NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Darvadstrocel for treating perianal fistula in Crohn's disease [ID960]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Darvadstrocel for treating perianal fistula in Crohn's disease [ID960]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Darvadstrocel for treating complex perianal fistula in Crohn's disease [ID960]
Pre-meeting briefing

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

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- with input from the Lead Team (Paul Robinson, Brian Shine and Pamela Mary Rees)

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Clinical effectiveness

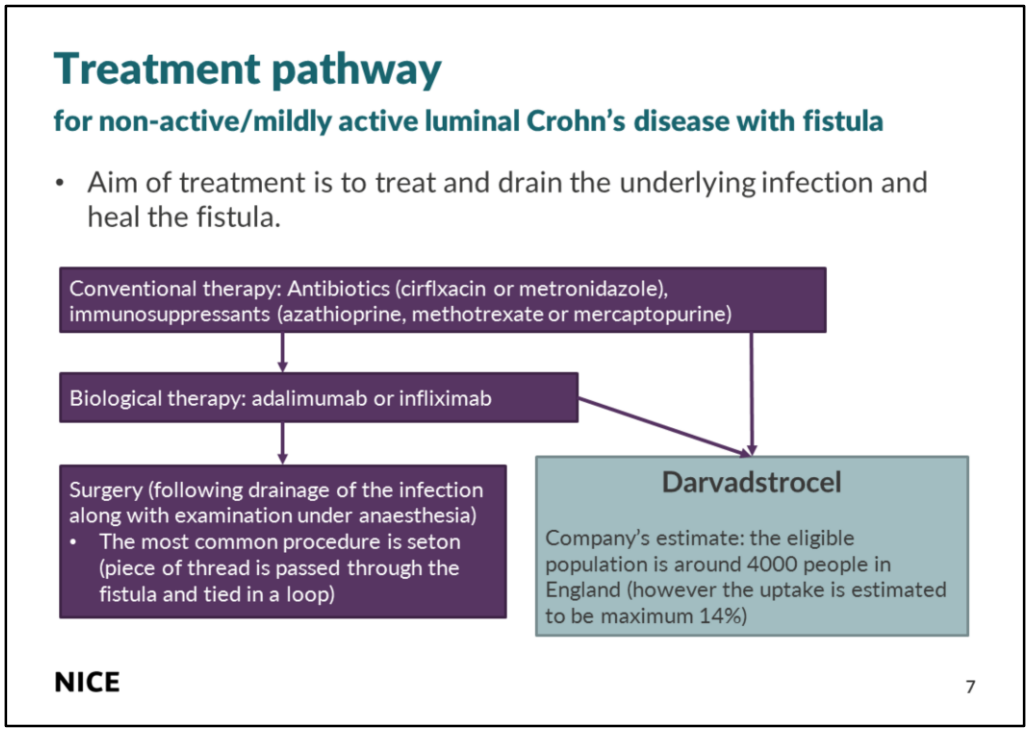
Key issues: clinical effectiveness

- Population not included in evidence base:
- people with more than two internal openings or more than thee external openings are excluded from the analyses by the company
- people with second administration at recurrence are excluded - no clinical trial evidence to support second administration
- Which patients would be eligible for darvadstrocel? How would they be defined in clinical practice? Would it be used after biologic therapy has failed?
- Generalisability to UK population- ADMIRE-CD trial did not include patients from the UK
- Are the comparators presented in the submission routinely given in UK clinical practice?
- Does the clinical trial evidence suggests that darvadstrocel is clinically effective compared with standard of care? In the model, post hoc analysis using an endpoint that was not the primary endpoint of the trial is used. Is it clinically effective at time to clinical and patient-centric (CPC) remission and relapse?
- Long-term safety/efficacy of darvadstrocel? Robust data beyond 52 weeks is limited, because of a protocol change at this point in the ADMIRE-CD trial.

Disease background

Crohn's disease with complex perianal fistula

- Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract (gut) that may affect any part of the gut from the mouth to the anus
- Inflammation of the gut can lead to tissue damage and ulceration. A complication of such tissue damage is the development of fistula
- A perianal fistula is an abnormal connection that develops between the bowel and the skin near the anus. The symptoms of perianal fistula include skin irritation around the anus, pain, passing of blood or pus when having a bowel movement and leakage of faecal matter. Fistulae are described as simple or complex depending on the location and whether there is a singular fistula tract or interlinking connections
- Faecal incontinence is also common, and is associated with high risk of septicaemia (blood-poisoning)
- Approximately 20% of people with Crohn's disease will develop a perianal fistula, and 30% of these people have recurrent fistulae
- High unmet need: Only a third of patients will have long lasting remission and only a small percentage of fistulae are permanently healed



Interventional procedures guidance 410 recommends that there are no major safety concerns with using a suturable biosynthetic plug to block the internal opening of the fistula. However, data on the efficacy of this procedure is limited and the guidance states that the procedure should only be used with special arrangements for clinical governance, consent and audit or research.

In ADMIRE-CD (the key clinical evidence) approx. 80% of people had biological therapy prior to darvadstrocel.
78% on the darvadstrocel arm and 80% on the control arm.

Surgical treatment of complex perianal fistulae has a recurrence rate of 25-50% (Yassin, APT 2014;40:741)

Decision problem (I)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adult with non-active/mildly active luminal Crohn's disease, with complex perianal fistulae which have shown an inadequate response to at least one conventional or biologic therapy		NA
Intervention	Darvadstrocel		NA
Comparator	Surgical management without darvadstrocel	Treatment consists of surgical treatment including examination under anaesthesia (EUA) and seton placement, as this correlates with the current standard of care in the UK, and was also used as the control arm for the ADMIRE-CD trial.	Fistulotomy, advancement flap procedures, insertion of biosynthetic plugs and fibrin glue are not commonly used in UK practice. ERG comments: agrees with the list of comparators presented in the submission

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Comment from company: A retrospective study in a tertiary hospital in London, and clinical opinion from a UK KOL Ad Board, indicated that EUA and seton placement were the most common surgical treatments.

Decision Problem (II)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	• Closure of fistula • Recurrence of fistula • Continence • Mortality • Adverse effects (AEs) of treatment • Health-related quality of life (HRQoL)	• Clinical and Patient Centred (CPC) remission • Combined remission • Clinical remission • AEs of treatment • HRQoL *For more details on the definition of outcomes in ADMIRE-CD trial see slide 18.*	Clinical outcomes presented as per ADMIRE-CD clinical trial. **ERG comments**: Continence is not reported in the submission. Clinical advisers stated that it is unlikely to differ between the two arms.

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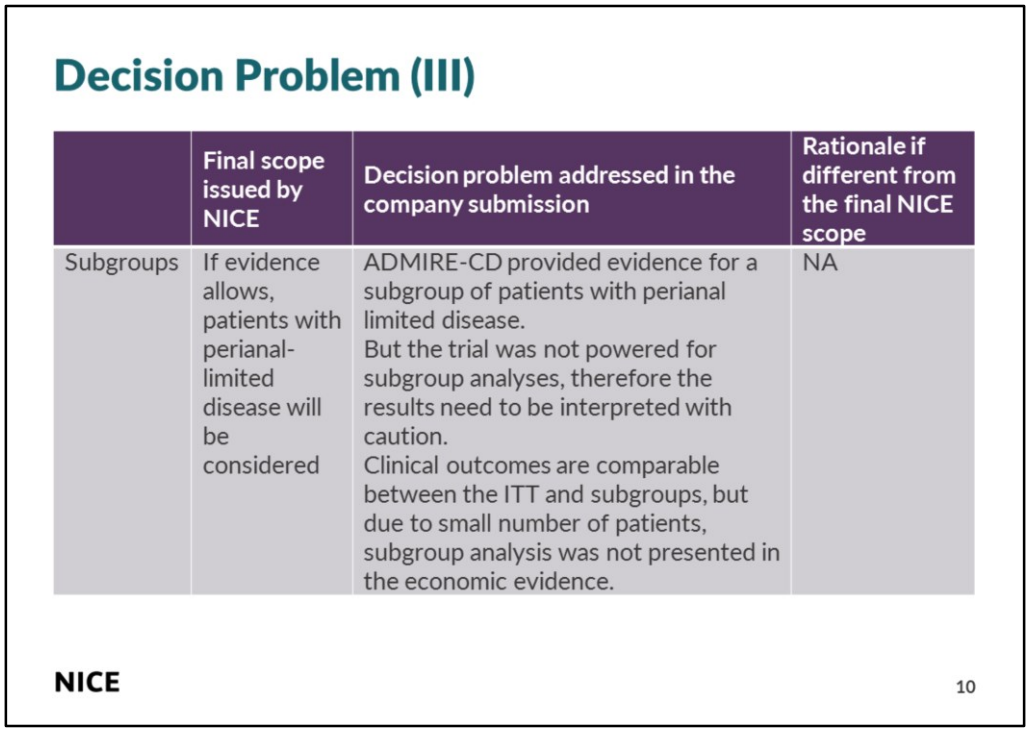
Faecal incontinence was missing from the company submission, because clinical experts were unable to identify adequately the required resource use, quality of life impact on patients and the clinical course of incontinence in fistulising disease. Therefore faecal incontinence was not included in the model by the company.

See also clarification response A3 on outcomes and section 3.4 of ERG report.



Decision Problem (III)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups	If evidence allows, patients with perianal-limited disease will be considered	ADMIRE-CD provided evidence for a subgroup of patients with perianal limited disease. But the trial was not powered for subgroup analyses, therefore the results need to be interpreted with caution. Clinical outcomes are comparable between the ITT and subgroups, but due to small number of patients, subgroup analysis was not presented in the economic evidence.	NA

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See section B.2.7 of CS and Figure 13.

Comments from the company: The patient group who have perianal limited disease may not have received nor be appropriate for biological treatment. Restricting darvadstrocel treatment to patients who have failed biological treatment might prevent these patients from adequate and timely treatment with darvadstrocel.

Technology darvadstrocel

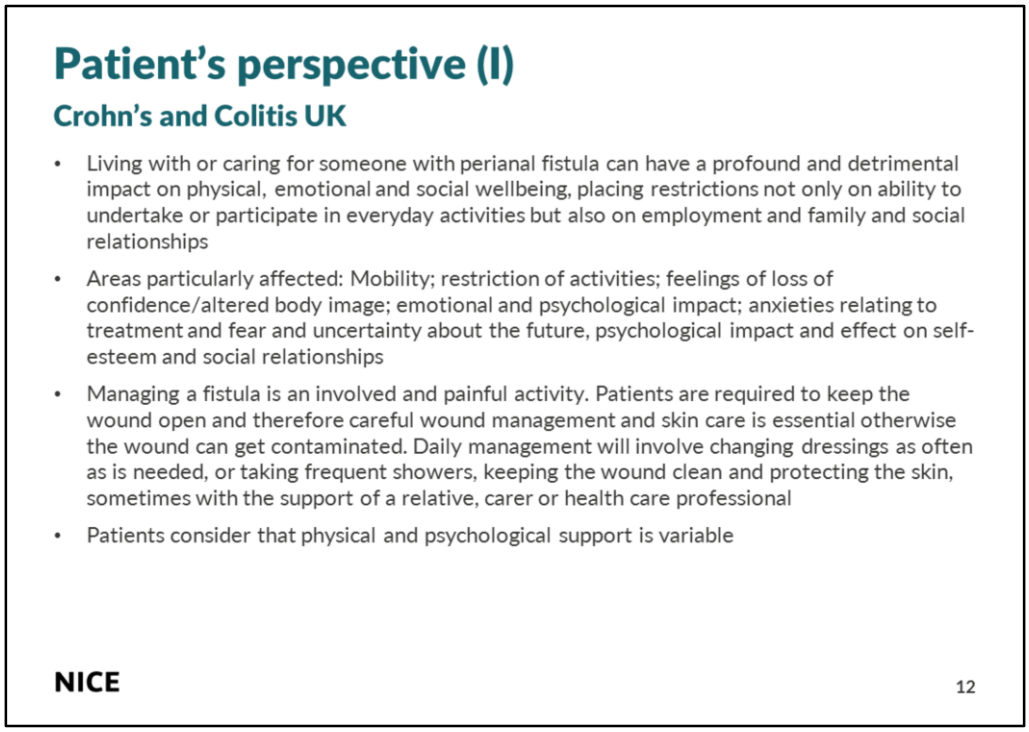
UK approved name	Darvadstrocel (Brand name: Alofisel)
Mechanism of action	Darvadstrocel is a suspension of expanded human adipose-derived stem cells of allogeneic origin. These stem cells have the potential to regulate the function of immune-cells including B lymphocytes, T-lymphocytes, NK cells, monocyte-derived dendritic cells and neutrophils resulting in local immunosuppression.
Marketing authorisation	Alofisel was granted EMA approval on 23rd March 2018. Indicated for the treatment of complex perianal fistulae in adult patients with non-active/mildly active luminal CD, when fistulae have shown an inadequate response to at least one conventional or biologic therapy. Darvadstrocel should be used after conditioning of the fistula.
Method of administration and dosage	The content of two vials (60 million cells) is injected into the fistula walls along the length of the fistula tract and two vials (60 million cells) injected around the internal opening during an examination under anaesthesia (EUA). Darvadstrocel will be added to current standard of care treatments as an additional procedure.
List price and average cost of a course of treatment	£13,500 per vial, £54,000 for one course of treatment A simple PAS has been approved by the Department of Health which provides a discount for one course of treatment.

Abbreviations: CD, Crohn's disease; NK, Natural Killer; PAS, Patient Access Scheme; SmPC, Summary of Product Characteristics; UK, United Kingdom

EPAR section 2.5.3

'There is insufficient data available on the effect and safety of repeated Alofisel administrations, whereas the need for additional treatment may be anticipated in a portion of the targeted population'

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004258/WC500246476.pdf



The patient organisation generated evidence through: social media channels and healthcare professionals and researchers. They have heard directly from patients and carers who have personal experience of living with or caring for someone living with perianal fistulising Crohn's disease.

Patient's perspective(II)

Crohn's and Colitis UK

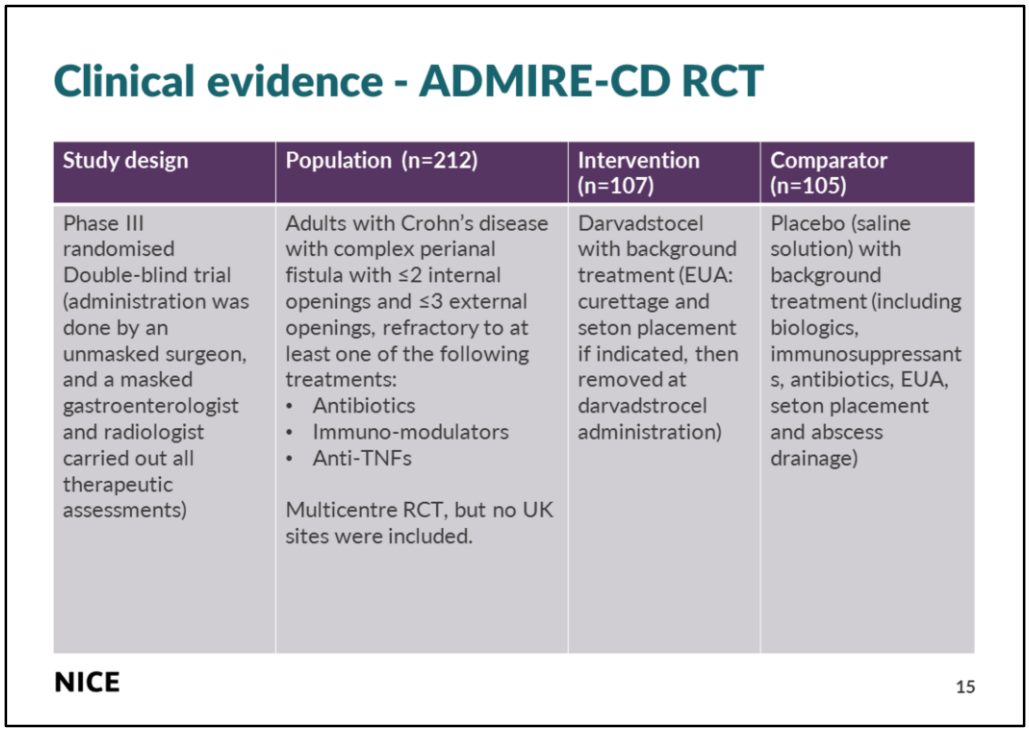
- Negative impact on sexual life, fewer pregnancies which puts additional burden on women in childbearing age
- Formation of a stoma does not guarantee that fistulae will not reoccur
- In summary, effective treatment options for perianal fistula are limited and suboptimal

- Treatment with darvadstrocel: would be welcomed by those who cannot tolerate or have found current drug treatments ineffective or wish to delay or avoid surgery
- Some patients may object to the use of stem cells
- If only available in limited centres, this might restrict access for some patients that could benefit

Clinical expert submissions

British Society of Gastroenterology and Royal College of Physicians

- Besides healing of the fistula tract, preventing discharge and abscess formation, darvadstrocel could also prevent recurrence, either in the same tract or formation of new tracts
- From the patient's point of view, most important endpoint is long-term remission rate (i.e. 1 year or longer)
- Treatment may be less effective in people with active proctitis
- Darvadstrocel requires a specific surgical treatment under anaesthetic to curette the fistulae tracts, and insert setons. A second anaesthetic is required at least 2 weeks later to ligate the internal fistulae opening and inject the stem cells. Currently treatments do not involve 2 EUA procedures. The second EUA has to be coordinated with delivery of the stem cell treatment to the hospital as it has a short shelf-life of about 24-48 hrs
- Would be used in specialist hospitals with surgical and medical experience of treating perianal Crohn's disease, because the procedure requires expertise from the surgeon. Additional training for colorectal surgeons might also be required
- Generalisability of ADMIRE-CD trial:
  - reflects UK clinical practice, although second EUA will need to be introduced together with darvadstrocel
  - in real life, remission rates for the placebo group would be lower, than in the study.



Clinical evidence - ADMIRE-CD RCT

Study design	Population (n=212)	Intervention (n=107)	Comparator (n=105)
Phase III randomised Double-blind trial (administration was done by an unmasked surgeon, and a masked gastroenterologist and radiologist carried out all therapeutic assessments)	Adults with Crohn's disease with complex perianal fistula with ≤2 internal openings and ≤3 external openings, refractory to at least one of the following treatments: • Antibiotics • Immuno-modulators • Anti-TNFs Multicentre RCT, but no UK sites were included.	Darvadstocel with background treatment (EUA: curettage and seton placement if indicated, then removed at darvadstrocel administration)	Placebo (saline solution) with background treatment (including biologics, immunosuppressants, antibiotics, EUA, seton placement and abscess drainage)

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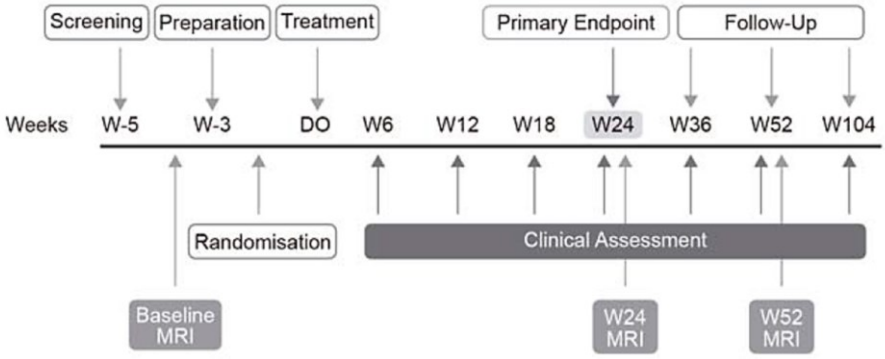
See section B.2.3 of CS

Definition of non-active or mildly active luminal Crohn's disease:

Crohn's Disease Activity Index (CDAI) ≤ 220, diagnosed at least 6 months earlier in accordance with accepted clinical, endoscopic, histological and/or radiological criteria

ADMIRE-CD trial was not performed in the UK, but company states that patients included were similar to those seen in UK clinical practice

Trial schema of ADMIRE-CD



Source: figure 7 of company submission

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Also see figure 1 of ERG report

Outcomes in ADMIRE-CD trial

- Primary endpoint
- Combined remission at week 24 (clinical remission* and MRI assessment)
- *clinical assessment of closure of all treated external openings that were draining at baseline, and the absence of collections > 2 cm of the treated perianal fistula in at least two of three dimensions, confirmed by masked central magnetic resonance imaging. Clinical assessment of closure: absence of draining despite gentle finger compression
- Post hoc analyses of outcomes
- Based on feedback from clinicians, the most relevant clinical outcome to patients with CD with perianal fistulae should include a component of pain and discharge in addition to clinical remission
- Time to clinical and patient-centric (CPC) remission (clinical remission and the patient does not experience any pain or discharge, as determined by a score equal to 0 in both the pain and discharge dimensions of the PDAI; no MRI assessment was included)
- Time to CPC relapse (time to relapse from CPC remission)

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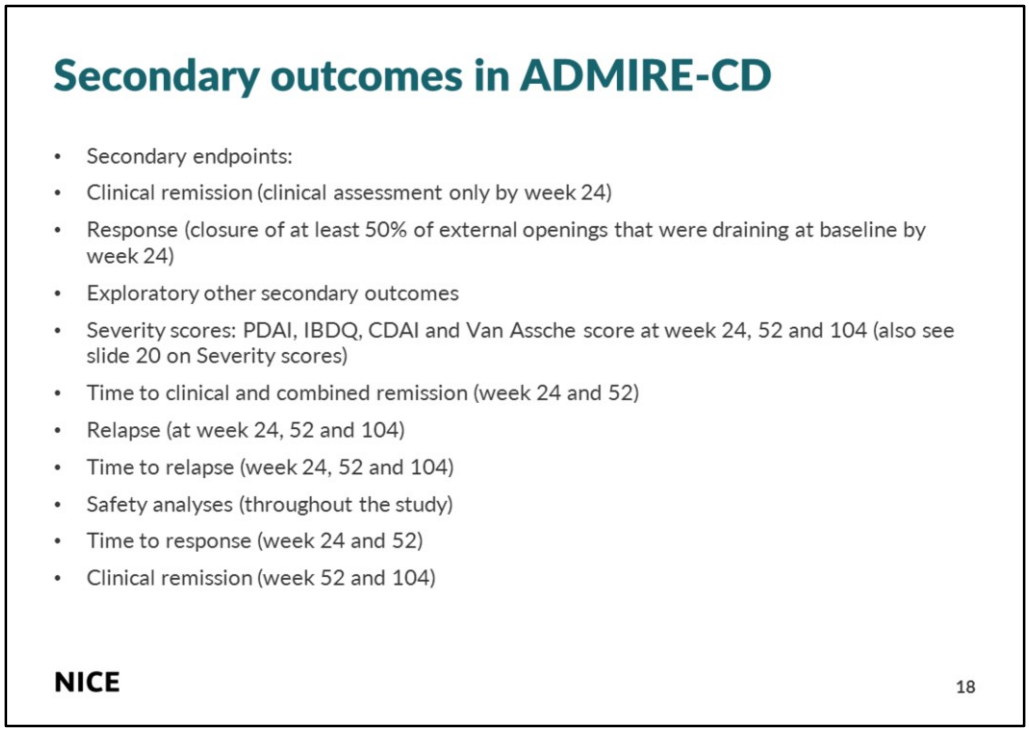

PDAI (Perianal Disease Activity Index)

IBDQ (Inflammatory Bowel Disease Questionnaire)

CDAI (Crohn's Disease Activity Index)

Van Assche score (MRI based score in assessing the disease activity and severity in Crohn's disease)

A short description of these scoring instruments is presented in Appendix D.1.4.

Van Assche Score focus on local perianal fistulising disease activity, the CDAI focuses on luminal CD severity. The only patient reported outcome instrument included was the IBDQ .

Severity scores

	IBDQ	CDAI	PDAI	Van Assche Score
Disease	CD	CD	Perianal Disease	Perianal Disease
Overview	Interview administered questionnaire	Patient 7-day diary	Investigator assessed	MRI-based score of perianal CD severity
Components	• Bowel symptoms • Systemic symptoms • Emotional function • Social functions Each question is rated on a 7-point Likert score from worst symptoms (score of 1) to no symptoms (score of 7)	• Liquid stools • Abdominal pain • General wellbeing • Presence of complications • Anti-diarrhoeals • Presence abdominal mass • Hct or PCV • Percentage deviation from standard weight	• Discharge • Pain/restriction of activities • Restriction of sexual activity • Type of perianal disease • Degree of induration Each category is graded on a 5-point Liket scale ranging from no symptoms (score of 0) to severe symptoms (score of 4)	• Number of fistula tracks score • Location score • Extension score • Hyperintensity on T-2 weighted images score • Collections (cavities >3 mm diameter) score • rectal wall involvement score
Range	Range from 32 to 224. Higher score indicates better wellbeing.	Range is from 0 to approx. 600. Higher score means more active/severe disease. <150: remission >450: severe disease	Range 0-20. Higher score means more severe disease.	Range from 0 to 24. Higher score means more severe disease Total score = the sum of the individual domain scores.

Abbreviations: CDAI, Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; Hct, Haematocrit; PCV, Packed cell volume; PDAI, Perianal Disease Activity Index

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Company submission appendix D.1.4.

ERG comment on outcomes

- The study was not powered to test changes in CPC remission and CPC relapse, but these outcomes were used to model relative treatment effect of darvadstrocel
- Both the company's and the ERG's clinical experts considered CPC remission the most relevant way to measure remission and relapse in people with non-active or mildly active luminal Crohn's disease with complex perianal fistula, that did not respond to conventional and/or biological therapy
- There is scarcity of historical evidence to externally validate the results
- The available efficacy data beyond 52 weeks were limited because a protocol change occurred in ADMIRE-CD when various patients had already finished the 52 week trial period. The CS states '...This resulted in a low level of patient data, and so generalisation of results beyond 52 weeks is difficult and should be approached with care'. As a result, there is uncertainty regarding the long-term efficacy and safety of darvadstrocel.

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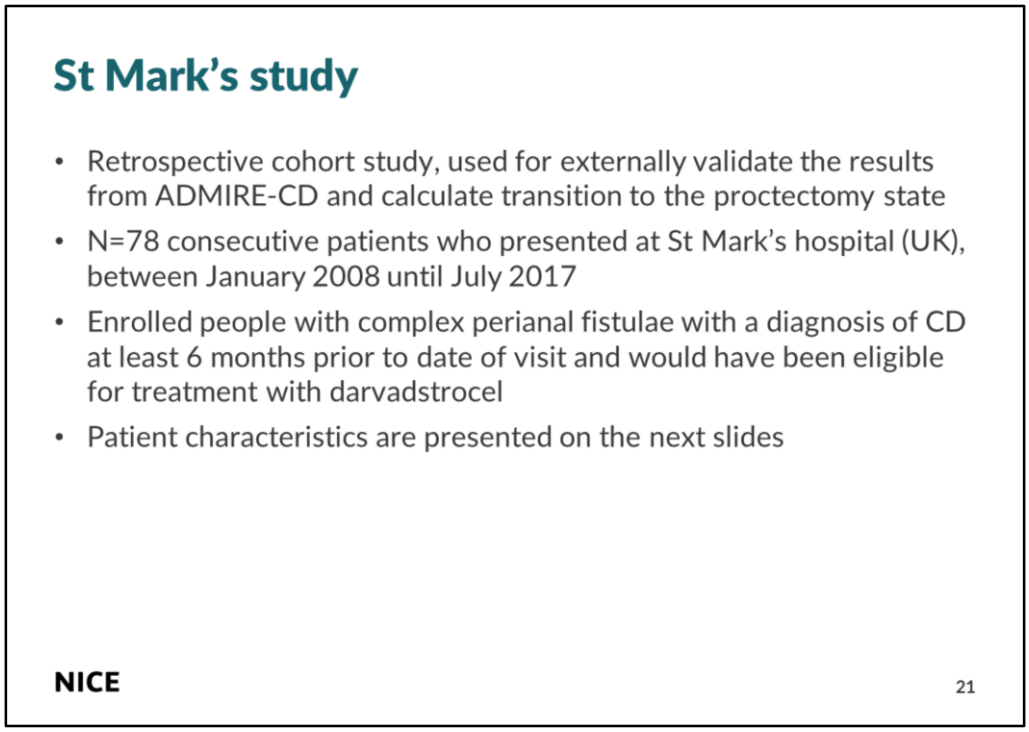

Source: B1.3.3 of Company submission and Appendix Q

Patient characteristics (I)

Baseline characteristic		ADMIRE-CD Darvadstrocel	ADMIRE-CD Control	St Mark's study
ITT population		(N=107)	(N=105)	(N=78)
Gender, male, n (%)		60 (56%)	56 (53%)	
Ethnic origin, n (%)	Caucasian	100 (93%)	96 (91%)	
	Black	4 (4%)	1 (1%)	
	Other	0 (0%)	1 (1%)	
	Missing	3 (3%)	7 (7%)	
Duration CD, years (SD)		12.1 (10.0)	11.3 (8.9)	
CD treatment in past 6 months, any, n (%)	Antibiotics	82 (77%)	74 (70%)	In the St Mark's study prior or current treatments were presented together.
	Immunos.	89 (83%)	77 (73%)	
	Anti-TNF	83 (78%)	84 (80%)	
Background CD treatment (stratification factor), n (%)	Anti-TNF	37 (35%)	33 (31%)	Anti-TNF
	Immunos.	16 (15%)	22 (21%)	Immunos.
	Anti-TNF AND Immunos.	28 (26%)	31 (30%)	Anti-TNF and Immunos.
	Neither	26 (24%)	19 (18%)	None

Abbreviations: CD - Crohn's disease; SD - Standard deviation; TNF - Tumour necrosis factor, NR - Not reported; Immunos. – immunosuppressants;

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Source table 9. of company submission B

St Mark's study: retrospective study from St Mark's hospital indicated that patients in ADMIRE-CD had a similar age, but were more likely to be male.

Highlighted in red: key differences between ADMIRE-CD and St Mark's study

Patient characteristics (II)

		ADMIRE-CD		St Mark's study
		darvadstrocel	control	
Other concomitant CD treatments (safety population), n/N (%)	Antibiotics Corticosteroids	56/103 (54%) 6/103 (5%)	41/102 (39%) 7/102 (6%)	
PDAI score (0 to 20, whereby a higher score indicates more severe perianal disease), mean (SD)		6.8 (2.5)	6.6 (2.9)	NR
Fistula internal openings (safety population), n/N (%)	0 1 2	0/103 (0%) 82/103 (80%) 21/103 (20%)	1/102 (1%) 90/102 (88%) 11/102 (11%)	NR
Fistula external openings (safety population), n/N (%)	1 2 >2	58/103 (56%) 37/103 (36%) 8/103 (8%)	73/102 (72%) 25/102 (25%) 4/102 (4%)	NR

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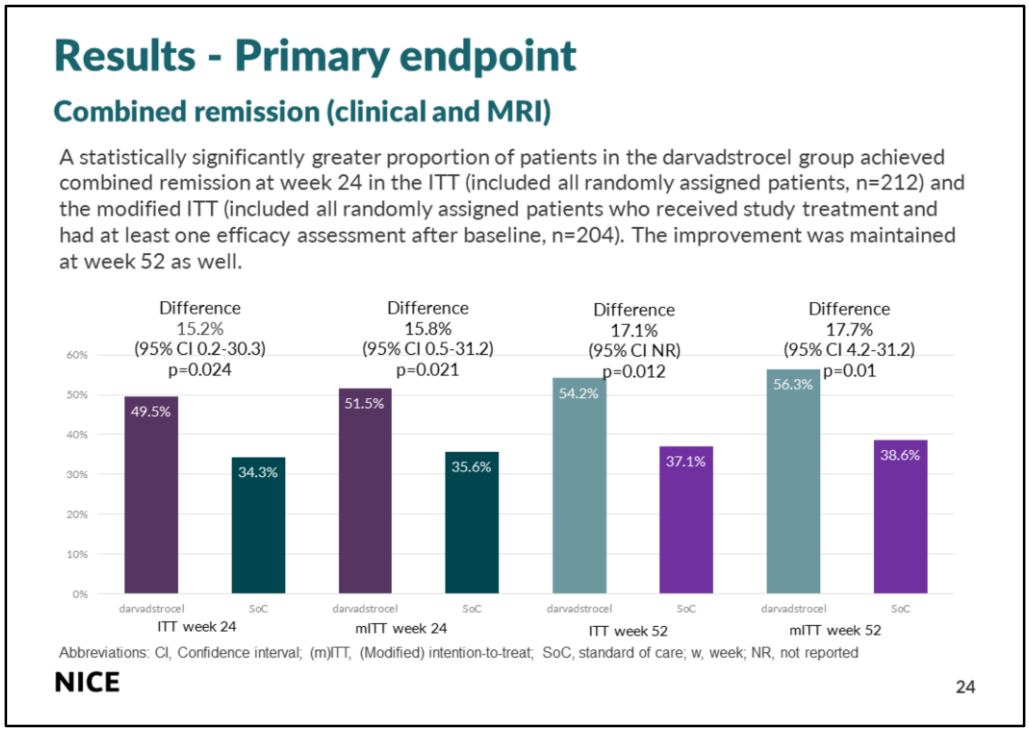
Source table 9. of company submission B

The proportion of patients with more than one internal fistula opening was slightly higher for patients randomised to darvadstrocel and patients randomised to darvadstrocel were more likely to have two internal openings (0%, 80% and 20% for 0, 1, 2 respectively [safety population, n=103]), compared with control treatment (1%, 88%, 11% respectively [safety population, n=102]).

A similar pattern was observed for external openings, the proportion of patients with more than one draining external fistula opening was slightly higher for patients randomised to darvadstrocel (56%, 36%, and 8%, for 1, 2 or >2 draining external openings, respectively [safety population, n=103]) compared with control treatment (72%, 25%, and 4%, respectively [safety population, n=102]).

Differences in the number of opening may indicate more severe disease, which according to clinical opinion is harder to treat



Source figure 8 and tables 12 and 13 of company submission B

Typographical error corrected on the notes page

Results - Primary and key secondary outcomes, ITT population, week 24 follow-up

	Darvadstrocel (N=107)	Control (N=105)
Combined remission (clinical remission and MRI)		
Combined remission, n (%)	53 (49.5%)	36 (34.3%)
Censored cases, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI)	0.74* (0.48, 1.14)	
Clinical remission		
Clinical remission, n (%)	[redacted]	[redacted]
Censored cases, n (%)		
Hazard ratio (95% CI)	0.57* (0.41, 0.79)	
Response		
Response, n (%)	[redacted]	[redacted]
Censored cases, n (%)	18 (16.8%)	30 (28.6%)
Hazard ratio (95% CI)	0.59* (0.43, 0.81)	

Abbreviations: CI, Confidence interval; ITT, Intention-to-treat
* HR below 1 indicates more patients with remission (i.e. better results) on the darvadstrocel arm

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Source: Table 15 company submission B and table 6 of ERG report

Combined remission was statistically significantly higher in the darvadstrocel group at week 24 in both ITT and mITT population.

With longer follow-up (52 weeks), the beneficial effect of darvadstrocel was maintained in the ITT population and in the mITT population as well.

Results - post hoc analyses

(used in the economic model)

	Darvadstrocel	Control	Hazard ratio (95% CI)
CPC remission (clinical remission and the patient does not experience any pain or discharge, as determined by a score equal to 0 in both the pain and discharge dimensions of the PDAI; no MRI assessment was included)			
Patients at risk	N=107	N=105	
CPC remission, n (%)	59 (55.1%)	43 (41.0%)	
Kaplan-Meier estimates, Median (95% CI), weeks[a]	28.7 (17.7, 37.0)	35.2 (24.4, NA)	0.61 (0.42, 0.91)
P-value			p=0.014
CPC relapse (time to relapse from CPC remission)			
Patients at risk	N=59	N=47	
CPC relapse, n (%)	30 (50.8%)	28 (59.6%)	
Kaplan-Meier estimates, Median (95% CI), weeks	48.7 (18.9, NA)	12.9 (12.0, 33.0)	1.38 (0.89, 2.12)
P-value			p=0.0262

CI, Confidence interval; CPC, Clinical and patient-centric
[a] Restricted mean with upper limit of 52 weeks

Also see slide 17 on the definition of these endpoints.

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Source: table 8 of ERG report and section B.2.6.4.1 of CS.

CPC remission in the ITT population improved statistically significantly.

Fewer patients relapsed with darvadstrocel as compared with control treatment.

Results - Disease severity

Outcome	Darvadstrocel (n=103)	Change from baseline	Control (n=101)	Change from baseline	Treatment difference (95% CI)	p-value
PDAI, mean (SD)						
Baseline	6.7 (2.5)		6.5 (2.8)			
Week 24	4.4 (3.6)	-2.3 (3.8)	5.1 (3.9)	-1.3 (3.5)	-0.8 (-1.8 to 0.2)	0.101
Week 52	4.4 (3.8)	-2.3 (4.1)	5.0 (4.0)	-1.4 (3.7)	-0.7 (-1.7 to 0.3)	0.186
IBDQ, mean (SD)						
Baseline	173.5 (31.6)		169.4 (36.1)			
Week 24	178.3 (34.6)	3.8 (25.5)	174.7 (36.2)	4.0 (25.6)	0.3 (-6.6, 7.3)	0.923
Week 52	176.1 (38.1)	2.1 (27.4)	172.7 (40.6)	1.7 (25.0)	0.7 (-6.7, 8.2)	0.849
CDAI, mean (SD)						
Baseline	87.8 (48.3)		93.3 (55.0)			
Week 24	92.5 (66.5)	5.7 (62.2)	94.1 (76.1)	2.2 (65.5)	1.8 (-16.0, 19.7)	0.839
Week 52	97.4 (82.7)	11.1 (80.5)	99.2 (77.8)	7.6 (67.3)	-1.3 (-19.6, 22.1)	0.906
Van Assche Score						
Baseline	9		9.4		NR	NR
Week 24	8.6	NR	9	NR	0.004 (-0.686, 0.694)	NR
Week 52	[redacted]	NR	[redacted]	NR	[redacted]	NR

CDAI, Crohn's Disease Activity Index; CI, Confidence interval; IBDQ, Inflammatory Bowel Disease Questionnaire; mITT, Modified intention-to-treat; PDAI, Perianal Disease Activity Index; SD, Standard deviation

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Trial did not include a preference-based measure of HRQoL. There are no disease-specific measures of HRQoL available for patients with perianal fistula. The only patient reported outcome measure included was the IBDQ.

Total PDAI scores in the mITT population decreased in both treatment groups at all visits (week 6, 12 and 18) and at week 24 (treatment difference, -0.8; 95% CI: -1.8 to 0.2; p=0.101) and week 52 (treatment difference, -0.7; 95% CI: -1.7 to 0.3; p=0.186),[9] with the improvement (i.e. decrease) being greater in the darvadstrocel group compared with the control group. However, the differences between treatments did not reach statistical significance (p > 0.05). Similarly, in the mITT population, there were no significant differences (p>0.05 for all) between the groups at weeks 24 or 52 for total and subdomain IBDQ, CDAI and Van Assche scores.

ERG critique of clinical evidence

- The key uncertainties in the clinical evidence for darvadstrocel relate to repeated administration, optimal dosing and long-term efficacy and safety
- In the post hoc analyses the HR and 95% confidence interval for CPC relapse is from a Gompertz model. The company presented the HRs in a non-standard way with below 1 indicating more patients with remission and above 1 indicating more patients with relapse
- It is unclear whether a Gompertz model was also used to estimate the HR for CPC remission

Safety and adverse events

Number patients (%)	Week 24		Week 52	
	Darv. N=103	Control N=102	Darv. N=103	Control N=102
TEAEs	68 (66.0%)	66 (64.7%)	79 (76.7%)	74 (72.5%)
Proctalgia	13 (12.6%)	11 (10.8%)	**15 (14.6%)**	**12 (11.8%)**
Anal abscess	12 (11.7%)	13 (12.7%)	**20 (19.4%)**	**14 (13.7%)**
Anal fistula	3 (3%)	6 (6%)	11 (10.7%)	8 (7.8%)
Nasopharyngitis	10 (9.7%)	5 (4.9%)	11 (10.7%)	5 (4.9%)
Treatment-related TEAEs	18 (17.5%)	30 (29.4%)	21 (20.4%)	27 (26.5%)
Withdrawn due to AEs	5 (4.9%)	6 (5.9%)	9 (8.7%)	9 (8.8%)
Treatment-related TESAEs in ≥2% of patients				
TESAEs	5 (5%)	7 (7%)	7 (6.8%)	7 (6.9%)
Anal abscess/fistula	5 (5%)	5 (5%)	7 (6.8%)	5 (4.9%)

AE, Adverse event; TEAE, Treatment-emergent adverse event; darv., darvadstrocel

In the economic model, only proctalgia and anal abscess were included as AEs based on results at 52 weeks.

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Source: table 22 of Company submission B; Table 11 of ERG report

Similar adverse events profile between darvadstrocel and the control arm of the trial.

TEAEs, defined as '*events with relationship certain, probable or possible with the study treatment*

serious AEs (TESAEs), defined as '*events that threaten patient life or functions*';[21] and severe TEAEs, defined as an event that '*causes a significant interference with function*'.

Many cases, the reported frequency of AEs was higher in the placebo arm than the treatment arm, because some AEs, including anal abscess and proctalgia, are associated with the indication and might represent treatment failure. As a result after 24 weeks, fewer patients treated with darvadstrocel compared with control experienced treatment-related TEAEs (17.5% of patients receiving darvadstrocel versus 29.4% receiving control), and the reported frequency of withdrawal from the trial to due TEAEs was similar between arms (4.9% of patients receiving darvadstrocel versus 5.9% receiving control). Clinical advice received by the ERG indicated that such outcomes should have been treated as efficacy outcomes

rather than AEs.

Cost effectiveness

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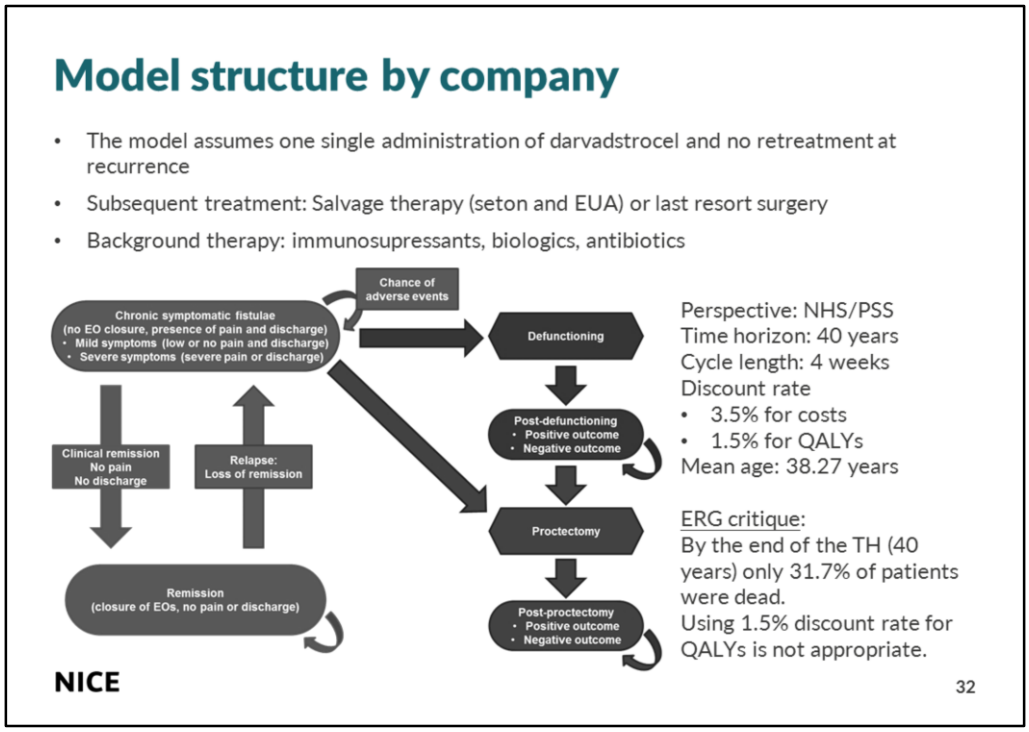
Key issues: cost effectiveness

- Time horizon 40 years – might not be long enough to capture the difference in costs and benefits
- Discount rate – company suggest to use 1.5% discount rate for benefits and 3.5% for costs
- Utility data – utility values are only available from a vignette study
- Extrapolation of time to relapse and time to remission
  - Choice of parametric curve
  - Model does not allow to fit parametric curves beyond 2 years, instead time-invariant probability was calculated
- Transitions to the defunctioning and proctectomy health states
- Missing transitions within the model structure
- Wastage of darvadstrocel – company model assumes no drug wastage



Patients enter the model in either one of the two CSF health states (40.1% mild, 59.9% severe) at a mean age of 38.27 years.
Transitions from CSF to remission is calculated fitting a Gompertz distribution to CPC remission, based on results from ADMIRE-CD.

