surgery was defined as a treatment failure.

§ The patients received initial infusions of infliximab (5 mg/kg) at 0, 2 and 6 weeks, with removal of their seton sutures planned after their second infusion of infliximab. The clinical response was documented at subsequent outpatient visits and classified as being either complete, partial or no response.

|| The number of patients who had perianal fistulas or CPF was not reported. A total of 87 patients with CD and active fistulas were enrolled; 34 patients (39%) had a single fistula, 24 (28%) had two fistulas, and 29 (33%) had three or more fistulas during the course of their disease, yielding a total number of fistulas of 169, of which 110 were perianal fistulas (79 complex perianal and 31 simple perianal fistulas).