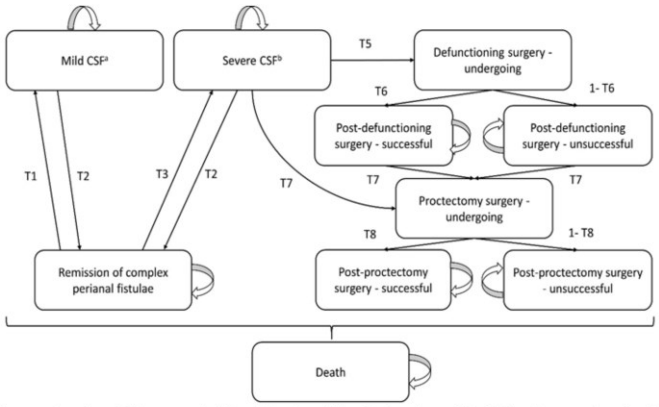
Transition to from remission to CSF health states is calculated fitting a Gompertz distribution to CPC relapse results and the probability that CSF is mild from ADMIRE-CD.

After completing one line of treatment with darvadstrocel or SOC patients go on to receive salvage therapy. Remission and relapse for people who have received salvage therapy was estimated by applying a HR based on an expert elicitation exercise to the respective time to event function for patients receiving standard care.

The defunctioning surgery (subsequent cycles) and the proctectomy surgery (subsequent cycles) were both split into successful and unsuccessful surgeries.
Transition to defunctioning surgery was calculated by fitting exponential distribution to individual patient level data from a subgroup with perianal fistulae in a prospective cohort study on surgical outcomes in people with perianal fistulae and Crohn's disease by Mueller et al. (2007). Annual probability of 3.75% was assumed for people with complex fistulising Crohn's disease receiving a defunctioning surgery over a median time horizon of 16 years.
Transition to proctectomy was calculated based on an analysis of the St Mark's retrospective dataset
Transitions to the proctectomy and defunctioning surgery health states are assumed not to be possible from either the remission or the mild CSF health states.

Patients who have had defunctioning surgery are not able to have this reversed in the model; as such, the only possible transitions from the defunctioning surgery states are to proctectomy or death.

Model diagram by the ERG



a – 40.1% of people start the model in this health state; b – 59.9% of people start the model in this health state; T1 – time to relapse * probability that a CSF is mild; T2– time to remission; T3 - time to relapse * (1- probability that a CSF is mild); T5 – time to defunctioning surgery; T6 – probability that a defunctioning surgery is successful; T7 – time to proctectomy; T8 – probability that a proctectomy is successful

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Patients enter the model in either one of the two CSF health states (40.1% mild, 59.9% severe) at a mean age of 38.27 years. Health state transitions are estimated over 520 4-weekly cycles (approximately 40 years); at this time point, only 31.7% of patients in each treatment group have died.

T2 is calculated fitting a Gompertz distribution to CPC remission results from ADMIRE-CD.

T1 and T3 are calculated fitting a Gompertz distribution to CPC relapse results and the probability that CSF is mild from ADMIRE-CD.

The Gompertz distributions are different in the darvadstrocel and standard care groups, as a treatment effect covariate (HR) is estimated for both the time to relapse and time to remission Gompertz distributions.

After one completed line of either darvadstrocel or standard care (defined as achieving remission or remaining in the CSF health state for more than 13 model cycles), patients go on to receive salvage therapy in both arms.

Remission and relapse for people who have received salvage therapy was estimated by applying a HR based on an expert elicitation exercise to the respective time to event function for

patients receiving standard care.

T5 was calculated by fitting exponential distribution to individual patient level data from a subgroup with perianal fistulae in a prospective cohort study on surgical outcomes in people with perianal fistulae and Crohn's disease by Mueller et al. (2007)

T7 was calculated based on an analysis of the St Mark's retrospective dataset.

Transitions to the death state from all states are based on general population life tables.

ERG critique on model assumptions

- Time horizon: By the end of the TH (40 years) only 31.7% of patients were dead. The ERG explored the impact of using a 60-years time horizon in the model
- Selection of time-to-event functions (Gompertz used in base case by the company):
  - Not adjusting for interval censoring might lead to bias, however it is unknown towards which direction
  - The ICER seems to be highly sensitive to the parametric curve selection, but the true impact is unknown
  - The company used a time-invariant probability to extrapolate time-to-event functions beyond 104 weeks, which seems to be arbitrarily chosen. The ERG considers that mixture cure models may have provided a more plausible long-term fit to the data.
- Missing transitions within the model: Data from the St Mark's study suggest that it was possible for people with: a successful defunctioning surgery to transition to an unsuccessful defunctioning surgery state; a successful proctectomy to transition to a unsuccessful proctectomy state; and an unsuccessful proctectomy to a successful proctectomy state, although these transitions are not possible in the model. The ERG explored the impact of adding these transitions to the model in exploratory analysis 6.

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See section 5.3.4.5, and 5.3.4.8 of ERG report

Clinical effectiveness inputs

Parameter type	Parameter	Source
Time-to-event parameters	Remission – darvadstrocel	CPC definition of remission in the ADMIRE-CD trial
	Remission – standard care	
	Relapse – darvadstrocel	CPC definition of relapse in the ADMIRE-CD trial
	Relapse – standard care	
	Remission – HR of salvage therapy versus standard care	Company's expert elicitation exercise
	Relapse – HR of salvage therapy versus standard care	
	Time to defunctioning surgery	Mueller et al. prospective cohort study
	Receiving a proctectomy surgery	Bell et al. prospective study

Subsequent therapies post progression

- If a patient does not respond to their initial treatment (either darvadstrocel or standard care) within one year or if the patient relapses after remission, they subsequently receive salvage therapy. Salvage therapy is similar to standard care in that one of the following treatments will be used: surgically managing the fistula; antibiotics; immunosuppressants and/or biologics
- The effectiveness of salvage therapy is calculated using a HR comparing time to treatment specific relapse relative to the control arm and using Gompertz model for extrapolation, based on clinical expert opinion
- After several failed lines of salvage therapy, last resort surgeries are considered. These consist of defunctioning surgery, in which the fistula is temporarily bypassed to allow healing, and proctectomy, in which a proportion of the bowel is permanently bypassed
- In the model the probabilities of undergoing proctectomy and defunctioning surgery are assumed to be constant with respect to time.

ERG critique on assumptions for subsequent therapies

- Elicitation of time to relapse and remission for people on salvage therapy:
  - Methodological rigour (no formal elicitation protocol, unclear what information was presented to the experts)
  - Design of the expert elicitation (the effectiveness of salvage therapy was only elicited as HR, which assumes that the proportional hazard assumption holds, but it is unclear whether this assumption was validated)
  - Estimation of uncertainty (the level of uncertainty was not elicited from the experts, therefore the uncertainty in the ICER might have been under- or overestimated).
- Transitions to the defunctioning and proctectomy health states: the model outputs do not match the data used to populate the model
  - Defunctioning: the data used to populate the model relate to all people with complex fistulising Crohn's disease, whereas the transition probability is only applied to a subset of the population (people with severe CSF) – the company's model underestimates the risk of receiving a defunctioning surgery for the severe CSF health state. This was explored in ERG exploratory analysis 2
  - Proctectomy: the data used to populate the model relates to all people with Crohn's disease with complex fistulae. The equal probability of transitioning to the proctectomy health state from the severe CSF and post-defunctioning health states may not be clinically plausible. This was explored in ERG exploratory analysis 2

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The company's exploratory analyses confirmed that altering the assumptions around subsequent therapies does not have a big impact on the ICER.

Modelling health-related quality of life

- Health-related quality of life (HRQoL) is principally determined by the time spent in the different model health states.
- HRQoL benefit is driven by time to remission, time to relapse and timing of defunctioning surgery or proctectomy and is split between mild and severe CSF
- Utility decrements for treatment emergent adverse events were applied, resulting in different HRQoL in the mild CSF (state 1) and severe CSF (state 2) health states across the three treatment groups (darvadstrocel, standard care or salvage therapy).
- No HRQoL measurement was included in ADMIRE-CD trial. It only included IBDQ as patient reported outcome measure, however mapping from IBDQ to EQ-5D to obtain utility values is not appropriate, because IBDQ is focused on luminal disease and not complex perianal fistulae

Vignette study (Fountain et al.)

- Utility values were derived from a vignette study (Fountain et al.)
- Vignettes were developed describing eight health states: (1) remission, (2) CSF with mild symptoms, (3) CSF with moderate symptoms, (4) abscess, (5) defunctioning surgery with positive outcome, (6) defunctioning surgery with negative outcome, (7) proctectomy with positive outcome and (8) proctectomy with negative outcome.
- Health state descriptions were derived with the input of both patients and clinicians.
- Valued using a time-trade off (TTO) methodology by both a representative sample of the general public (n=835) and by a sample of patients with Crohn's disease, but not specifically CSF (n=162)
- The values generated by the general public sample were used in the company's base case analysis; the values from Crohn's disease patients were explored in a sensitivity analysis.

Utility values used in the model

Health state		Mean utility	Standard deviation	Standard error	95% confidence interval
Remission		0.865	0.24	0.008	[0.85; 0.88]
Chronic symptomatic fistulae	Mild symptoms	0.578	0.44	0.015	[0.55; 0.61]
	Severe symptoms	0.383	0.50	0.017	[0.35; 0.42]
Abscess		0.223	0.55	0.019[a]	[0.19;0.26]
Defunctioning	Undergoing	Assumed equal to CSF with severe symptoms			
	Successful	0.567	0.46	0.016	[0.54; 0.60]
	Unsuccessful	0.193	0.56	0.019	[0.15; 0.23]
Proctectomy	Undergoing	Assumed equal to CSF with severe symptoms			
	Successful	0.564	0.50	0.017	[0.53; 0.60]
	Unsuccessful	0.202	0.57	0.020	[0.16; 0.24]

Abbreviations: CSF, chronic symptomatic fistulae. Notes: **, assumed equal to chronic symptomatic fistulae with severe symptoms. Source: Takeda, data on file.
a calculated by ERG
Source: table 16 of ERG report, adapted from table 46 of company submission

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Utility values are not age adjusted.

Disutilities associated with treatment emergent adverse events:

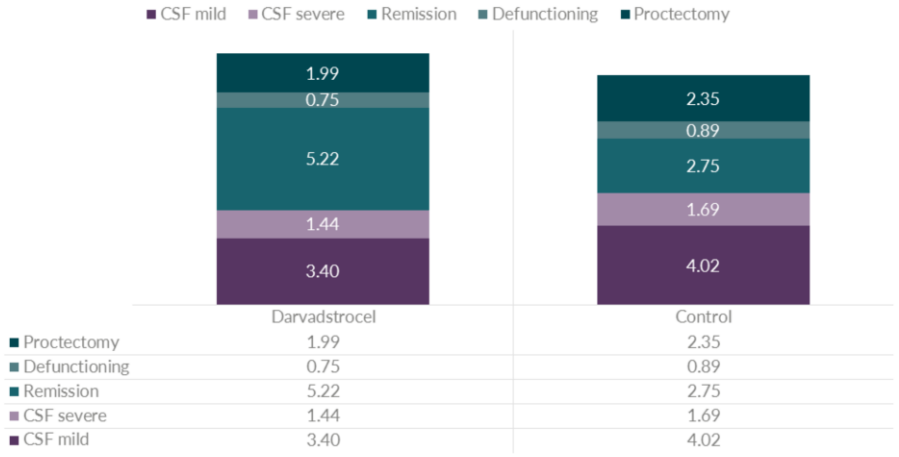
Abscess: The vignette study measured the utility of CSF with abscess as a separate health state, the company incorporated a utility decrement associated with abscess into the model by calculating the difference between the utility values for CSF with abscess and CSF with severe symptoms. This resulted in a mean disutility of 0.16 (SE 0.026, 95% CI 0.11 to 0.21).

Proctalgia: The company's model assumes that there is no additional decrement associated with proctalgia as this event may be experienced by patients having CSF and was therefore already accounted for within the HSUVs for CSF

ERG critique on utility values

- ERG agrees with not mapping IBDQ to EQ-5D from the ADMIRE-CD trial
- Using utility values obtained from direct valuation of health states vignettes is not consistent with the NICE Reference case, but the valuations of the vignettes by the general population were closer to the Reference Case than those obtained from the sample of patients with Crohn's disease
- Face validity of utility values – experts considered that
  - utility values for CSF with severe symptoms were slightly higher than expected
  - utility values for the CSF with mild symptoms were underestimated
  - utility values for a successful outcome following surgery were underestimated, which would underestimate the benefits to patients of a successful surgical procedure
- The benefits of defunctioning or proctectomy surgery may be underestimated (Fountain et al.) therefore the ERG explored the impact of using alternative utility values for the CSF mild, successful defunctioning surgery and successful proctectomy health states (exploratory analysis 7).

Total QALYs accrued by health state company's model, using 3.5% discount rate



	Darvadstrocel	Control
Proctectomy	1.99	2.35
Defunctioning	0.75	0.89
Remission	5.22	2.75
CSF severe	1.44	1.69
CSF mild	3.40	4.02

Abbreviations: QALY:, quality-adjusted life years; CSF, chronic symptomatic complex perianal fistulae

NICE

Costs and health care resource use

Health state related inpatient, outpatient resource use and associated costs	Expert opinion, NHS Reference Costs 2016-17, PSSRU, NICE TA 329, NICE DG11
Darvadstrocel acquisition cost (including PAS)	Company
Frequency of use for different surgical and drug treatments for complex perianal fistulae	ADMIRE-CD trial, expert opinion
Unit costs of surgical procedures used to treat complex perianal fistulae	NICE MIB 102, NICE MIB 105, NHS Reference Costs 2016-17
Unit costs and dosing related to drug treatments	BNF, SmPC, NICE TA187

- The only differences in the model pathways between the darvadstrocel and standard care arms are that in the initial CSF health states (either mild or severe) patients in the darvadstrocel arm receive a single course of darvadstrocel in addition to the standard care treatments during examination under anaesthesia (EUA).

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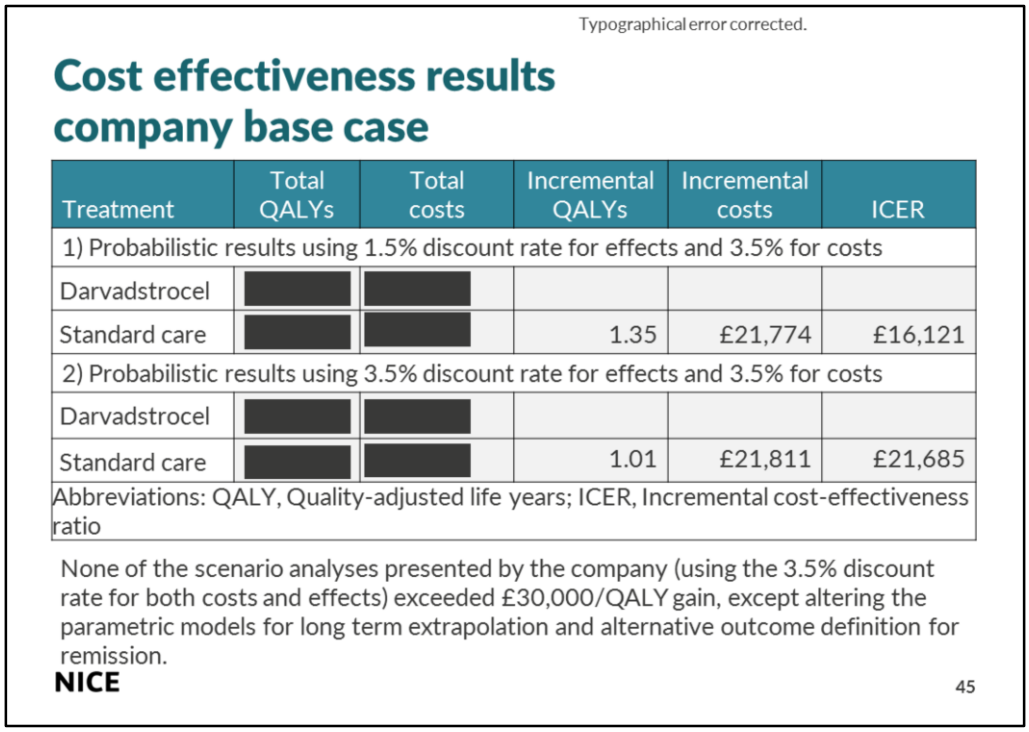
For individual cost items, see section B.3.5 of company submission and Tables 17, 18 and 19 of ERG report.

ERG critique on cost calculations and resource use

- Wastage of darvadstrocel: the company assumed no wastage, because during the ADMIRE-CD trial, no wastage was observed on the darvadstrocel arm
- A sensitivity analysis, assuming 5% wastage for darvadstrocel minimally increased the ICER
- The ERG considered that 5% wastage was likely to represent an upper limit of the impact of wastage in clinical practice



Typographical error corrected.

Cost effectiveness results company base case

Treatment	Total QALYs	Total costs	Incremental QALYs	Incremental costs	ICER
1) Probabilistic results using 1.5% discount rate for effects and 3.5% for costs					
Darvadstrocel	[redacted]	[redacted]			
Standard care	[redacted]	[redacted]	1.35	£21,774	£16,121
2) Probabilistic results using 3.5% discount rate for effects and 3.5% for costs					
Darvadstrocel	[redacted]	[redacted]			
Standard care	[redacted]	[redacted]	1.01	£21,811	£21,685

Abbreviations: QALY, Quality-adjusted life years; ICER, Incremental cost-effectiveness ratio

None of the scenario analyses presented by the company (using the 3.5% discount rate for both costs and effects) exceeded £30,000/QALY gain, except altering the parametric models for long term extrapolation and alternative outcome definition for remission.

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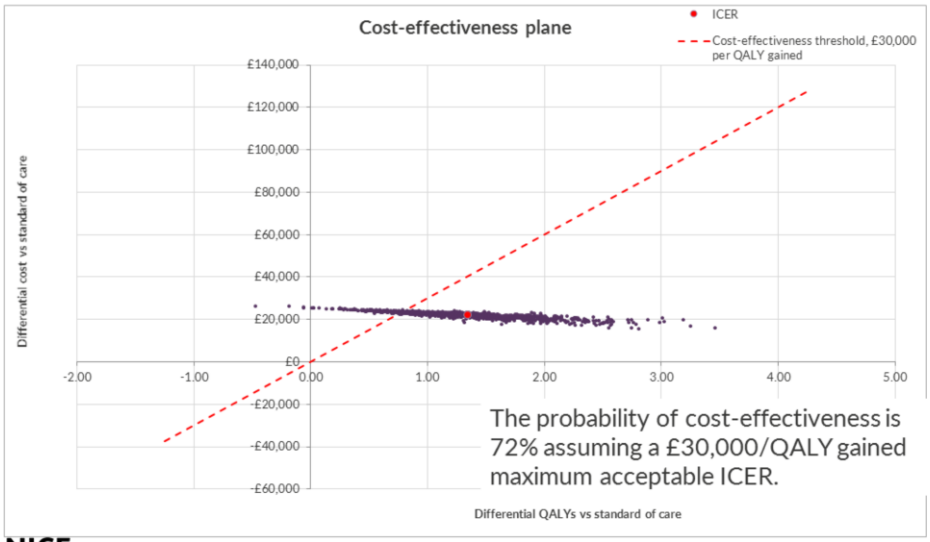
Source: Clarification response B7 and table

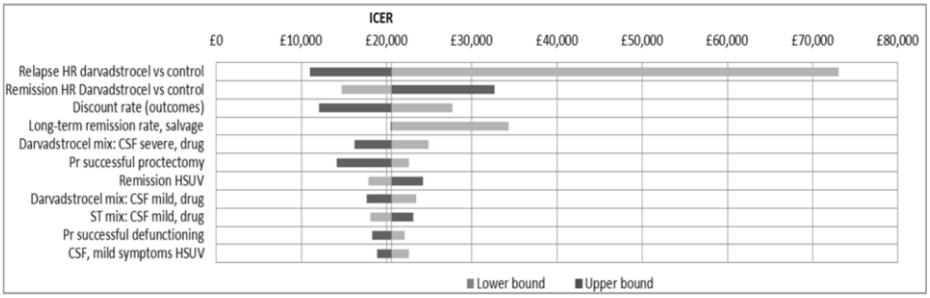
PSA scatter plot using 3.5% discount rate



The probability of cost-effectiveness is 72% assuming a £30,000/QALY gained maximum acceptable ICER.

NICE

Tornado diagram one way sensitivity analyses, using 3.5% discount rate



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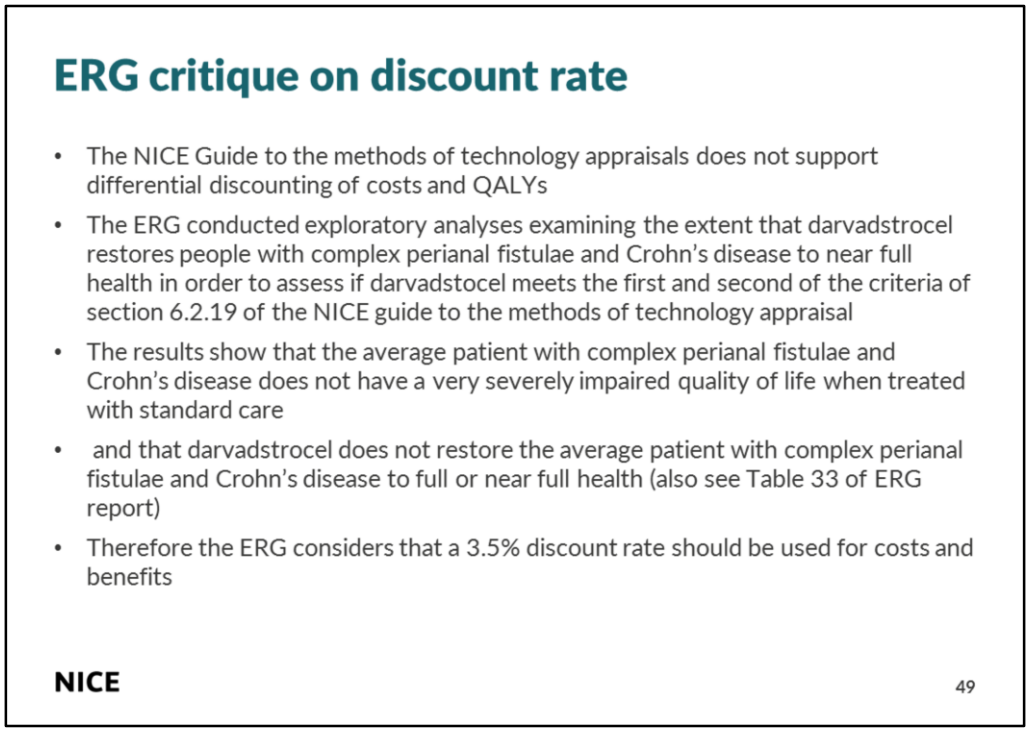
The model parameter with the highest impact is the hazard ratio for the relative effectiveness for darvadstrocel vs SoC on time to CPC relapse and CPC remission.

Altering the discount rate for benefits.

Source clarification response B7

Discount rate

- Company base case uses a discount rate of 3.5% for costs and 1.5% for benefits, as the company claims that section 6.2.19 of the NICE guide to the methods of technology appraisal 2013 applies
- Section 6.2.19 lists the following criteria:
  - when treatment restores people who would otherwise die or have a very severely impaired life
  - restores to full or near full health
  - sustained over a very long period (normally at least 30 years)
  - A discount rate of 1.5% for both costs and benefits may be considered
  - the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs



Source: section 5.5 of ERG report, exploratory analysis 5

Main issues identified by the ERG

- Is a discount rate of 1.5% for QALYs applicable according to Section 6.2.19 of the NICE Methods Guide
- the impact of using alternative time to relapse and time to remission time to event functions;
- the impact of using alternative time to event functions;
- adoption of a 40-year time horizon; by this time point, only 31.7% of people have died in each group, ERG explored applying a 60-year time horizon
- the data used to populate the transitions to the defunctioning and proctectomy health states
- the impact of under predicting utility values for the CSF mild, successful defunctioning surgery and the successful proctectomy health states
- missing transitions within the model structure
- wastage of darvadstrocel

ERG exploratory analyses (I) using 3.5% discount rates

Treatment	Total QALYs	Total costs (with PAS)	ICER
Company's base case			
Darvadstrocel	[redacted]	[redacted]	-
Standard care			-
Incremental	1.05	£21,639	£20,591
1) Correction of implementation errors			
Darvadstrocel	[redacted]	[redacted]	-
Standard care			-
Incremental	1.05	£21,666	£20,700
2c) Proctectomy and defunctioning surgery calibrated			
Darvadstrocel	[redacted]	[redacted]	-
Standard care			-
Incremental	0.96	£23,241	£24,115
2d) Proctectomy and defunctioning surgery probabilities were obtained from the St Mark's retrospective cohort study			
Darvadstrocel	[redacted]	[redacted]	-
Standard care			-
Incremental	0.95	£24,530	£25,530
3) Long term remission and relapse rates for salvage therapy are obtained from the salvage therapy arm			
Darvadstrocel	[redacted]	[redacted]	-
Standard care			-
Incremental	1.05	£21,628	£20,540

Exploratory analyses suggest that the ICER is sensitive to the time to event functions and any under prediction of the utility values for the CSF mild, successful defunctioning surgery and/or the successful proctectomy surgery health states.
Including additional transitions within the company's model structure has only a minor impact on the ICER.

Abbreviations: QALYs – quality-adjusted life years; PAS – patient access scheme; ICER – incremental cost-effectiveness ratio; ERG – Evidence Review Group

ERG exploratory analyses (II) using 3.5% discount rates

Treatment	Total QALYs	Total costs (with PAS)	ICER (£ per QALY gained)
4) Time horizon is set to 60 years (replication of the company's scenario analysis)			
Darvadstrocel	[redacted]	[redacted]	-
Standard Care			-
Incremental	1.10	£21,706	£19,719
ERG base case: 1 + 2c + 3 + 4			
Darvadstrocel	[redacted]	[redacted]	-
Standard care			-
Incremental	1.01	£23,978	**£23,176**
6) ERG base case + Inclusion of missing transitions			
Darvadstrocel	[redacted]	[redacted]	-
Standard Care			-
Incremental	1.11	£21,655	£19,452
7) ERG base case + CSF mild, successful defunctioning surgery and successful proctectomy health states have the same utility value as the remission health state			
Darvadstrocel	[redacted]	[redacted]	-
Standard Care			-
Incremental	0.37	£23,738	£63,721

Abbreviations: QALYs – quality-adjusted life years; PAS – patient access scheme; ICER – incremental cost-effectiveness ratio; ERG – Evidence Review Group

ERG exploratory analyses (III) using 3.5% discount rates

8) ERG base case + Using different parametric distributions for the time to relapse and time to relapse

Time to remission function	Time to relapse function	Total costs			Total QALYs			ICER
		Darv	SC	Incr.	Darv	SC	Incr.	
Gompertz (base case)	Gompertz (base case)	[redacted]	[redacted]	£23,378	[redacted]	[redacted]	1.01	£23,176
Generalised gamma	Gompertz (base case)			£24,033			0.82	£29,200
Gompertz (base case)	Log-normal			£25,084			0.21	£119,514
Generalised gamma	Log-normal			£25,146			0.18	£143,131

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Abbreviations: QALYs – quality-adjusted life years; Darv - darvadstrocel; SC – standard of care; incr. - incremental; ICER – incremental cost-effectiveness ratio

Innovation

- Clinicians consider darvadstrocel innovative and results in significantly higher long-term healing rates
- This is a highly innovative technology, in the context of current suboptimal treatments for this particularly difficult and debilitating complication of Crohn's Disease, and has the potential to represent a step-change in its management
- Darvadstrocel is the only licenced treatment for CD patients who have complex perianal fistulae
- It represents a new and novel treatment paradigm, and will be the first licensed allogenic stem cell treatment in the UK.

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See section B2.12 of company submission

Equality

- There are particular implications for women of child-bearing age, due to potential reduction in fertility associated with pelvic surgery and obstetric complications.
- The need for frequent wound cleaning and dressing may also impact on those following particular religious practices

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Darvadstrocel for treating complex perianal fistula in Crohn's disease [ID960]

Document B

Company evidence submission

April 2018

File name	Version	Contains confidential information	Date
Darvadstrocel NICE Section B	**1.0**	**Yes**	**12 April 2018**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

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Contents

List of Tables

List of Figures

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Darvadstrocel is indicated for the treatment of complex perianal fistulae in adult patients with non-active/mildly active luminal Crohn's disease, when fistulae have shown an inadequate response to at least one conventional or biologic therapy. Darvadstrocel should be used after conditioning of fistula (see B.1.2.2 of this submission for methods of administration).

Darvadstrocel was previously referred to as Cx601.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adult with non-active/mildly active luminal Crohn's disease, with complex perianal fistulae which have shown an inadequate response to at least one conventional or biologic therapy	As per the NICE scope	No difference
Intervention	Darvadstrocel	As per the NICE scope	No difference
Comparator(s)	Surgical management without darvadstrocel	Treatment consists of surgical treatment including EUA and seton placement, as this correlates with the current standard of care in the UK, and was also used as the control arm for the ADMIRE-CD trial.	Fistulotomy, advancement flap procedures, insertion of biosynthetic plugs and fibrin glue are not commonly used in UK practice. Rather, a retrospective study in a tertiary hospital in London, and clinical opinion from a UK KOL Ad Board, indicated that EUA and seton placement were the most common surgical treatments.

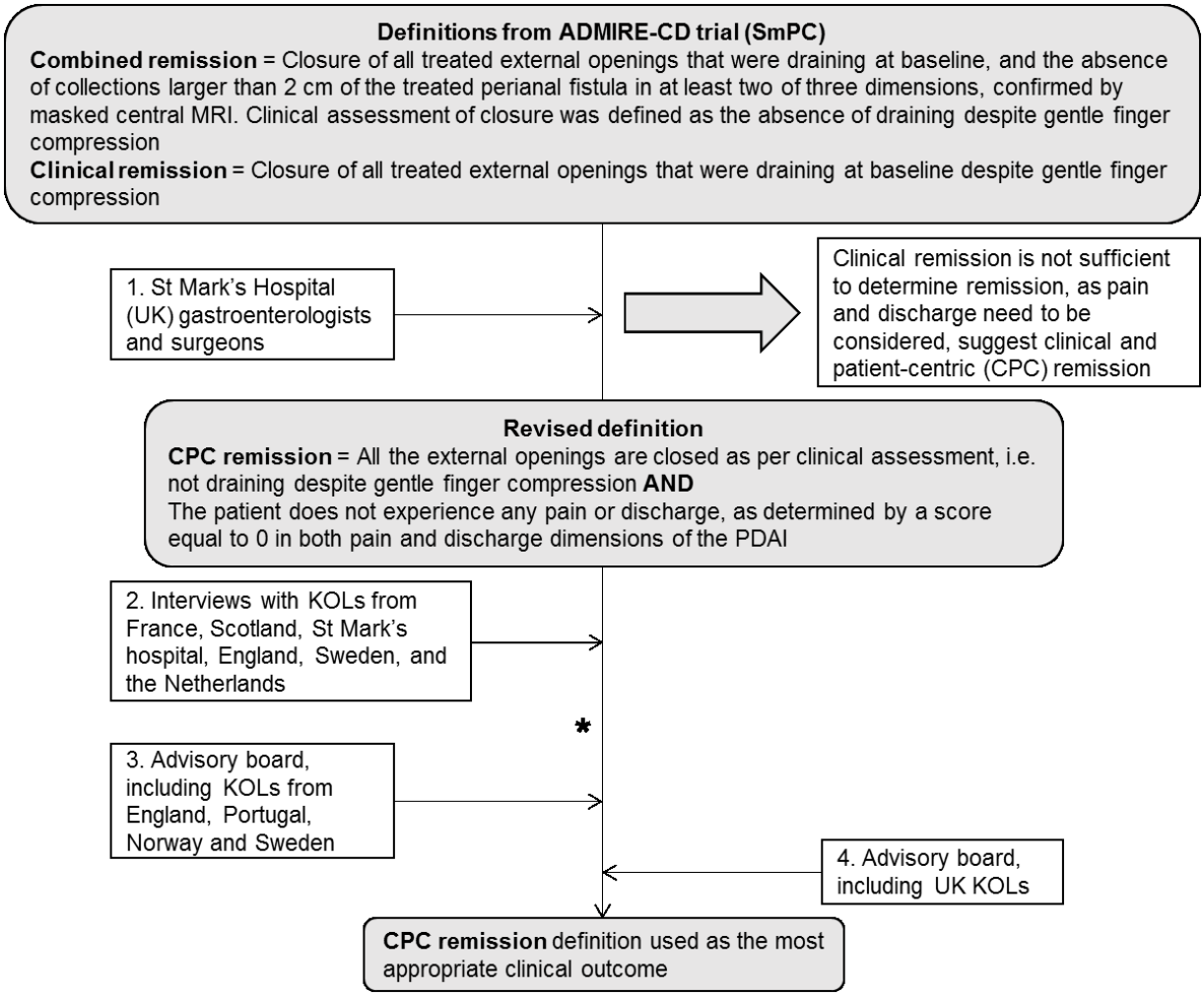
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: Closure of fistula Recurrence of fistula Continence Mortality Adverse effects of treatment Health-related quality of life	CPC remission[1] Combined remission[2] Clinical remission[3] Adverse effects of treatment Health-related quality of life	Clinical outcomes as reported in the key clinical trial ADMIRE-CD. In addition Clinical and Patient Centred (CPC) remission was added, as clinical experts recommended that the clinical outcome of most relevance should include a component of pain and discharge in addition to clinical remission. Pain and discharge scores were taken from the PDAI outcome recorded in the ADMIRE-CD trial
Subgroups to be considered	If evidence allows, patients with perianal-limited disease will be considered	While the key clinical trial data provided evidence for a subgroup of patients with perianal limited disease, the trial was not powered for subgroup analyses, therefore the results need to be interpreted with caution. Clinical outcomes are comparable between the ITT and subgroups, and due to small n, are presented in clinical evidence (Section B.2.7) but not in the economic model. The patient group who have perianal limited disease may not have received nor be appropriate for biological treatment. Restricting darvadstrocel treatment to patients who have failed biological treatment might prevent these patients from adequate and timely treatment with darvadstrocel	No difference

Source: (NICE 2018)
Abbreviations: CD, Crohn's disease; CPC: Clinical and patient-centric; NICE, National Institute for Health and Care Excellence; PDAI, Perianal Disease Activity Index

[1] CPC remission is defined as all the external openings are closed as per clinical assessment, i.e. not draining despite gentle finger compression (i.e. the clinical remission definition of ADMIRE-CD); AND the patient does not experience any pain or discharge, as determined by a score equal to 0 in both pain and discharge dimensions of the PDAI
[2] Combined remission is defined as the clinical assessment of closure of all treated external openings that were draining at baseline, and the absence of collections larger than 2 cm of the treated perianal fistula in at least two of three dimensions, confirmed by MRI. Clinical assessment of closure was defined as the absence of draining despite gentle finger compression.
[3] Clinical remission is defined as closure of all treated external openings that were draining at baseline despite gentle finger compression

Whilst the key outcomes from the key clinical trial (ADMIRE-CD) were combined remission and clinical remission, gastroenterologists and surgeons from the St Mark's Hospital (UK) advised that a more clinically appropriate outcome should also include pain and discharge. This revised definition has been validated by clinical experts in Europe, including 9 clinical experts from the UK (see Figure 1).

Figure 1: Process to determine the definition of remission



Abbreviations: CPC, Clinical and patient-centric; KOL, Key opinion leader; MRI, Magnetic resonance imaging; PDAI, Perianal Disease Activity Index; SmPC, Summary of Product Characteristics; UK, United Kingdom. Notes: * denotes bespoke model development (see Table 25 for further detail)

A definition of possible surgical therapies for perianal fistulae in patients with Crohn's disease (CD) is provided in Table 2.

Table 2: Definition of surgical options (NICE 2017d)

Surgery	Detail
Advancement flap procedures	Surgical method involving closure of the internal opening of the fistula with a flap of tissue and cleaning out the fistula tract (NICE 2017d)
Biosynthetic plug	A conical plug, usually made of porcine intestinal submucosa, is pulled into the tract until it blocks the internal opening, and is sutured in place at the internal opening. The external opening is not completely sealed so that drainage of the fistula can continue (NICE 2011)
Examination under anaesthesia (EUA)	Inspection of the fistula tract, whilst under sedation. The most common procedure in the treatment of perianal fistulae in CD. The procedure can also include curettage, cleaning of the fistula tract, placement of a seton, as well as allowing a physician the opportunity to examine the fistula tract and determine the location of the internal opening(s)
Fibrin glue	A formulation injected into the fistula tract in an attempt to seal it (NICE 2017d)
Fistulotomy	Surgery to cut open the whole length of the fistula, from the internal opening to the external opening, before the surgeon cleans out the contents and flattens it out (NICE 2017d)
Ligation of the inter-sphincteric fistula tract (LIFT)	Involves opening the space between the muscles to access the fistula tract (NICE 2017d)
Seton	Threading a stitch (seton) through the fistula tract and back out through the anus where it is loosely tied. Two types of seton may be used; a silicone draining seton, or a silk or polyester cutting seton (NICE 2017d)
Video assisted anal fistula treatment (VAAFT)	A surgical kit for treating anal fistulae. The system comprises 1) a video telescope (fistuloscope) to allow surgeons to see inside the fistula tract, a unipolar electrode for diathermy of the internal tract. 2) This is connected to a high frequency generator. 3) A fistula brush and forceps for cleaning the tract and clearing any granulation tissue (NICE 2017d)
Last resort surgeries	
Defunctioning – colostomy	Surgical exteriorisation of the colon after segmental resection and before re-anastomosis, as a way of reducing inflammation and improving outcomes
Defunctioning – ileostomy	An artificial opening created in the ileum and brought to the surface of the abdomen for the purpose of evacuating faeces
Proctectomy	Surgical resection of the rectum

B.1.2 Description of the technology being appraised

Appendix C presents the Summary of Product Characteristics (SmPC) and the European Public Assessment Report (EPAR). The following table presents the technology being appraised.

Table 3: Technology being appraised

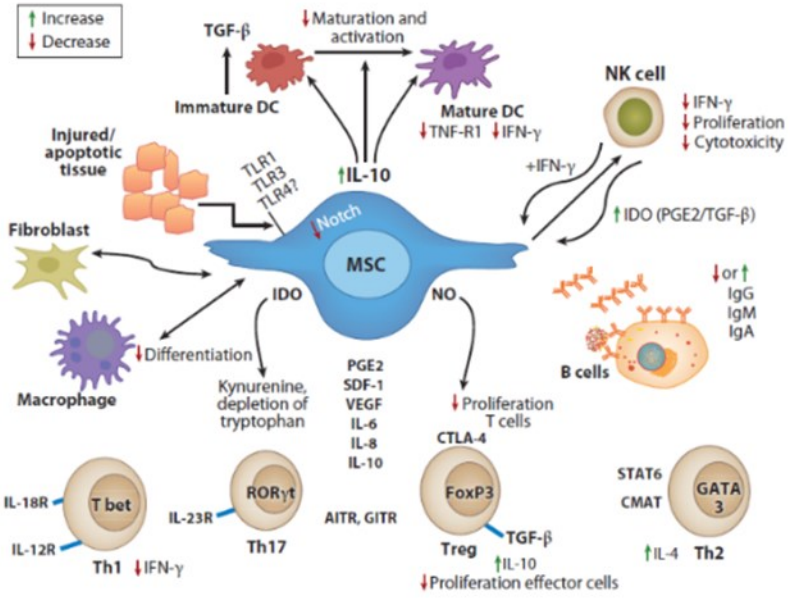
UK approved name and brand name	Darvadstrocel (Alofisel®)
Mechanism of action	Darvadstrocel is a suspension of expanded human adipose-derived stem cells of allogeneic origin. These stem cells have the potential to regulate the function of immune-cells including B lymphocytes, T-lymphocytes, NK cells, monocyte-derived dendritic cells and neutrophils resulting in local immunosuppression.
Marketing authorisation/CE mark status	Alofisel was granted EMA approval on 23rd March 2018 for the indication as detailed in this submission.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Darvadstrocel is indicated for the treatment of complex perianal fistulae in adult patients with non-active/mildly active luminal CD, when fistulae have shown an inadequate response to at least one conventional or biologic therapy. Darvadstrocel should be used after conditioning of the fistula.
Method of administration and dosage	Darvadstrocel is a cell suspension with 120 million cells (4 vials) being given as a single administration. The content of two vials (60 million cells) is injected into the fistula walls along the length of the fistula tract and two vials (60 million cells) injected around the internal opening during an Examination Under Anaesthesia (EUA). This procedure is done by a specialist physicians experienced in the diagnosis and treatment of conditions for which darvadstrocel is indicated.
Additional tests or investigations	No additional tests or investigations are required beyond current standard of care in the UK.
List price and average cost of a course of treatment	£13,500 per vial, £54,000 for one course of treatment
Patient access scheme (if applicable)	A simple patient access scheme has been submitted to the DH, with a cost of £[redacted] for one course of treatment

Abbreviations: CD, Crohn's disease; EUA, Examination under anaesthesia; NK, Natural Killer; SmPC, Summary of Product Characteristics; UK, United Kingdom

B.1.2.1 Mechanism of action

Darvadstrocel is a cellular therapy comprising of expanded adipose-derived mesenchymal stem cells (eASCs). These eASCs are isolated from 'lipoaspirates', which is the material extracted by liposuction from healthy adult donors. Darvadstrocel cells are expanded in culture and cryopreserved until use. eASCs are immune-privileged and can be administered without the need for either human leukocyte antigen matching, or administration of immunosuppressive drugs.

Figure 2: Darvadstrocel mechanism of action



Source: (Singer 2011)

Mesenchymal stem cells (including eASC) primarily work by downregulating immune response. This in turn facilitates the repair of damaged tissues. Mesenchymal stem cells also have the potential to differentiate into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells) and adipocytes (fat cells), however it is unknown to what extent, if any, this is involved in their efficacy for tissue repair.

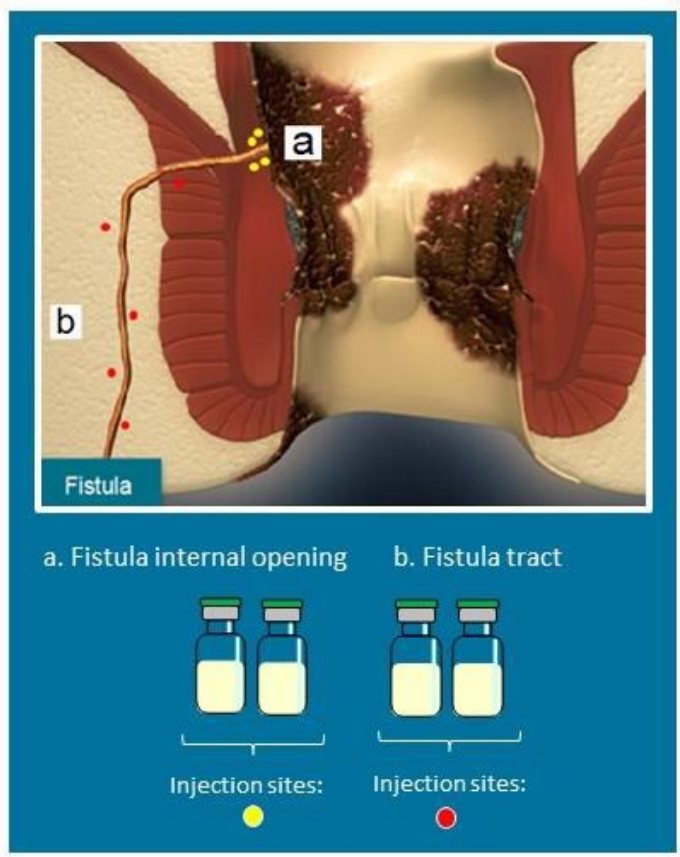
The unique mechanism of action of darvadstrocel involves a diverse range of regenerative and immunosuppressant properties by secretion of soluble factors and modulation of immune cell function (Singer 2011, Gao 2016); see Figure 2). Darvadstrocel acts by abolishing the inflammation which results in repair of the fistula tract.

B.1.2.2 Method of administration and dosage

Before administration of darvadstrocel, the surgeon must perform conditioning of the fistula tract and ensure that no abscesses are present. In case of an abscess, incision and drainage are needed, and setons should be placed, if appropriate, in accordance with routine surgical procedures. The administration procedure takes place two to four weeks later, and involves the injection of darvadstrocel into the tissues surrounding the tract. Four vials, each containing approximately 30 million cells, will be administered to each patient, with the

contents of two vials injected around the fistula tract and the other two vials injected around the fistula internal opening (see Figure 3). Each procedure is anticipated to take approximately 60 minutes. Each of these procedures is similar to the examination under anaesthesia (EUA)/seton placement procedure currently used as standard of care in the National Health Service (NHS). It should be noted that this same procedure is also done where other agents with healing intent are used e.g. biologics. When administering biologics to a patient with a chronic perianal fistula, it is vital to ensure no abscess is present, and so patients will have two visits similar to those used for administration of darvadstrocel.

Figure 3: Darvadstrocel administration sites



Source: (Tigenix 2016a)

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Perianal fistula in Crohn's disease

A perianal fistula is defined as an abnormal passageway or tunnel which develops between the rectum and the skin in the perianal area. Fistulae are characterised by local inflammation that is exacerbated by faecal and bacterial contamination. Chronic complications of Crohn's Disease (CD) may include the development of fistulae as the inflammation in CD tends to penetrate the whole thickness of the bowel wall and this can damage the bowel wall in the form of ulcers and abscesses. As these develop, a hole can start to form which then

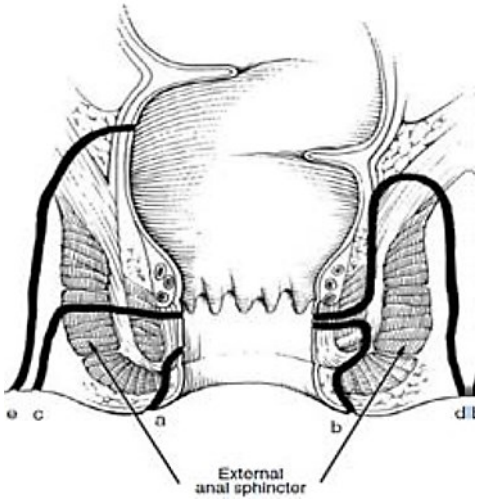
becomes a tunnel creating a fistula. Ongoing inflammation around the fistula tract inhibits healing, making the healing of complex perianal fistulae in patients with CD extremely challenging. Few pharmacological treatments exist for complex perianal fistulae and repeated surgical procedures are usually required (Sands 2004, Domenech 2005, Gionchetti 2017). These complex perianal fistulae are much more difficult to treat than the cryptoglandular fistulae that occasionally affect otherwise healthy patients.

Cryptoglandular fistulae and perianal fistulae in patients with CD have a number of key differences, impaired healing rates are observed in CD patients due to inflammatory changes in the bowel leading to significantly lower remission rates, also cryptoglandular fistulae are normally low/superficial with no sphincter involvement, hence they are typically treated with relatively aggressive surgical procedures such as fistulotomy, which have a high probability of achieving complete fistula healing. However perianal fistulae in patients with CD often originate from higher in the rectum thus involving the sphincter muscles rendering fistulotomy as not normally being considered in this group due to the serious consequences associated with even minor damage to the anal sphincter of patients with CD and the associated risk of incontinence.

Perianal fistulae can be divided into either 'simple' or 'complex' categories according to classification systems such as those developed by Parks and the American Gastroenterological Association (AGA) (Sandborn 2003). However, the ECCO consensus guidelines note that there is no clinical consensus for classifying perianal fistula in CD into simple and complex variants (Gionchetti 2017) (see also Appendix L). In the literature the majority of perianal fistulae in CD patients are reported as being complex (approximately 75%; see Appendix L).

In general, perianal fistulae are classed as complex if the primary tract is high in origin, thereby having sphincter involvement or has multiple branches with more than one internal or external opening (see Figure 4). In some definitions the presence of inflammatory bowel disease (IBD) also results in classifying a fistula as complex.[4]

Figure 4: Perianal fistulae



Source: (Sandborn 2003)
Simple (low) perianal fistula: a: Superficial; b: Inter-sphincteric;
Complex (high) perianal fistula: c: Trans-sphincteric; d: Supra-sphincteric; e: Extra-sphincteric

[4] See https://emedicine.medscape.com/article/776150-overview, accessed 7 March 2018

A recent costing report conducted by NICE (NICE 2015a) reported the prevalence of CD as 0.2% and the incidence 0.01%, resulting in 85,533 prevalent patients and 4,500 new patients in England. However there is currently no UK data available to estimate the number of those CD patients who have a complex perianal fistula. A recent Dutch population-based cohort study, including 1,162 patients with CD (diagnosis between 1991 and 2008), may reflect the UK with regards to incidence rates of perianal fistulae in patients with CD (Gottgens 2017). The overall cumulative risk of at least one perianal fistula was 8.3% after one year, 11.6% after five years, and 15.8% after ten years, with a slightly lower 5-year risk in the more recent cohort (10.3% in the 2006-2011 era) (Gottgens 2017). Applying the 1-year risk from Gottgens (2017) to the English prevalence and incidence data, results in 7,473 CD patients with perianal fistulae in England. Risk factors for developing perianal fistulae in CD patients were a young age (18-40 years) and colonic or ileocolonic disease location at diagnosis as compared with ileal location (Gottgens 2017). Of the 161 primary perianal fistulae that were diagnosed. In the Dutch study most patients received antibiotics (82.6%), 89% of patients received some type of surgery for patients with high perianal fistulae; mainly seton and mucosal advancement flap interventions) and over half received biologics with or without immunosuppressants (up to 54% in the 2006-2011 era).

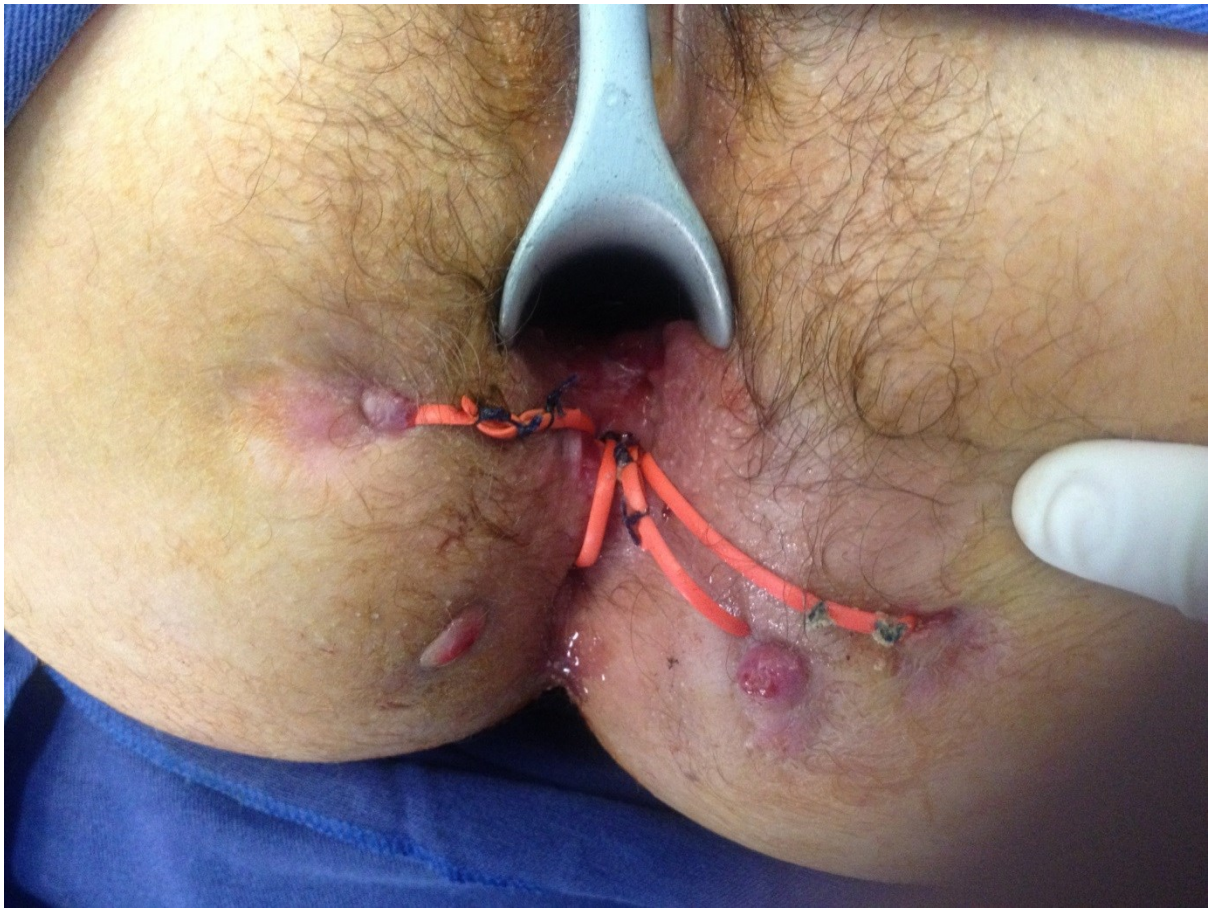
B.1.3.2 Burden of illness in patients with complex perianal fistulae

Complex perianal fistula is a debilitating and relapsing disease affecting between 12–16% of CD patients (Chaparro 2011, Gottgens 2017). Patients face a significant impact on their quality of life (QoL) suffering pain, anal discharge, anal incontinence, restrictions to activity, impaired sex life, and emotional distress. Current treatment options are associated with poor sustained remission rates and healing rates (see Section B.2).

Symptoms of a perianal fistula which significantly affect a patients QoL include persistent anal and/or abdominal pain, perianal inflammation, pain during defaecation, continuous malodorous drainage (pus, blood, and faecal material), incontinence, skin irritation around the anus and fever (due to the development of abscesses) (Marzo 2015, Gionchetti 2017). If an abscess is present, this results in severe pain, fever and requires surgical drainage of the abscess (often as an unplanned procedure). As complex perianal fistulae in CD patients extend beyond the anal sphincter, the patient may develop faecal incontinence. This faecal incontinence could be due to damage caused by the perianal disease itself, as inflammation within the fistula tract can cause further ulceration damaging surrounding tissue, the formation of additional branches off the main fistula tract, or due to certain surgical treatment options which may permanently damage the sphincter. Perianal fistulae result in considerable morbidity, causing significant impairment in QoL with serious clinical and psychological consequences (Gionchetti 2017).

Figure 5 shows a patient with a Chronic Symptomatic Fistula with setons in place. This is an example of patients in this 'mild' health state and helps to demonstrate the significant QoL burden on these patients.

Figure 5: A patient with a chronic symptomatic fistula with setons in place



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Complex perianal fistulae in patients with CD result in high morbidity and a significant impairment in QoL (Mahadev 2011, Mahadev 2012, Riss 2013). In a cross-sectional study evaluating QoL in CD patients with perianal fistulae, 42% stated that they would trade some amount of life expectancy for cure of perianal disease (Mahadev 2011), on average, patients would trade 6.5% of life expectancy which translates into 5.3 years. Patients were most averted to anal incontinence (85%), anal pain (81%), anal discharge (78%), physical activity restriction (77%), and loss of independence (77%) (Mahadev 2011). Mahadev (2012) also suggested that mental health issues are an important consideration for CD patients with perianal fistulae, with 73% of the patients reported feeling depressed, 33% felt life was not worth living, 13% had suicidal feelings and 42% were willing to trade five years of life expectancy for a cure (Mahadev 2012).

Currently, no valid instruments are available to measure the QoL in CD patients with perianal fistulae (Vignette study; Appendix R) and no study has reported utility values using generic instruments such as the EQ-5D or Short-Form, 6 dimensions (SF-6D) for this population (see Section B.3.4). A review of the literature identified only one paper that reported estimates of health-related utility for CD patients with perianal fistulae and cannot be considered robust due to the ambiguity around the methods used to derive the data, including whether a vignette approach was used, details of the vignettes/health states and the methods used in their development. It was therefore not possible to align the reported values with the health states included in our economic model (see Section B.3.4.3).

Takeda commissioned a vignette study to identify and estimate the health state utility values for CD patients with perianal fistulae (Appendix R). A vignette approach does not measure changes in health as reported by patients, as specified by NICE in its recommended approach (TSD 11; (Brazier 2011)). However, since the ADMIRE-CD trial and the literature review did not identify appropriate utility values, and mapping was infeasible, a vignette study was performed. In the study, the utility values were elicited using description of the health states. The vignettes were designed for compatibility with the health economic model structure and developed using qualitative research with patients, and were validated by UK clinical experts. Two separate surveys were performed: one based on a representative sample of the UK general public (n=835), and one administered to CD patients (n=162). The results of the study demonstrate that the perceived QoL burden of fistula in CD is substantial. Using the results from the UK general public, it was indicated that having active perianal disease resulted in utility values of 0.55 and 0.35 for chronic symptomatic fistula with mild and severe symptoms respectively, compared to a utility of 0.87 when in remission. The utility of remission is aligned with the English population norm for healthy 35-44 year olds (0.888) (Janssen 2018), note that the mean age in the key clinical trial was 38 years (Panes 2016). Defunctioning surgery and proctectomy with positive outcome resulted in a utility of 0.58 and 0.38 respectively. Unsuccessful surgery had much lower values, 0.19 for defunctioning surgery with negative outcome and 0.20 for proctectomy with negative outcome. The utility values elicited from the patient survey were slightly higher than those from the general population, although low utility values were elicited for the fistula with severe symptoms, abscess and unsuccessful surgery states.

In a UK study of IBD patients (CD, ulcerative colitis, other IBD; with or without perianal fistulae), health-related QoL (HRQoL) was found to be significantly affected by faecal incontinence. This study included a random sample of people from a national Crohn's and colitis organisation (Norton 2013). A total of 3,264 (32.6%) respondents to a survey were included in the analysis of which 47% had CD, 49% had ulcerative colitis, 4% had other IBD, and no diagnosis was given by 0.2%. HRQoL information was collected using the Inflammatory Bowel Disease Questionnaire (IBDQ). Continence issues were assessed using the International Consultation on Incontinence Questionnaire for Bowels (ICIQ-B). Greater bowel control (from the ICIQ-B) was positively correlated with QoL (from the ICIQ-B) ($P < 0.001$). Lower bowel control was negatively correlated with social function ($P < 0.001$) (Norton 2013). Significant associations were found in multivariable analyses between faecal incontinence and age ($P = 0.005$), gender ($P < 0.001$), anal stretch ($P = 0.004$), anal fistula surgery ($P < 0.001$), colorectal surgery ($P \leq 0.001$), and urinary incontinence ($P \leq 0.001$). The study was not specific for CD patients with perianal fistula, however it indicated that faecal incontinence has a negative impact on the HRQoL, which is of relevance as many current surgical options for complex perianal fistulae impact on this, although this impact is not included in the economic model.

There is very limited evidence from UK studies reporting the direct costs of complex perianal fistulae. In a recent retrospective UK study of patients with CD and treated with infliximab, the annual in-patient elective procedures for drainage of abdominal, peri-rectal abscesses, corrections of fistulae and treatment of severe anal fistulae reduced from £752 pre-infliximab to £539 post-infliximab (Lindsay 2008). As the study provided costings for patients with CD, rather than CD patients with complex perianal fistulae, the resource impact of complex perianal fistulae only was not presented.

The mean annual costs for pharmacological treatment (excluding infliximab) in fistulising CD was estimated to range from £3,300–£10,368 (NICE 2010, Dretzke 2011). Current ECCO guidelines recommend biologics as a first-line treatment, with the mean cost for infliximab use in fistulising CD estimated to be £8,808–£12,584 (NICE 2010, Dretzke 2011). Up to 90%

of patients have been estimated to require surgery, with a median of six procedures to achieve healing (Bell 2003). Direct costs are 19 times higher for patients needing surgery compared to patients under medical therapy (Boschetti 2016). It should be noted that this study was not specific to the treatment of complex perianal fistulae in patients with CD, the patient population included 38.1% of patients with perianal lesion and 19% of patients had a history of surgery for perianal lesions. Complex perianal fistulae have a considerable economic burden on the health system due to their chronic and recurrent nature. The lack of standardised treatment approach results in heterogeneity in costs incurred per patient (Buchanan 2011, Chaparro 2013). Relapsed/recurrent patients incur higher costs compared with those in remission, as they require a combination of pharmacological treatment and (multiple) surgical procedures (Cohen 2008).

In summary, patients with complex perianal fistulae as a complication of CD have a low HRQoL and are associated with a high cost of care.

B.1.3.3 Current clinical pathway of care

The NICE guideline for the management of Crohn's disease (CG152), does not include a specific section on the clinical pathway of care for the treatment of CD patients with perianal fistula (NICE 2012). There are no other guidelines or technology appraisals published by NICE that specifically examine the treatment of complex perianal fistula in CD patients (see Table 4).

Table 4: NICE guidance of relevance for current clinical pathway of care

NICE documents	Title	Relevance for perianal fistula in CD
NICE Guideline 152 (NICE 2012)	Crohn's disease: management (2012)	Not relevant; some reference to medical treatment of CD patients with perianal fistulae, however no clinical care pathway for perianal fistula provided
NICE Technology Appraisal 187 (NICE 2010)	Infliximab and adalimumab for the treatment of Crohn's disease (2010)	Not relevant; provides information on medical treatment of CD patients with perianal fistulae. However, the appraisal does not match the final NICE scope, i.e. it focussed on the treatment of active luminal CD with some patients also having perianal disease not limited to perianal fistulae.
NICE Technology Appraisal 352. Review date August 2018 (NICE 2015c)	Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy (2015)	Not relevant; perianal fistula not considered
NICE Technology Appraisal 456. Review date July 2020 (NICE 2017c)	Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy	Not relevant; perianal fistula not considered
NICE interventional procedures guidance 410. (NICE 2011)	Closure of anal fistula using a suturable bioprosthetic plug (2011)	Not relevant; not commonly used in the UK to treat perianal fistula in CD patients
NICE Medtech innovation briefing 102 (NICE 2017d)	VAAFT for treating anal fistulae (2017)	Not relevant; provides information on current surgical practices in the UK, although not specific for CD patients with perianal fistula

Abbreviations: CD, Crohn's disease; NICE, National Institute for Health and Care Excellence; VAAFT, Video-assisted anal fistula treatment

Within the UK, the most relevant guidelines are published by ECCO, which are European-based consensus guidelines on the diagnosis and management of CD, including the treatment of perianal fistulae (Gionchetti 2017). Other guidance/consensus documents that are published are: NHS pathway 2017 [within the NICE Medtech innovation briefing; (NICE 2017d)], The Association of Coloproctology of Great Britain and Ireland (ACPGBI) guidance (Lee 2017a), and global consensus statements (Gecse 2014) (See Appendix L).

For patients with a simple perianal fistula (i.e. uncomplicated low anal fistula), it is suggested to drain the perianal abscess if present, followed by simple surgical opening of the fistula (fistulotomy). For patients diagnosed with a complex perianal fistula (the relevant patient population), medical imaging is recommended along with mandatory EUA abscess drainage and loose seton placement, with the timing of seton removal varying depending on

the subsequent therapy given. If present, active luminal CD should be treated in conjunction with appropriate surgical management of the fistulae. Biological treatments such as infliximab are recommended first-line therapies after adequate surgical drainage. Addition of ciprofloxacin to biologic therapies improves short term outcomes of perianal fistula. To enhance the effect of biologics in complex fistulising disease, a combination of biologic treatment with thiopurines may be considered. The recommended therapies for continuing treatment for perianal fistula are pharmaceutical treatment (thiopurines and/or biologics), seton drainage, or combined pharmaceutical treatment with seton drainage.

The treatment of complex perianal fistulae in adult CD patients refractory to conventional or biologic treatment is not well identified in most consensus statements, and this results in a heterogeneous standard of care, with Multi-Disciplinary Teams (MDTs) deciding the approach based on experience. The current guidelines and consensus statements do not provide clear preference for the different surgical treatments for the treatment of patients who have complex perianal fistula and are refractory to conventional or biologic therapy. For patients with complex perianal fistulae, cutting setons and fistulotomy are not recommended due to the high risk of incontinence (Lee 2017a). No preference is provided for the other surgical treatments such as EUA, draining setons, fibrin glue, fistula plugs, advancement flaps, LIFT and/or VAAFT, due to the heterogeneity of the disease and the paucity of high quality evidence on the clinical effectiveness and safety for patients with complex perianal fistulae (see Section B.2.9).

Takeda commissioned a retrospective study to investigate the current treatment practices in this patient group. Data was collected retrospectively from 78 patients in terms of hospital visit date from January 2008 until July 2017 who met criteria that indicated that they would have been eligible for treatment with darvadstrocel: diagnosis of CD at least 6 months prior to date of visit and presence of complex perianal fistulae (Appendix Q). St. Mark's hospital is a tertiary hospital that specialises in intestinal and colorectal medicine and is a national and international referral centre for intestinal and colorectal disorders. Data was extracted in regards to hospital visits, relevant procedures, tests and medications. All subsequent visits and treatment data for these patients were included regardless of whether or not the patients would continue to be eligible for darvadstrocel. The median follow-up was 2.6 years.

All patients had received biologic treatment either in the past (61.5%) or as their current treatment (38.5%) and most patients had received an immunosuppressant (66.7%). All patients had received some form of surgery by the end of the follow up period, a median of 2.6 years. The most common surgical treatments performed in patients with complex perianal fistulae as a complication of CD were EUAs with or without other interventions (56%, 44/78), EUA with drainage of abscess or sepsis (26%, 20/78), seton insertion (26%, 20/78), proctectomy (19%, 15/78), defunctioning colostomy (8%, 6/78), VAAFT (6%; 5/78) and defunctioning ileostomy (5%, 4/78). These surgical treatments are in line with the current UK consensus statements and ECCO guidelines.

A summary of the treatments received by patients considered to be eligible for darvadstrocel in the St Mark's study are presented in Table 5.

Table 5: Treatments at follow-up in St Mark's study in at least four patients (median follow-up 2.6 years)

Treatment	Number of patients (n=78)	%	Range of treatments per patient
Any biologic	**65**	**83.3%**	
Adalimumab	48	61.5%	(1-36)
Infliximab	32	41.0%	(1-23)
Vedolizumab	13	16.7%	(3-13)
Any immunosuppressant	**52**	**66.7%**	
Thiopurines	43	55.1%	(2-36)
Methotrexate	11	14.1%	(2-7)
Tacrolimus	4	5.1%	(3-8)
Any surgery	**78**	**100.0%**	
Surgical interventions			
EUA (+/- other interventions)	**44**	**56.4%**	
EUA	20	25.6%	(1-2)
EUA / drainage of abscess or sepsis	20	25.6%	(1-5)
EUA / seton insertion	20	25.6%	(1-3)
VAAFT	5	6.4%	(1-2)
Last-resort surgery			
Proctectomy	15	19.2%	(1-1)
Defunctioning - colostomy	6	7.7%	(1-1)
Defunctioning - ileostomy	4	5.1%	(1-1)

Source: St Mark's report (Appendix Q)
Abbreviations: EUA, Examination under anaesthesia; VAAFT, Video-assisted anal fistula treatment.
* At the St Mark's hospital, VAAFT was used as part of a clinical trial as an alternative to a EUA

There is a high unmet medical need for treatment of complex perianal fistula(e) in patients with CD who are refractory to antibiotics, immunosuppressants, and/or biologics. There is inconsistent advice regarding the preferred surgical treatments in this setting and regardless of the initial approach taken, the majority of patients require multiple surgical interventions, with more invasive treatments that have a high impact on patients HRQoL (Lee 2017b). Up to 38% of complex perianal fistulae may require last-resort surgical intervention, including defunctioning stoma or proctectomy (Geltzeiler 2014) (Appendix Q).

B.1.3.4 Proposed clinical pathway of care

It is apparent that there is a high unmet medical need for treatment of CD patients with complex perianal fistula(e) who are refractory to antibiotics, immunosuppressants, or biologics.

Regardless of the initial medical and surgical approach taken, the majority of patients require multiple surgical interventions, with more invasive treatments that have a high

impact on patients HRQoL (Lee 2017b). Due to the low healing rates seen with the various surgical procedures discussed above, there is often a reluctance to remove a seton as this can result in the build-up of collections in the fistula tract which can lead to abscess formation and new fistula tract growth (branching of the original fistula tract). This may explain the predominant use of EUA/seton placement in the UK as the main palliative surgical intervention in the UK to provide symptomatic relief for patients.

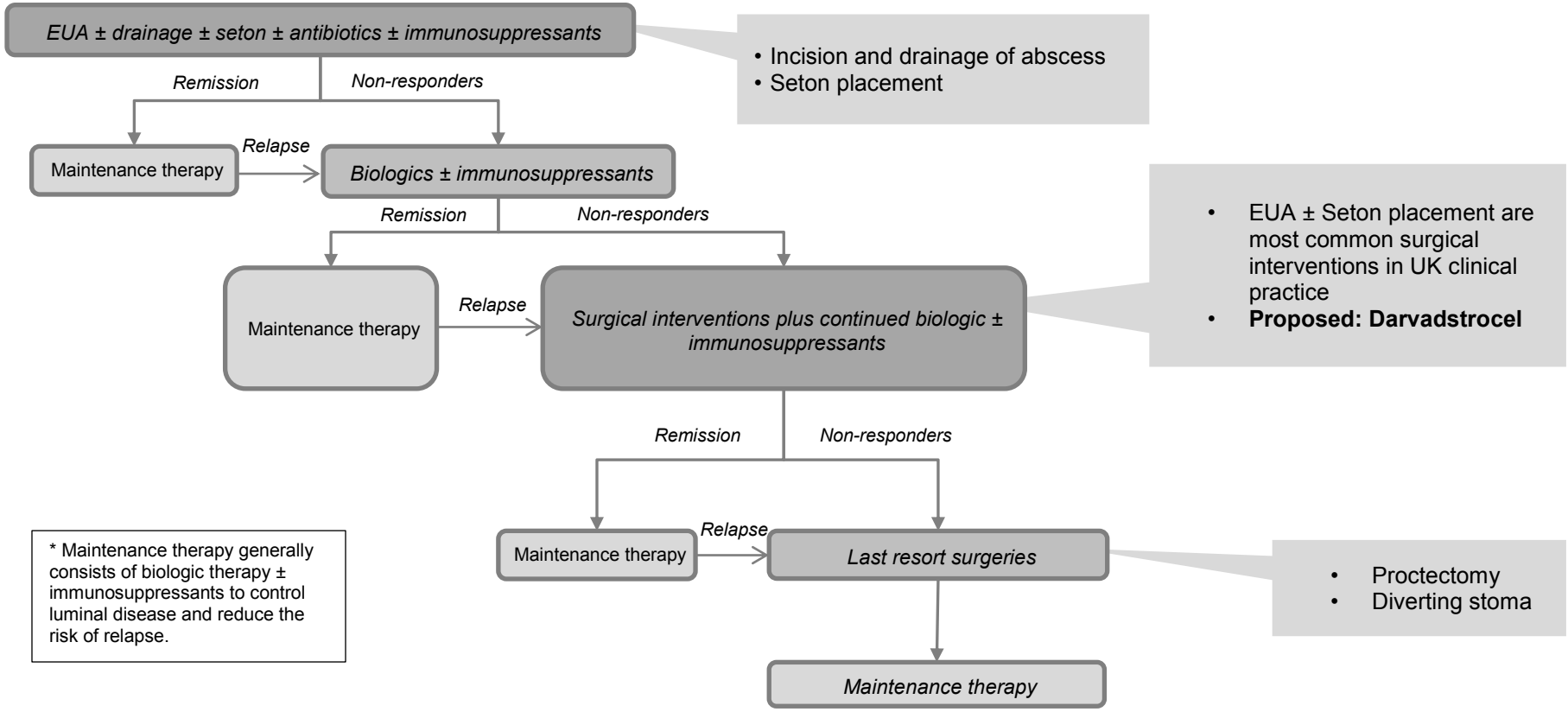
In a retrospective study in a tertiary hospital in London, the most common treatments were EUAs, seton placement, diverting stoma, and proctectomy (Appendix Q). EUAs and seton placement are not curative and can be considered to be of palliative intent, while diverting stoma and proctectomy can be considered last-resort surgery. The high percentage of patients receiving proctectomy indicates that there is a high unmet need for curative treatments.

Adipose-derived mesenchymal stem cells are a new approach for the treatment of complex perianal fistula in CD patients, because of their anti-inflammatory and immunosuppressant potential. Darvadstrocel is allogenic expanded adipose-derived stem cells, and this medication is the first to provide targeted treatment for complex perianal fistulae in patients with CD. Within the Association of Coloproctology of Great Britain and Ireland (ACPGBI) consensus statements, darvadstrocel is seen as a potential new treatment for CD patients with perianal fistulae (Lee 2017a). Darvadstrocel is indicated for the treatment of complex perianal fistula in adult patients with non-active/mildly active luminal CD, when fistula(e) have shown an inadequate response to at least one conventional or biologic therapy. Patients can receive darvadstrocel in addition to conventional therapies after failure of an antibiotic, immunosuppressant or biologic, and may replace current less effective treatments such as EUAs or draining setons (see Figure 6), as well as using darvadstrocel alone as a curative treatment to achieve healing of a complex perianal fistula, which would also lead to a reduction in the need for last-resort surgery (defunctioning or proctectomy).

Darvadstrocel is a valuable and much needed intervention in the treatment of complex perianal fistula in patients with CD. Darvadstrocel targets patients with complex perianal fistulae who currently have a limited choice of treatments that provide a low likelihood of positive outcomes in regards to HRQoL and fistula healing. Currently, there is a lack of a standardised treatment approach which results in a heterogeneous standard of care, with physicians deciding the approach based on experience, and darvadstrocel could help to standardise the treatment approach for complex perianal fistula in patients with CD, and give patients hope of a life free of complications.

Darvadstrocel will generally be used after biologic therapy except where this is contraindicated or unsuitable e.g. for patients with perianal limited disease. Although these patients have a fistula they have no symptoms of luminal CD in which case use of a biologic is unsuitable for two reasons 1) no evidence for effectiveness of biologics in this group and 2) biologic therapy may be required at a later stage to treat emerging luminal disease.

Figure 6: Current and proposed clinical treatment pathway



EUA: Examination under Anaesthesia

B.1.4 Equality considerations

There are no equality considerations relevant for the use of darvadstrocel in the treatment of complex perianal fistulae in patients with CD.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) of biomedical literature databases was undertaken in accordance with the NICE methods guide (NICE 2013) in order to identify clinical trials relevant to the NICE decision problem. This systematic review assessed the efficacy, HRQoL, safety, and tolerability outcomes associated with key interventions in the treatment complex perianal fistula in patients with CD. A broad strategy was applied, whereby the search was not limited to darvadstrocel treatment only. The SLR was performed to assess the clinical effectiveness (including safety and tolerability) of treatments used for the management of complex perianal fistulae in patients with CD.

The full search strategy and details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are summarised in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The SLR identified one Phase III randomised clinical trial (RCT), ADMIRE-CD (Panes 2016, Panes 2017a), and one single arm Phase I/II study (de la Portilla 2013) applicable to the decision problem. ADMIRE-CD is the pivotal trial and forms the evidence base for the efficacy, safety and tolerability of darvadstrocel in patients with complex perianal fistula and CD which is the population relevant for the Decision Problem (Section B.1). The de la Portilla study (2013) provides supportive information on the efficacy and safety of darvadstrocel, although due to the single-arm status of the study is considered supplementary information (details on methods and results are presented in Appendix D.1.5).

Only one RCT was identified in the clinical systematic literature review that evaluated darvadstrocel in CD patients with complex perianal fistula (Panes 2016, Panes 2017a). This is the only study relevant to the decision problem described in Section B.1.1; i.e. it is the only study that has assessed the use of darvadstrocel in the treatment of complex perianal fistulae in adult patients with non-active/mildly active luminal CD, where fistulae have shown an inadequate response to at least one conventional or biologic therapy (details of the trial are outlined in Table 6).

The data presented in Sections B.2.2 to B.2.7 are from the ADMIRE-CD trial and are from both published and unpublished sources (Panes 2016, Tigenix 2016a, Panes 2017a).

Table 6: Clinical effectiveness evidence

Study	ADMIRE-CD, Cx601-0302 (Panes 2016, Panes 2017a)				
Study design	Phase III, randomised, double-blind trial. Treatment was administered by an unmasked surgeon, with a masked gastroenterologist and radiologist assessing the therapeutic effect. Randomisation was stratified according to concomitant treatment at randomisation (anti-TNF, immunosuppressant, both, or neither)				
Population (n=212)	CD patients with complex perianal fistula, refractory to at least one of the following treatments: antibiotics, immuno-modulators or induction or maintenance anti-TNFs				
Intervention(s) (n=107)	Darvadstrocel with background treatment				
Comparator(s) (n=105)	Control				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	Trial provides highest level evidence on the clinical effectiveness of darvadstrocel compared with the most appropriate comparator (standard of care currently used in UK clinical practice)				
Reported outcomes specified in the decision problem	Combined remission at week 24,clinical remission, response, time to clinical remission, time to response, relapse, safety outcomes *Post hoc*: Time to CPC remission; time to CPC relapse				
All other reported outcomes	CDAI, PDAI, Van Assche				

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CPC: Clinical and patient-centric; PDAI, Perianal Disease Activity Index; TNF, Tumour necrosis factor

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design

As stated in the Decision Problem (Section B.1.1), the main comparator for darvadstrocel in this patient population is examination under anaesthesia (EUA) with curettage.

The most common treatment in the UK consists of background therapy, including biologics, immunosuppressants, antibiotics, EUA, seton placement and abscess drainage. ADMIRE-CD provides clinical data for a direct comparison of darvadstrocel with this treatment. A methodological overview of ADMIRE-CD can be found in Appendix D. Patients had all failed at least one medical therapy, and approximately 77.6% of the darvadstrocel group, and 80% of the control group were previously using biologics (Tigenix 2016a).

This is the only RCT that specifically aims to evaluate the treatment of complex perianal fistula in patients with CD. Due to the rarity of the disease, and the under-representation in research literature, ADMIRE-CD can be considered a large trial.

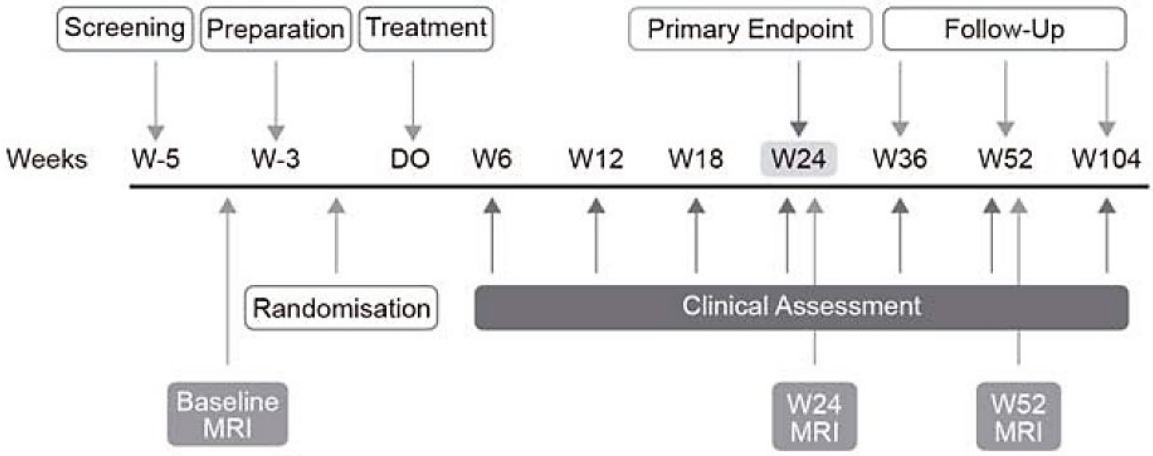
ADMIRE-CD included adult patients (≥18 years) with non-active or mildly active luminal CD with treatment-refractory draining complex perianal fistulae. The study took place across seven EU countries (Austria, Belgium, France, Germany, Italy, the Netherlands, and Spain)

and Israel. Patients were randomised to either darvadstrocel (n=107) or placebo (control treatment) (n=105). Eligible patients had to be refractory to at least one of the following treatments; antibiotics (defined as no response after one month of treatment), the immunosuppressants azathioprine, 6-mercaptopurine or methotrexate (defined as no response after three months), or treatment with a biologic therapy. Further details, including the exclusion criteria used in the trial, are detailed in Table 7. The trial visit schema is detailed in Figure 7.

Following the screening visit, patients were given a baseline MRI and scheduled for a preparation visit. During this visit a EUA was undertaken to prepare the fistula for darvadstrocel administration. The procedure included curettage of the fistula tract in all patients, and seton placement if clinically indicated. Randomisation was performed after the preparation visit.

Following randomisation into treatment groups, patients are administered either darvadstrocel (intervention) or an identical volume of saline solution (comparator), alongside EUA. This procedure is done by specialist physicians experienced in the diagnosis and treatment of conditions for which darvadstrocel is indicated. 50% of the solution is injected around the internal fistula opening and 50% into the fistula walls along the length of the fistula tract.

Figure 7: Planned visit schema



Source: Supplement of (Panes 2016). Abbreviations: MRI, Magnetic resonance imaging; W, Week

Due to the distinct appearance of a cell suspension it was difficult to blind the administration of darvadstrocel. Therefore, the double-blind trial design was maintained by administering the treatment by an unmasked surgeon, and using a masked gastroenterologist and radiologist to carry out all therapeutic assessments. Surgeons were not permitted to share information about the treatment used in the surgical procedure with the gastroenterologist or radiologists, and were also not allowed to participate in any clinical assessment of the fistula during the study. The radiologists (who centrally read MRI scans) were provided with figures to identify the treated fistulae, but were masked to patient data, order of examinations, and treatment received.

The following table provides a summary of the trial methodology.

Table 7: Comparative summary of trial methodology

Trial	ADMIRE CD
Location	49 hospital sites in eight countries (Austria, Belgium, France, Germany, Israel, Italy, Netherlands, Spain), from July 6th 2012, to July 27th 2015.
Trial design	Phase III, randomised, double-blind trial. Treatment was administered by an unmasked surgeon, with a masked gastroenterologist and radiologist assessing the therapeutic effect. Patients were randomised via centrally located computer-generated randomisation list in a ratio of 1:1. Randomisation was stratified according to concomitant treatment at randomisation (anti-TNF, immunosuppressant, both, or neither).
Detailed eligibility criteria for participants (inclusion criteria)	Male or (non-pregnant) female aged ≥18 years who signed informed consent* and met the following criteria: CD patients with non-active or mildly active luminal CD defined by a CDAI ≤ 220, diagnosed at least 6 months earlier in accordance with accepted clinical, endoscopic, histological and/or radiological criteria. Presence of complex perianal fistula with ≤2 internal openings and ≤3 external openings, assessed by clinical examination and MRI. Fistula must have been draining for ≥6 weeks prior to the inclusion. A complex perianal fistula is defined as a fistula that met one or more of the following criteria during its evolution: High inter-sphincteric, trans-sphincteric, extra-sphincteric or supra-sphincteric Presence of ≥ 2 external openings (tracts) Associated collections *[redacted]

Trial	ADMIRE CD
Detailed eligibility criteria for participants (exclusion criteria)	• Presence of dominant luminal active CD requiring immediate therapy • Concomitant rectovaginal fistulae • Patient naïve to specific treatment for perianal fistula in CD including antibiotics • Presence of an abscess or collections > 2 cm, unless resolved in the preparation procedure (week -3 to day 0) • Rectal and/or anal stenosis and / or active proctitis, if this means a limitation for any surgical procedure • Patient who underwent surgery for the fistula other than drainage or seton placement • Patient with a diverting stoma • Patient with ongoing steroid treatment or treated with steroids in the last 4 weeks • Renal or hepatic impairment • Malignant tumour or patients with a prior history of any malignant tumour, including any type of fistula carcinoma • Current or recent history of abnormal, severe, progressive, uncontrolled hepatic, haematological, gastrointestinal (except CD), endocrine, pulmonary, cardiac, neurological, psychiatric, or cerebral disease • Congenital or acquired immunodeficiency's • Known allergies or hypersensitivity to antibiotics including but not limited to penicillin, streptomycin, gentamicin, aminoglycosides; HSA (Human Serum Albumin); DMEM (Dulbecco Modified Eagle's Medium); materials of bovine origin; local anaesthetics or gadolinium (MRI contrast) • Contraindication to MRI scan, (e.g., due to the presence of pacemakers, hip replacements or severe claustrophobia) • Major surgery or severe trauma ≤6 months • Patients previously treated with eASCs • Subjects who need surgery in the perianal region for reasons other than fistulae at the time of inclusion in the study, or for whom such surgery is foreseen in this region in the 24 weeks after treatment administration
Trial drugs **darvadstrocel (n=107) and PBO (n=105)**	Two weeks before treatment administration, all patients underwent a preparatory procedure during which EUA and fistula curettage were performed. If indicated a seton was placed. If a seton was placed, this was removed at the administration visit. During the administration procedure, a second EUA and fistula curettage were performed and either a 24 mL dose of darvadstrocel containing 120 million eASCs (treatment group; n=107) or an identical volume of saline solution (control group; n=105) was injected at multiple sites into the tissue adjacent to all fistula tracts and internal openings. This dose was selected to be sufficient to treat up to three fistula tracts per patient.

Trial	ADMIRE CD
Permitted and disallowed concomitant medication	After investigational product administration, patients could be treated with antibiotics for no more than 4 weeks. Immunosuppressants and anti-TNF drugs were maintained at stable doses throughout the study. Initiation or dose increases of these drugs were not allowed. A steroid course was permitted to treat occurrences of luminal disease during the study, with a starting dose of 40 mg tapered over a maximum of 12 weeks.
Primary outcomes (including scoring methods and timings of assessments)	**Combined remission at week 24**; defined as the clinical assessment of closure of all treated external openings that were draining at baseline, and the absence of collections larger than 2 cm of the treated perianal fistula in at least two of three dimensions, confirmed by masked central MRI (BioClinica, Munich, Germany). Clinical assessment of closure was defined as the absence of draining despite gentle finger compression.
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	**Efficacy analysis at week 24** *Key Secondary:* Clinical remission; defined as closure of all treated external openings that were draining at baseline despite gentle finger compression, as clinically assessed by week 24 Response defined as closure of at least 50% of all treated external openings that were draining at baseline, as clinically assessed by week 24
Pre-planned subgroups	On the ITT and mITT analyses for the primary and key secondary outcomes the following subgroup analyses were to be performed at week 24: Randomisation stratification factors: i.e. concomitant anti-TNFs and/or concomitant immunosuppressant treatments: 1) Anti-TNF + Immunosuppressant; 2) Anti-TNF only; 3) Immunosuppressant only; 4) Neither TNF nor Immunosuppressant.

Source: (Panes 2016) and (Tigenix 2016a)
Abbreviations:; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; EO, External opening; IBDQ, Inflammatory Bowel Disease Questionnaire; IO, Internal opening; MRI, Magnetic resonance imaging; PDAI, Perianal Disease Activity Index; QoL, Quality of life; SAE, Serious adverse event; TEAE, Treatment emergent adverse event; TESAE, Treatment emergent serious adverse event; TNF, Tumour necrosis factor.

B.2.3.1.1 Changes in protocol

For ADMIRE-CD, the original protocol (version 1.0), dated 13 December 2011, was followed by five protocol amendments. In addition to administrative edits, notable changes included extending the trial duration from 24 weeks to 104 weeks, additional assessment intervals, clarification of reasons for study completion, explanation of statistical analysis, an extended recruitment phase to achieve target numbers, and addition of immunological analysis of blood samples to allow assessment of alloreactivity in study patients (further details provided in Appendix M).

B.2.3.2 Trial drugs and concomitant medications

Two weeks before treatment administration, all patients underwent EUA, and fistula curettage was performed. A seton was placed if indicated. If a seton was placed, this was removed just before administration of the treatment.

A single injection of 120 million darvadstrocel cells was distributed into the tissue adjacent to all fistula tracts and internal openings. This dose was selected to be able to treat up to three fistula tracts per patient, (n=107). Washing with saline was performed to prevent cell loss in the dead space of the syringe. Patients in the control group (n=105) received an identical volume of saline solution (i.e., 24 mL).

Patients were permitted to continue concurrent treatments for the patients' condition (e.g. biologics, immunosuppressants, etc).

The following medications were permitted after darvadstrocel administration:

- Antibiotics to treat the fistula during the study, provided no more than four weeks of continued treatment
- Immunosuppressants could be maintained at a stable dose, however new treatment was not allowed. A decrease in dose or suspension was allowed.
- Anti-TNFs maintained at stable doses. No new treatment was allowed.
- Use of aminosalicylate (5-ASA) from the time of treatment administration, and thereafter, a decrease in dose was permitted if required.
- Medications taken for other conditions were also allowed.

B.2.3.3 Trial outcomes

The pre-specified primary and secondary outcomes for ADMIRE-CD are summarised in Table 8. The primary outcome was combined remission at week 24, defined as the clinical assessment of closure of all treated external openings that were draining at baseline, and the absence of collections larger than 2 cm within the perianal fistula in at least two of three dimensions, confirmed by masked central MRI. The clinical assessment of closure was defined as the absence of draining despite gentle finger compression.

Secondary outcomes were segmented into two key outcomes (clinical remission and response at 24 weeks) and various additional secondary outcomes (time to clinical remission, time to response, relapse, time to relapse, PDAI, IBDQ, CDAI and Van Assche

score at week 24, 52 and 104). Clinical remission was defined as closure of all treated external openings that were draining at baseline despite gentle finger compression. Response was defined as closure of at least 50% of all treated external openings that were draining at baseline. Clinical remission and response were considered key secondary outcomes because of statistical hierarchy in testing (see Section B.2.4).

Disease severity was measured using the PDAI, CDAI, and Van Assche scores. A short description of these scoring instruments is presented in Appendix D.1.4. While the PDAI and Van Assche Score focus on local perianal fistulising disease activity, the CDAI focuses on luminal CD severity. The only patient reported outcome instrument included was the IBDQ (a short description is also presented in Appendix D.1.4). The IBDQ does not focus on local perianal fistulising disease, rather on systemic bowel disease (e.g. luminal CD).

Table 8: Pre-planned trial outcomes for ADMIRE-CD

Outcomes	ADMIRE-CD
Primary outcome	Combined remission at week 24, defined as the clinical assessment of closure of all treated external openings that were draining at baseline, and the absence of collections larger than 2 cm of the treated perianal fistula in at least two of three dimensions, confirmed by masked central MRI (BioClinica, Munich, Germany). Clinical assessment of closure was defined as the absence of draining despite gentle finger compression.
Key secondary outcomes	Clinical Remission defined as closure of all treated external openings that were draining at baseline despite gentle finger compression, as clinically assessed by week 24 Response defined as closure of at least 50% of all treated external openings that were draining at baseline, as clinically assessed by week 24
Exploratory other secondary outcome(s)	**At week 24 and 52:** Time to combined remission Time to clinical remission Time to response Van Assche score **At week 52:** Combined remission Response **At week 24, 52 and 104:** Relapse defined, in patients with clinical remission at previous visit, as reopening of any of the treated external openings with active drainage as clinically assessed, or the development of a perianal collection >2 cm of the treated perianal fistula confirmed by centrally blinded MRI assessment Time to Relapse in patients with Clinical Remission PDAI IBDQ CDAI score **At week 52 and 104:** Clinical remission **Safety analyses throughout the study** AEs including: TEAEs, TEAEs related to study treatment, TESAEs, TESAEs related to study treatment, TEAEs leading to study withdrawal, AEs related to surgical procedure(s) to provide study treatment, deaths Only SAEs will be reported between week 52 and week 104. • Physical examination • Vital signs • Laboratory tests (biochemistry, haematology, urinalysis)
***Post hoc* Analyses**	Time to CPC remission Time to relapse of CPC remission

Source: (Panes 2016, Tigenix 2016a)
Abbreviations: AE, adverse event; CDAI, Crohn's Disease Activity Index; CPC, clinical and patient-centric; IBDQ, Inflammatory bowel disease questionnaire; MRI, magnetic resonance imaging; PDAI, Perianal disease activity index; SAE, Serious adverse event; TEAE, Treatment emergent adverse event; TESAE, Treatment emergent serious adverse event;

Two additional *post hoc* analyses were performed, based on feedback from clinical experts (see Section B1.1). Clinical experts indicated that the clinical outcome of most relevance to CD patients with perianal fistulae should include a component of pain and discharge in addition to clinical remission. Therefore, additional *post hoc* analyses were performed using a clinical and patient-centric (CPC) definition of remission as a more clinically relevant outcome. A patient is considered to achieve CPC remission from complex perianal fistulae when:

- All the external openings are closed as per clinical assessment, i.e. not draining despite gentle finger compression (i.e. the clinical remission definition of ADMIRE-CD); AND
- The patient does not experience any pain or discharge, as determined by a score equal to 0 in both the pain and discharge dimensions of the PDAI (Sahnan 2018)

The time to CPC remission was the outcome used in the economic model, because expert clinical opinion indicated that this outcome represented more accurately the decision algorithm used in clinical practice (See Figure 1 in Section B.1.1). The *post hoc* analyses for time to CPC remission were performed using all available data from the ADMIRE-CD trial. In addition, to time to CPC remission, time to relapse from CPC remission was included as an additional *post hoc* analysis.

B.2.3.4 Patient characteristics

ADMIRE-CD was well randomised with consistency between the two treatment groups (Panes 2016); the majority of patients had received at least one treatment for CD in the past six months (91.6% darvadstrocel and 94.3% control). In the darvadstrocel group 45% (48/107) patients compared with 30% (31/105) patients in the control group had more than one fistula tract. Of the 212 randomly assigned patients, 95% (201/212) had a seton placed during the preparation visit (98% [105/107] patients in the darvadstrocel group and 91% [96/105] patients in the control group).

At randomisation, a smaller proportion of patients in the darvadstrocel group (15.0%) compared with the control group (21.0%) were recorded as taking immunosuppressants, and 24.3% were recorded as taking neither anti-TNF agents nor immunosuppressants (compared to only 18.1% of the control group).

When compared with control treatment, a higher proportion of patients treated with darvadstrocel reported that they had previously been treated with antibiotics (76.6% vs. 70.5%, for darvadstrocel and control treatment, respectively) or immunosuppressants (83.2% vs, 73.3%), while the previous use of biologics was similar (77.6% vs. 80.0%). No differences were observed in the mean baseline of PDAI, IBDQ, CDAI, and Van Assche scores.

The proportion of patients with more than one draining external fistula opening was slightly higher for patients randomised to darvadstrocel (56.1%, 36.4%, and 6.5%, for 1, 2 or >2 draining external openings, respectively) compared with control treatment (73.3%, 22.9%, and 2.9%, respectively). A similar pattern was observed for internal openings, and patients randomised to darvadstrocel were more likely to have two internal openings, compared with patients randomised to control treatment (19.6% vs. 10.5%, respectively). This may indicate that the patients randomised to darvadstrocel had more severe perianal fistulising disease in comparison to those randomised to the control treatment.

A comparison with patients from the retrospective study from St Mark's hospital indicated that patients in ADMIRE-CD had a similar age, but were more likely to be male. In addition, patients in the St Mark's study were more likely to have been previously treated with a biologic, as compared to the patients in the ADMIRE-CD trial (see Table 9).

Table 9: Characteristics of participants in the studies across treatment groups in ADMIRE-CD (ITT) and St Mark's retrospective study

	ADMIRE-CD		St Mark's study
Baseline characteristic	**darvadstrocel**	**Control**	
	(N=107)	(N=105)	(N=78)
Age, years (SD)	39.0 (13.1)	37.6 (13.1)	[redacted] year *
Gender, male, n (%)	60 (56%)	56 (53%)	[redacted]
Ethnic origin, n (%)			
Caucasian	100 (93%)	96 (91%)	[redacted]
Black	4 (4%)	1 (1%)	[redacted]
Other	0 (0%)	1 (1%)	[redacted]
Missing	3 (3%)	7 (7%)	[redacted]
Weight, kg (SD)	73.9 (15.0)	71.3 (14.9)	[redacted]
Duration CD, years (SD)	12.1 (10.0)	11.3 (8.9)	[redacted]
CD treatment in past 6 months, any, n (%)			
Antibiotics	82 (77%)	74 (70%)	
Immunosuppressants	89 (83%)	77 (73%)	
Anti-TNF	83 (78%)	84 (80%)	
Concomitant CD treatment (stratification factor), n (%)			
Anti-TNF	37 (35%)	33 (31%)	[redacted]~
Immunosuppressants	16 (15%)	22 (21%)	[redacted]~
Anti-TNF AND Immunosuppressants	28 (26%)	31 (30%)	[redacted]~
Neither	26 (24%)	19 (18%)	[redacted]~
Other concomitant CD treatments (safety population), n/N (%)			
Antibiotics	56/103 (54%)	41/102 (39%)	[redacted]
Corticosteroids	6/103 (5%)	7/102 (6%)	[redacted]
PDAI score (0 to 20, whereby a higher score indicates more severe perianal disease), mean (SD)	6.8 (2.5)	6.6 (2.9)	NR

	ADMIRE-CD		St Mark's study
Fistula internal openings (safety population), n/N (%)			
0	0/103 (0%)	1/102 (1%)	NR
1	82/103 (80%)	90/102 (88%)	
2	21/103 (20%)	11/102 (11%)	
Fistula external openings (safety population), n/N (%)			
1	58/103 (56%)	73/102 (72%)	NR
2	37/103 (36%)	25/102 (25%)	
>2	8/103 (8%)	4/102 (4%)	
CDAI score (0 to 600, whereby a higher score indicates more severe disease), mean (SD)	88.7 (48.8)	94.2 (58.7)	NR
IBDQ total score (32 to 224, whereby a higher score indicates better quality of life), mean (SD)	174.1 (31.2)	169.1 (36.7)	NR
C-reactive protein (nmol/L), mean (SD)	81.9 (123.8)	64.8 (102.9)	NR
Haemoglobin (g/L), mean (SD)	134 (13)	135 (13)	NR

Source: (Panes 2016, Tigenix 2016a), Appendix Q
Abbreviations: CD - Crohn's disease; SD - Standard deviation; TNF - Tumour necrosis factor, NR - Not reported
* Only age brackets reported, median bracket
~ Prior or current treatment

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The planned sample size in ADMIRE-CD was 208 patients (104 randomised to each group). The sample size was sufficient to detect a minimum 25% difference in the percentage of patients with combined remission between darvadstrocel and control treatment (anticipated minimum combined remission rates were 50% for darvadstrocel and 25% for control treatment) with a two-sided type I alpha error level of 0.025, 80% power, and allowing for 20% of patients to discontinue the trial.

Efficacy analyses were done in the following populations:

- Intention-to-treat (ITT) population; which included all randomly assigned patients (n=212)
- Modified ITT (mITT) population; which included all randomly assigned patients who received study treatment and had at least one efficacy assessment after baseline (n=204; seven patients did not receive treatment and one patient did not have any follow-up assessments)

The primary endpoint was also analysed in the per-protocol population, which included all randomised and treated patients who had both an MRI after baseline and clinical fistula assessment, with no major protocol deviations that affected the primary endpoint.

The two key secondary efficacy endpoints (clinical remission and response) were also analysed in the secondary per-protocol population, defined as all randomised and treated patients who had at least one clinical fistula assessment after baseline, with no major protocol deviations that affected these secondary end points.

Treatment Emergent Adverse Events (TEAEs) were analysed in the safety population, defined as all patients who received study treatment (n=205).

Table 10 presents a summary of the statistical analysis in the ADMIRE-CD trial.

Table 10: Summary of statistical analyses in ADMIRE-CD

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
To evaluate the efficacy and safety of darvadstrocel compared to control for the treatment of perianal fistulising CD over 24, 52 and 104 weeks	**Primary outcome** The primary endpoint was analysed using a stratified Cochran-Mantel-Haenszel test, adjusting for randomisation strata (i.e., CD treatments at randomisation), with a two-sided type I error level of 0.025. Treatment differences were expressed with 97.5% CIs. The primary analysis was conducted on the ITT population. **Key secondary outcomes** To address the issue of multiplicity, the two key secondary endpoints (clinical remission and response by week 24) were grouped into a short-term group with a gatekeeping method by Hochberg's testing procedure to control the overall type I error, with the primary efficacy endpoint acting as the gatekeeper. Statistical significance was tested with a two-sided type I error level of 0.05. **Other secondary outcomes** No statistical adjustment for multiplicity was made for non-key secondary endpoints. Percentages and treatment differences were expressed with 95% CIs calculated with a Wald's asymptotic method. Time to clinical remission and response were analysed with Kaplan-Meier estimates, supplemented with HRs from a stratified Cox-proportional model. Cox regression was done with adjustment for the randomisation stratum. For patients without an event (clinical remission, response, or relapse), censoring was applied at the date of the last visit at which the patient was observed. **Safety outcomes** Safety outcomes were presented with descriptive statistics.	212 patients recruited into trial; n= 107 darvadstrocel, and n= 105 control. The sample size was sufficient to detect a minimum 25% difference in the percentage of patients with combined remission between darvadstrocel and control (anticipated minimum combined remission rates were 50% for darvadstrocel and 25% for control) with a two-sided type I alpha error level of 0.025, 80% power, and allowing for 20% of patients to discontinue the study.	A non-response or non-remission was imputed if an MRI scan or clinical assessment was not done after baseline by week 24 and if a rescue event took place before week 24. A rescue event was defined as antibiotic treatment for more than 4 weeks; corticosteroids at 40 mg prednisone equivalent for at least 12 weeks; new anti-TNF compared with baseline treatment for at least 8 weeks; new immunosuppressant compared with baseline treatment for at least 12 weeks; or a surgical intervention for the treated fistula. The effects of rescue events and missing data conventions on efficacy were explored in supportive and sensitivity analyses of the primary endpoint.

Source: (Panes 2016, Tigenix 2016a)
Abbreviations: CD, Crohn's disease; CI, Confidence interval; HR, Hazard ratio; ITT, Intention-to-treat; MRI, Magnetic resonance imaging; TNF, Tumour necrosis factor

No interim analysis was planned or performed for this trial. The analysis after week 24 was the primary analysis. Analyses up to weeks 52 and 104, respectively, are follow-up analyses.

Subgroup analyses were performed in the ITT and mITT populations for the primary and key secondary efficacy outcomes at week 24. Within this report, only the results for the randomisation stratification factors are presented (i.e. concomitant anti-TNFs and immunosuppressants, concomitant anti-TNFs only, concomitant immunosuppressants only, or none of these two concomitant medications). All subgroup analyses should be interpreted with caution as in some instances the number of patients in each subgroup was small, making interpretation of the results difficult.

For the *post hoc* analyses, time to CPC remission and time to relapse from CPC remission, the reference population was the ITT, and the baseline time for the analysis was set as visit 0, i.e. treatment administration. Patients were censored at the time of their early termination visit, if any. In the case of missing dates for early termination visits, the dates were imputed as the day after the patients' last visit with a known date.

Achievement of CPC remission was determined only based on complete data on both the fistula status and PDAI scores, so that partially complete records reporting fistula status only, PDAI scores only, or none of the two, were considered not to contribute to events.

Log-rank analyses were performed to estimate the median time to CPC remission and median time to relapse from CPC remission. The results are presented as median time with its 95% confidence interval. In addition, the hazard ratio was estimated for darvadstrocel compared with control treatment.

B.2.4.1 Participant flow in the relevant randomised controlled trials

A total of 289 patients were enrolled and screened for participation in ADMIRE-CD, with 107 patients randomised to darvadstrocel and 105 patients randomised to control treatment, and were included in the intention-to-treat (ITT) and safety analysis sets. At the 24 week follow-up, 19 patients (17.8%) discontinued in the darvadstrocel arm, and 22 patients (21.0%) discontinued in the control arm. The CONSORT diagram is presented in Appendix D.2. The main reasons for discontinuation were substantial clinical deterioration (both arms), adverse events (AEs) (both arms), and patient decision/withdrawal of consent (control arm) (see Table 11).

Table 11: Patient disposition in ADMIRE-CD

Disposition	Darvadstrocel	Control
Patients randomised (ITT population)	107	105
Patients discontinuing before week 24, n (%)*		
Substantial clinical deterioration	7 (36.8%)	4 (18.2%)
Adverse event	7 (36.8%)	6 (27.3%)
Major protocol deviation	3 (15.8%)	1 (4.5%)
Withdrew consent, patient decision	1 (5.3%)	5 (22.7%)
Did not meet inclusion criteria	0 (0%)	2 (9.1%)
Other	1 (5.3%)	1 (18.2%)
Patients completed 24 weeks, n (%)	88 (82.2%)	83 (79.0%)
Patients completed 24 weeks follow-up and entered follow-up 52 weeks	84 (78.5%)	80 (76.2%)
Patients discontinuing between week 24 and 52, n (%)*		
Patients decision	2 (14.3%)	2 (10.5%)
Adverse event	4 (28.6%)	3 (15.8%)
Surgical procedures for other reasons than fistula		1 (5.3%)
Significant clinical deterioration	7 (50%)	7 (36.8%)
Major protocol deviation (worsening CD requiring change in therapy)	1 (7.1%)	6 (31.6%)
Patients completed 52 weeks, n (%)	70 (65.4%)	61 (58.1%)
Patients completed 52 weeks follow-up and entered in follow-up 104 weeks	[redacted]	[redacted]

Source: (Panes 2016, Panes 2017a, Tigenix 2017)
Abbreviations: CD, Crohn's disease
*Percentage is of the patients who discontinued

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

An assessment of the quality of the relevant clinical effectiveness evidence is presented in Appendix D.3. The ADMIRE-CD was a well performed clinical trial with a low risk of bias.

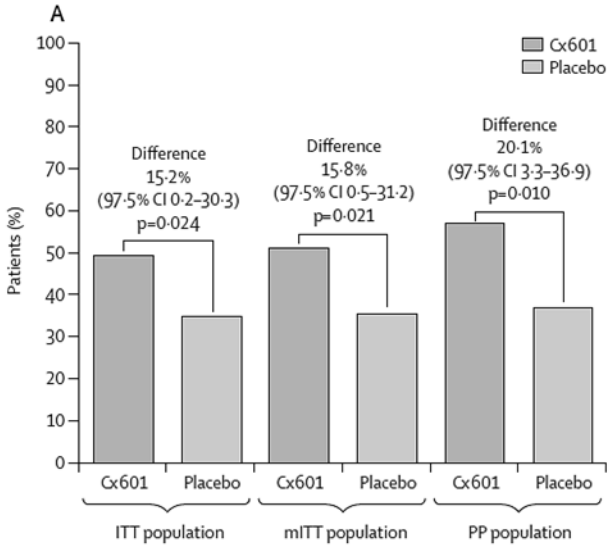
While the ADMIRE-CD trial was not performed in the UK, patients included were similar to those seen in UK clinical practice (see Section B.2.3.4). To adjust for treatment practices, where clinicians would prefer the CPC remission above combined remission, *post hoc* sensitivity analyses have been performed using this outcome (see Section B.2.4). CPC remission does not bias the results in favour of darvadstrocel, rather it better represents the assessment carried out in UK clinical practice.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Primary outcome – combined remission at week 24

A significantly greater proportion of patients in the darvadstrocel group than the control group achieved the primary endpoint of combined remission[5] at week 24 in the ITT population (50% vs. 34%, respectively, difference 15.2%, 97.5% CI: 0.2 to 30; p=0.024) (see Figure 8 and Table 12). The results were confirmed in the mITT and sensitivity analyses.

Figure 8: Combined remission at week 24



Source: Figure 1 from (Panes 2016)

Abbreviations: CI, Confidence interval; darvadstrocel, Allogeneic; expanded, adipose-derived stem cells; (m)ITT, (Modified) intention-to-treat; Placebo, Control treatment; PP, Per protocol

[5] Clinical remission is defined as the clinical assessment of closure of all treated external openings that were draining at baseline, and the absence of collections larger than 2 cm of the treated perianal fistulae in at least two of three dimensions, confirmed by masked central MRI.

Table 12: Combined remission, primary and supportive analyses at week 24

Population	Darvadstrocel		Control		Difference (%)	97.5% CI	p-value
	n/total N (%)	95% CI	n/total N (%)	95% CI			
ITT*	53/107 (49.5%)	40.1, 59.0	36/105 (34.3%)	25.2, 43.4	15.2%	0.2, 30.3	0.024
mITT	53/103 (51.5%)	41.8, 61.1	36/101 (35.6%)	26.3, 45.0	15.8%	0.5, 31.2	0.021
Sensitivity analyses							
Sensitivity 1	52/107 (48.6%)	n.r.	34/105 (32.4%)	n.r.	16.2%	1.3, 31.1	0.014
Sensitivity 2	53/107 (49.5%)	n.r.	36/105 (34.3%)	n.r.	15.2%	0.2, 30.3	0.024
Sensitivity 3	53/107 (49.5%)	n.r.	36/105 (34.3%)	n.r.	NA	NA	0.017

Source: (Panes, et al. 2016)
Abbreviations: CI, Confidence interval; (m)ITT, (Modified) intention-to-treat; NA, Not applicable; n.r., Not reported
* Primary analysis of the ADMIRE-CD trial
Sensitivity analysis 1: ITT, non-response/non-remission imputed for all missing data and after rescue therapy (no LOCF)
Sensitivity analysis 2: ITT, missing = non-response/non-remission after LOCF applied. Rescue medication not considered as failure
Sensitivity analysis 3: ITT, missing = non-response/non-remission after LOCF applied. Logistic analysis including stratification factor and number of baseline external openings as factors
Rescue therapy was defined as corticosteroids at 40 mg prednisone equivalent for ≥12 weeks; new anti-TNF compared with baseline therapy for ≥8 weeks; new immunosuppressant compared with baseline therapy for ≥12 weeks; or surgical intervention for the treated fistula

With longer follow-up (52 weeks), the statistically significant improvement in the percentage of patients who achieved combined remission with darvadstrocel compared with control treatment was maintained (see Table 13).

Table 13: Combined remission, longer follow-up, mITT population

Population	Darvadstrocel		Control		Difference (%)	97.5% CI	p-value
	n/total N (%)	95% CI	n/total N (%)	95% CI			
mITT week 24	53/103 (51.5%)	41.8, 61.1	36/101 (35.6%)	26.3, 45.0	15.8%	0.5, 31.2	0.021
mITT week 52	58/103 (56.3%)	[redacted]	39/101 (38.6%)	[redacted]	17.7%	4.2, 31.2*	0.010

Source: (Panes 2016, Panes 2017a)
Abbreviations: CI, Confidence interval; (m)ITT, (Modified) intention-to-treat; NA, Not applicable; n.r., Not reported
*95% CI reported

B.2.6.2 Key secondary outcome – Clinical remission and response at week 24

Both key secondary outcomes (clinical remission[6] and response[7] at week 24) resulted in numerically higher rates favouring darvadstrocel compared with control (see Table 14). At week 24, of the patients treated with darvadstrocel, 53.3% achieved clinical remission, while

[6] Clinical remission was defined as closure of all treated external openings that were draining at baseline despite gentle finger compression.
[7] Response was defined as closure of at least 50% of all treated external openings that were draining at baseline.

only 41.0% of the control patients achieved clinical remission (p=0.064). Darvadstrocel treatment resulted in rapid and sustained clinical remission from week 6 to week 24. Response was achieved in 66.4% of the patients treated with darvadstrocel compared with 53.3% of the control patients (p=0.054).

Table 14: Key secondary outcomes ADMIRE-CD, ITT population[a]

	Darvadstrocel N=107 n (%)	Control N=105 n (%)	Difference % (95%CI) [b]	p-value [b]
Clinical remission				
Week 6	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	57 (53.3%)	43 (41.0%)	12.3% (-1.0, 25.7)	0.064
Week 52[c]	61 (59.2%)	42 (41.6%)	17.6% (4.1, 31.1)	0.013
Week 104[d]	[redacted]	[redacted]	[redacted]	[redacted]
Response				
Week 6	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	71 (66.4%)	56 (53.3%)	13.0% (-0.1, 26.1)	0.054
Week 52[c]	68 (66.0%)	56 (55.4%)	10.6% (-2.8, 23.9)	0.128
Week 104	n.r.			

Source: Table 2 of (Panes 2016), Table 25, p116 of the (Tigenix 2016b), Table 26, p96 of the (Tigenix 2016a) and Table 26, p117 of the (Tigenix 2016b), (Tigenix 2017), and (Panes 2017a)
Abbreviations: CI, Confidence interval; n.r., Not reported
[a] Last observation carried forward rules applied. Treatment failure is imputed after rescue therapy.
[b] Difference in remission rate was calculated using Wald's stratified asymptotic method. For difference in Remission rate (darvadstrocel – Placebo) p-value is from Cochran-Mantel-Haenszel test, randomisation strata as stratification variables
[c] mITT population
[d] mITT population for patients who completed the 52 weeks follow-up and entered the follow-up 104 weeks

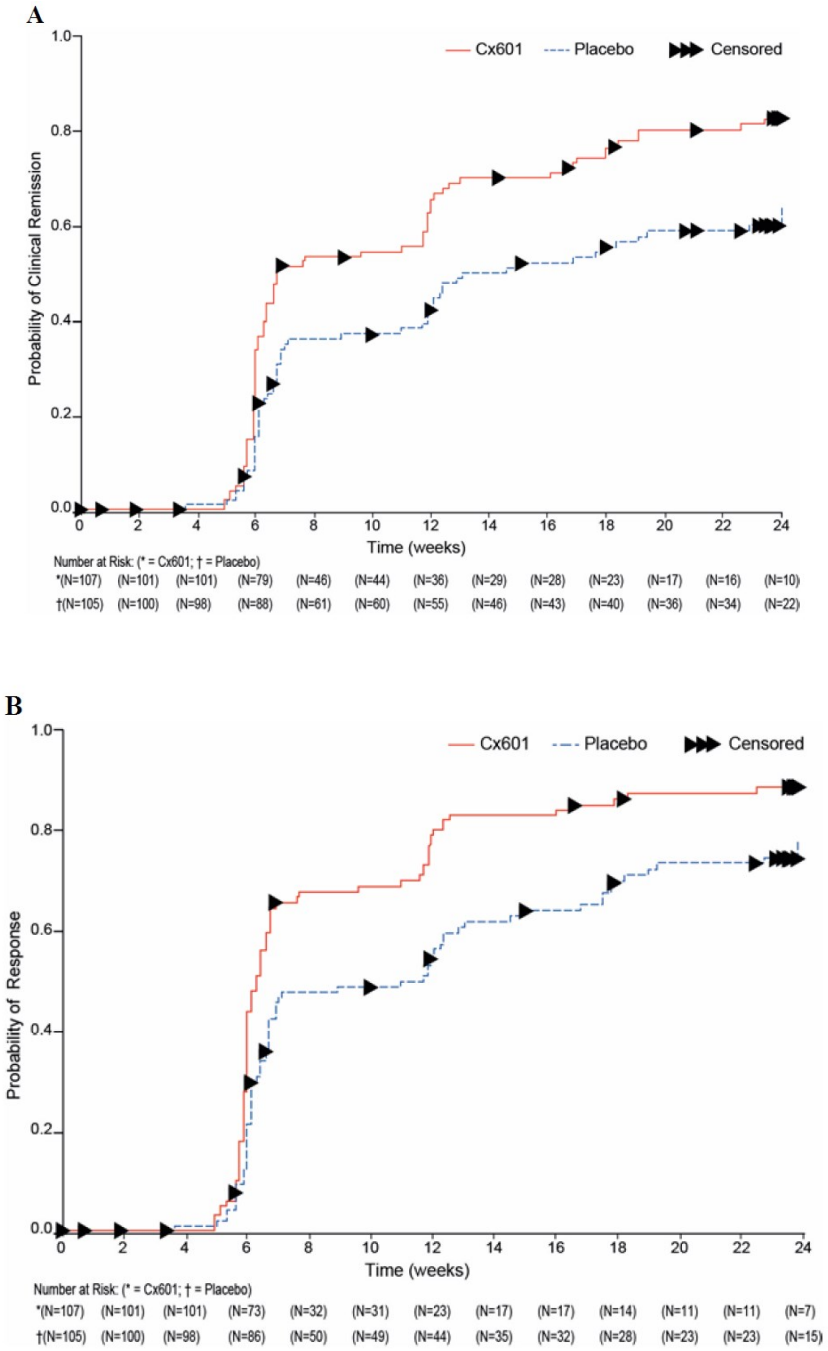
B.2.6.3 Other secondary outcomes

B.2.6.3.1 Time to event results

For those patients achieving clinical remission, the time to achieve this was statistically significantly faster by 7.9 weeks for darvadstrocel compared with control treatment (6.7 vs. 14.6 weeks, respectively) (see Figure 9 and Table 15). Similarly, for those patients achieving a response, the time to response was statistically significantly faster by 5.4 weeks with darvadstrocel, compared to control treatment (6.3 vs. 11.7 weeks, respectively) (see Figure 9 and Table 15).

Time to combined remission was similar between darvadstrocel and control treatment (see Table 15). This lack of difference was due to the inclusion of MRI measurement to assess whether a patient had a combined remission, as MRI measurements were only performed at week 24 and week 52.

Figure 9: Kaplan-Meier plots of clinical remission (A) and response (B) in the ITT population of the ADMIRE-CD trial, week 24



Source: Supplement of (Panes 2016)

Abbreviations: ITT = intention to treat; Placebo = control treatment

Table 15: Time to combined remission, clinical remission and response of perianal fistula by Week 24, ITT Population

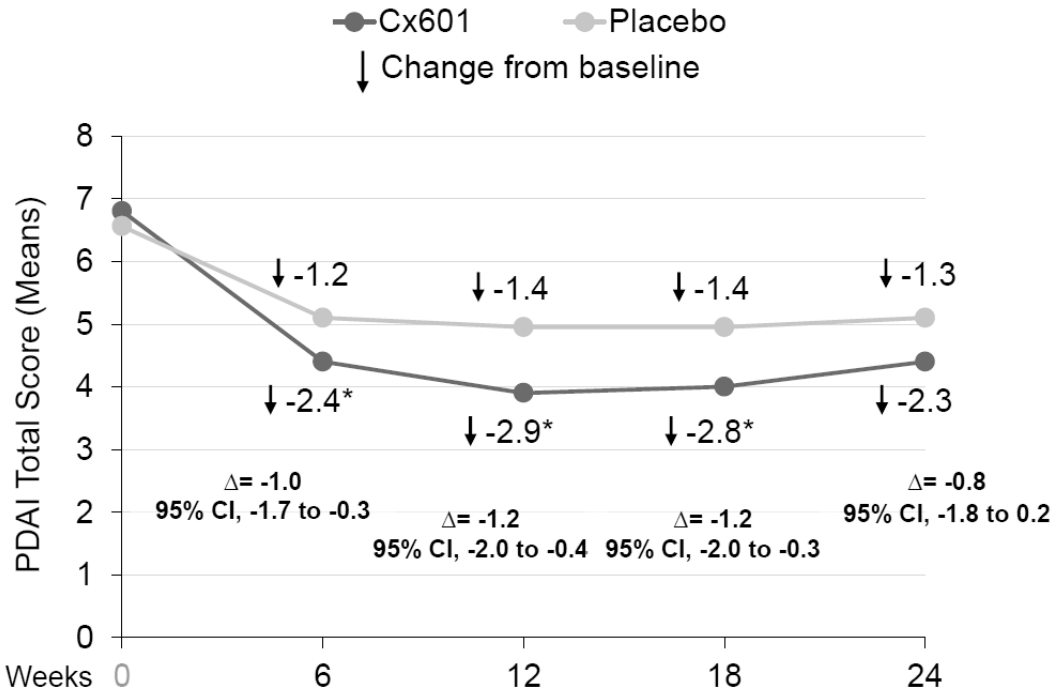
	Darvadstrocel (N=107)	Control (N=105)	Hazard Ratio (95% CI)
Combined remission			
Combined remission, n (%) *	xx (xx%)	xx (xx%)	
Censored cases, n (%)	xx (xx%)	xx (xx%)	
Kaplan-Meier Estimates, Median (95% CI), weeks	25.0 (24.7, 26.1)	28.1 (24.7, 36.0)	0.74 (0.48, 1.14)
Clinical remission			
Clinical remission, n (%)*	xx (xx%)	xx (xx%)	
Censored cases, n (%)	xx (xx%)	xx (xx%)	
Kaplan-Meier Estimates, Median (95% CI), weeks	6.7 (6.4, 11.9)	14.6 (11.9, 22.9)	0.57 (0.41, 0.79)
Response			
Response, n (%)*	xx (xx%)	xx (xx%)	
Censored cases, n (%)	18 (16.8%)	30 (28.6%)	
Kaplan-Meier Estimates, Median (95% CI), weeks	6.3 (6.0, 6.6)	11.7 (6.7, 12.9)	0.59 (0.43, 0.81) 0.62 (0.45, 12.9)

Figures have been rounded to 1 decimal place
Source: (Panes 2016), and Table 23 and pages 92-94 of (Tigenix 2016a)
Abbreviations: CI, Confidence interval; ITT, Intention-to-treat
* Achieved at least once during the 24-week follow-up

B.2.6.3.2 PDAI score

The PDAI scores in the mITT population decreased over time in both groups, with a larger decrease of 1.0 to 1.2 points observed with darvadstrocel treatment compared with control treatment at 6, 12, and 18 weeks Figure 10. Individual domain scores followed the same trend (Table 16).

Figure 10: PDAI[#] score over time in ADMIRE-CD, mITT population



Source: adapted from (Panes 2016)

Abbreviations: CI, Confidence interval; Cx601, Darvadstrocel; mITT, Modified intention-to-treat; PDAI, Perianal Disease Activity Index; Placebo, Control treatment

* The 95% CI for between-group difference was derived from an analysis of covariance (ANCOVA) model with treatment group and stratum as factors and baseline value as covariate, and asterisk indicated that the 95% CI did not cross 0.

PDAI score ranges from 0-20, whereby a higher score indicates more severe disease

Table 16: Individual domain scores of the PDAI over time in ADMIRE-CD, mITT population

	Darvadstrocel		Control		Treatment difference (95% CI)
	N	mean (SD)	N	mean (SD)	
Discharge					
Baseline	xxx	xx (xx,xx)	xxx	xx (xx,xx)	
6 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
12 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
18 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
24 weeks	103	1.00 (1.138)	99	1.24 (1.126)	-0.288 (-0.606, 0.030)
Pain					
Baseline	xxx	xx (xx,xx)	xxx	xx (xx,xx)	
6 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
12 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
18 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
24 weeks	103	0.65 (0.997)	99	0.74 (1.065)	-0.098 (-0.369, 0.173)
Restriction of sexual activity					
Baseline	xxx	xx (xx,xx)	xxx	xx (xx,xx)	
6 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
12 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
18 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
24 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
Type of perianal disease					
Baseline	xxx	xx (xx,xx)	xxx	xx (xx,xx)	
6 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
12 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
18 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
24 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
Degree of induration					
Baseline	xxx	xx (xx,xx)	xxx	xx (xx,xx)	
6 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
12 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
18 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)
24 weeks	xxx	xx (xx,xx)	xxx	xx (xx,xx)	xx (xx,xx)

Source: Table 14.1.4.1.2 of CSR
Abbreviations: CI, Confidence interval; mITT, Modified intention-to-treat; SD, Standard deviation
Bold is significant difference, p-value ≤0.05

B.2.6.3.3 CDAI, IBDQ and Van Assche Score

Not unexpectedly, darvadstrocel did not have an effect on instruments designed primarily to assess the impact of luminal CD, such as the CDAI or IBDQ (see Table 17). Since patients with active luminal disease were excluded from the study, CDAI scores were low and IBDQ scores were high throughout as expected.

There were no differences in the Van Assche score at week 24 or week 52 (see Table 17). Although changes in the Van Assche score have a good correlation with clinical response of the perianal fistula to immunosuppressive therapy, and the index has been partially validated in small studies to show the score is responsive to medical therapy, the Van Assche score has several limitations which may explain the absence of any change between weeks 24 and 52. The main limitation in the index is that it has not been fully validated, and responsiveness of each individual item of the score was not determined. In addition, there is no cut-off to define clinically significant improvement or remission (Panes 2017c).

Table 17: Results of other secondary outcomes in the ADMIRE-CD trial, mITT population

Outcome	Darvadstrocel	Control	Treatment difference (95% CI)	p-value
IBDQ#, mean (SD)				
Baseline	173.5 (31.6)	169.4 (36.1)	n.r.	n.r.
Week 24	178.3 (34.6)	174.7 (36.2)	n.r.	n.r.
Change from baseline	3.8 (25.5)	4.0 (25.6)	0.3 (-6.6, 7.3)	0.923
Week 52	176.1 (38.1)	172.7 (40.6)	n.r.	n.r.
Change from baseline	2.1 (27.4)	1.7 (25.0)	0.7 (-6.7, 8.2)	0.849
CDAI$, mean (SD)				
Baseline	87.8 (48.3)	93.3 (55.0)	n.r.	n.r.
Week 24	92.5 (66.5)	94.1 (76.1)	n.r.	n.r.
Change from baseline	5.7 (62.2)	2.2 (65.5)	1.8 (-16.0, 19.7)	0.839
Week 52	97.4 (82.7)	99.2 (77.8)	n.r.	n.r.
Change from baseline	11.1 (80.5)	7.6 (67.3)	-1.3 (-19.6, 22.1)	0.906
Van Assche Score^				
Baseline	9.0	9.4	n.r.	n.r.
Week 24	8.6	9.0	0.004 (-0.686, 0.694)	n.r.
Change from baseline	n.r.	n.r.	n.r.	n.r.
Week 52	xx	xx	xx (xx, xx)	n.r.
Change from baseline	n.r.	n.r.	n.r.	n.r.

Source: Supplement of (Panes 2016); CSR week 52 (Tables 14.2.2.10.2.2.1, 14.2.2.11.2.2.2, 14.2.2.12.2.1.1), and (Panes 2017a)

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, Confidence interval; IBDQ, Inflammatory Bowel Disease Questionnaire; mITT, Modified intention-to-treat; PDAI, Perianal Disease Activity Index; SD, Standard deviation

IBDQ score ranges from 32 to 224, whereby a higher score indicates a better quality of life

$ CDAI score ranges from 0 to 600, whereby a higher score indicates that the disease is more active / severe

^ Van Assche score ranges from 0-22, whereby a higher score indicates more severe disease

B.2.6.4 *Post hoc* analyses

B.2.6.4.1 Time to CPC remission

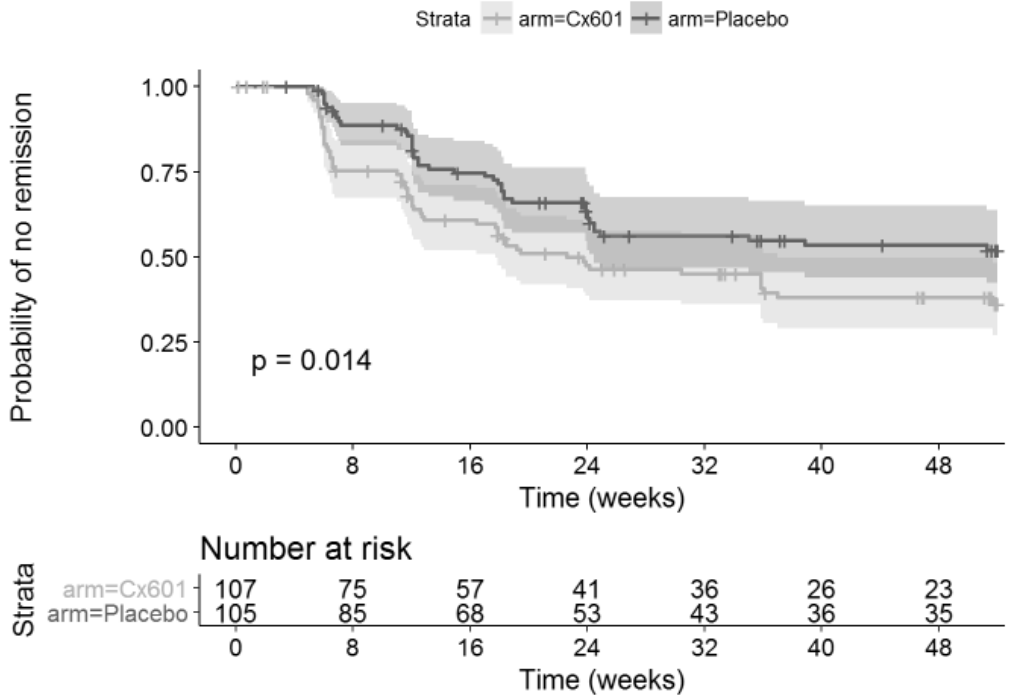
As presented in Section B.2.3.3, *post hoc* analyses were performed on the time to CPC remission, as this outcome was considered by clinical experts the most relevant outcome in clinical practice.

Figure 11 shows the Kaplan-Meier curves for the two trial arms in the ADMIRE-CD trial. It should be noted that as the event is preferable, a smaller area under the curve indicates both a faster and increased access to remission. The time to remission was significantly shorter for the darvadstrocel arm when compared to control (log-rank test: X_1^2=6.0, p=0.014), aligned with the statistically significant improvement of the primary outcome of ADMIRE-CD (see Section B.2.6.1). It is worth noting that zero events occurred in the first

four weeks after treatment administration, due to the schedule of assessment as per the trial protocol – the first clinical assessment was scheduled six weeks (SD: 2 weeks) after treatment. This analysis yields very similar results to the combined remission results published for the ITT population in the ADMIRE-CD trial (Panes 2016).

A summary of the Kaplan-Meier estimates is reported in Table 18.

Figure 11: Time to CPC remission, ITT population



Source: *Post hoc* analyses of ADMIRE-CD, data on file

Abbreviations: CPC, Clinical and patient-centric; Cx601, Darvadstrocel; Placebo, Control treatment

Table 18: Time to CPC remission, ITT Population

	Darvadstrocel (N=107)	Control (N=105)	Hazard Ratio (95% CI)
CPC remission, n (%)	59 (55.1%)	43 (41.0%)	
Kaplan-Meier Estimates, Median (95% CI), weeks*	28.7 (17.7, 37.0)	35.2 (24.4, NA)	0.61 (0.42, 0.91)
Log-rank test			X_1^2=6.0, p=0.014

Source: *Post hoc* analyses of ADMIRE-CD, data on file
Abbreviations: CI, Confidence interval; CPC, Clinical and patient-centric
* Restricted mean with upper limit of 52 weeks

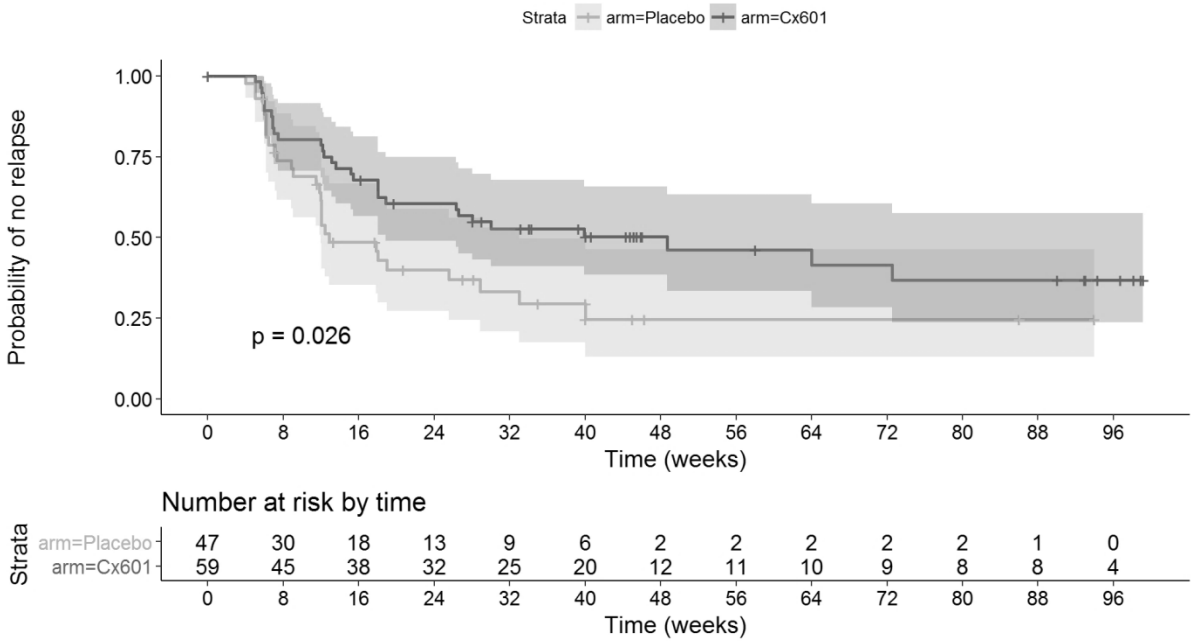
B.2.6.4.2 Time to relapse from CPC remission

As presented in Section B.2.3.3, *post hoc* analyses were performed on the time to CPC relapse, as this outcome was considered by the clinical experts as the most relevant outcome.

Figure 12 shows the Kaplan-Meier curves for the two trial arms in the ADMIRE-CD trial. The two curves are clearly separated, as also confirmed by the rejection of the null hypothesis of no difference using a log-rank test (X_1^2=4.9; p=0.0262).

In the trial, 47 and 59 patients achieved CPC remission respectively in the control and darvadstrocel arm; 28 and 30 of patients lost CPC remission and relapsed before the end of the follow-up. The median time to relapse of CPC remission was substantially and statistically significantly longer in the darvadstrocel arm than in the control arm, with half of the events occurring after 48.7 versus 12.9 weeks in the two arms, highlighting that treatment with darvadstrocel led to sustained CPC remission in the ADMIRE-CD trial.

Figure 12: Time to relapse from CPC remission, ITT population



Source: *Post hoc* analyses of ADMIRE-CD, data on file

Abbreviations: CPC, Clinical and patient-centric; Cx601, Darvadstrocel; Placebo, Control treatment

Table 19: Time to CPC relapse, ITT Population

	Darvadstrocel (N=107)	Control (N=105)	Hazard Ratio (95% CI)
Patients at risk	N=59	N=47	
CPC relapse, n (%) *	30 (50.8%)	28 (59.6%)	
Kaplan-Meier Estimates, Median (95% CI), weeks	48.7 (18.9, NA)	12.9 (12.0, 33.0)	1.38 (0.89, 2.12)
Log-rank test			X_1^2=4.9, p=0.0262

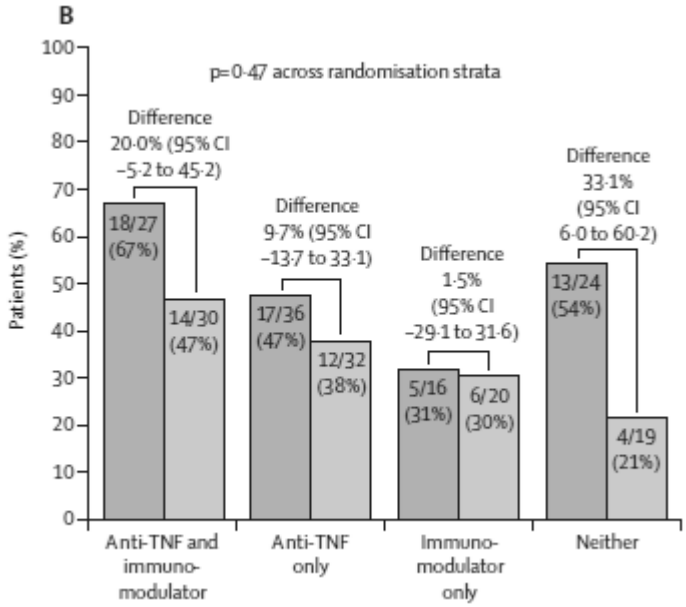
Source: *Post hoc* analyses of ADMIRE-CD, data on file
Abbreviations: CI, Confidence interval; CPC, Clinical and patient-centric; NA, Not available

B.2.7 Subgroup analysis

In the mITT population, the effect of darvadstrocel on combined remission was proportionally greater than control in the four randomisation strata (see Figure 13), with the difference between groups being greatest in patients receiving neither (difference 33.1%, 95% CI: 6.0 to 60.2) or both anti-TNF and immunosuppressant treatments (20.0%, 95% CI: –5.2 to 45.2) at randomisation, however, the difference in the treatment effect between the four stratification groups was not significant (p=0.47). The trial was not powered for the subgroup analyses due to the small patient numbers in these subgroups.

The ITT analysis demonstrates a benefit of darvadstrocel treatment on both achievement of remission and maintenance of remission (reflected in a lower relapse rate). Both of these factors contribute significantly to the effective treatment of patients with complex perianal fistula. Due to low patient numbers during the 52 week follow up, it is not possible to analyse the relapse rates within these subgroups, and so this data is not included in the economic model.

Figure 13: Results of combined remission for the stratification groups in ADMIRE-CD, 24 weeks, mITT population



Source: Figure 2 of (Panes 2016)
Abbreviations: CI, Confidence interval; mITT, Modified intention to treat; TNF, Tumour necrosis factor
Pink, Darvadstrocel; Blue, Control
Stratification was by concomitant therapy: anti-TNF and immunosuppressant, anti-TNF only, immunosuppressant only, or neither

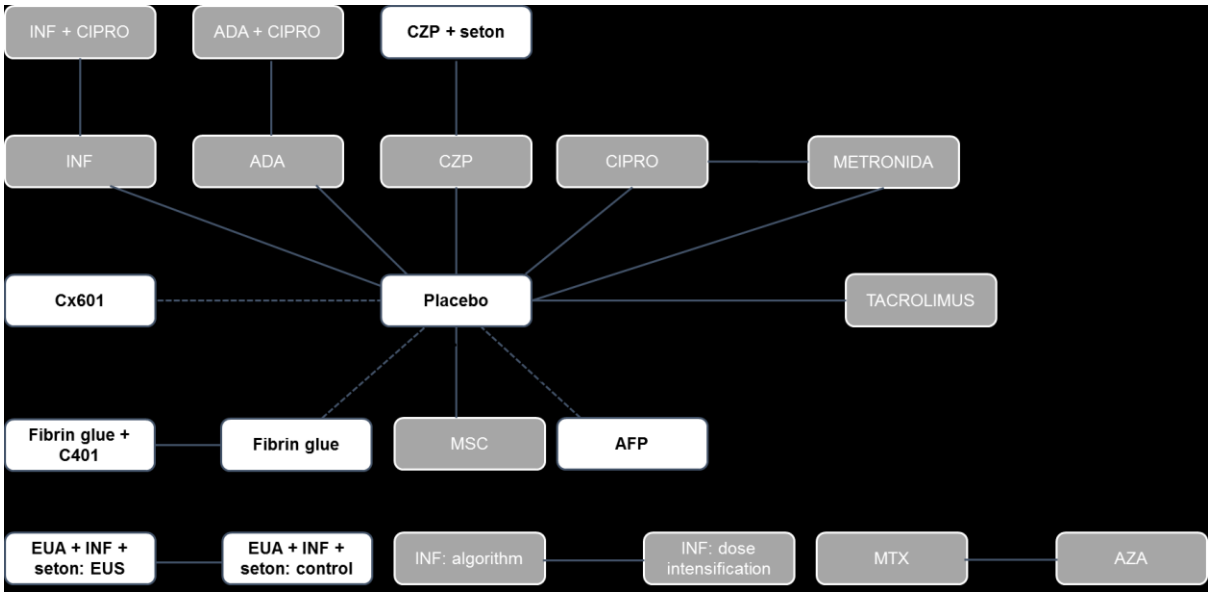
B.2.8 Meta-analysis

A meta-analysis was not possible as only one study included darvadstrocel in the target CD patient population with complex perianal fistula.

B.2.9 Indirect and mixed treatment comparisons

Details of the search to identify RCTs relevant for consideration in a network meta-analysis (NMA) are presented in Section B.2.1. A network diagram used to consider for inclusion in a NMA is provided below (Figure 14). Of the 19 RCTs identified by the systematic review, only six trials included stem cell therapy or surgical treatments (Garcia-Olmo 2009, Grimaud 2010, Schwartz 2015, Wiese 2015, Panes 2016, Senejoux 2016), and only the ADMIRE-CD trial used darvadstrocel (Panes 2016). The Wiese 2015 trial was excluded from comparison, due to a lack of common comparator connecting to the ADMIRE-CD trial (Wiese 2015).

Figure 14: Randomised controlled trials contributing to the master evidence network



Abbreviations: AFP, Anal Fistula Plugs; ADA, Adalimumab; AZA, Azathioprine INF, Infliximab; CIPRO, Ciprofloxacin; CZP, Certolizumab Pegol; EUS, endoscopic ultrasound; EUA, Examination under Anaesthesia; METRONIDA, Metronidazole; MSC, Mesenchymal Stromal Cells; MTX, Methotrexate
Note: Placebo group is not a true representation of a placebo response for all the studies connected to the network. For few studies the observational group or control group was assumed as placebo treated group to facilitate linking of Cx601 through common comparator
*Patients in both the treatment groups received standard of care, so placebo group is not true representative of placebo effect; ^Placebo group represents observational group after seton removal alone (Control group); **Placebo group represents patients under observation

For the remaining five trials selected for inclusion in the evidence network, a feasibility assessment was conducted to evaluate comparability across studies including study design, patient demographics and availability of data. Details on these studies are presented in Appendix D.4. Considering heterogeneity across trials, the following assumptions were made to compare darvadstrocel to the surgical interventions in the remaining trials:

- Studies reporting results at the time point window of 4 weeks on either side of primary or secondary efficacy endpoints of the ADMIRE-CD trial were considered for analysis
- Studies reporting results for at least 10 patients in each treatment arm were included

Based on these inclusion criteria, three of the five remaining relevant RCTs were excluded. The Garcia-Olmo 2009 trial was excluded due to a sample size of 7 patients (Garcia-Olmo 2009). Schwartz 2015 was excluded as it only reported on PDAI score (Schwartz 2015). Grimaud 2011 was an open label study which only reported on a subgroup of patients with complex perianal fistulae in CD, prior therapy details for this subgroup of patients were not reported. In addition, the endpoint for assessment of fistula closure was at 10 weeks, compared to 24 weeks in the ADMIRE-CD trial (Grimaud 2010).

The remaining two RCTs, ADMIRE-CD and Senejoux 2016 trials were considered for inclusion. Although darvadstrocel could be compared to anal fistula plugs for complete response through these trials, the analysis may not estimate true treatment effect due to variations in the patient population. Fistula plugs are not commonly used for the patient population relevant to this submission, and direct evidence is available for the main comparator treatment used in UK clinical practice. Senejoux 2016 only included a subgroup of patients with complex perianal fistulae in CD, and the proportion of patients who were refractory to conventional therapy was not reported (Senejoux 2016). Additionally, the placebo used in the ADMIRE-CD trial was not a true placebo as EUA, curettage and seton placement were conducted in both arms of the study which is an active treatment and represents the most commonly conducted surgical intervention in UK clinical practice.

Following the feasibility assessment, it was concluded that an NMA could not be conducted due to a lack of comparable RCTs and considerable heterogeneity in the studies identified by the systematic review. The assessment found a high level of variability in the comparators, outcomes, patient populations, and sample size across studies.

B.2.10 Adverse reactions

Darvadstrocel is well tolerated, with a similar safety profile as control treatment (see Table 20, Table 21, and Table 22).

No statistical analyses were performed between the two treatment groups. Approximately two-thirds of the patients treated with either darvadstrocel or control experienced a TEAE. Most TEAEs were mild or moderate in intensity. After 24 weeks, fewer patients treated with darvadstrocel compared with control experienced treatment-related TEAEs (17% vs. 29%, for darvadstrocel and control, respectively) (see Table 20).

The most commonly reported TEAEs were proctalgia, anal abscess, and nasopharyngitis with no differences between darvadstrocel and control (see Table 21). The most common treatment-related TEAEs were anal abscess and proctalgia. Anal abscess and proctalgia are associated with fistulae and represent treatment failure rather than being caused by the treatment. Five (5%) of 103 patients in the darvadstrocel group, and six (6%) of 102 in the control group withdrew from the study because of TEAEs. A similar percentage of patients in the darvadstrocel and control group experienced serious TEAEs (17% vs. 14%, respectively), the most common of which was anal abscess (darvadstrocel 9% vs. control 7%). Five (5%) of the patients in the darvadstrocel group versus seven (7%) in the control group experienced serious TEAEs. Five patients (5%) in each group had serious a TEAE of anal abscess. No deaths occurred during the trial. The safety profile at 52 weeks was similar to that observed at week 24.

Table 20: Summary of treatment-emergent adverse events and treatment-emergent serious adverse events up to Week 24 in ADMIRE-CD, safety population

	TEAE		TESAEs	
	darvadstrocel N=103	Control N=102	darvadstrocel N=103	Control N=102
	n (%)	n (%)	n (%)	n (%)
TEAEs/TESAEs	68 (66.0%)	66 (64.7%)	18 (17.5%)	14 (13.7%)
Withdrawn TEAEs leading to study withdrawal	5 (4.9%)	6 (5.9%)	4 (3.9%)	4 (3.9%)
Intensity of TEAEs				
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Treatment related	18 (17.5%)	30 (29.4%)	5 (4.9%)	7 (6.9%)
Outcome of TEAEs/TESAEs				
Death	[redacted]	[redacted]	[redacted]	[redacted]
Not recovered	[redacted]	[redacted]	[redacted]	[redacted]
Recovered with sequelae	[redacted]	[redacted]	[redacted]	[redacted]
Recovered without sequelae	[redacted]	[redacted]	[redacted]	[redacted]
Changed intensity	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 3,(Panes 2016); Table 32, p108 of (Tigenix 2016a)
Abbreviation: TEAE, Treatment-emergent adverse event; TESAE, Treatment-emergent serious adverse event

Table 21: TEAEs, treatment-related TEAEs, severe TEAEs and TESAEs up to Week 24 in ≥5 patients in either treatment group, of ADMIRE-CD, safety population

Number patients (%)	TEAE		Treatment related TEAE		Severe TEAE		TESAE	
	darvadstrocel N=103	Control N=102	darvadstrocel N=103	Control N=102	darvadstrocel N=103	Control N=102	darvadstrocel N=103	Control N=102
Number of patients	68 (66%)	66 (64.7%)	18 (17.5%)	30 (29.4%)	[redacted]	[redacted]	18 (17.5%)	14 (13.7%)
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proctalgia	13 (12.6%)	11 (10.8%)	5 (4.9%)	9 (8.8%)	[redacted]	[redacted]		
Diarrhoea	7 (6.8%)	3 (2.9%)						
Abdominal pain	4 (3.9%)	6 (5.9%)						
Anal fistula	3 (3%)	6 (6%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and Infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anal abscess	12 (11.7%)	13 (12.7%)	6 (5.8%)	9 (8.8%)	[redacted]	[redacted]	9 (8.7%)	7 (6.9%)
Nasopharyngitis	10 (9.7%)	5 (4.9%)						
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]						
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]				
Fistula discharge	[redacted]	[redacted]	1 (<1.0%)	2 (2.0%)				
Skin and Subcutaneous tissue disorders	[redacted]	[redacted]						

Number patients (%)	TEAE		Treatment related TEAE		Severe TEAE		TESAE	
Injury, Poisoning and procedural complications	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)				
Procedural pain			xx (xx%)	xx (xx%)				
Investigations	xx (xx%)	xx (xx%)						

Source: Table 3, (Panes 2016); Table 33, p110 of (Tigenix 2016a); Table 34, p112 of (Tigenix 2016a); Table 35, p113 of (Tigenix 2016a), Table 38, p118 of (Tigenix 2016a)

Abbreviations: TEAE, Treatment-emergent adverse event; TESAE, Treatment-emergent serious adverse event

Table 22: Longer-term safety from ADMIRE-CD, safety population

Number patients (%)	Week 24		Week 52	
	darvadstrocel N=103	Control N=102	darvadstrocel N=103	Control N=102
TEAEs	68 (66.0%)	66 (64.7%)	79 (76.7%)	74 (72.5%)
Treatment-related	18 (17.5%)	30 (29.4%)	21 (20.4%)	27 (26.5%)
Withdrawn due to AEs	5 (4.9%)	6 (5.9%)	9 (8.7%)	9 (8.8%)
Treatment-related AEs in ≥5% of patients				
Anal abscess	6 (5.8%)	9 (8.8%)	[redacted] 13 (12.6%)*	[redacted] 16 (15.7%)*
Proctalgia	5 (4.9%)	9 (8.8%)	5 (4.9%)	8 (7.8%)
Serious TEAEs	18 (17.5%)	6 (5.9%)	25 (24.3%)	21 (20.6%)
Treatment-related	5 (4.9%)	7 (6.9%)	7 (6.8%)	7 (6.9%)
Serious treatment-related AEs in ≥2% of patients				
Anal abscess	5 (5%)	5 (5%)	7 (6.8%)*	7 (6.9%)*

Source: Table 3, (Panes 2016); Table 2 (Panes 2017b); Table 43, (Tigenix 2016b); (Panes 2017a)

Abbreviations: AE, Adverse event; TEAE, Treatment-emergent adverse event

* Anal abscess/fistula included the following preferred terms: anal abscess, anal fistula, fistula, fistula discharge and infected fistula.

Procedure-emergent, and non-treatment-emergent adverse event rates up to week 24, were similar for darvadstrocel and placebo (see Table 23).

Table 23: Procedure-emergent, non-treatment-emergent adverse events up to Week 24 in ≥2 patients in either treatment group of ADMIRE-CD, safety population

Number patients (%)	darvadstrocel N=103	Control N=102
Number of patients with PENTEs	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Infections and Infestations	[redacted]	[redacted]
Injury, Poisoning and procedural complications	[redacted]	[redacted]
Procedural pain	[redacted]	[redacted]

Source: Table 36, p114 of (Tigenix 2016a)

Abbreviations: PENTE, Procedure-emergent, non-treatment-emergent adverse event

Blood samples from 63 darvadstrocel-treated and 60 placebo-treated patients were analysed for the presence of donor-specific antibodies at baseline and week 12. Ten (16%) patients

in the darvadstrocel group and nine (15%) in the placebo group had pre-existing IgG HLA class I antibodies at baseline. At week 12, 18 (34%) of 53 darvadstrocel-treated patients and none of the placebo-treated patients who tested negative at baseline generated anti-HLA class I antibodies. There were no immune reactions or TEAEs associated with the development of donor-specific antibodies, and no association between positivity for donor-specific antibodies and therapeutic response.

Appendix F details the AEs observed in the single arm darvadstrocel study (de la Portilla 2013). The safety profile of darvadstrocel in this study is consistent with those found in ADMIRE-CD.

The RCTs considered in Section B.2.9 did not present comparable AEs. Therefore, no network meta-analyses for AEs were performed.

B.2.11 Ongoing studies

No additional trials or studies including darvadstrocel will be available in the next 12 months for CD patients with complex perianal fistulae.

B.2.12 Innovation

Darvadstrocel is the only licenced treatment for CD patients who have complex perianal fistulae. It represents a new and novel treatment paradigm, and will be the first licensed allogenic stem cell treatment in the UK.

Darvadstrocel offers a novel treatment option with curative intent for complex perianal fistula in adult patients with non-active or mildly-active luminal CD, where fistulae are refractory to conventional or biologic agents, or in patients intolerant to such treatments (a group who currently have few effective therapies available). Additionally, the overarching clinical benefit of darvadstrocel is the long-term reduction in the need for last-resort surgeries, which often negatively impacts the mental health of CD patients, as well as their ability to seek employment, have relationships and maintain a normal and active life (see Section B.1.3.2). The main advantage of darvadstrocel is that it is a localised treatment with minimal side effects and sustained clinical efficacy. Darvadstrocel provides the opportunity for fistula healing in patients who are currently offered only palliative treatment (e.g. a permanent seton), and this is an important subgroup within the darvadstrocel eligible population.

The innovative properties of darvadstrocel discussed above will lead to an impactful and positive change in the management of perianal fistula, in CD patients.

B.2.13 Interpretation of clinical effectiveness and safety evidence

ADMIRE-CD demonstrates a superior clinical efficacy and tolerability profile when compared to current treatment options, and offers a novel approach in a group of difficult to treat CD patients with perianal fistula. Results from the clinical study support the use of darvadstrocel

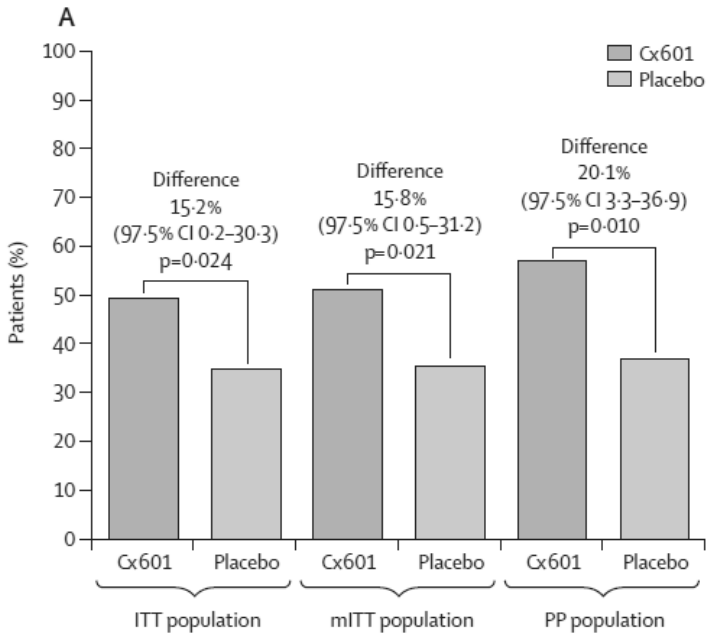
as an effective well-tolerated treatment option for adult CD patients with chronic symptomatic perianal fistulae in the UK.

B.2.13.1 Principal findings of the clinical evidence base

The key clinical evidence for darvadstrocel is derived from the pivotal Phase III randomised, double-blind ADMIRE-CD trial evaluating the efficacy, safety and tolerability of darvadstrocel versus control treatment in CD patients with complex perianal fistula. The primary outcome, combined remission, was defined as the clinical assessment of closure of all treated external openings that were draining at baseline, and the absence of collections larger than 2 cm of the treated perianal fistula in at least two of three dimensions, confirmed by MRI. Clinical assessment of closure was defined as the absence of draining despite gentle finger compression.

ADMIRE-CD met its primary objective, demonstrating a significant improvement in combined remission at 24 weeks with darvadstrocel versus control treatment in CD patients with complex perianal fistula. This was seen as an improvement in combined remission of 15.2% for darvadstrocel versus control treatment (49.5% vs. 34.3%, [97.5% CI: 0.2% to 30.3%, p-value = 0.024]) see Figure 15. Additionally, of patients with combined remission at week 24, a greater proportion of those treated with darvadstrocel versus control had no relapse at week 52 (75.0% vs. 55.9%).

Figure 15: Combined remission at week 24



Source: Figure 1 from (Panes 2016)

Abbreviations: CI, Confidence interval; darvadstrocel, Allogeneic; expanded, adipose-derived stem cells; (m)ITT, (Modified) intention-to-treat; Placebo, Control treatment; PP, Per protocol

The ADMIRE-CD trial also demonstrated the consistent superiority of darvadstrocel versus control treatment across the key secondary and other secondary outcomes:

- The clinical remission improved by 12.3% at week 24 (53.3% vs. 41.0%; 95% CI: -1.0% to 25.7%, p-value = 0.064);

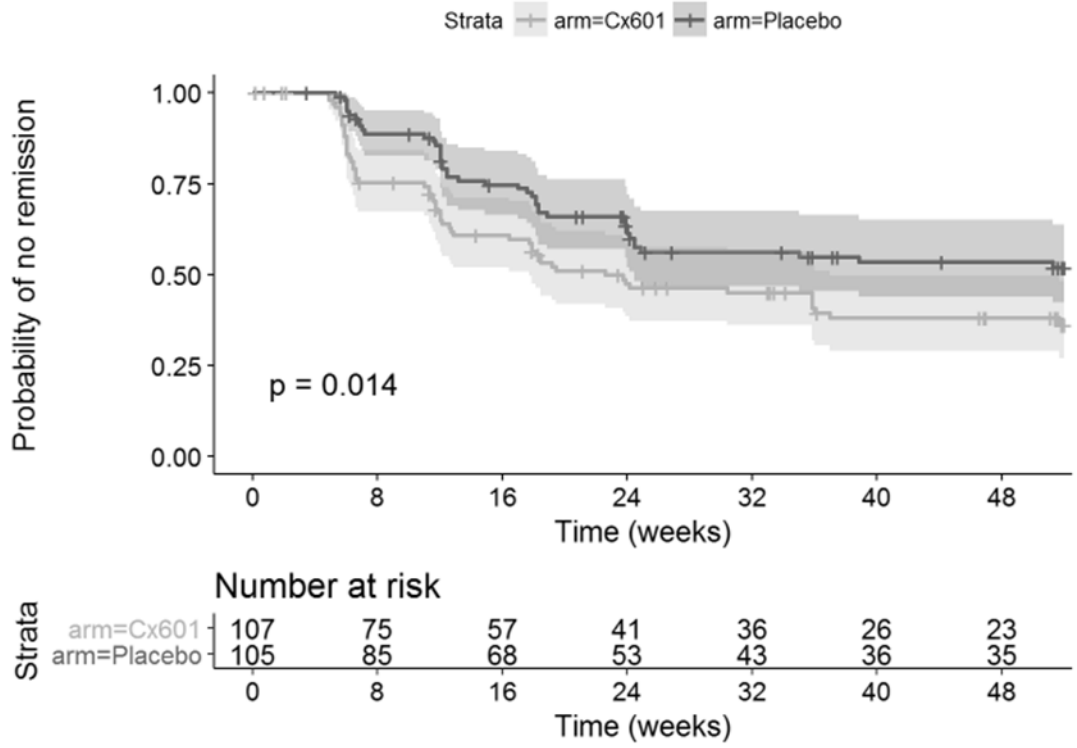
- The response improved by 13.0% at week 24 (66.4% vs. 53.3%, 95% CI: -0.1% to 26.1%, p-value = 0.054);
- The time to clinical remission was 7.9 weeks faster (6.7 vs. 14.6 weeks; HR: 0.57 [95% CI: 0.41 to 0.79]);
- The time to response was 5.4 weeks faster (6.3 vs. 11.7 weeks; HR: 0.59 [95% CI: 0.43 to 0.81]); and
- A greater improvement from baseline in PDAI at 6, 12 and 18 weeks (statistical difference between 1.0 and 1.2 points between the darvadstrocel and control treatment over time).

Two additional *post hoc* analyses were performed, based on feedback from clinical experts. Clinical experts indicated that the clinical outcome of most relevance to CD patients with perianal fistulae should include a component of pain and discharge in addition to clinical remission. Therefore, additional *post hoc* analyses were performed using the CPC definition of remission as a more clinically relevant outcome. A patient is considered to achieve CPC remission from complex perianal fistulae when:

- All the external openings are closed as per clinical assessment, i.e. not draining despite gentle finger compression (i.e. the clinical remission definition of ADMIRE-CD); AND
- The patient does not experience any pain or discharge, as determined by a score equal to 0 in both pain and discharge dimensions of the PDAI

The *post hoc* analyses of time to CPC remission, and time to loss of CPC remission, confirmed the primary and key secondary outcomes, i.e. darvadstrocel is superior to control treatment. In time to CPC remission, there is a 14.1% improvement in the darvadstrocel group (55.1% vs. 41.0%), and the median time to CPC remission is 6.5 weeks faster (28.7 vs. 35.2 weeks, HR 0.61; 95% CI: 0.42 to 0.91), see Figure 16. Additionally, fewer patients relapsed with darvadstrocel as compared with control treatment (50.8% vs. 59.6%, respectively). The time to loss of CPC remission was extended with darvadstrocel compared to control (48.7 vs. 12.9 weeks; HR: 1.38 (95% CI: 0.89 to 2.12).

Figure 16: Time to CPC remission, ITT population



Source: *Post hoc* analyses of ADMIRE-CD, data on file
Abbreviations: CPC, Clinical and patient-centric; Cx601, Darvadstrocel; Placebo, Control treatment

The beneficial effect observed at week 24 (combined remission in darvadstrocel 51.5%, control 35.6%; p=0.021) was sustained at week 52; a significantly greater proportion of patients receiving darvadstrocel vs control achieved combined remission (56.3% vs. 38.6%; p=0.010), and clinical remission (59.2% vs. 41.6%; p=0.013) at week 52. Of patients with combined remission at week 24, a greater proportion of those treated with darvadstrocel versus control had no relapse at week 52 (75.0% vs. 55.9%). Additionally, limited data at week 104 supports the sustained efficacy, with xx% of darvadstrocel patients showing clinical remission (compared to xx% of the control group).

Darvadstrocel is a localised treatment and clinical trial data show that darvadstrocel is well tolerated, with a similar safety profile compared with control treatment. The safety profile of darvadstrocel is consistent in the Phase I/II and Phase III studies. Table 24 below summarises the longer-term safety of darvadstrocel versus control during the ADMIRE-CD trial. It can be seen that generally, AEs are reported less often for the darvadstrocel group, in comparison to control, at both week 24 and 52.

Table 24: Longer-term safety from ADMIRE-CD, safety population

Number patients (%)	Week 24		Week 52	
	darvadstrocel N=103	Control N=102	darvadstrocel N=103	Control N=102
TEAEs	68 (66.0%)	66 (64.7%)	79 (76.7%)	74 (72.5%)
Treatment-related	18 (17.5%)	30 (29.4%)	21 (20.4%)	27 (26.5%)
Withdrawn due to AEs	5 (4.9%)	6 (5.9%)	9 (8.7%)	9 (8.8%)
Treatment-related AEs in ≥5% of patients				
Anal abscess	6 (5.8%)	9 (8.8%)	[redacted] 13 (12.6%)*	[redacted] 16 (15.7%)*
Proctalgia	5 (4.9%)	9 (8.8%)	5 (4.9%)	8 (7.8%)
Serious TEAEs	18 (17.5%)	6 (5.9%)	25 (24.3%)	21 (20.6%)
Treatment-related	5 (4.9%)	7 (6.9%)	7 (6.8%)	7 (6.9%)
Serious treatment-related AEs in ≥2% of patients				
Anal abscess	5 (5%)	5 (5%)	7 (6.8%)*	7 (6.9%)*

Source: Table 3, (Panes 2016); Table 2 (Panes 2017b); Table 43, (Tigenix 2016b); (Panes 2017a)

Abbreviations: AE, Adverse event; TEAE, Treatment-emergent adverse event

* Anal abscess/fistula included the following preferred terms: anal abscess, anal fistula, fistula, fistula discharge and infected fistula.

The current standard of care in the UK for CD patients who have complex perianal fistula that is refractory to conventional or biologic therapy is continued medical treatment (antibiotics, immunosuppressants and/or biologics) and repair surgery (such as the use of seton placement and EUAs). The supportive care in the ADMIRE-CD trial included the same background and concomitant treatment as that observed in a retrospective study in a UK hospital (Appendix Q).

B.2.13.2 Evidence from other sources for the comparator

The comparator is surgical treatment, such as EUA + seton placement. These are the most common treatments in clinical practice in the UK for adult patients with CD who have a complex perianal fistula that is refractory to conventional or biologic therapy.

An SLR was performed to identify relevant evidence on the efficacy of repair surgical treatment. The SLR identified 19 RCTs, and of these, only six trials included darvadstrocel or surgical treatments (setons, fibrin glue, anal fistula plug, EUA and seton) (Garcia-Olmo 2009, Grimaud 2010, Schwartz 2015, Wiese 2015, Panes 2016, Senejoux 2016). Following the feasibility assessment, it was concluded that an NMA could not be conducted due to a lack of comparable RCTs and considerable heterogeneity in the studies identified by the systematic review. The assessment found a high level of variability in the comparators, outcomes, patient populations, and sample size across studies (see Section B.2.9 for further detail).

B.2.13.3 Strengths of current database

The key clinical evidence for darvadstrocel is derived from the pivotal Phase III randomised, double-blind ADMIRE-CD trial, evaluating the efficacy, safety, and tolerability of darvadstrocel and a control treatment, in CD patients with complex perianal fistula. For patients, the most clinically relevant outcome is prolonged remission. Data up to 104 weeks demonstrated a sustained effect with darvadstrocel, in comparison to control. UK clinical experts deemed that remission defined by clinical remission and the absence of pain or discharge would be the most clinically relevant outcome. The results of the *post hoc* analysis confirmed the results of ADMIRE-CD trial in that it supported darvadstrocel as superior to the control treatment.

Due to the lack of effective treatment for CD patients with complex perianal fistulae who are refractory to conventional or biologic therapy, the current treatment practice is poorly defined. A recent retrospective study of the St Mark's Hospital identified that the most common surgical treatments are EUAs and seton placements. The results from the St Mark's Hospital were confirmed at an advisory board of gastroenterologists and surgeons in the UK. The treatment in the control arm of the ADMIRE-CD trial appeared to be similar to treatments identified in the retrospective study, therefore the ADMIRE-CD trial reflects UK clinical practice.

B.2.13.4 Limitations of the current evidence base

In regards to the current evidence base, a small number of limitations were identified. The patient relevant outcome of CPC remission was assessed using a *post hoc* methodology and was not pre-specified. However, all available evidence was included and the results were similar to the primary and key secondary outcomes, i.e. darvadstrocel was more beneficial than the control treatment.

An unforeseen drawback to this current evidence base is that the efficacy data available beyond 52 weeks was limited. This is due to the changes in the protocol whereby the trial duration was extended beyond 104 weeks, which occurred when various patients had already finished the 52 week trial period. This resulted in a low level of patient data, and so generalisation of results beyond 52 weeks is difficult and should be approached with care.

As highlighted previously in the document, the lack of sufficient power for the subgroup analysis stratified by concomitant medications makes the interpretation of these analyses more difficult.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review search was performed to identify relevant cost-effectiveness studies with the aim of comparing structural assumptions, inputs and predicted outcomes between the analyses and the de novo economic model, in accordance with the NICE methods guide (NICE 2013). Keywords related to the disease area and to cost-effectiveness analyses, such as quality-adjusted life year (QALY), incremental cost-effectiveness ratio (ICER), cost-benefit and cost-utility, were used to search for relevant evidence. The search was performed on Embase, MEDLINE, MEDLINE In-process, Cochrane Central Register of Controlled Trials (CENTRAL), National Health Service economic evaluation database (NHS EED), conference abstracts, Research Papers in Economics (RePEc), and the Cost-Effectiveness Analysis (CEA) registry.

The methods and results of published cost-effectiveness analyses available for darvadstrocel are presented in Appendix G. The completed Philipp's and Drummond's checklists are available in an Excel file in the Appendix.

Two cost-effectiveness studies were identified in the literature review for the management of perianal fistulae in patients with CD (Arseneau 2001, Lindsay 2008), however one study was not relevant, as the cost-effectiveness study used the US perspective (Arseneau 2001).

Lindsay et al. (2008) performed a cost-utility analysis of infliximab for the treatment of active luminal and fistulising CD compared to standard of care. Transition probabilities were derived from the ACCENT I and ACCENT II trials, reporting the relative effectiveness of infliximab compared to placebo in fistulising CD. Lindsay et al. used a Markov model to measure the accrual of direct costs associated to hospital visits, treatment and diagnostic procedures over time. Quality of life was measured in QALYs, by attaching health state utilities derived from a Spanish EQ-5D survey on 200 CD patients and clinical expert opinion. Over a 5 year time horizon, infliximab was shown to be associated with an incremental cost per QALY estimated equal to £29,752. Scenario analyses around the base case assumptions resulted in ICERs in a range comprised between £27,047 and £44,026, with patient body weight being the most influential factor affecting relative-effectiveness (Lindsay 2008).

B.3.2 Economic analysis

The models identified in the literature (see Section B.3.1) were considered inadequate for the assessment of the cost-effectiveness analysis of darvadstrocel as a specific treatment for complex perianal fistula in CD patients, as previous models examined a patient population treated for both luminal and fistulising CD (irrespective of disease complexity). Therefore we developed a *de novo* health economic model for the purpose of this submission.

B.3.2.1 Health economic model development

As the literature review did not identify model structures sufficiently detailed for the cost-effectiveness analysis of darvadstrocel for the treatment of complex perianal fistula in CD patients, a *de novo* model was designed. The health economic model was created through a

stepped model conceptualisation phase. Expert clinical input from UK gastroenterologists and surgeons was used to identify health states, define clinically relevant remission (CPC remission) and model structure (see Table 25). The conceptual model was presented to a multidisciplinary panel of experts from the St Mark's Hospital Academic Institute in London (a specialised centre in gastrointestinal and bowel diseases). A more detailed description of the conceptualisation phase is provided in Appendix N.

Table 25: Timeline of model development

Consul-tation	Date	Experts consulted	Purpose	Definition of remission	Disease states	Other aspects
1	01/02/17	St Mark's Hospital (UK) clinicians (1 gastroenterologist 5 surgeons, 1 radiologist and 1 nurse)	Model framework validation meeting	Clinical remission is not sufficient to determine remission, as pain and discharge need to be considered, suggest CPC remission*	Mild and severe Chronic Symptomatic Fistula (CSF) with or without abscess with severity being dictated by level of pain and discharge. Remission: patients with no pain, no discharge and closed external openings. Defunctioning abdominal surgery, e.g. colostomy, with positive or negative outcome (relating to resolution of fistula) Proctectomy, with positive or negative outcome All-cause mortality	
2	24/02/17 - 14/03/17	Interviews with KOLs from France, Scotland, England, Sweden, the Netherlands	Blinded clinical validation of model structure	Agreed with CPC remission as being most appropriate to reflect clinical practice	1) Remission 2) CSF - low management (palliative care) and high management 3) Abdominal surgery 4) Death from all causes	AEs to be included: proctalgia and anal abscess (based on trial data analysis)
First draft of economic model, incorporating feedback on definition of remission, disease states, AEs from St Mark's Hospital clinicians and blinded European KOLs						
3	05/09/17	Advisory board, including KOLs from England, Portugal, Norway and Sweden	Clinical validation of the economic model structure and clinical outcomes	Agreed with CPC remission as being most appropriate to reflect clinical practice	Agreed with the health states	Provided information on resource use, AEs cost; long-term efficacy, confirm utility values from Vignette study, composition of treatment mixes
Second draft of economic model, no changes in the model structure compared with version 1, however inputs updated aligned with advisory boards						
4	13/12/17	Two health economic	Economic Model			No changes in model

Consul-tation	Date	Experts consulted	Purpose	Definition of remission	Disease states	Other aspects
		modelling experts from the UK	validation			structure
5	01/18 – 03/18	NICE PReliminary Independent Model Advice (PRIMA)	Economic Model review. Advice on the verification of the computerised model, model fit, its transparency and usability and any errors found in the technical documentation provided by the company			A small mathematical error was identified. In the HRQoL-Control and HRQoL – Darvadstrocel sheets the following functions were incorrect: =SUM(BE5:INDEX(BE5:BE785,timeHorizon*13)). The function should read =SUM(BE6:INDEX(BE6:AL786,timeHorizon*13)).
6	08/02/18	UK Advisory Board with 7 clinical experts and 1 Health Economist	Clinical validation of the economic model structure and clinical outcomes			Composition of treatment mixes, validation of HSUs, and clinical outcomes of the economic model
Final version of economic model, no changes in the model structure compared with version 1, however inputs updated aligned with UK advisory board, and mathematical error corrected						

* CPC remission is defined as: Closure of all treated external openings that were draining at baseline defined as the absence of draining despite gentle finger compression, and no pain and no discharge as defined by a score of 0 on the pain and discharge categories of the Perianal Disease Activity Index (PDAI)

B.3.2.2 Patient population

The target patient population in the model consists of adults with complex perianal fistula and non-active or mildly active luminal CD, who are refractory to at least one of the following treatments: antibiotics, immunosuppressants or induction/maintenance biologics treatment. This is in line with the final NICE scope, as highlighted in Section B 1.1.

B.3.2.2.1 Population characteristics

The target population of the cost-effectiveness analysis is in line with the patient population studied in the pivotal Phase III ADMIRE-CD RCT. This population consists of adults, aged 18 years or older, with complex perianal fistula and non-active or mildly active luminal CD, who were refractory to antibiotics, immunosuppressants, induction, or maintenance biologic treatment (Best 1976, Panes 2016). In particular, patients with rectovaginal fistulae, diverting stomas, and those who had not received previous treatment for perianal fistulising CD were not considered.

The economic model defines the baseline population characteristics based on the ADMIRE-CD RCT. Three baseline population demographics were included in the model: average body weight (used to estimate the average drug dosage required for therapies with weight-based dosages, such as infliximab), average age, and average gender proportions (used to reproduce the age- and gender-specific mortality throughout the time horizon based on national mortality statistics).

Table 26: Population characteristics included in the economic model

Population characteristics	Average	Standard error	95% Confidence interval
Body weight (kg)	72.57	1.03	[70.55; 74.60]
Average age (years)	38.27	0.90	[36.51; 40.04]
Proportion male (%)	54.72%	3.42%	[48.02%; 61.42%]
Abbreviations: kg, kilogram. Source: ADMIRE-CD trial (Panes 2016)			

B.3.2.2.2 Split of symptomatic fistulae by severity

In addition to baseline demographics, the proportion of patients who have mild or severe fistula symptoms was also included in the economic model as suggested by the clinical experts. The proportion of patients experiencing mild or severe symptoms while having chronic symptomatic fistulae is derived from the ADMIRE-CD trial data according to a classification based on a subset of the dimensions of PDAI (Irvine 1995), which range from a score of 0 (least severe) to 4 (most severe) (Table 27). The classification was suggested by the St Mark's expert panel and subsequently validated by further interviews with international clinical experts (see Section B.3.2.1; Table 25). Clinical experts interviewed agreed that it was appropriate to identify no or mild symptoms by the PDAI dimension levels 0 and 1. Therefore, if patients with active fistulae had scores of 0 or 1 in both pain and discharge dimensions, their symptoms were deemed mild. Otherwise, if the score associated to at least one of the two dimensions was 2 or higher, the symptoms were categorised as severe (Table 28).

Table 27: Classification of fistulae symptoms severity based on PDAI scores

CSF health state classification	PDAI dimension scores (Irvine 1995)	
	Pain/restriction of activities	Discharge
Mild symptoms	0: no activity restrictions 1: mild discomfort, no restriction	0: no discharge 1: minimal mucous discharge
Severe symptoms	2: moderate discomfort, some limitation activities 3: marked discomfort, marked limitation 4: severe pain, severe limitation	2: moderate mucous or purulent discharge 3: substantial discharge 4: gross faecal soiling

Abbreviations: CSF, Chronic symptomatic fistulae; PDAI, Perianal Disease Activity Index. Source: (Irvine 1995)

Table 28: Definition of remission and chronic symptomatic fistulae health states based on clinical remission, pain, and discharge status

Health state	Symptoms	Clinical remission*	Pain component of PDAI**	Discharge component of PDAI**
Remission	None	Yes	0	0
Chronic symptomatic fistulae	Mild	Yes or No	0-1	0-1
	Severe	Yes or No	2-4	2-4
			2-4	0-1
			0-1	2-4

Notes: *, clinical remission is defined as the absence of draining despite gentle finger compression according to the definition of clinical remission in the ADMIRE-CD trial; **, the symptom levels are classified according to the Perianal Disease Activity Index (PDAI) dimensions (Irvine 1995) and validated by clinical experts as: 0, no symptoms; 0 to 1, mild or none; 2 or greater or severe symptoms (Table 27).

The rationale for the analysis of the split between mild and severe symptoms for the chronic symptomatic fistulae health state is based upon clinical opinion that one aim of current treatment is to achieve the CSF Mild health state, as this limits the impact on patients QoL and it is therefore considered a good outcome; whereas the CSF Severe health state is treated very differently and has a more significant impact on the patient's QoL and medical resource used. Additionally, the split was created to inform the proportion of patients who would enter the economic model with mild or severe symptoms, as well as the proportion of patients who, after a relapse, would experience mild or severe symptoms. Given the two-fold use of this parameter in the model, as well as the assumption of equilibrium between the two health state sub-categories when moving into the model, it was considered that a simple average across all observations, irrespective of visit time and characteristics of the disease trajectory such as previous relapses, was a reasonable, easily interpretable, and simple approach.

The proportion of patients with chronic symptomatic fistulae with mild or severe symptoms over the ADMIRE-CD trial follow-up was calculated by taking the average proportions across all observations over time of only those patients who had symptomatic fistulae (e.g. missing data and patients in clinical remission were excluded).

Table 29 reports the proportion of observations in patients with chronic symptomatic fistulae by treatment arm, and collated for all available observations in the follow-up time. The proportion of patients with mild symptoms who received treatment with darvadstrocel was greater than in the control arm, but the difference was not significant (two-sided test of equality in proportions with Yates' continuity correction: X_1^2=1.4039, p=0.2361). In addition, no changes over time were observed in the percentage of patients with mild or severe symptoms in the ADMIRE-CD trial. The trial design focussed on an attempt to heal the fistula tract rather than control symptoms, as is the case in clinical practice. Therefore, no changes over time where observed in the ADMIRE-CD trial, but changes are observed in the model to reflect clinical practice.

Table 29: Proportion of observations of chronic symptomatic fistulae patients with mild symptoms

	Trial arm		
	Darvadstrocel	**Control**	**Pooled**
Observations in patients with symptomatic fistulae, N	222	274	496
Mild symptomatic fistulae, n (%)	96 (43.2%)	103 (37.6%)	199 (40.1%)
95% CI of the proportion	[33.33%; 53.15%]	[28.24%; 46.95%]	[35.81%; 44.43%]
Abbreviations: CI, confidence interval			

As no significant difference between the two trial arms was observed, the proportion of CD patients with perianal fistulae that had mild symptoms at model entrance was assumed to be equal to 40.1%. Similarly, within the economic model, when patients had a relapse and transitioned to the chronic symptomatic fistulae health state, it was assumed that 40.1% of these patients had mild symptoms.

B.3.2.3 Model structure

The economic model structure chosen was a semi-Markov state transition model at a cohort level. This model structure was selected as it allows sufficient flexibility given the gaps in medical literature, while capturing the necessary chronological importance of re-treatments with salvage therapy (including palliative surgery such as EUA/seton placement) and last-resort surgery. This structure was considered more appropriate than a decision tree model, semi-Markov model or patient-level simulation model. A decision tree model was considered an inappropriate model structure, because of the inflexibility in the inclusion of the temporal effects when considering a relapsing-remitting disease trajectory. A hybrid response-based decision tree model followed by a natural history simulation semi-Markov model was also considered inappropriate as it was thought to be a simplification of a fully semi-Markov model and did not allow sufficient flexibility in the response-based structure. Lastly, a patient-level simulation model was discarded due to the lack of transparency of such a model structure and limited relevant input data in the literature.

The model includes the CPC definition of remission based on expert clinical opinion to represent more accurately the decision algorithm used in clinical practice. The CPC remission definition allows the production of a Kaplan-Meier curve for time to remission and time to response without resorting to the use of the much weaker end-point of clinical remission (see Sections B.2.6.4.1 and B.2.6.4.2). Additionally, the pain and discharge components of the PDAI are required to model the CSF Mild and CSF Severe health states

therefore CPC remission links the three main health states together using similar data (see Section B.2.6.3.2).

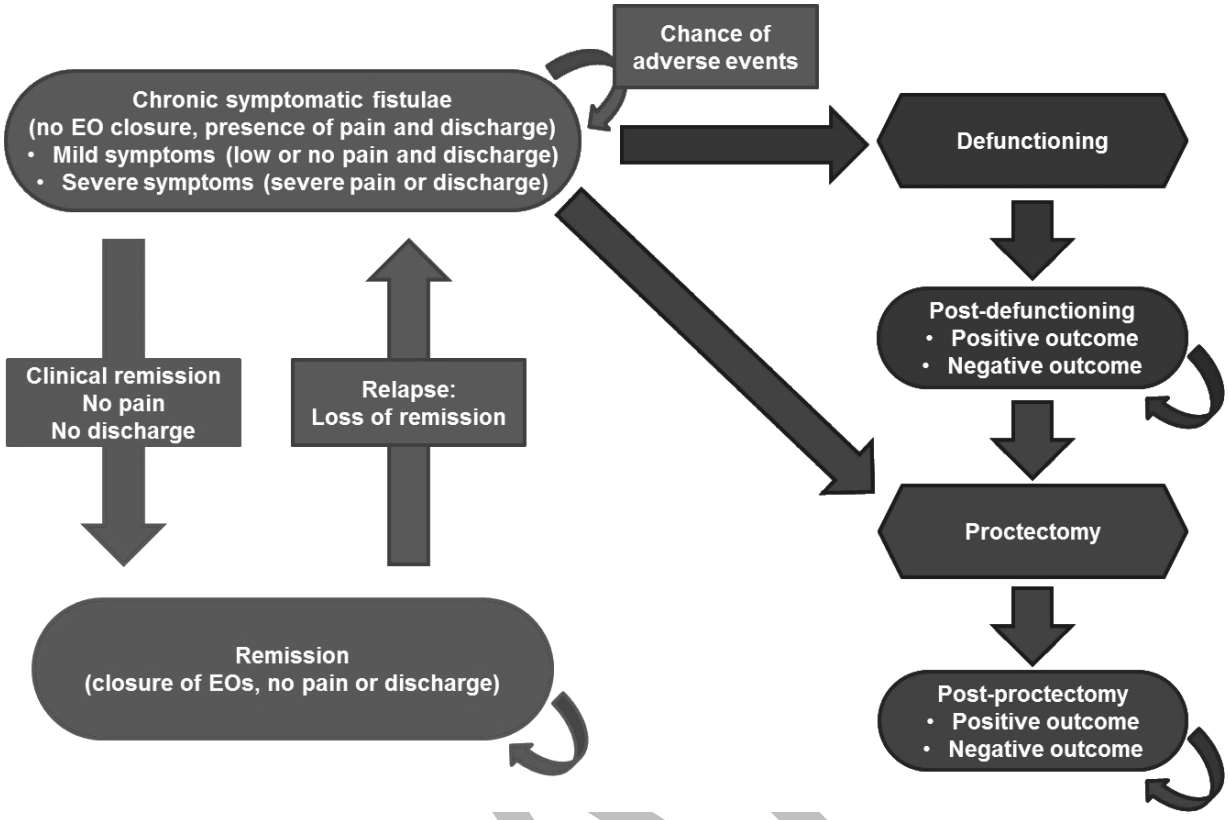
Five main health states are included in the model structure:

- Remission, using the CPC definition of remission; i.e. clinical remission, no pain and no discharge. Remission could be described as asymptomatic, well-controlled perianal disease with CD symptoms.
- Chronic symptomatic fistulae; including patients who did not achieve remission and/or are experiencing fistula-related symptoms of varying degrees. Occurrence of perianal abscess events is possible from this health state, and these are assumed to be resolved in an average of four weeks. The chronic symptomatic fistulae state if further partitioned into two groups based on the severity of the patients' symptoms classified using a subset of the dimensions of PDAI (Table 25), i.e. mild and severe symptoms as described in Section B.3.2.2.2.
- Defunctioning surgery; comprising one tunnel state of four weeks representing the time in which patients undergo surgery and the short-term recovery post-procedure. The patient may spend longer in the recovery health state, but for simplicity, a four-week tunnel state is used. After surgery the patients transition into a long-term post-defunctioning surgery health state and are partitioned into two groups according to the outcome of defunctioning surgery (successful and unsuccessful), which is based upon resolution of the symptoms related to the fistula tract.
- Proctectomy; including a tunnel state (as described above) and a post-proctectomy health state subdivided into successful and unsuccessful proctectomy, analogously to defunctioning surgery.
- Death from any cause, age- and gender-specific. No disease-related mortality is assumed. There is some mortality risk associated with last resort surgery but this is low, its exclusion could under-represent the benefits of darvadstrocel.

Additionally, it should be noted that there is a significant recovery period for patients who have undergone defunctioning or proctectomy surgery and this is associated with poor quality of life. This period of recovery is not included, but this exclusion may lead to an under-reporting of the QALY gained by darvadstrocel patients in the model.

An illustration of the simplified model structure is shown in Figure 17.

Figure 17: Simplified model diagram



Abbreviations: EO, external opening. Note: death health state not shown.

The model structure allows the following transitions between the main health states:

- From chronic symptomatic fistulae to CPC remission, according to time-varying transition probabilities representing time to remission;
- From CPC remission to chronic symptomatic fistulae, according to time-varying time to CPC relapse;
- From chronic symptomatic fistulae to undergoing defunctioning surgery, based on the probability of chronic symptomatic fistulae patients to undergo defunctioning surgery conditional on the severity of their symptoms;
- From chronic symptomatic fistulae to undergoing proctectomy, based on the probability of patients with chronic symptomatic fistulae to undergo proctectomy conditional on the severity of their symptoms;
- From post-defunctioning surgery to undergoing proctectomy, based on the probability of patients who have undergone defunctioning requiring a proctectomy;
- From any health state to death, according to age- and gender-specific general population mortality.

Based on the CPC definition of remission and on the classification of the severity of the symptoms in the chronic symptomatic fistulae health state, living patients in the model who did not enter the last-resort surgery pathway are classified according to the clinical remission status, pain, and discharge levels (Table 28).

A cohort-based multi-state Markov state transition model was developed to simulate the costs and effectiveness of treatment of complex perianal fistulae in CD patients. A time

horizon of 40 years is set as the base case value to adequately capture the long-term benefits of the introduction of darvadstrocel, whilst also limiting the impact of uncertainty associated to the extrapolation of the long-term clinical outcomes compared to a lifetime time horizon. The time horizon could be considered to incorporate substantial uncertainty, particularly related to the management of patients treated with salvage therapy as these would be subjected to repeated treatments for several years continuously if not in remission. The 40-year limit was chosen to limit the impact of this uncertainty while also preserving a long enough time to demonstrate the long-term benefits of treatment with darvadstrocel. Sensitivity analyses assessing the impact of different time horizons in the economic analyses are reported in Section B.3.8.2.

The cycle length of the model is set equal to four-weekly cycles, with one year composed of 13 model cycles for a total of 52 weeks. This cycle length was selected as it was considered a natural measure for schedules of assessment, as well as cycle lengths of maintenance treatments such as infliximab and adalimumab. Additionally, four weeks is also a common divisor of 24, 52, and 104 weeks, which are the data cuts available from the ADMIRE-CD RCT, making it simpler to validate the intermediate model outcomes without resorting to a shorter cycle length.

No cycle correction is applied as patients enter the model in a tunnel state and accumulate costs dependent on the timing of the health state membership, and not on the transition between health states such as the darvadstrocel drug acquisition and administration costs. The application of a cycle correction would have resulted in either misallocating outcomes to the incorrect cycles by shifting part of the cost of darvadstrocel to the second model cycle when all patients would have received it in the first cycle and effectively delaying the entrance of some patients in the model, or in underestimating the outcomes due to misallocation of health state membership, by considering some patients in the first cycle of treatment, when they would incur the darvadstrocel costs, as already having transitioned in the second cycle of treatment. Consequently, cycle correction is not applied, and the four-weekly cycle length is considered to be sufficiently short so that the bias reduction due to cycle correction would be negligible.

The model was programmed in Microsoft Excel® 2010 and used visual basic for applications for probabilistic and deterministic sensitivity analyses. In line with the NICE reference case, cost-effectiveness was assessed in terms of the cost per Quality Adjusted-Life Years (QALY) gained.

Costs were discounted at a rate of 3.5% per annum, while health outcomes were discounted at a rate of 1.5% per annum. It was considered that a non-reference discount rate of 1.5% per annum for health outcomes was applicable, as darvadstrocel demonstrates long term healing potential in this population with a significant impact on QoL as discussed in Section B.1.3.2, and as per the NICE methods guide (NICE 2013b). Darvadstrocel is an important and much needed intervention in the treatment of complex perianal fistula(e) in patients with CD, a disease that has a high unmet need. Additionally, the disease complex perianal fistula(e) often affects young people and has with a median age of onset of 15-30 years, and so the benefit of an effective treatment in this young population is likely to provide long term health benefits (>30 years) and that would be life-changing. As darvadstrocel is administered as a single course of treatment and complex perianal fistula(e) is an orphan disease this is unlikely to commit the NHS to significant irrecoverable costs.

B.3.2.4 Clinical pathway in the model

As discussed in Section 1.3, clinical guidance on the treatment of complex perianal fistulae in CD patients in the UK is not well documented in the clinical pathway of care (see Section B.1.3.3). Within the final NICE scope, surgery is considered the most appropriate comparator for this patient population. The most common surgeries in the UK for CD patients with perianal fistulae include EUA and seton placement (Appendix Q).

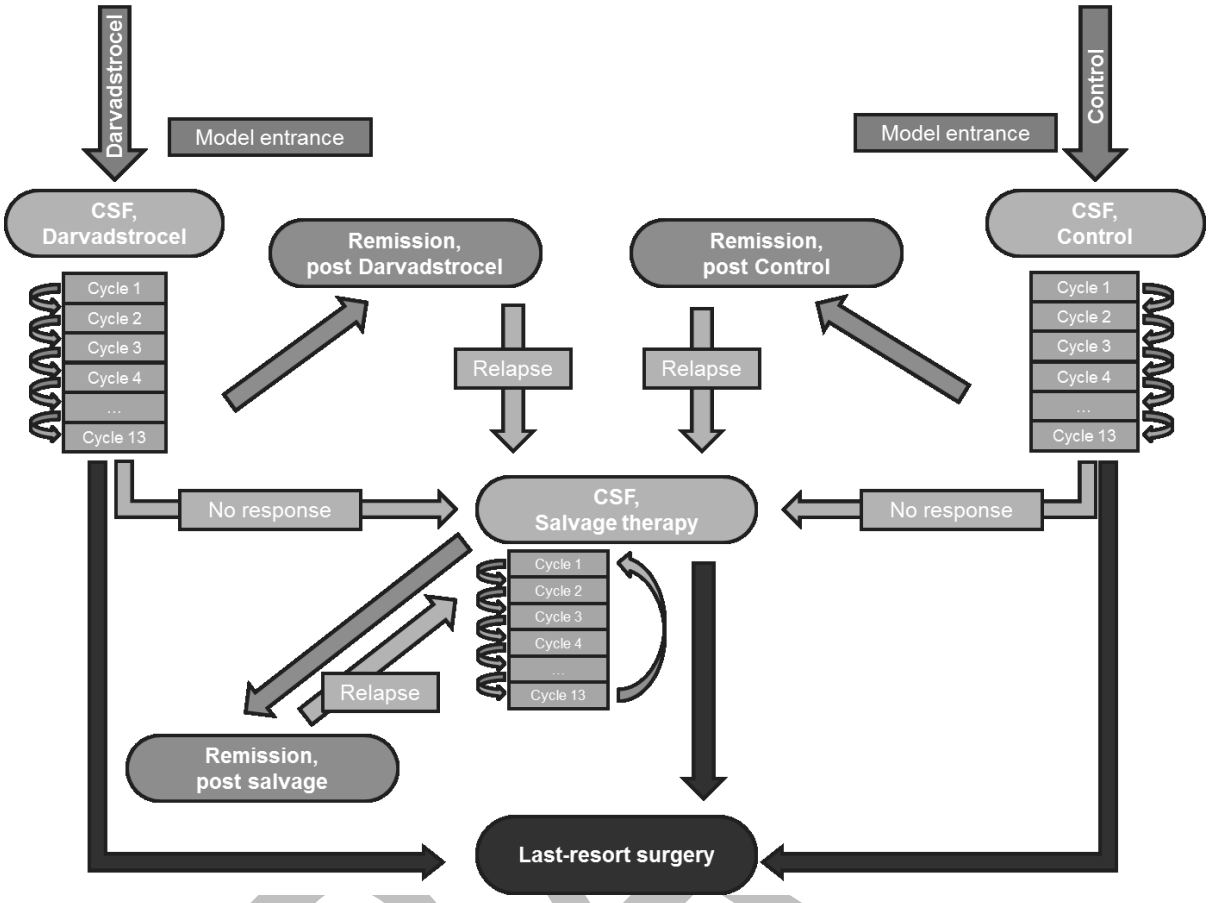
At model entrance, patients are assumed to be in the chronic symptomatic fistula health state and initiating treatment with either the darvadstrocel treatment mix or the control treatment mix. The two cohorts of patients compared in the model differ only by the treatment offered at the beginning of the model. The control cohort receives a mix of medical and surgical treatments defined as control treatment mix. Patients in the intervention cohort, or darvadstrocel cohort, receive the same mix of medical and surgical treatments in addition to a single intralesional injection of darvadstrocel at model entrance, denominated darvadstrocel treatment mix (Panes 2016). The treatments in the darvadstrocel and control treatment mix are set conditional to the severity of the symptoms experienced by patients with chronic symptomatic fistula(e), i.e. mild or severe symptoms.

Patients not responding to initial therapy, either with the darvadstrocel or control treatment mix, are assumed to switch to a subsequent treatment mix, designated as 'salvage therapy'. According to clinical experts and clinical guidelines, salvage therapy is likely to be different from the control treatment mix, as the offer of surgical procedures is increased for non-responding or relapsing patients after medical therapy (Gionchetti 2017). Additionally, it is common in clinical practice to escalate infliximab and adalimumab doses for these patients (NICE 2010). Due to an increasing risk of abscess formation and subsequent new fistula tract development in patients who have failed to achieve healing and in whom a draining seton is not in place, the most common aim of salvage therapy is to maintain patients in a mild health state (i.e. CSF Mild) rather than to heal the fistula tract.

A time to next treatment for non-responding patients has been incorporated into the model structure to allow patients to cycle through multiple therapies if not responding to current treatment. If patients do not respond (i.e. do not transition to the remission health state) after a set amount of time, they are assumed to have failed the current therapy and are assumed to receive another course of treatment. According to the NICE TA187 assessing infliximab and adalimumab for the treatment of CD, "infliximab or adalimumab should be given as a planned course of treatment until treatment failure […] or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed […] to determine whether ongoing treatment is still clinically appropriate" (NICE 2010). Based on the NICE TA187, the model allows a maximum time to next treatment equal to 52 weeks, which can be varied in 4-week decrements down to a minimum time of four weeks in the economic model.

Non-responding and relapsing patients are considered exchangeable as their previous treatment of disease trajectory is not assumed to have any impact on the subsequent transition probabilities or resource use. A detailed model structure for the model pathway prior to last-resort surgery is shown in Figure 18. Patients are allowed to stay in the initial chronic symptomatic fistula health state, receiving the darvadstrocel or control treatment mix depending on their cohort, for up to 52 weeks or 13 times 4-week cycles. If they do not respond after this time (i.e. transition to the remission health state) or relapse after having achieved remission, patients move to the chronic systemic fistulae salvage therapy health state, in which they receive the salvage therapy treatment mix.

Figure 18: Model structure



Abbreviations: CSF, chronic symptomatic fistulae

B.3.2.5 Intervention technology and comparators

Darvadstrocel is indicated for the treatment of complex perianal fistula(e) in adult patients with non-active/mildly active luminal CD, when fistula(e) have shown an inadequate response to at least one conventional or biologic therapy.

The comparators considered within the economic analysis, as per the NICE final scope, are surgical therapy, e.g. seton placement and EUAs. As stated in the Decision Problem (Section B.1.1), the main comparator for darvadstrocel in the population of interest, complex perianal fistulae in CD patients that are refractory to conventional or biologic therapy, is control treatment as defined in the ADMIRE-CD trial, as this included EUA and seton placement which accounts for >90% of all surgical procedures conducted in the UK (Appendix Q).

In the base case analysis, the darvadstrocel treatment mix (darvadstrocel in addition to the control treatment) is compared to the control treatment mix.

The treatment mixes in the economic model are based on the line of therapy (initial or subsequent) and health state. The denomination of the treatment mixes, by model arm (i.e. darvadstrocel or control) and health state are shown in Table 30. Based on clinical expert opinion, maintenance treatments in the remission and last-resort surgery health states are also included. It is assumed that the treatment mix in these health states is irrespective of previously received therapies.

Table 30: Denominations of treatment mixes by model arm and health state

Health state		Darvadstrocel	Control
Initial treatment	**Chronic symptomatic fistulae, mild**	Darvadstrocel treatment mix	Control treatment mix
	Chronic symptomatic fistulae, severe		
Salvage therapy	**Chronic symptomatic fistulae, mild**	Salvage therapy treatment mix (mild)	
	Chronic symptomatic fistulae, severe	Salvage therapy treatment mix (severe)	
Remission		Remission treatment mix	
Successful defunctioning		Successful defunctioning treatment mix	
Unsuccessful defunctioning		Unsuccessful defunctioning treatment mix	
Successful proctectomy		Successful proctectomy treatment mix	
Unsuccessful proctectomy		Unsuccessful proctectomy treatment mix	
Abbreviations: chronic symptomatic fistulae, chronic symptomatic fistulae.			

B.3.3 Clinical parameters and variables

In the economic model, treatment effectiveness is described by two transition probabilities conditional on treatment received:

- **Achievement of remission**, determining the transition between the chronic symptomatic fistulae and remission health state. Time to remission is conditional on the treatment mix received in the current chronic symptomatic fistulae state, i.e. darvadstrocel, control or salvage therapy (see Section B.3.3.1);
- **Relapse from remission**, regulating the opposite transition from remission to the chronic symptomatic fistulae health state. Time to relapse depends on the treatment mix received at the time to achievement of remission, i.e. darvadstrocel, control or salvage therapy (see Section B.3.3.2).

The base case treatment effectiveness is CPC remission and relapse from CPC remission, based on *post-hoc* statistical analyses of the ADMIRE-CD trial data (Panes 2016), see Section B.2.3.3. As described in Section B.2.3.3, the term CPC remission was created following discussion with clinical experts from St Mark's Hospital and Academic Institute (a specialised centre in gastrointestinal and bowel diseases based in London). This term was used to embody both clinical endpoints, and patient-centric remission (an endpoint which is more representative of routine clinical practice). The base case economic model did not use the primary outcome (combined remission) of the ADMIRE-CD trial, because of two reasons:

1. Clinical expert opinion considered that the CPC remission provided a more robust outcome from a clinical practice perspective.
2. Combined remission, the primary outcome of ADMIRE-CD trial includes MRI measurements, which were only performed at week 24 and 52. Therefore time to

event estimates are less sensitive than CPC remission, which was measured at weeks 6, 12, 18, 24, 36, 52 and 104.

In sensitivity analyses, the primary and key secondary outcome of the ADMIRE-CD trial were included, see Table 31 for details of the definitions included.

Table 31: Clinical endpoints used in the definitions of remission

	Remission definition	Clinical remission *	PDAI criteria **	MRI criteria ***	ADMIRE-CD
Base case	CPC	Yes	Yes	No	Post-hoc analysis
Sensitivity 1	Clinical	Yes	No	No	Key secondary outcome
Sensitivity 2	CPC + MRI	Yes	Yes	Yes	-
Sensitivity 3	Combined (Clinical + MRI)	Yes	No	Yes	Primary outcome

Abbreviations: CPC, clinical and patient-centric; MRI, magnetic resonance imaging.

Notes: *, clinical remission was defined as closure of all treated external openings that were draining at baseline despite gentle finger compression; **, PDAI criteria were defined as no pain and no discharge as assessed on the respective dimensions of the Perianal Disease Activity Index (PDAI) (Irvine 1995); ***, MRI criteria were defined as absence of collections greater than 2 centimetres of the treated perianal fistulae confirmed by masked central magnetic resonance imaging (MRI).(Panes 2016)

Each of the darvadstrocel, control, and salvage therapy treatment mixes is associated with mix-specific probabilities of remission and relapse. Salvage therapy is assumed to have the same effectiveness irrespective of the previous therapy received by patients, i.e. darvadstrocel or control. Additionally, no difference in treatment effectiveness is assumed between mild and severe chronic symptomatic fistulae patients on both the remission and relapse dimensions. This is because the actual symptom severity of patients is assumed to fluctuate over time as described in Section B.3.2.2.2. Using a single measurement of the severity of the symptoms at baseline may bias the results against darvadstrocel treatment as numerically more patients in the darvadstrocel arm had mild symptoms than those in the control arm.

B.3.3.1 Time to remission

B.3.3.1.1 Time to CPC remission (base case)

Standard survival analyses were performed to describe the distribution of the time to CPC remission events during the trial follow-up time (up to 104 weeks). The data were analysed using the semi-parametric Kaplan-Meier estimators and then by fitting fully parametric survival models to the data. The aim of these analyses was to identify an appropriate and accurate parametric model to describe the outcomes over time as well as extrapolate them over time when appropriate.

The exponential model was considered the preferred statistical model *a priori*. This was because the exponential model assumes a constant rate, and therefore probability, of the events throughout time. This property would have allowed the incorporation of the results of the survival analysis in the economic model while maintaining a simple structure. When the exponential model was found not to fit appropriately, standard parametric and piecewise exponential models were considered.

As recommended by NICE and based on the Technical Support Document (TSD) number 14, the six most common families of parametric models were assessed for best fit to the trial data (Latimer 2013). These were the exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma models. The goodness of fit of the parametric models was tested visually and by comparing the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), indexes which measure the adequacy of fit to the data. Analyses of violations of the proportional hazards and accelerated failure assumptions were not conducted to explore the reliability of parametric extrapolations beyond the observed follow-up, as no extrapolation was performed for the time to achievement of remission.

The reference population was the ITT, and the baseline time for the analysis was set as week 0, i.e. treatment administration. Patients were censored at the time of their early termination visit, if any. In the case of missing dates for early termination visits, the dates were imputed as the day after the patients' last visit with a known date.

Given the uncertainty associated to the potential effectiveness of the therapies, in particular for salvage therapy whose efficacy was based on the control arm of the ADMIRE-CD trial, parametric survival models were used to describe the underlying mechanism of achievement of remission.

Because of the structural absence of events during the first four weeks from treatment administration, standard parametric models were fitted using a 4-week offset to improve the fit to the observed outcomes.

Based on both the AIC and BIC, the two best-fitting statistical models are the generalised gamma and Gompertz models (see Table 32).

Table 32: Goodness of fit measures, parametric models for time to remission

Parametric model	AIC	BIC
Generalised gamma	931.1734	944.3866
Gompertz	946.2664	956.1763
Log-normal	946.6324	956.5423
Log-logistic	954.7821	964.6920
Weibull	965.6205	975.5305
Exponential	980.8393	987.4459

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

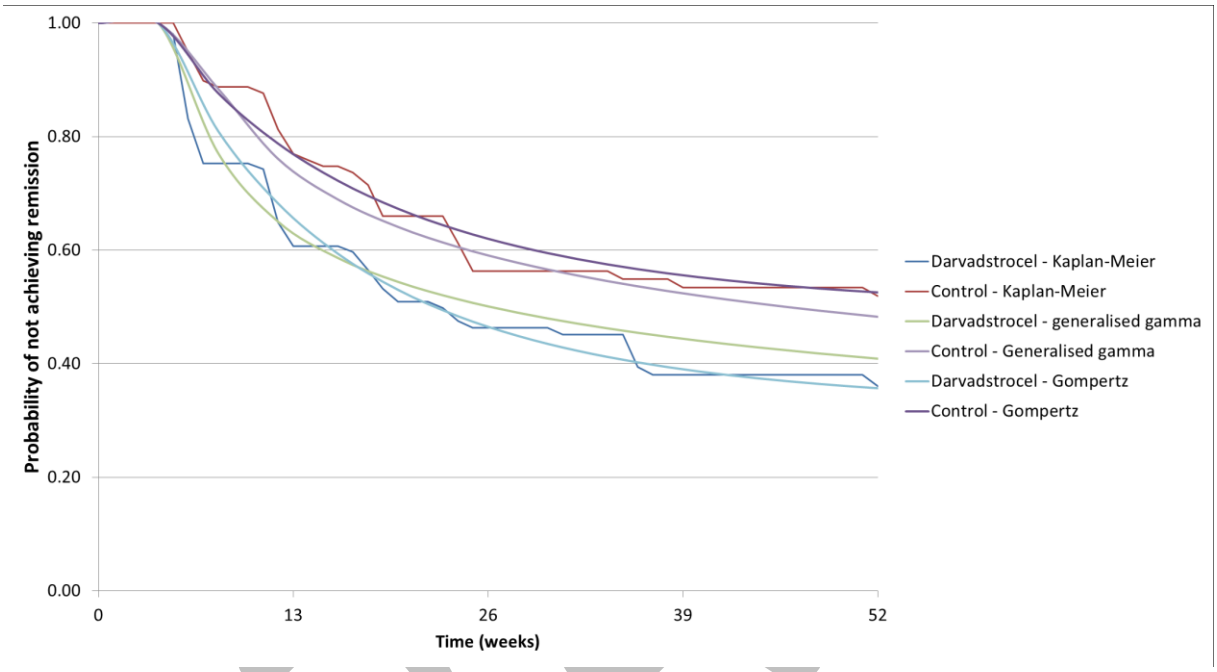
Both the generalised gamma and Gompertz curves, shown in Figure 19, fit the observed data reasonably well. The Gompertz model was chosen as the base case model because:

- The one-year Gompertz model estimates were deemed appropriate and clinically plausible by an interdisciplinary panel of international clinical experts. Furthermore, the underlying assumption for the generalised gamma model is that all patients would achieve remission over time. On the other hand, the Gompertz model predicts remission probabilities decreasing to zero with time, which was deemed more plausible by the experts;
- The Gompertz model is more accurate in predicting the 52 week probability of remission at visual assessment;
- The salvage therapy effectiveness was modelled using a HR applied to the control treatment curve, based on clinical expert opinion (detailed in Section B.3.3.3). As the

application of a HR to a non-proportional hazards model would not be methodologically correct, the Gompertz model was preferred over the generalised gamma (NICE 2016)

The Gompertz model parameters are reported in Table 33 and Table 34. The generalised gamma model is tested as an alternative parametric model for CPC remission in sensitivity analyses.

Figure 19: Parametric model fit to CPC remission, two best-fitting parametric models



Abbreviations: CPC, Clinical and patient-centric

Table 33: Gompertz parametric model coefficients, CPC remission

Gompertz parametric model	Transformed scale	Normal scale (MLE)	Standard deviation (MLE)	Z test
Shape		-0.052075	0.009654	Z=-5.39; p<0.001
Rate		-3.311080	0.187982	Z=-17.61; p<0.001
Darvadstrocel HR vs. Control	2.121	0.471345	0.200651	Z=2.35; p=0.019
Abbreviations: HR, hazard ratio; MLE, maximum likelihood estimate.				

Table 34: Base case clinical inputs, Gompertz model for time to CPC remission

Gompertz parametric model	Coefficient (normal scale)	Variance-covariance matrix		
		Shape	Rate	Darvadstrocel HR vs Control
Shape	-0.044984	0.000062	-0.000797	0.000049
Rate	-3.319662	-0.000797	0.031555	-0.021879
Darvadstrocel HR vs. Control	0.387899	0.000049	-0.021879	0.038260

Abbreviations: HR, hazard ratio; NA, not applicable; SoC, standard of care; ST, salvage therapy.

B.3.3.1.2 Time to clinical remission (sensitivity analysis)

Time to remission was also analysed according to the definition of clinical remission as defined in the ADMIRE-CD trial, i.e. closure of all treated external openings that were draining at baseline despite gentle finger compression. The statistical approach to the analysis corresponded to the one used for the CPC remission. The results of the statistical analyses are summarised below.

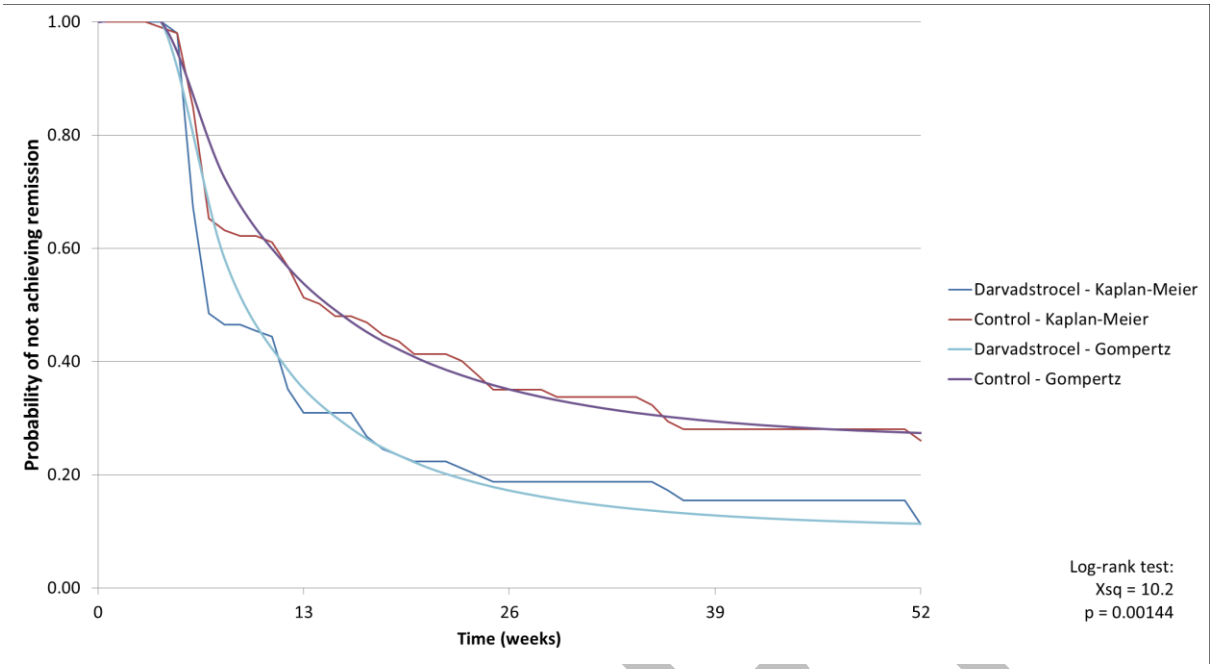
The AIC and BIC indices for the goodness of fit of the standard parametric models, offset by a 4-weekly cycle as in the CPC remission analysis (as the same schedule of assessment was applied) are reported in Table 35. While the generalised gamma resulted in the best fit, the parametric curve showed signs of non-convergence, as the curve does not fit the observed data appropriately. The log-normal, log-logistic, and Gompertz ranked similarly in terms of AIC and BIC. The Weibull and exponential models were markedly the worst fits to the clinical data. Note that the parameters did not converge to a maximum likelihood estimate, indicating that the AIC and BIC are not meaningful.

Table 35: Standard parametric model goodness of fit indices, time to clinical remission

Parametric model	AIC	BIC
Generalised gamma (not converged)	1017.138	1030.331
Log-normal	1083.342	1093.237
Gompertz	1089.373	1099.268
Log-logistic	1091.477	1101.372
Weibull	1127.301	1137.196
Exponential	1156.866	1163.463
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.		

Based on the parametric model chosen in the base case, Gompertz model was selected as the most appropriate parametric function to describe time to clinical remission in the economic model. As shown in Figure 20, the model fits the data very well.

Figure 20: Gompertz parametric model fit, time to clinical remission.



The Gompertz model coefficients are reported in Table 36.

Table 36: Gompertz parametric curve coefficients, time to clinical remission

Gompertz parametric model	Transformed scale	Normal scale (MLE)	Standard deviation (MLE)	Z test
Shape		-0.06849	0.0099120	Z=-6.91; p<0.001
Rate		-2.38452	0.1490092	Z=-16.00; p<0.001
Darvadstrocel HR vs. Control	1.9295	0.51828	0.1652992	Z=3.14; p=0.001
Abbreviations: HR, hazard ratio; MLE, maximum likelihood estimation (scale)				

B.3.3.1.3 Time to CPC remission + MRI and combined remission (sensitivity analyses)

The proportions of patients achieving remission with and without the MRI criteria were assessed for both definitions of remission (i.e. CPC and clinical), separately for the two arms at the two visits in which the MRI was performed. A HR-based approach was adopted in order to estimate the time to remission rates from both CPC remission and clinical remission to remission which includes the MRI component (i.e. both CPC remission + MRI and combined remission).

The number of patients with CPC remission but not CPC + MRI remission was not greater than three patients per arm at either visit. For both remission definitions, the rate ratio of non-MRI to MRI remissions results are lower for control than darvadstrocel at week 24, and vice versa at week 52. The confidence interval associated to the rate ratio did not indicate

any significant difference between the arms. Therefore, no differential effect due to the addition of MRI as an additional criterion to achieve remission is included in the analysis.

The rate ratio pooled with respect to treatment allocation shows a slight increase between week 24 and week 52, of approximately 0.05 for both CPC and clinical remission. However, the increase was not deemed sufficient to grant a time-varying approach as the differences appeared to be due to a very low number of patients not achieving the additional MRI criteria.

Consequently, the HR adjustment was operated as a single HR reduction applied to the time to CPC and clinical remission survival curve. The HR is calculated by pooling both treatments and visit time points to increase the data used to guide the calibration of the curves.

Operationally, the HR is estimated based on the rate ratio between the relative frequency of clinical remissions and the relative frequency of combined remission. The 95% confidence intervals for the HRs are calculated on the logarithmic scale. The resulting estimates are reported in Table 37. The HR is applied to the time to CPC remission and clinical remission curves and is assumed to be independent to time and treatment.

Table 37: Hazard ratios applied for the calibration of the remission curves to incorporate MRI criterion in the definition of achievement of remission

Definition comparison	HR	se [ln(HR)]	95% CI
CPC vs. CPC + MRI	0.922	0.135	[0.708, 1.200]
Clinical vs. Combined	0.896	0.111	[0.721; 1.113]

Abbreviations: CI, confidence interval; CPC, clinical and patient-centric; HR, hazard ratio; ln, logarithm; MRI, magnetic resonance imaging; se, standard error

B.3.3.2 Time to relapse

The strategy for the analysis of time to relapse data was similar to the approach used to analyse the time to remission data. The events over time were assessed for treatment effect visually and using a non-parametric log-rank test. Analogous to remission, the *a priori* preferred method for incorporation of the outcomes over time into the economic model was a fully parametric exponential model. This model of analysis was selected due to its simplicity, and it memoryless property, thus resulting in the ability to apply a single transition probability constant over time.

In contrast, with the time to achievement of remission data, there was a need to extrapolate the outcomes observed during the limited trial duration until the end of the time horizon of the economic model. For this purpose, the suitability of modelling treatment effect in a proportional hazards or accelerated failure time framework was assessed. The appropriateness of proportional hazards models was tested using the Grambsch-Therneau test, and the cumulative log-hazard plot, and for accelerated failure time models the linearity of the quantile-quantile plot of survival distributions associated to the two treatment arms was assessed (Collett 2015).

Similar to time to remission, time to relapse from remission is also measured according to the following definitions:

1. Time to relapse from CPC remission (Base case analysis)
2. Time to relapse from clinical remission (Scenario analysis 1)

3. Time to relapse from CPC remission + MRI (Scenario analysis 2)
4. Time to relapse from combined remission (Scenario analysis 3)

In addition, within a semi-Markov model structure, modelling each probability of relapse as dependent on model time inception and time elapsed since entry in remission is unfeasible. Therefore, time to relapse was modelled in two stages:

- Short-term relapse (base case: ≤2 year) – Sections B.3.3.2.1 and B.3.3.2.3
- Long-term relapse (base case:>2 year) – Section B.3.3.2.4

B.3.3.2.1 Time to relapse from CPC remission

The appropriateness of proportional hazards models was tested using the Grambsch-Therneau test. This test did not highlight any deviation from proportionality of the hazards (ρ=0.0297; X^2=0.0496; p=0.824). This confirmed the appropriateness of the proportional hazards assumption for time to relapse from CPC remission. Details of the results are presented in Appendix O.

Equivalent to the approach used for the analysis of time to CPC remission, offset standard parametric models were fitted to the observed data. As no relapse events could be structurally observed during the first four weeks from CPC remission, a 4-week offset was included when fitting the standard parametric model to the time to relapse from CPC remission data, analogous to the analysis of time to CPC remission. The AIC and BIC associated to each of the parametric curves fitted is reported in Table 38.

Table 38: Goodness of fit measures, parametric models for time to relapse from CPC remission

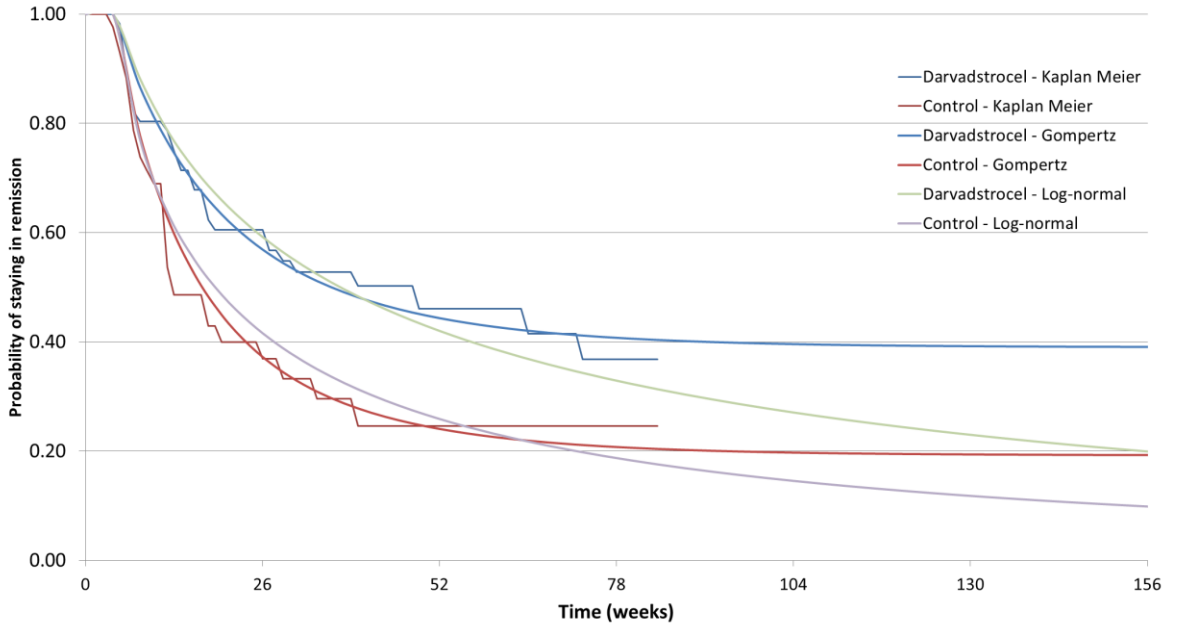
Parametric model	AIC	BIC
Gompertz	517.572	525.327
Log-normal	518.216	525.971
Log-logistic	521.644	529.399
Generalised gamma*	522.156	532.496
Weibull	528.702	536.457
Exponential	539.436	544.606

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion. Notes: *, as the Prentice parameterisation of the generalised gamma distribution yielded unstable estimates as confirmed by visual assessment, the Stacy parameterisation was used instead, as it provided a reasonable visual fit to the observed data. The alternatives were specified using the *gengamma* or *gengamma.orig* distribution arguments, respectively, in *flexsurvreg*.(Stacy 1962, Prentice 1974, Jackson 2016)

The two best-fitting models in terms of AIC and BIC are the Gompertz and log-normal models, shown in Figure 21. The long-term extrapolations differ substantially between the two parametric models. The log-normal model predicted that all patients would eventually relapse. In contrast, the Gompertz function remains relatively stable after about 100 weeks, as the relapse rates decrease towards zero, implying approximate non-relapsing CPC remission for patients who have been in CPC remission for approximately two years.

The assumptions used in the economic model for time to relapse from CPC remission is that some patients will achieve or remain in CPC remission over time. This is in line with clinical expert's opinions (surgeons and gastroenterologists from across the UK and EU). Furthermore, as already stated in Section B.3.3.1, the effectiveness associated with salvage therapy is expressed using a HR comparing time to treatment-specific relapse relative to the control arm, and therefore a proportional hazards model such as the Gompertz is considered methodologically more appropriate than the second-best fitting log-normal model, as the latter is an accelerated failure time model. Therefore, the Gompertz curve is selected as the preferred modelling approach in the base case scenario. The alternative parametric models tested and a piecewise exponential approach are provided as scenario analyses in the economic model.

Figure 21: Parametric model fit to time to relapse from CPC remission data, two best-fitting parametric models



Abbreviations: CPC, Clinical and patient-centric

The Gompertz coefficient estimates included in the economic model are reported in Table 39 and the base case clinical inputs are presented in Table 40.

Table 39: Gompertz parametric model coefficients, time to relapse from CPC remission

Gompertz parametric model	Transformed scale	Normal scale (MLE)	Standard deviation (MLE)	Z test
Shape	0.9593	-0.0415	0.0105	Z=-3.97; p<0.001
Rate	0.0685	-2.6812	0.2205	Z=-12.16; p<0.001
Darvadstrocel HR vs. Control	0.5709	-0.5605	0.2683	Z=-2.09; p=0.037

Abbreviations: HR, hazard ratio; MLE, maximum likelihood estimate

Table 40: Base case clinical inputs, Gompertz model for time to relapse from CPC remission

Gompertz model	Coefficient (normal scale)	Variance-covariance matrix		
		Shape	Rate	darvadstrocel HR vs control
Shape	-0.0415455	0.0001096	-0.0011264	-0.0004236
Rate	-2.6811743	-0.0011264	0.0486103	-0.0326843
Darvadstrocel HR vs. control	-0.5604564	-0.0004236	-0.0326843	0.0720074
Abbreviations: HR, hazard ratio; NA, not applicable; SoC, standard of care; ST, salvage therapy				

B.3.3.2.2 Time to relapse from clinical remission

For the scenario analysis using the clinical remission definition, the time to relapse from clinical remission was calculated as a secondary outcome of the trial.

No separation in the curves for darvadstrocel and control was observed in the time to relapse from clinical remission (X_1^2=0.4; p=0.5150). The tails of the Kaplan-Meier curves of darvadstrocel and control treatment diverged after week 48 post-achievement of clinical remission, but there were few events as there were few patients at risk at that time point.

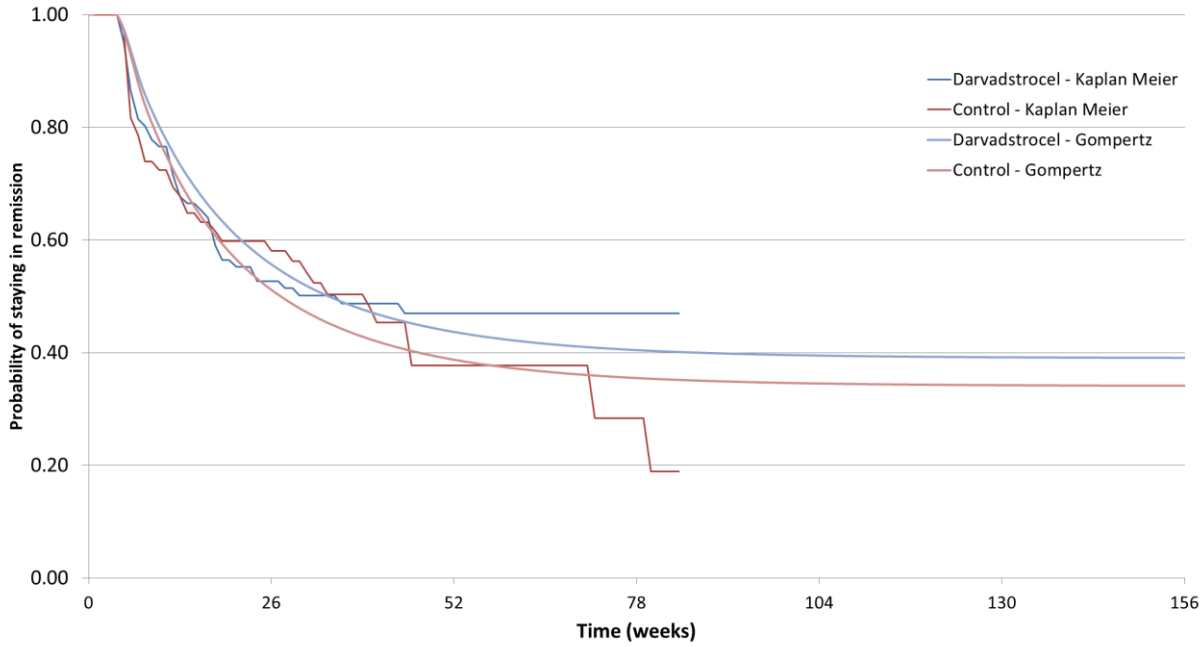
The AIC and BIC indexes for the goodness of fit of the standard parametric models, offset by a 4-weekly cycle as in the clinical remission analysis (as the same schedule of assessment was applied) are reported in Table 41. The log-normal model resulted in the best fit, followed by the generalised gamma, log-logistic and Gompertz, which ranked similarly. The Weibull and exponential models were markedly the worst fits to the observed data.

Table 41: Standard parametric model goodness of fit indexes, time to relapse of clinical remission

Parametric model	AIC	BIC
Log-normal	749.776	758.747
Generalised gamma	754.526	766.488
Log-logistic	756.516	765.487
Gompertz	757.079	766.050
Weibull	763.665	772.636
Exponential	791.794	797.774
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.		

All parametric models tested, as well as the piecewise exponential approach, are available in the economic model. Similar to the time to relapse from CPC remission, the Gompertz model was adopted as the preferred model in the scenario analysis, as proportional hazards could be applied (Figure 22).

Figure 22: Gompertz parametric model fit, time to relapse from clinical remission.



The Gompertz model coefficients are reported in Table 42.

Table 42: Gompertz parametric curve coefficients, time to relapse of clinical remission

Gompertz parametric model	Transformed scale	Normal scale (MLE)	Standard deviation (MLE)	Z test
Shape	0.9566	-0.0443	0.0089	Z=-4.98; p<0.001
Rate	0.0478	-3.0423	0.1975	Z=-15.40; p<0.001
Darvadstrocel HR vs. Control	0.8738	-0.1349	0.2246	Z=-0.60; p=0.55

Abbreviations: HR, hazard ratio; MLE, maximum likelihood estimation (scale).

B.3.3.2.3 Time to relapse from CPC + MRI remission and combined remission

Time to relapse from CPC + MRI or combined remission could not be calculated, due to the limited time points that combined remission was reported in the ADMIRE-CD trial. Therefore, the time to relapse from CPC remission and clinical remission, respectively were used as proxies.

B.3.3.2.4 Long-term relapse modelling

Within a semi-Markov model structure, modelling each probability of relapse as dependent of model time inception, and time elapsed since entry in remission, is unfeasible. Therefore, short-term and long-term times to relapse from remission were modelled separately. In the base case, the long-term relapse modelling started after two years.

Observed trial data indicates that, while a substantial proportion of patients in remission relapse relatively quickly, the probability of relapse decreases drastically with time, which suggests that some patients may remain in remission for an extended period (Colombel 2009). In support of this argument, the best-fitting Gompertz model estimates the probability of relapse approaching zero with time, suggesting long-term remission for some patients.

Clinical experts (surgeons and gastroenterologists from across the EU and the UK) were presented with the Gompertz model, as well as alternative log–normal parametric model. The clinical experts considered the Gompertz model to most accurately predict long-term relapse, while they did not consider the alternative log-normal parametric model to be plausible due to the high relapse rates at later times, and the underlying assumption that all patients would eventually relapse (Consultation 3 05/09/17, see Table 25).

After two years in remission, the probability of relapse is assumed to remain constant, and is calculated based on the average rate of the associated curve between year 2 and 3. The time-varying horizon is chosen based on clinical opinion, as the experts indicated that it was unlikely, but not impossible, that patients who had not relapsed within two years would relapse after that. The 2-year horizon is also consistent with the flattening trend associated to the base case Gompertz curves described in Section B.3.3.1.1. The long-term relapse rate is modelled dependently on the treatment-specific parametric curve, and can be varied independently to carry out scenario analyses.

The 4-weekly long-term relapse rate, based on the Gompertz model are shown in Table 43.

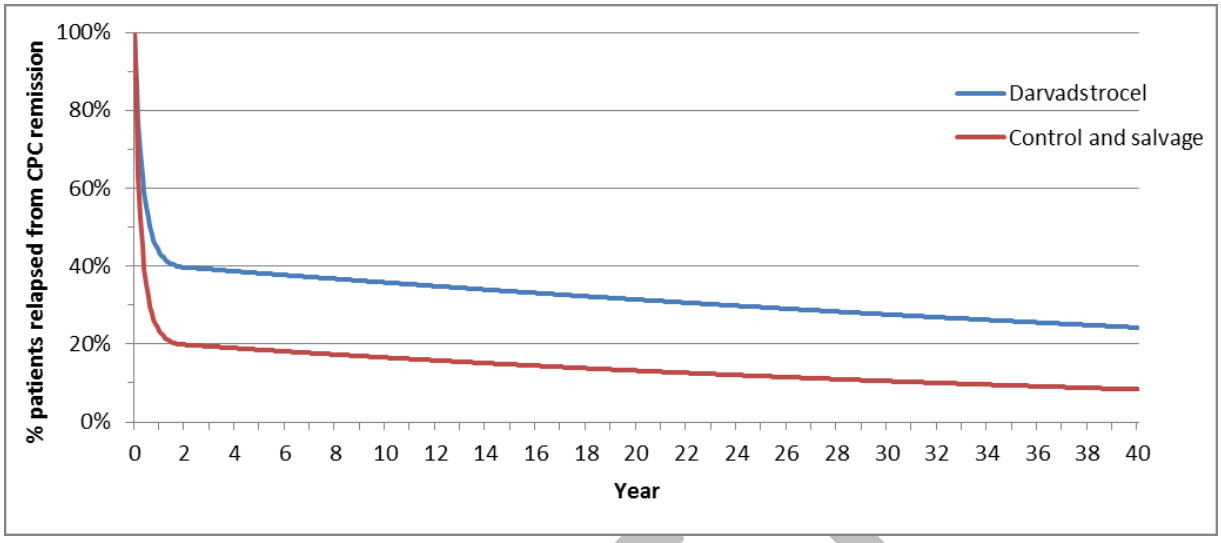
Table 43: Long-term relapse rates from remission by treatment mix, Gompertz model

Long-term 4-weekly relapse rate	CPC	Clinical	CPC + MRI	Combined
Darvadstrocel	0.00100	0.00077	0.00100	0.00077
Control treatment	0.00175	0.00089	0.00175	0.00089
Salvage therapy	0.00175	0.00089	0.00175	0.00089

Abbreviations: CPC, Clinical and patient-centred

The resulting time to relapse over the 40-year time horizon of the model is presented in Figure 23. The modelled long-term relapse rates for a patient who achieved CPC remission at 2 years is 39.0% for darvadstrocel, 57.9% for control treatment, and 57.9% for salvage treatment. During a UK advisory board with clinical experts (Consultation 6 08/02/18, see Table 25) it was stated that patients in radiological remission at 2 years have a 5% lifetime risk of relapse. Within the economic model the differential relapse rates incorporated in all treatment arms are higher than that considered appropriate by UK clinical experts, which can be considered a conservative assumption.

Figure 23: Long-term relapse from CPC remission modelled in the economic model



Abbreviations: CPC, Clinical and patient-centred

B.3.3.3 Treatment effectiveness

Two clinical endpoints, time to remission and time to relapse, are used to model treatment-specific effectiveness for darvadstrocel, control and salvage therapy treatment mixes. Time to CPC remission and time to relapse from CPC remission determine the time-varying transition probabilities between the chronic symptomatic fistulae and remission health states, and remission and chronic symptomatic fistulae health state, respectively. Due to the lack of available data, no difference in treatment effectiveness is assumed for patients with mild or severe chronic symptomatic fistula symptoms, i.e. the probability of achieving remission from the mild or severe chronic symptomatic fistula symptoms health state is similar for each treatment arm. However, the probability of treatment failure (i.e. defunctioning surgery or proctectomy) is different depending on whether a patient is in the mild or severe chronic symptomatic fistula symptoms health state.

There was limited efficacy beyond 12 months identified in the systematic literature review. In randomised controlled trials, with a follow-up of two years (Colombel 2009), the complete healing of perianal fistulae while being treated with biologics was approximately 31% (Colombel 2009). However, the evidence at 2 years was not comparative. No long-term evidence was available for salvage therapies such as surgical treatments.

Due to a lack of available data, the treatment effectiveness of salvage therapy was elicited from clinical expert opinion. An international panel of clinical experts from UK, Portugal and Sweden (Consultation 3 05/09/17; see Table 25) was presented with several scenarios representing different projections associated to relative treatment effectiveness of salvage therapy compared to the control arm derived from the ADMIRE-CD trial, separately for CPC remission and relapse from CPC remission. The scenarios were modelled based on different HRs compared to the control arm for ease of interpretability and inclusion in the economic analysis. The experts considered salvage therapy to be less effective than control in bridging patients to CPC remission, but did not consider the proportion of relapses from CPC remission or the speed of relapses to differ between the two interventions. Therefore, the experts considered the most plausible HRs for time to CPC remission to be 0.60 and for time to relapse from CPC remission to be 1.00. Clinicians agreed that given the lack for

comparative data, it would be too optimistic to assume salvage therapy as effective as control treatment. Additional details are reported in Appendix P (Consultation 3 05/09/17; Table 25).

For the base case, the remission rates are not conditional only on time since start of the re-treatment (i.e. the transition probabilities reset at each re-treatment) but are conditional on time since initiation of the first treatment in salvage therapy. It is assumed that patients do not respond to re-treatment with salvage therapy, i.e. only in the first cycle is there a treatment effect, in order to reflect the use of long-term seton placement which is the most common treatment strategy seen in real-life care, reflecting a treatment goal of palliation (maintaining patients in the CSF mild health state) rather than fistula healing at this stage in the treatment pathway.

The base case treatment effectiveness inputs for time to remission and relapse used in the model are shown in Table 44. The treatment effectiveness of salvage therapy is set to HR = 0.6 of the control treatment, and then applied constantly over time regardless of the number of retreatments received.

Table 44: Treatment effectiveness for darvadstrocel vs. control and control vs. salvage

Gompertz model HR	Time to remission		Time to relapse from remission	
	Darvadstrocel vs. Control	Control vs. salvage *	Darvadstrocel vs. Control	Control vs. salvage
Base case – CPC	1.474	0.600	0.571	1.00
Scenario 1 – Clinical	1.674	0.600	0.874	1.00
Scenario 2 – CPC + MRI	0.922 * CPC	0.600	0.571**	1.00
Scenario 3 – Combined	0.896 * clinical	0.600	0.874**	1.00

Abbreviations: CPC, Clinical and patient-centred; HR, hazard ratio

Notes: * For salvage therapy, the time to remission rate was only applied to the first treatment. It is assumed that patients do not respond to re-treatment with salvage therapy

** Due to the lack of MRI data available for time to relapse from CPC + MRI remission and time to relapse from combined remission, the hazard ratio for time to CPC remission and clinical remission was applied, respectively

B.3.3.4 Last-resort surgery use and outcomes

One of the aims of treatment for patients with complex perianal fistulae and CD is to reduce defunctioning surgeries such as temporary colostomy and ileostomy, as well as resectioning of the rectum (such as proctectomy). Defunctioning surgeries and proctectomies are recommended in clinical guidelines after failure of pharmaceutical or other surgical treatments (Gionchetti 2017). As there is no evidence associating specific treatments to a reduced or increased likelihood of accessing last-resort surgeries, the probability of patients undergoing defunctioning or proctectomy are conditional on the health state of the patient, and are not treatment-specific.

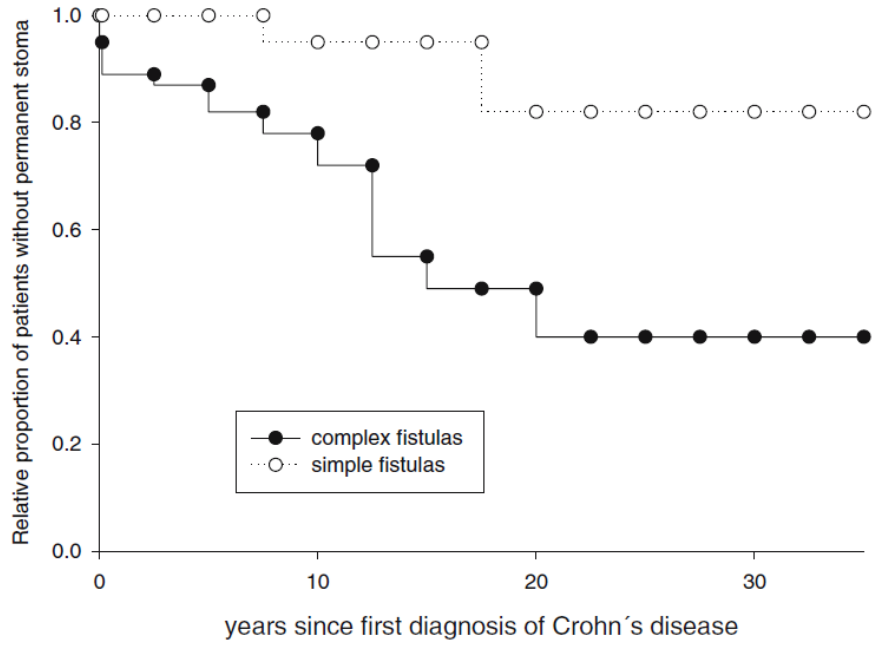
B.3.3.4.1 Probability of defunctioning surgery

The probability of requiring a permanent defunctioning surgery was estimated based on a German study (Mueller 2007). Mueller and colleagues analysed the risk of permanent stomas in 102 consecutive CD patients who presented with the first manifestation of a perianal fistula or a perianal abscess in a single German outpatient department (Ludwig-Maximilians University; Munich) between 1992 and 1995. Follow-up data was available for 97 patients, with a median follow-up from the first diagnosis of CD, of 16 years (range: 8-37 years). There were 50 male and 47 female patients, with a median age of 23 years. A total of 46 patients (52%) had complex fistulae, defined as rectovaginal and/or presenting three or more perianal openings. Of these 46 patients, 34 required a temporary stoma (74%) and 23 a permanent stoma (50%). Time-to-permanent stoma data was available for the subgroup of complex perianal fistulae patients in the form of a Kaplan Meier curve with an associated risk table.

The heterogeneity between the complex perianal fistulae population as defined in the ADMIRE-CD trial and by Mueller *et al*. (2007) was substantial, for example; in the Muller study, the patients were seen more than 20 years ago and therefore the surgical management may not be up to date. Additionally, the definition of a complex perianal fistula was not aligned between the two studies, and there were geographical (German vs. UK) and local (variations in between centres) differences in the typical management of the disease. Taking these considerable differences into account, a conservative approach was used.

The rate of receiving permanent stomas from the study by Mueller (2007) to estimate the probability of defunctioning surgery was preferred, because the base case economic model structure does not allow defunctioning reversal, to reflect UK clinical practice, and also because clear time to event data was available. The Kaplan Meier curve available from the publication (see Figure 24) was digitised and the pseudo-individual patient data was reconstructed (Guyot 2012). An exponential curve was then fitted to the pseudo-individual patient data and an annual event probability equal to 3.7528% was obtained.

Figure 24: Time to permanent stoma in complicated Crohn's disease with simple and complex fistulae, Mueller *et al*. (2007)



Patients at risk								
A	42	42	36	21	9	3	2	2
B	46	38	34	23	10	3	2	0

Source: Figure 2 from (Mueller 2007)

The probability of successful outcomes after defunctioning surgery is based on the St Mark's retrospective study, and set equal to 62%, as detailed in Appendix Q. This probability was validated by clinical experts during an advisory board (Consultation 4 13/08/17; Table 25). Before the availability of the retrospective study of St Mark's Hospital, clinical experts advised that the probability of successful outcomes after defunctioning surgery was approximately 50% (Consultation 1 01/02/17; Table 25).

B.3.3.4.2 Probability of proctectomy

The probability of patients receiving proctectomy was based on a retrospective data analysis from the St Mark's Hospital in the UK (Bell 2003). The authors reported the clinical course of 169 fistulae in 87 patients with Crohn's disease-related fistulae requiring intervention between January 1993 and December 1994. Of the 169 fistulae, 110 (65%) were perianal, with the rest either recto-vaginal (27/169, 16%) or from other sites (32/169, 19%). Complex fistulae amounted to 80% of the total (135/169), based on the Parks *et al*. (1976) classification (Parks 1976).

Eighteen patients with fistulae required proctectomy (18/87, 21%), which resulted in healing for 10 of them (10/18, 56%). The median number of treatments prior to proctectomy was 12 (range: 3-18), with a median time of 6 years from first presentation of fistulating disease to proctectomy (range: 12 weeks to 28.2 years). In particular, rectal involvement was associated with an increased risk of proctectomy, while the presence of a rectovaginal fistula was not (Bell 2003).

The number of proctectomies and the time to proctectomy by fistulating disease complexity (i.e. simple or complex fistulae) was not reported. The annual probability of receiving a proctectomy is therefore based on the entire sample by assuming a constant average rate of the events in the median time at risk (as the mean was not available). This estimate appears to be conservative however the percentage of patients receiving last resort surgery as predicted by the model matches the rate expected by clinical experts (Consultation 6 08/02/18; see Table 25). This check was done to ensure a sensible rate of last resort surgery was being modelled. The rate is then converted to an annual probability.

In the model base case, the annual probability of proctectomy is assumed to be null for chronic symptomatic fistula patients with mild symptoms, according to clinical expert opinion, while chronic symptomatic fistula patients with severe symptoms are associated with a yearly probability of 3.85% to undergo a proctectomy. Due to lack of data, the same 3.85% probability of receiving a proctectomy is conservatively assumed for patients who underwent defunctioning surgery; however, clinical experts from the St Mark's Hospital confirmed that at least 9 out of 10 defunctioned patients would eventually go on to receive proctectomy; therefore, the rate of proctectomy events derived from Bell *et al.* (2003) is likely to underestimate the transition probability from the post-defunctioning surgery health state.

Bell *et al.* (2003) indicated a relatively low healing rate post proctectomy (10/18, 56%); however, healing was not defined by the authors, and thus it is unclear whether it can be considered a long-term outcome as per the model definition (Bell 2003). Analogously to the probability of positive outcomes (successful) defunctioning surgery, the likelihood of positive outcomes after proctectomy is based on the St Mark's retrospective data analysis, with a probability equal to 80%.

B.3.3.5 Safety inputs

Adverse events are included in the evaluation to account for the potential QoL burden of experiencing events while on treatment. In order to exclude rare occurrences and identify relevant differences between therapies, TRAEs occurring in at least 5% of patients in the ADMIRE-CD trial arms, are included in the economic analyses. Only two events were identified based on this definition; anal abscess and proctalgia, based on the 52-week follow-up trial data (see Section B.2.10).

For all other health states, except for darvadstrocel-chronic symptomatic fistulae and control treatment-chronic symptomatic fistulae, treatment-specific TRAEs were not considered because of the lack of homogeneous data. Based on the available data, it is not considered feasible or reasonable to isolate the single component causing the occurrence of TEAEs. Therefore, the TRAE rates for salvage therapy, post-surgery, and remission are based on clinical expert opinion (Consultation 3 05/09/17; Table 25). The base case model inputs are reported in Table 45.

Table 45: Annual probability of experiencing treatment-related adverse events by treatment mix

Event	Darvadstrocel	Control	Salvage therapy	Post-surgery	Remission
Anal abscess	x/xx (xx%)	x/xx (xx%)	12.00%	12.00%	0.00%
Proctalgia	5/103 (4.85%)	8/102 (7.84%)	14.50%	14.50%	0.00%
Source	ADMIRE-CD trial		Clinical expert opinion		

TRAEs are assumed to occur during the whole treatment period by applying the annual probability of events to all treated patients, assuming constant rates of events during treatment.

B.3.3.6 Mortality

No robust evidence could be identified that showed that there is a significant impact of increased mortality for patients with complex perianal fistulae as a complication of CD when compared to age- and gender-matched general population. Therefore, mortality was included based on the age- and gender-specific 2013-2015 life table data on general population mortality for England and Wales (Office for National Statistics 2017). In the economic model, mortality was weighted by gender based on the initial proportion of male and female patients in the ADMIRE-CD trial (Panes 2016), and was applied based on the average age of patients in the model at each cycle.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

Currently, there are no perianal fistula specific QoL instruments available, and so no such instrument was included in the ADMIRE-CD trial (see Section B.2.6 for further detail).

B.3.4.2 Mapping

Consideration was given to a mapping approach to estimate EQ-5D utility values, but was not possible due to a lack of valid instruments available to measure QoL in patients with complex perianal fistulae as a complication of CD (Appendix R).

Two instruments, the CDAI and PDAI are commonly used in clinical trials; however, these are measures of disease activity and do not measure QoL. Mapping relies on a degree of conceptual overlap between the source and target measure (Longworth 2011, Petrou 2015). An assessment of the content of CDAI and PDAI found that whilst some items may be considered to reflect components of HRQoL (e.g. the presence of abdominal pain), most items are clinical indicators, and therefore the conceptual overlap with EQ-5D is limited.

A similar finding has been reported in an empirical study which attempted to map the CDAI to the EQ-5D (Buxton 2007). Despite this being a well-designed study using a large dataset (n=3,575 observations), it was not possible to develop a valid mapping algorithm between the CDAI and EQ-5D. The authors concluded that the poor performance of CDAI as a predictor of utility reflects its main role as clinical indicator of disease activity, rather than as a measure of HRQoL.

Mapping from the IBDQ, was not appropriate as this generic bowel disease instrument has not been designed to measure QoL associated with a complex perianal fistula but rather that associated with the luminal disease.

B.3.4.3 Health-related quality-of-life studies

Currently, no valid instruments are available to measure the HRQoL in patients with complex perianal fistulae (see Appendix R) and no study has reported utility values using generic instruments such as the EQ-5D or Short-Form, 6 dimensions (SF-6D) for this population (see Section B.3.4).

A literature review was conducted to identify published HRQoL studies reporting utility values in patients with fistulae or/and CD or in patients undergoing surgical procedures typically undergone by patients with CD. The searches used to identify studies, inclusion/exclusion criteria, and a full description and quality assessment of studies considered relevant to decision-making in England are provided in Appendix H. In summary, 37 unique published studies were included. Only two of these provided data specifically for fistula health states.

A study by Arseneau (2001) reported a US-based cost-utility analysis of treatments (infliximab and combination metronidazole) for perianal fistula in CD (Arseneau 2001). The paper also included brief details of utility estimation of fistula health states in CD. Direct elicitation was conducted with 32 CD patients (17 fistulising and 15 non-fistulising) and 20 healthy individuals using the standard gamble technique. The mean utility values estimated by CD patients for fistulae treated with infliximab and combination metronidazole were 0.73 and 0.69 respectively. The same health states were valued by a healthy sample at 0.77 and 0.75 respectively. Improved fistula treated with infliximab and mercaptopurine (6-MP)/metronidazole were valued 0.85 and 0.81 by CD patients; 0.91 and 0.88 by the general public. Perianal abscess was valued as 0.62 and 0.72 by CD patients and the general public respectively.

Few details were provided in the paper as to how the utility data were generated. It is not possible to determine the patient characteristics of the sample studied but this appears to be an early cohort as 6-MP/metronidazole was the main comparator and studies examining surgical treatment where excluded from the reported literature review. This would suggest that this patient cohort is very different to that being examined in this appraisal. Furthermore, the approach used to elicit the utility values is unclear; including whether a vignette approach was used, details of the vignettes/health states and the methods used in their development. It was therefore not possible to align the reported values with the health states included in our economic model.

A study by Grucela (2012) measured utility in patients with fistula undergoing anorectal surgery using the EQ-5D (Grucela 2012). It was considered to be of fair quality but did not report data separately for patients with CD. It reported mean EQ-5D values in patient with fistula-in-ano of 0.82 pre-fistulotomy and 0.87 post-fistulotomy. The tariff set used in this study was not reported. As the study population did not match the population for the economic model (patients with complex perianal fistulae in CD), these values were not included in the economic model.

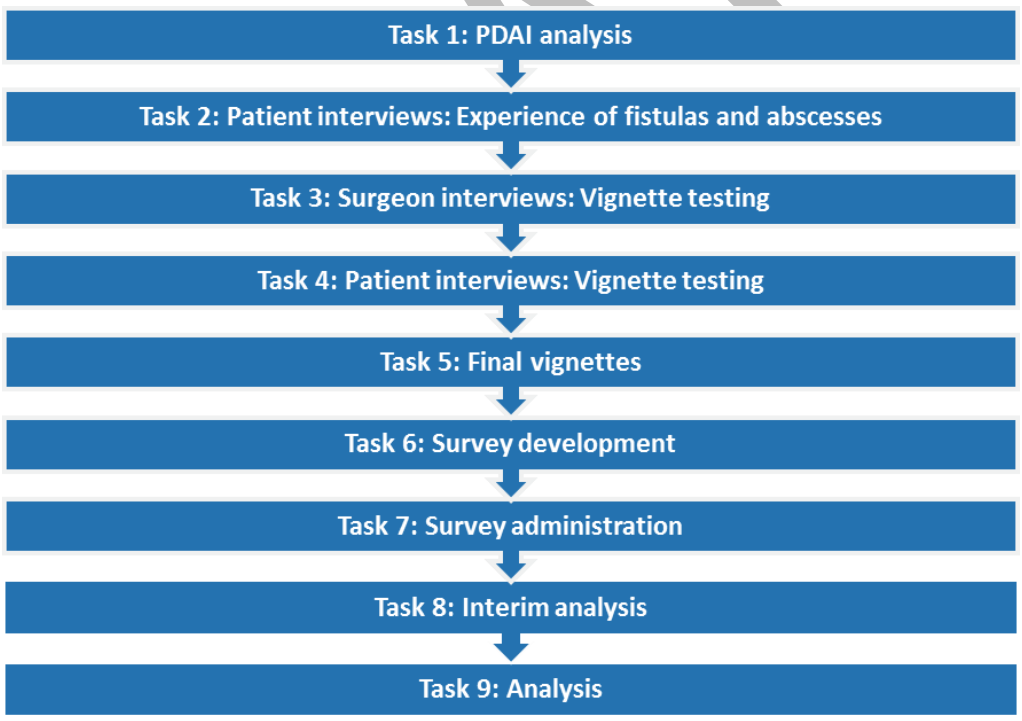
The remaining studies did not report utility data for patients with complex perianal fistula in CD. None of the studies reporting utility estimates associated with surgery states reported data for patients with CD.

B.3.4.4 Vignette study

A vignette approach does not measure changes in health as reported by patients, as specified by NICE in its recommended approach (TSD 11) (Brazier 2011). However, since the ADMIRE-CD trial and the literature review did not identify appropriate utility values, and mapping was infeasible, a vignette study was performed by a consultancy group, PHMR, under the guidance of Louise Longworth, to elicit health state utility values (HSUVs) for inclusion in the economic model (see Appendix R). Vignette approaches to utility elicitation have previously been considered by NICE as valid, most recently in an appraisal of a treatment for short bowel syndrome (NICE 2017b).

The aim of the study was to develop descriptions of health states, or 'vignettes', relating to fistulae in CD patients and to value these to generate utility data. The vignettes were designed to reflect different severities of complex perianal fistula in CD patients including surgical states, aligned with the health states included in the health economic model. In-depth interviews were conducted with CD patients who had experienced fistulae to explore how fistulae (and any associated surgery) affected their QoL. Draft vignettes were developed based on the findings of the interviews and validated with clinicians. A second set of interviews with patients was then conducted to further validate the vignettes. The key steps undertaken during this study are shown in Figure 25. Details on the steps are provided in Appendix R. The final vignettes used in the survey are described below.

Figure 25: Key steps undertaken for the vignette study



Health State 1: Remission

You have a condition that causes inflammation of the gastrointestinal tract. This inflammation can occur within your intestines, anywhere from near your mouth to your anus. People with this condition can experience stomach cramps and a need to go to the toilet urgently.

Some people with this condition can experience fistulae, which are small holes or openings, near the anus. However, your condition is well controlled. You do not have pain associated with the fistulae and do not experience any discharge from around the anus. Your daily activities are not restricted and there are no physical restrictions on your sexual activity as a result of fistulae.

Health State 2: Chronic Symptomatic Fistulae with mild symptoms

You have a condition that causes inflammation of the gastrointestinal tract. This inflammation can occur within your intestines, anywhere from near your mouth to your anus. People with this condition can experience stomach cramps and a need to go to the toilet urgently.

Because of the condition, you also experience fistulae, which are small holes or openings, near the anus. These sometimes cause you mild discomfort and a small amount of mucous sometimes leaks from the fistulae opening. You have no or slight restrictions on your daily activities. You have slight physical restrictions on your sexual activity.

Health State 3: Chronic Symptomatic Fistulae with severe symptoms

You have a condition that causes inflammation of the gastrointestinal tract. This inflammation can occur within your intestines, anywhere from near your mouth to your anus. People with this condition can experience stomach cramps and a need to go to the toilet urgently.

Because of the condition, you also experience fistulae, which are small holes or openings, near the anus. These sometimes cause you moderate or marked discomfort. You experience moderate or substantial discharge from the fistulae openings, which contains mucous, pus and/or poo. Your daily activities are moderately to markedly restricted as a result of the fistulae. You have moderate or marked physical restrictions on your sexual activity.

Health State 4: Abscess

You have a condition that causes inflammation of the gastrointestinal tract. This inflammation can occur within your intestines, anywhere from near your mouth to your anus. People with this condition can experience stomach cramps and a need to go to the toilet urgently.

Because of the condition, you also experience fistulae, which are small holes or openings, near the anus. These fistulae are infected and an abscess has developed. This causes you severe pain and you may experience swelling around your anus. Your daily activities are moderately to severely restricted as a result of the infected fistulae. You have moderate to severe physical restrictions on your sexual activity.

Health State 5: Defunctioning surgery with positive outcome

You have a condition that causes inflammation of the gastrointestinal tract. It has not been possible to control your symptoms with drugs, and you have had an operation. Before the operation you regularly experienced severe pain and an urgent need to go to the toilet. You also experienced a regular and substantial discharge of mucus, pus and/or poo from around your anus.

The operation diverted digestive waste away from the affected area of your gastrointestinal tract, to give it a chance to heal. It also re-routed part of your intestine to an opening, or stoma, so that waste products may be emptied into an external bag attached to your abdomen. The operation was a success but you still have mild discomfort from the fistulae. A small amount of mucous may sometimes leak from the fistulae but your daily activities are not restricted. You have slight physical restrictions on your sexual activity.

Health State 6: Defunctioning surgery with negative outcome

You have a condition that causes inflammation of the gastrointestinal tract. It has not been possible to control your symptoms with drugs, and you have had an operation. Before the operation you regularly experienced severe pain and an urgent need to go to the toilet. You also experienced a regular and substantial discharge of mucus, pus and/or poo from around your anus.

The operation diverted digestive waste away from the affected area of your gastrointestinal tract, to give it a chance to heal. It also re-routed part of your intestine to an opening, or stoma, so that

waste products may be emptied into an external bag attached to your abdomen. The operation has not completely relieved your symptoms and you still regularly experience moderate to severe pain. You also experience a regular and substantial discharge of mucus, pus and/or poo from the fistula openings. Your daily activities are severely restricted as a result of the fistulae. You have moderate to severe physical restrictions on your sexual activity.

Health State 7: Proctectomy with positive outcome

You have a condition that causes inflammation of the gastrointestinal tract. It has not been possible to control your symptoms with drugs, and you have had an operation to remove your back passage (rectum). Before the operation you regularly experienced severe pain and an urgent need to go to the toilet. You also experienced a regular and substantial discharge of mucus, pus and/or poo from around your anus.

The operation removed your back passage (rectum). It also re-routed part of your bowel to an opening, or stoma, so that waste products may be emptied into an external bag attached to your abdomen. It is not possible to reverse the operation and you will always require the stoma and external bag.

The operation was a success and you do not have any pain or discharge from around the anus. Your daily activities are not restricted. You have slight physical restrictions on your sexual activity.

Health State 8: Proctectomy with negative outcome

You have a condition that causes inflammation of the gastrointestinal tract. It has not been possible to control your symptoms with drugs, and you have had an operation to remove your back passage (rectum). Before the operation you regularly experienced severe pain and an urgent need to go to the toilet. You also experienced a regular and substantial discharge of mucus, pus and/or poo from around your anus.

The operation removed your back passage (rectum). It also re-routed part of your bowel to an opening, or stoma, so that waste products may be emptied into an external bag attached to your abdomen. It is not possible to reverse the operation and you will always require the external bag.

The operation has not completely relieved your symptoms and you still regularly experience moderate to severe pain. You also experience discharge from the surgery wound which has not fully healed. Your daily activities are severely restricted as a result of the surgery wound. You have moderate to severe physical restrictions on your sexual activity.

Samples of the general public and patients with CD were used to obtain utility values for each health state. In addition to eight health states for the economic model, the CD patients were asked to value their current heath state. A detailed overview and description of the approaches and methodologies used to estimate the utility values are provided in an accompanying document to this report (Appendix R). The time-trade-off (TTO) method of valuation was used. This is a choice-based technique, which is also used to value the EQ-5D instrument. Specific elements of the standard EuroQol valuation protocol were also adopted to maximise consistency with EQ-5D valuations: a composite (lead time) TTO framework, description of the anchors ('full health' and 'dead'), time horizon for the health states, the iteration procedure and starting point for valuation (Oppe 2016).

Although standardised measures of HRQoL are preferred, vignette studies conducted with a high level of rigour are an alternative credible research tool. The validity of the methodology is enhanced by conducting extensive qualitative work with patients to construct the vignettes, using techniques such as in-depth interviews and focus groups. The credibility of the vignette can also be further improved by independent verification of the patient's descriptions. Methods have been developed for constructing vignettes using pertinent HRQoL data from clinical studies and this provides some quantitative bases for their construction (TSD11) (Brazier 2011).

The general public survey was administered online to 1,040 respondents and was reflective of the UK general population in terms of age and gender. A total of 205 respondents displayed logical inconsistency in their responses and were excluded. 835 respondents were included in the final analysis and the mean values followed a logical pattern from least to most severe health states (highest to lowest utility) – see Table 46. The 'remission' state of non-active perianal CD was valued highest (mean 0.87; 95% CI 0.85-0.88) followed by 'Chronic Symptomatic Fistulae with mild symptoms' (mean 0.58; 95% CI 0.55 – 0.61). Successful proctectomy and defunctioning surgery had mean utility values of 0.57 and 0.56 respectively. Defunctioning surgery with negative outcome and proctectomy with negative outcome had mean utility values of 0.19 and 0.21 respectively. Chronic symptomatic fistulae with severe symptoms and abscess had mean values of 0.38 and 0.22. Standard deviations ranged from 0.24 to 0.57, with narrow deviation for the mild health state and a widening of the range as health states increased in severity. Respondents with family or friends with CD valued all of the health states higher and this was statistically significant for four health states in the public survey.

The values were validated with an international panel of clinical experts and were deemed appropriate to describe the HRQoL of complex perianal fistulae in CD patients.

Table 46: Vignette study results, general population sample

Health state		Observations	Mean utility	Standard deviation	Standard error	95% confidence interval
Remission		835	0.865	0.24	0.008	[0.85; 0.88]
Chronic symptomatic fistulae	**Mild symptoms**	835	0.578	0.44	0.015	[0.55; 0.61]
	Severe symptoms	835	0.383	0.50	0.017	[0.35; 0.42]
Defunctioning**	**Undergoing**	-	0.383	0.50	0.017	[0.35; 0.42]
	Successful	835	0.567	0.46	0.016	[0.54; 0.60]
	Unsuccessful	835	0.193	0.56	0.019	[0.15; 0.23]
Proctectomy**	**Undergoing**	-	0.383	0.50	0.017	[0.35; 0.42]
	Successful	835	0.564	0.50	0.017	[0.53; 0.60]
	Unsuccessful	835	0.202	0.57	0.020	[0.16; 0.24]

Abbreviations: CSF, chronic symptomatic fistulae. Notes: **, assumed equal to chronic symptomatic fistulae with severe symptoms. Source: Takeda, data on file.

The CD patient survey was administered online to 201 respondents. A total of 19.4% of respondents who provided inconsistent responses were excluded from the analysis, leaving a sample of 162 respondents included in the analysis. One third of the participants in the patient study had experienced perianal fistula, 36.4% had experienced perianal abscess, 26.5% had experienced abdominal abscess and nearly half (46.9%) of them had undergone surgery for CD. Results are presented in Table 47. The 'remission' state of non-active perianal CD was valued highest at 0.89 followed by 'Chronic Symptomatic Fistulae with mild symptoms, which was valued 0.66. Defunctioning surgery and proctectomy with positive outcome were given mean utility values of 0.54 and 0.57 respectively. Defunctioning surgery with negative outcome and proctectomy with negative outcome had mean utility values of 0.28 and 0.28 respectively. Standard deviations ranged from 0.24 to 0.54, with narrow

deviation for remission and wide range for others. The mean utility value reported for participants' current health state was 0.71.

Table 47: Vignette study results, Crohn's disease patients sample

Health state		Observations	Mean utility	Standard deviation	Standard error	95% confidence interval
Remission		162	0.894	0.24	0.019	[0.86; 0.93]
Chronic symptomatic fistulae	**Mild symptoms**	162	0.657	0.41	0.032	[0.59; 0.72]
	Severe symptoms	162	0.433	0.46	0.036	[0.36; 0.51]
Defunctioning**	**Undergoing**	-	0.433	0.46	0.036	[0.36; 0.51]
	Successful	162	0.541	0.51	0.040	[0.46; 0.62]
	Unsuccessful	162	0.278	0.54	0.042	[0.19; 0.36]
Proctectomy**	**Undergoing**	-	0.433	0.46	0.036	[0.36; 0.51]
	Successful	162	0.568	0.52	0.041	[0.49; 0.65]
	Unsuccessful	162	0.279	0.55	0.043	[0.19; 0.36]

Abbreviations: CSF, chronic symptomatic fistulae. Notes: *, treatment-related adverse events decrement; **, assumed equal to chronic symptomatic fistulae with severe symptoms. Source: Takeda, data on file.

The utility values elicited from a representative sample of the UK general public are used in the economic model base case, in accordance to NICE guidance (NICE 2013b). The results based on the CD patient's survey are explored in scenario analyses.

B.3.4.5 Adverse reactions

The results of the vignette study were adapted to estimate the disutility associated with perianal abscess events. This was because in the economic model abscess were considered as events occurring while patients were in the chronic symptomatic fistulae health state and not as a separate health state. To estimate the disutility associated to abscesses, it was conservatively assumed that this would be equal to the difference between the HSUV associated to severe chronic symptomatic fistulae and the active perianal abscess utility. The associated standard error was calculated based on an assumption of no correlation between the measures as: $se(disutility_{abscess}) = \sqrt{se(\text{HSUV}_{CSF\ severe})^2 + se(\text{HSUV}_{abscess})^2}$.

The disutility value associated to proctalgia was conservatively assumed to be null, as by definition of chronic symptomatic fistulae the patients could experience pain, and was therefore considered to be already accounted for by the chronic symptomatic fistulae HSUVs. The disutilities associated to the two included TEAEs are reported in Table 48.

Table 48: Disutilities associated to treatment-related adverse events, general population sample

Adverse event	Disutility	Standard error	95% Confidence Interval
Anal abscess	0.16	0.026	[0.11; 0.21]
Proctalgia	0.00	0.000	[0.00; 0.00]

B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

The HSUVs applied in the model are presented in **Error! Not a valid bookmark self-reference.**.

Table 49: Summary of utility values for cost-effectiveness analysis

State		Base case population		Sensitivity analysis		Reference in submission (section and page number)	Justification
		Utility value: mean	95% CI	Utility value: mean	95% CI		
Health state							
Remission		0.865	[0.85; 0.88]	0.894	[0.86; 0.93]	Table 45, page 99	The pivotal trial did not report HSU, the SLR did not identify appropriate HSU, and therefore a Vignette study was performed. Values from the general population were used as the base case, while patient values were applied as a sensitivity analysis.
Chronic symptomatic fistulae	**Mild symptoms**	0.578	[0.55; 0.61]	0.657	[0.59; 0.72]		
	Severe symptoms	0.383	[0.35; 0.42]	0.433	[0.36; 0.51]		
Defunctioning**	**Undergoing**	0.383	[0.35; 0.42]	0.433	[0.36; 0.51]		
	Successful	0.567	[0.54; 0.60]	0.541	[0.46; 0.62]		
	Unsuccessful	0.193	[0.15; 0.23]	0.278	[0.19; 0.36]		
Proctectomy**	**Undergoing**	0.383	[0.35; 0.42]	0.433	[0.36; 0.51]		
	Successful	0.564	[0.53; 0.60]	0.568	[0.49; 0.65]		
	Unsuccessful	0.202	[0.16; 0.24]	0.279	[0.19; 0.36]		
Adverse events - disutility							
Anal abscess		0.16	[0.11; 0.21]	0.091	[-0.01; 0.20]	Table 48, page 100	The disutility value associated to proctalgia was conservatively assumed to be null, as by definition of chronic symptomatic fistulae the patients could experience pain, and was therefore considered to be already accounted for by the chronic symptomatic fistulae HSUVs.
Proctalgia		0.00	[0.00; 0.00]	0.000	[0.00; 0.00]		

Abbreviations: CI, Confidence interval; HS, health state; AR, adverse reaction. Notes: *, treatment-related adverse events decrement; **, assumed equal to chronic symptomatic fistulae with severe symptoms.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Relevant cost and health resource use data were identified from various sources including previous NICE appraisals, a systematic review of published costing studies, the British National formulary, NHS reference costs, PSS research unit reports, and the summary of product characteristics for in-scope comparators. Appendix I presents the search strategy and methodology to identify relevant cost and healthcare resource data.

The systematic review identified two studies relating to the economic burden of complex perianal fistula in CD, both conducted in Spain in a multicentre setting. In addition, five studies which reported on the economic burden of perianal fistula in CD, irrespective of disease complexity, were identified. Three of the five studies reported disease burden or health care resource use associated with perianal fistula in CD treated with infliximab, while the remaining two were economic evaluation studies, as discussed in Section B.3.1.

Table 50 below summarises the cost per disease management resource unit. As the SLR did not find many relevant studies relating to the cost and use of resources for the chronic perianal fistula subgroup of CD individuals, the majority of sources used to identify the most applicable cost and health resources were the St Mark's study, expert opinions from a range of specialist clinical practitioners from the UK, and the ADMIRE-CD trial.

Table 50: Cost per disease management resource unit

Resource	Unit cost, £	Source
GP visit	37.00	Unit Costs of Health and Social Care 2017, PSSRU. Cost per surgery consultation lasting 9.22 minutes (Curtis 2017)
Gastroenterologist visit	149.76	National Schedule of Reference Costs, year 2016-2017. Gastroenterology, consultant led. Outpatient, service code 301 (Gov.uk 2017)
Surgeon visit	127.09	National Schedule of Reference Costs, year 2016-2017. Colorectal surgery, consultant led. Outpatient, service code 104 (Gov.uk 2017)
Nurse appointment	51.15	National Schedule of Reference Costs, year 2016-2017. Specialist nursing, stoma care services, adult, face to face. Code N24AF (Gov.uk 2017)
Nutritionist visit	81.33	National Schedule of Reference Costs, year 2016-2017. Dietetics, consultant led. Service code 654 (Gov.uk 2017)
MRI	162.23	National Schedule of Reference Costs, year 2016-2017. Magnetic resonance imaging scan of one area, with post contrast only, 19 years and over (RD02A, outpatient) (Gov.uk 2017)
Endoscopy	182.10	National Schedule of Reference Costs, year 2016-2017. Diagnostic flexible sigmoidoscopy, 19 years and over (FZ54Z, outpatient) (Gov.uk 2017)
Stoma care	1,961.00	Estimated average annual cost of stoma care cost, assumed to be incurred by all surgery patients (TA329 costing statement, Appendix A) (NICE 2015b)

Resource	Unit cost, £	Source
Computerised tomography scan	85.56	National Schedule of Reference Costs, year 2016-2017. Computerised tomography of one area without contrast, 19 years and over (RD020A) (Gov.uk 2017)
Colonoscopy	334.76	National Schedule of Reference Costs, year 2016-2017.Diagnostic colonoscopy, 19 years and over (FZ51Z, outpatient) (Gov.uk 2017)
Blood count	1.69	National Schedule of Reference Costs, year 2016-2017. Integrated blood services (DAPS03) (Gov.uk 2017)
C-reactive protein	1.13	National Schedule of Reference Costs, year 2016-2017. Clinical biochemistry (DAPS04) (Gov.uk 2017)
Haemoglobin	3.06	National Schedule of Reference Costs, year 2016-2017. Haematology (DAPS05) (Gov.uk 2017)
Faecal calprotectin	22.79	NICE DG11 (2013): Faecal calprotectin diagnostic tests for inflammatory disease of the bowel; ELISA test (NICE 2013a)
Abbreviations: DG, diagnostic guidance; GP, general practitioner; ELISA, enzyme-linked immunosorbent assay; MRI, magnetic resonance imaging; NICE, National Institute for Health and Care Excellence; PSSRU, Personal and Social Services Research Unit.		

The economic model includes the following costs:

- Darvadstrocel cost and resource use
- Background treatment and salvage therapy cost and resource use
- Health state costs
    - Routine disease management
    - Last-resource surgical procedures
- Costs of adverse events

B.3.5.1 Darvadstrocel costs and resource use

The total cost of a single intralesional injection of darvadstrocel is £[redacted], based on the PAS price for a pack of four vials required per injection, equating to a [redacted] discount from the list price. Darvadstrocel is delivered during an examination under anaesthesia (EUA), in addition to a EUA conducted at the conditioning visit (Table 51). Within ADMIRE-CD, patients in the control arm received a placebo (saline) injections, however they also received two EUAs (1 at the conditioning visit and a second 2-4 weeks later) in the same way as for patients in the darvadstrocel arm. The costs of the EUAs conducted at the conditioning visit are excluded from the economic model as it would be equal in both treatment arms. A EUA is associated with the same cost obtained from the National Schedule of Reference Costs as the cost for intermediate anal procedures, validated based on NICE MIB 102 and 105 (Gov.uk 2017, NICE 2017a, NICE 2017d). This is because no substantial differences in the resources used could be identified between the procedures. The cost of the EUA is applied in the first cycle.

Table 51: Costs of darvadstrocel and control treatment plus administration

Cost (£)	Darvadstrocel	Control	Source
Darvadstrocel	xxxxx	-	
Examination under Anaesthesia	1,170.21	1,170.21	National Schedule of Reference costs, year 2016-2017. Code FZ22C: intermediate anal procedures, 19 years and over, with CC score 0, day case. (Gov.uk 2017) NICE MIB 102, NICE MIB 105 (NICE 2017a, NICE 2017d)
Total cost in first cycle	xxxxx	1,170.21	

B.3.5.2 Treatment mix

The treatments in the control arm are based on the ADMIRE-CD trial and include antibiotics, immunosuppressants, biologics and seton placement to represent the conditioning visit. For the darvadstrocel arm, the same control treatment is provided in addition to darvadstrocel treatment at the start of the model. Within the base case, no dose escalation of biologics is assumed for the darvadstrocel and control arms. The use of a EUA in both groups allows for a direct comparison between the two arms of the study. The treatments included in the darvadstrocel and control treatment arm of the model are presented in Table 52.

Table 52: Treatment mix in the darvadstrocel and control arms

Treatment mix	Darvadstrocel	Control	Sources and assumptions
Darvadstrocel	100%	0%	All patients treated with darvadstrocel in the darvadstrocel treatment mix
Antibiotics			
Ciprofloxacin	29.76%	29.76%	Based on ADMIRE-CD data
Metronidazole	38.05%	38.05%	Metronidazole and metronidazole benzoate
Immunosuppressants			
Azathioprine	46.23%	46.23%	Azathioprine and azathioprine sodium
Methotrexate	0%	0%	All patients on immunosuppressants assumed to receive azathioprine
6-MP	0%	0%	Based on ADMIRE-CD data
Biologics			
Adalimumab	33.59%	33.59%	Imputed based on proportion in the concomitant treatment randomisation stratum and biologic use up to week 52 in ADMIRE-CD
Infliximab	27.26%	27.26%	
Adalimumab dose escalation	0%	0%	Assumption (no dose escalation)
Infliximab dose escalation	0%	0%	
Vedolizumab	0%	0%	Based on ADMIRE-CD data
Surgery			
Seton (+ EUA)	95%	95%	Based on ADMIRE-CD data
Fistulotomy	0%	0%	Patients receiving the initial treatment mix assumed not to receive additional reparative surgeries over that used in the ADMIRE-CD trial
Anal plug	0%	0%	
Fibrin glue (+ EUA)	0%	0%	
Rectal flap	0%	0%	
VAAFT	0%	0%	
EUA	0%	0%	Based on ADMIRE-CD data

Source: (Panes 2016)

Abbreviations: 6-MP, 6-mercaptopurine; EUA, examination under anaesthesia; VAAFT, video-assisted anal fistula treatment

Additionally, following advice from clinical experts (gastroenterologists and surgeons based across the UK), treatment in the remission and the post-surgery health states was also considered within the model. The compositions of salvage treatment mixes by health state are detailed in Table 53.

Due to the limited information in the public literature, the medical and surgical treatments in the included health states are based on clinical expert validation of data received from a single centre service evaluation conducted at St Marks Hospital (Appendix Q). In general UK clinical experts validated the St Marks data as being representative of UK clinical practice. A number of differences were seen, especially related to biologic use (including dose escalation) that advisors believed was driven by local commissioning restrictions placed on the use of these agents, to account for this and represent the most plausible treatment use across the UK, the treatment mix compositions were obtained by averaging across the clinical expert answers to a questionnaire administered at a UK clinical advisory board. In all salvage therapy health states, patients will receive medical therapy and some surgical treatments (e.g. EUA/seton placement, anal plug,). In addition, dose escalation of adalimumab and infliximab is also assumed in the severe chronic symptomatic fistula, (un)successful defunctioning surgery, and (un)successful proctectomy health states.

Table 53: Salvage therapy treatment mixes

Treatment mix	Remission	Chronic symptomatic fistulae		Defunctioning		Proctectomy		Sources and assumptions
		Mild	Severe	Successful	Unsuccessful	Successful	Unsuccessful	
Antibiotics								
Ciprofloxacin	0.00%	11.25%	11.25%	0.00%	0.00%	0.00%	0.00%	Clinical expert opinion
Metronidazole	11.20%	55.28%	63.59%	18.56%	57.81%	1.09%	32.66%	
Immunosuppressants								
Azathioprine	51.32%	46.37%	52.50%	58.99%	46.88%	45.01%	52.50%	Clinical expert opinion
Methotrexate	7.29%	9.05%	4.38%	0.00%	5.84%	11.66%	0.00%	
6-MP	10.00%	7.50%	10.00%	11.88%	11.88%	0.00%	0.00%	
Biologics								
Adalimumab	31.76%	30.65%	36.55%	21.32%	27.03%	12.86%	25.47%	Clinical expert opinion
Infliximab	32.39%	30.65%	36.55%	21.32%	27.03%	12.86%	25.47%	
Adalimumab dose escalation	4.92%	5.94%	3.94%	3.38%	10.21%	0.75%	8.75%	
Infliximab dose escalation	4.92%	5.94%	3.94%	3.38%	10.21%	0.75%	8.75%	
Vedolizumab	8.24%	8.67%	9.07%	5.08%	7.69%	3.36%	7.36%	
Surgery								
EUA (+Seton)	5.21%	20.56%	16.25%	11.54%	11.96%	0.00%	2.50%	Clinical expert opinion
Fistulotomy	0.00%	1.51%	5.25%	0.00%	5.84%	0.00%	0.00%	
Anal plug	0.00%	12.50%	8.75%	0.00%	0.00%	0.00%	0.00%	
Fibrin glue (+ EUA)	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	
Rectal flap	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	

Abbreviations: DE, dose-escalated; EUA, examination under anaesthesia; 6-MP, 6-mercaptopurine.

For medical therapies, drug acquisition costs are calculated based on available formulations; pack sizes, unit costs and price per mg for each (combination of) treatment included in the model. The dosing information and the drug acquisition costs were sourced from the British National Formulary (BNF) and the European Medicines Agency (EMA) labels when not available (Joint Formulary Committee 2018). Whenever multiple dosage alternatives are available, the option resulting in the lowest cost is chosen. For weight-based dosages, the formulation resulting in the lowest average acquisition cost is selected, as no vial or tablet wastage is assumed in the model. The therapy schedule for dose-escalated biologic therapies, i.e. infliximab and adalimumab, is based on NICE Technology Appraisal (TA) 187 and has been validated by clinical experts (NICE 2010).

Surgical procedure costs include all costs related to the treatment itself with no associated administration costs, as the costs associated to administration route and treatment itself cannot be separated. When this is possible, e.g. for EUA/seton placement, the procedure cost includes the cost of the device or drug administered, while the administration cost includes the cost of resources required to deliver treatment (e.g. EUA). The costs for fistulotomy and video-assisted anal fistula treatment (VAAFT), available from a recent NICE Medtech Innovation Briefing (MIB), are equal to £1,169.00 and £1,195.40 respectively. The acquisition costs of the VAAFT equipment are not considered in the analyses (NICE 2017d). As no reliable costs could be identified available for other surgical procedures, i.e. anal plug, these are associated to the same cost as fistulotomy. This is under the assumption that the resources needed to perform the procedures, e.g. healthcare professional time and equipment required, would not be substantially different between them.

Due to the heterogeneity of the treatment administration schedules considered in the model, the costs associated to the initial treatments (i.e. darvadstrocel and control) are modelled separately for the first and follow-up therapy cycles to estimate accurately the timing of the occurrence of costs. The treatment costs for the salvage therapy, remission and post-surgery treatment mixes are averaged over the re-treatment time as a simplification given that these treatment mixes are assumed equal irrespective of previous therapy received.

The treatment dosing, unit costs, total drug and procedural costs per cycle by treatment included in the base case model scenario are reported in Table 52, Table 53, and Table 54.

Table 54: Drug acquisition and procedural costs of included treatments

Treatment costs	Unit descriptor	Dose per unit	Cost per unit, £	Dosage per administration	Admin per cycle	Units per admin	Cost per cycle, £		Source
							First cycle	Follow-up cycles	
Antibiotics									
Ciprofloxacin	Tablet	500 mg	0.09	500 mg	56	1	4.98	4.98	BNF (Joint Formulary Committee 2018)
Metronidazole	Tablet	400 mg	0.20	15 mg/kg	28	2.72*	14.88	14.88	BNF (Joint Formulary Committee 2018)
Immunosuppressants									
Azathioprine	Tablet	50 mg	0.04	2.25 mg/kg	28	3.27*	3.56	3.56	BNF (Joint Formulary Committee 2018)
Methotrexate	Tablet	2.5 mg	0.05	17.50 mg	4	7	1.51	1.51	BNF (Joint Formulary Committee 2018)
6-MP	Tablet	50 mg	1.97	1.25 mg/kg	28	1.81*	99.88	99.88	BNF (Joint Formulary Committee 2018)
Biologics									
Adalimumab	Vial	40 mg	352.14	40 mg	2	1	704.28	704.28	BNF, TA187 (NICE 2010, Joint Formulary Committee 2018)
Infliximab	Vial	100 mg	377.00	5 mg/kg	0.5	3.63*	684.01	684.01	BNF, TA187 (NICE 2010, Joint Formulary Committee 2018)
Adalimumab dose escalation	Vial	40 mg	352.14	40 mg	4	1	1,408.56	1,408.56	BNF, TA187 (NICE 2010, Joint Formulary Committee 2018)
Infliximab dose	Vial	100 mg	377.00	10 mg/kg	0.5	7.26*	1,368.02	1,368.02	BNF, TA187 (NICE 2010, Joint Formulary Committee

Treatment costs	Unit descriptor	Dose per unit	Cost per unit, £	Dosage per administration	Admin per cycle	Units per admin	Cost per cycle, £		Source
							First cycle	Follow-up cycles	
escalation									2018)
Vedolizumab	Vial	300 mg	2,050,00	300 mg	0.5	1	1,025.00	1,025.00	BNF (Joint Formulary Committee 2018)
Surgery									
Seton	Procedure	1 unit	0.00	1 unit	1	1	0.00	0.00	Cost of setons assumed to be approximately null
Fistulotomy	Procedure	1 unit	1,170.21	1 unit	1	1	1,170.21	0.00	MIB102, MIB105, NHS FZ22E (NICE 2017a, NICE 2017d, Joint Formulary Committee 2018)
Anal plug	Procedure	1 unit	1,170.21	1 unit	1	1	1,170.21	0.00	MIB102, MIB105, NHS FZ22E (NICE 2017a, NICE 2017d, Joint Formulary Committee 2018)
Fibrin glue	Procedure	1 unit	724.19	1 unit	1	1	724.19	0.00	Permacol®, MIB105 (NICE 2017a)
Rectal flap	Procedure	1 unit	1,170.21	1 unit	1	1	1,170.21	0.00	MIB102, MIB105, NHS FZ22E (NICE 2017a, NICE 2017d, Joint Formulary Committee 2018)

Abbreviations: BNF, British National Formulary; DE, dose escalated; EUA, examination under anaesthesia; kg, kilogram; mg, milligram; MIB, Medtech innovation briefing; NA, not applicable; NHS, National Health Service; TA, technology appraisal; VAAFT, video-assisted anal fistula treatment; 6-MP, 6-mercaptopurine. * As per the previous NICE consideration; average value based upon body weight and distribution of vials

B.3.5.2.1 Treatment administration

Four administration routes are identified for the treatments considered in the economic analysis, in addition to a "No administration" category used for surgical procedures not differentiating between costs associated to the treatment itself and to treatment administration.

The drug administration costs for intravenous (IV) treatments include the cost of a day case inflammatory bowel disease, without interventions, with CC Score 0 (FD02H), as used for vedolizumab (NICE 2015a) (it should be noted that the tariff code has changed since this vedolizumab submission). No administration costs are included for oral treatments. Similarly, no costs are assumed for subcutaneous (SC) drugs, as it is assumed that patients will self-administer. Treatments delivered during a EUA are associated with the same cost obtained from the National Schedule of Reference Costs as the cost for intermediate anal procedures, validated based on NICE MIB 102 and 105 (NICE 2017a, NICE 2017d, Joint Formulary Committee 2018). Similar costs are applied because no substantial differences in the resources used could be identified between the procedures. Surgical procedures are not associated with administration costs to avoid duplicating the cost of the healthcare resources required, unless treatment is administered during EUA, as in the case of darvadstrocel and seton placement/removal. The costs associated to each administration type are reported in Table 55.

Table 55: Unit costs, resource use, and total administration costs used in the model (per administration)

Administration type	Cost, £	Source
EUA	1,170.21	National Schedule of Reference costs, year 2016-2017. Code FZ22C: intermediate anal procedures, 19 years and over, with CC score 0, day case. NICE MIB 102, NICE MIB 105 (NICE 2017a, NICE 2017d, Joint Formulary Committee 2018)
IV infusion	284.49	National Schedule of Reference costs, year 2016-2017. Code FD02H: Inflammatory Bowel Disease without Interventions, with CC Score 0, day case (Joint Formulary Committee 2018), as used in TA352 (NICE 2015a)
SC injection	0.00	Assumption, self-administered by patients
Oral	0.00	Assumption, self-administered by patients

Abbreviations: CC, complications and comorbidities; EUA, examination under anaesthesia; IV, intravenous; MIB, Medtech Innovation Briefing; NICE, National Institute for Health and Care Excellence; SC, subcutaneous.

The administration costs per cycle by treatment are summarised in Table 56.

Table 56: Administration costs per 4-week cycle by treatment

Treatment	Form of administration	First cycle costs, £	Follow-up cycle costs
Antibiotics			
Ciprofloxacin	Oral	0.00	0.00
Metronidazole	Oral	0.00	0.00
Immunosuppressants			
Methotrexate	Oral	0.00	0.00
6-MP	Oral	0.00	0.00
Azathioprine	Oral	0.00	0.00
Biologics			
Adalimumab	SC injection	0.00	0.00
Infliximab	IV infusion; every 8 weeks	142.25	142.25
DE adalimumab	SC injections	0.00	0.00
DE infliximab	IV infusion; every 4 weeks	284.49	284.49
surgery			
Seton	EUA	1,170.21	90.02*
Fistulotomy	None	0.00	0.00
Anal plug	None	0.00	0.00
Fibrin glue	EUA	1,170.21	90.02*
Rectal flap	None	0.00	0.00

Abbreviations: DE, dose-escalated; VAAFT, video-assisted anal fistula treatment; 6-MP, 6-mercaptopurine. Notes: *, based on a re-treatment time of 13 cycles; None denotes no additional cost to procedure.

B.3.5.2.2 Summary cost of treatment mix

A summary of the treatment mix and administration costs in the included health states in the first and follow-up cycles is presented in Table 57.

Table 57: Treatment mix therapy costs in first and follow-up cycles

Treatment costs/cycle	First 4-week cycle, £			Follow-up 4-week cycle, £		
	Treatment	Administration	Total	Treatment	Administration	Total
Treatment arm – background treatments only						
Darvadstrocel arm	431.82	1,150.48	1,582.29	431.82	38.78	470.60
Control arm	431.82	1,150.48	1,582.29	431.82	38.78	470.60
Further health states						
Remission	611.83	65.64	677.47	611.83	65.64	677.47
Salvage therapy treatment mix						
CSF - mild	670.91	79.95	750.86	670.91	79.95	750.86
CSF - severe	667.84	121.59	789.43	667.84	121.59	789.43
Post last-resort surgery treatment mix						
Defunctioning,						
successful	422.79	50.89	473.69	422.79	50.89	473.69
unsuccessful	725.91	79.10	805.01	725.91	79.10	805.01
Proctectomy,						
successful	203.93	20.79	224.72	203.93	20.79	224.72
unsuccessful	632.85	64.18	697.03	632.85	64.18	697.03
Source	Treatment mix composition: Table 52 (darvadstrocel and control), Table 53 (salvage) Costs: Table 54 (treatment) and Table 55 (administration)					

Abbreviations: CSF, Chronic symptomatic fistulae

B.3.5.3 Health-state unit costs and resource use

Published costing studies examining complex perianal fistulae in patients with CD were identified via a systematic literature review (search date 22 January 2018) of biomedical literature databases in accordance with the NICE methods guide (NICE 2013b). The review covered:

- published peer-reviewed costing studies
- costing data used in models submitted to the NICE STA process
- unpublished data held by the company

The approaches used to identify studies in the review, and a full description and quality assessment of studies considered relevant to decision-making in England are provided in Appendix I.

In total, 5 unique published studies were included, of which 1 reported UK costs relevant to clinical practice in England (Lindsay 2008).

Since the literature did not provide information on the healthcare resource utilisation for all included health states, the healthcare resource utilisation was based on clinical expert opinion (Consultation 3 05/09/17; Table 25). The experts interviewed were asked to

complete a table with the types of visits and monitoring tests the target population would require in the different health states.

During Consultation 2 (24/02/17 – 14/03/17; Table 25), the clinical experts identified five types of healthcare professional visits: general practitioner (GP) visits, gastroenterologist visits, surgeon visits, nurse appointments and nutritionist visits. The following monitoring and laboratory test resources are included: MRI, endoscopy, stoma care, CT-scan, colonoscopy, blood count, c-reactive protein, haemoglobin, and faecal calprotectin. The 4-weekly frequencies estimated based on the experts' opinions are reported in Table 29 in Appendix J.

Based on the individual resource costs and frequencies by health state, the disease-related costs per 4-weekly model cycle are shown in Table 58.

Table 58: Routine disease management costs by health state per 4-weekly cycle

Health state		Visits, £	Monitoring and testing, £	Total per cycle, £
Remission		31.70	16.12	47.82
Chronic symptomatic fistulae	Mild symptoms	52.04	23.63	75.67
	Severe symptoms	99.35	52.14	151.49
Defunctioning surgery	Undergoing	746.38	542.59	1288.97
	Successful	39.21	167.57	206.78
	Unsuccessful	117.66	196.02	313.68
Proctectomy	Undergoing	924.62	635.84	1560.46
	Successful	48.06	160.62	208.68
	Unsuccessful	154.34	188.75	343.09

Notes: Costs are calculated per tunnel state period of four weeks, representing the time in which patients undergo surgery and the short-term recovery post-procedure

B.3.5.4 Last resource surgical procedures costs

The costs associated to last-resort surgical procedures, i.e. defunctioning surgery and proctectomy, are extracted from the National Schedule of Reference Costs (year 2015-2016) using HRG codes derived by mapping relevant procedure codes using the NHS grouper, as reported in Table 59. The costs represent a one-off expense to deliver surgery, and do not include any follow-up monitoring. Defunctioning surgery is assumed to include any surgeries resulting with the opening of a diverting ostomy potentially including (partial) colon resection but no resection of the rectum, such as colostomy, ileostomy and jejunostomy. Proctectomy is assumed to include any surgical procedure resulting in the resection of the rectum, with or without (partial) resection of the colon, such as proctectomy and pan-proctocolectomy.

Table 59: Last-resort surgery costs

Last-resort surgery	Cost, £	Source
Defunctioning surgery	5,034.24	National Schedule of Reference Costs, year 2016-2017. Weighted average of Major Small Intestine Procedures, elective, 19 years and over, codes FZ67C-F (Gov.uk 2017)
Proctectomy	11,925.05	National Schedule of Reference Costs, year 2016-2017. Weighted average of Very Complex Large Intestine Procedures, elective, 19 years and over, codes FZ73C-F (Gov.uk 2017)

B.3.5.5 Adverse reaction unit costs and resource use

As already detailed in Section B.3.3.3, TRAEs occurring in at least 5% of patients in the ADMIRE-CD trial arms, are included in the economic analyses, and based upon this definition, only two events were identified; anal abscess and proctalgia. The management of anal abscesses require incision and drainage via a EUA which can be performed in the outpatient or day care setting, and its associated cost is extracted from the National Schedule of Reference Costs for the year 2015-2016 (Gov.uk 2017). The greater cost of anal abscess reflects the range of severities at presentation and can include, increased hospital time, additional procedures compared to (elective) seton placement, and possible emergency care. For proctalgia, in the absence of any data on the TRAE management, the associated costs are estimated based on an assumed management including a GP visit and the cost of analgesics. The unit costs for each adverse event were based on various sources, as summarised in Table 60.

Table 60: Cost per adverse events used in the model

Adverse event	Total cost per event , £	Source
Anal abscess	2,303.00	National Schedule of Reference costs, year 2015-2016. Weighted average of codes FZ22C-E: intermediate anal procedures, 19 years and over, day case (Gov.uk 2017)
Proctalgia	50.00	Assumption based on a cost of £13.00 for analgesics, and £37.00 for 1 GP visit
Abbreviations: CC, complications or comorbidities; GP, general practitioner.		

The total costs due to TRAEs in the different treatment mixes are presented in Table 61. For all other treatment mixes, treatment-specific TRAEs were not considered because of the lack of homogeneous data. The total cost due to TRAEs for the health states of remission and post-surgery were also calculated. The annual probability of anal abscess and proctalgia whilst in remission is 0.00%, and the average TRAE management cost was £0. The annual probability of anal abscess whilst in the post-surgery health state is 12.00%, and for proctalgia this is slightly higher at 14.50%. The average management cost per 4-week cycle for TRAEs in the post-surgery health state is £23.13.

Based on the available data, it is not considered feasible or reasonable to isolate the single component causing the occurrence of TRAEs. Therefore, the TRAE rates for salvage therapy, post-surgery, and remission are based on clinical expert opinion (Consultation 3 05/09/17; Table 25). The cost of management of these TRAEs was calculated using the costs outlined in Table 60.

Table 61: Annual probability of adverse events and costs per 4-weekly treatment cycles, by treatment mix

Treatment mix	Annual probability		Average adverse events management cost per 4-week cycle of treatment
	Anal abscess	Proctalgia	
Darvadstrocel	7.77%	4.85%	14.47
Control arm	8.82%	7.84%	16.62
Salvage therapy	12.00%	14.50%	23.13

B.3.5.6 Summary resource use and costs

Table 62 presents the total cost per cycle for each health state.

Table 62: Costs included in the economic model

Health state		Treatment + administration	Background treatment + administration		Monitoring and visits*	Adverse events*	Surgical procedure	Total per cycle	
		1st cycle	1st cycle	Follow-up cycle				1st cycle	Follow-up cycle
Darvadstrocel arm		[redacted]	1,582.29	470.60	121.07	14.47		[redacted]	606.14
Control arm		1,170.71	1,582.29	470.60	121.07	16.62		2,890.69	608.29
Remission		-	677.47	677.47	47.82	0.00		725.29	725.29
Chronic symptomatic fistulae	Mild symptoms	-	750.86	750.86	75.67	23.13		849.66	849.66
	Severe symptoms	-	789.43	789.43	151.49	23.13		964.05	964.05
Defunctioning surgery	Undergoing	-			1,288.97		5,034.24	6,323.21	NA
	Successful	-	473.69	473.69	206.78	23.13		703.60	527.40
	Unsuccessful	-	805.01	805.01	313.68	23.13		1,141.82	925.90
Proctectomy	Undergoing	-			1,560.46		11,925.05	13,485.51	NA
	Successful	-	224.72	224.72	208.68	23.13		456.53	481.12
	Unsuccessful	-	697.03	697.03	343.09	23.13		1,063.25	922.97
Cross reference		Table 51	Table 57		Table 58	Table 61	Table 59		

Notes: *, Adverse events and monitoring visits are applied to both the 1st cycle and follow up cycles

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A summary of the variables applied in the economic model is provided in Table 63. Details on the distributions are provided in the Excel model.

Table 63: Summary of variables applied in the economic model

Model parameter	Value	Reference in submission
Baseline characteristics		
Average body weight, kg (95% CI)	72.57 (70.55, 74.60)	Table 26, B.3.2.2.1
Average age, year (95% CI)	38.27 (36.51, 40.04)	
% Male patients, %	54.72%	
Patients with mild symptoms (%)	40.1%	Table 29, B.3.2.2.2
Clinical parameters		
Time to remission		
- Darvadstrocel	CPC remission – Gompertz curve;	Table 34 and Table 44 Section B.3.3.1.1and B.3.3.3
- Control		
- Salvage therapy	HR 0.60 vs. control treatment; no repeat efficacy assumption	
Time to relapse from remission		
- Darvadstrocel	Relapse from CPC remission – Gompertz curve	Table 40 and Table 44 Section B.3.3.2.1and B.3.3.3
- Control		
- Salvage therapy	Same probability as control treatment	
Long term relapse rate (>2 year)		
- Darvadstrocel	0.0010	The probability of relapse is assumed to remain constant. Section B.3.3.2.4
- Control	0.0018	
- Salvage therapy	0.0018	
Probability defunctioning surgery		
CSF mild CSF mild, salvage	0.00	Section B.3.3.4.1
CSF severe CSF severe, salvage	0.04	
Successful	0.62	
Probability proctectomy		
CSF mild CSF mild, salvage	0.00	Section B.3.3.4.2
CSF severe	0.04	

Model parameter	Value		Reference in submission
CSF severe, salvage defunctioning			
Successful	0.80		
Health state utility values			
Remission	0.87		Vignette study; Table 46, Section B.3.4
CSF, mild	0.58		
CSF, severe	0.38		
Undergoing defunctioning	0.38		
Undergoing proctectomy	0.38		
Defunctioning, successful	0.57		
Defunctioning, unsuccessful	0.19		
Proctectomy, successful	0.56		
Proctectomy, unsuccessful	0.20		
Disutility			
Abscess	0.16		Table 48, Section B.3.4.5
Proctalgia	0.00		
TEAEs			
Annual probability	**Anal abscess**	**Proctalgia**	
Darvadstrocel	7.77%	4.85%	ADMIRE-CD, Table 61, Section B.3.5.5
Control	8.82%	7.84%	
Salvage	12.00%	14.50%	Clinical expert opinion; Table 61, Section B.3.5.5
Health state costs per cycle	**First cycle**	**Follow-up cycle**	Table 62, Section B.3.5
Darvadstrocel arm	[redacted]	606.14	
Control arm	2,890.69	608.29	
Remission	725.29	725.29	
CSF mild	849.66	849.66	
CSF severe	964.05	964.05	
Under defunctioning	6,323.21	NA	
Under proctectomy	703.60	527.40	
Defunctioning, successful	1,141.82	925.90	
Defunctioning, unsuccessful	13,485.51	NA	
Proctectomy, successful	456.53	481.12	
Proctectomy, unsuccessful	1,063.25	922.97	

Abbreviations: CSF, chronic symptomatic fistulae; HR, Hazard Ratio; TEAEs, Treatment-emergent adverse events

B.3.6.2 Assumptions

A summary of the key assumptions in the base case model is outlined in Table 64.

Table 64: Summary of basic structural assumptions

Aspect	Details	Justification/comments	Cross-reference
Model structure	Semi-Markov model Memory used to accurately represent the variation of probabilities of remission and relapse over a limited time	Simple, flexible structure to capture the chronic nature of the condition Based on review of clinical data, natural history of the disease, available data and consultation with clinical experts	B.3.2.3
Patient population	Adults with non-active or mildly active luminal CD, who have a CPF that is refractory to conventional or biologic therapy	Using the ADMIRE-CD RCT inclusion criteria, in line with the approved indication and Final NICE scope (Panes 2016, NICE 2018)	B.3.2.2
Treatments	Intervention: darvadstrocel treatment mix Comparator: Control treatment mix	The treatments are aligned with the ADMIRE-CD trial. The St Marks study confirmed that the control treatment mix was aligned with current clinical practice, which consists of medical treatments for the underlying CD and/or perianal fistulae (i.e. antibiotics, immunosuppressants, and/or biologics) and surgical treatments (most commonly seton placement and EUAs). Darvadstrocel is given in addition to the control treatment mix	B.3.2.5
Health states	• Remission • CSF, mild symptoms • CSF, severe symptoms • Defunctioning surgery (successful) • Defunctioning surgery (unsuccessful) • Proctectomy (successful) • Proctectomy (unsuccessful) • Death	Expert clinical input from UK gastroenterologists and surgeons was used to identify the variety of health states that could be entered during the duration of the model	B.3.2.1 B.3.2.3
Effectiveness	• Time to CPC remission • Time to relapse from CPC remission	Considered by clinical experts to be the most accurate representation of the decision algorithm used in clinical practice Salvage efficacy only applied in first treatment	B.3.3

Aspect	Details	Justification/comments	Cross-reference
Time horizon	Base case set to 40 years Modifiable up to 60 years	The disease is a chronic condition without additional risk of mortality User-modifiable time horizon between 1 and 60 years In the ADMIRE-CD trial, the mean age at baseline was 39.0 years within the darvadstrocel group, and 37.6 years within the control group	B.3.2.3
Cycle length	Four-weekly cycles	Natural measure of scheduled assessments and therapy cycles in ADMIRE-CD Greater common divisor of 24, 52 and 104, i.e. the data cuts available from the ADMIRE-CD RCT	B.3.2.3
Country	England	NICE guidance	-
Model perspective	NHS and PSSRU	The base-case scenario focuses on direct costs to the NHS as per NICE guidance.	-
Discount rates	Costs: 3.5% annually Benefits: 1.5% annually	As recommended by NICE (NICE 2013b)	B.3.2.3
Analytical software	Microsoft® Excel 2010 with Visual Basic for Applications	Flexible, accessible, and transparent software	B.3.2.3

Abbreviations: CD, Crohn's Disease; CHMP, The Committee for Medicinal Products for Human Use; CPC, clinical and patient-centric; EUA, Examination under anaesthesia; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal and Social Services Research Unit; RCT, randomised clinical trial

B.3.7 Base-case results

At the end of the 40-year time horizon in the economic model, darvadstrocel resulted in more patients achieving CPC remission than control treatment (13.9% vs. 6.4%, respectively) (see Table 65). In contrast fewer proctectomies were observed with darvadstrocel than with control treatment (25.3% vs. 29.4%, respectively). Similarly, the percentage of patients who would receive a defunctioning surgery is also reduced at the end of the model (5.8% vs. 6.6%, respectively).

Table 65: Percentage of patients in the different health states at the end of the model time horizon

% patients in health state at 40 year	Darvadstrocel	Control
Remission	13.9%	6.4%
CSF, mild	20.2%	22.9%
CSF, severe	3.1%	3.0%
Defunctioning	5.8%	6.6%
Proctectomy	25.3%	29.4%
Death	31.7%	31.7%
Abbreviations: CSF, Chronic symptomatic fistula(e)		

The results of the deterministic base case analysis are provided in Table 66. The disaggregated costs and QALYs are presented in Appendix J.

The base case results are presented as a pairwise comparison between the control scenario and the scenario considering the addition of darvadstrocel to background therapy. In the base case scenario, the cost per QALY gained when comparing the introduction of darvadstrocel to the current management is £15,471 with a total cost of darvadstrocel per administration of £[redacted].

The addition of darvadstrocel to the background therapy results in increased quality of life for patients but at a greater cost than the current control treatment in addition to background therapy. The increase in discounted quality-adjusted life years (QALYs) is equal to 1.40, a gain approximately equivalent to extending life for about 17 months in perfect health. It is worth noting that no differences in mortality are associated to the introduction of darvadstrocel, and therefore this substantial QALY gain is purely due to an increase in patients' quality of life.

Table 66: Base-case results

Treatment	Total costs (£) With PAS applied	Total LYG	Total QALYs	Incr cost with PAS applied	Incr LYG	ICER (cost / LYG)	Incr QALYs	ICER (cost / QALY)
Control	[redacted]	36.65	[redacted]					
Darvadstrocel	[redacted]	36.65	[redacted]	21,639	0.00	N/A	1.40	15,471
Abbreviations: ICER, incremental cost-effectiveness ratio; incr, Incremental; LYG, life years gained; N/A, Not applicable; QALYs, quality-adjusted life years.								

B.3.8 Sensitivity analyses

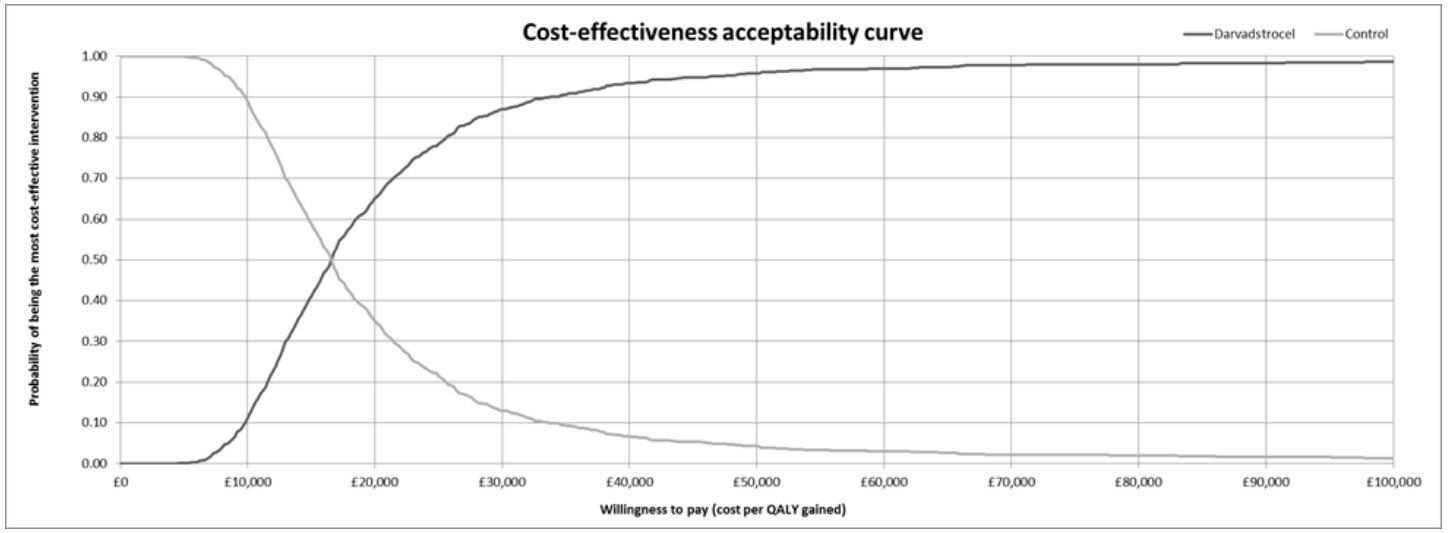
B.3.8.1 Probabilistic sensitivity analysis

A summary of the probabilistic distributions used in the sensitivity analysis is provided in Table 63. Further details on the derivation of sampling parameters (e.g. alpha and beta for individual distributions) are available in the Excel model.

The average PSA results over 1,000 simulations are summarised in Table 67. The probabilistic results indicate a significant increase in QALYs (95% credible interval, CrI, [0.35; 2.51]) alongside a significant increase in costs (95% CrI, [£18,276; £24,369]) for the comparison between darvadstrocel and control. The PSA results indicate that the uncertainty associated to the comparison is propagated appropriately through the model parameters.

The cost-effectiveness acceptability curve (CEAC) estimates the probability of cost-effectiveness for different willingness to pay thresholds, quantifying the degree to which a treatment is preferred (Baio 2017). The CEAC associated to the comparison between darvadstrocel and control is shown in Figure 26. The break-even point, i.e. the willingness to pay threshold in correspondence of which the CEAC values are equal and therefore there is no preference for any of the compared treatment strategies, lies at approximately £16,000 per QALY gained. The probability of darvadstrocel increases steadily from about £8,000 per QALY gained and takes over the control CEAC curve, reaching a probability of 0.65 in correspondence of a willingness to pay threshold equal to £20,000 per QALY.

Figure 26: Cost-effectiveness acceptability curve, probabilistic base case



Abbreviations: QALY, quality-adjusted life year.

Table 67: Probabilistic results

Treatment	Costs Mean	QALY Mean	Incremental cost, mean (95% CrI)	Incremental QALY mean (95% CrI)	Probabilistic ICER	Probability cost effective at £20,000	Probability cost effective at £30,000
Control	[redacted]	[redacted]					
Darvadstrocel	[redacted]	[redacted]	21,774 (18,276, 24,369)	1.35 (0.35, 2.51)	16,121	0.65	0.87
Abbreviations: QALYs, quality-adjusted life years; CrI, Credible interval							

B.3.8.2 Deterministic sensitivity analysis

Each parameter in the one-way sensitivity analysis was varied between its lower and upper 95% confidence interval, by 30% to 100% of its mean value if statistical measures of variance were not available. Further details on the variations in parameters are available in the Excel® model.

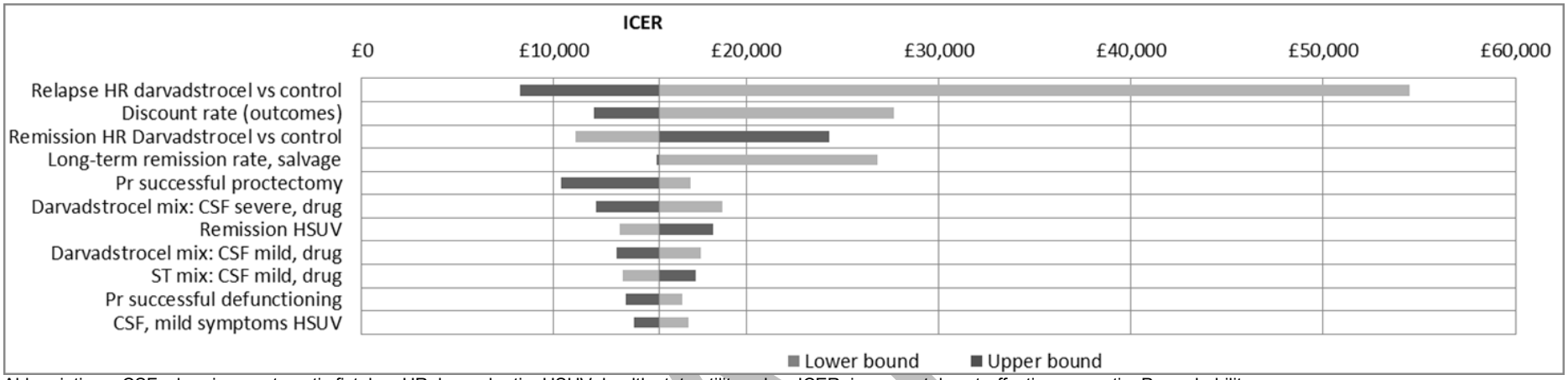
The results of the one-way sensitivity analyses on the different model outcomes explored are reported graphically as tornado plots for the ten most influential parameter variations in Figure 27.

The model parameters with the most impact on the model outcomes are the HRs comparing darvadstrocel and control relative treatment effectiveness on time to CPC relapse and CPC remission. These inputs are varied in the one-way sensitivity analyses based on the 95% CIs based on the survival analysis, and therefore the CI limits represent extreme scenarios, as the probability that the CI would not include the true HR (i.e. the CI limits being less extreme than the true ratio) is 5%.

The relative treatment effectiveness of salvage therapy compared to control is also influential in the model, although not at as much as the relative effect of darvadstrocel compared to control. It is worth noting that, as the salvage therapy relative effectiveness was elicited based on clinical expert opinion, no estimates of uncertainty are available and therefore the variation in the OWSAs is based on an arbitrarily large variation, assuming a 15% coefficient of variation for the estimates.

Other parameters influencing the model outcomes are the discount rate for health effects, as the main clinical benefit of darvadstrocel is sustained remission and is accrued on the long term, and the drug acquisition cost of darvadstrocel. The probability of proctectomies being successful (varied between 0% and 100%) is influential as it is associated to maintenance treatment post-surgery, with a lower overall treatment mix cost for successful proctectomies. As patients in the control arm are projected to receive more last-resort surgeries, a greater success rate decreases the cost differences between the two model arms.

Figure 27: One-way sensitivity analysis tornado plot, ICER



Abbreviations: CSF, chronic symptomatic fistulae; HR, hazard ratio; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; Pr, probability

B.3.8.3 Scenario analysis

The uncertainty associated with the selected data sources, as well as structural and modelling assumptions, is explored via deterministic scenario analysis. Scenario analyses, involving the variation of single or a small set of key model parameters, are outlined in Table 68. The ICER value ranged from £11,380 (gained from a 0% discount rate for costs and QALYs) to £23,761 (resulting from utilising a time horizon of 20 years), which was the most impactful scenario. The next most impactful scenario resulted from increasing the discount rate to 3.5% for costs and QALYs, which provided an ICER of £20,591. All scenarios presented resulted in ICERs below £24,000 per QALY.

A scenario of interest was the exclusion of biologic usage within salvage therapy and keeping all other assumptions as per the base case. Biologics are used to treat luminal CD which is out of scope for this appraisal. It is not possible to split biologic usage between luminal CD and chronic perianal fistula and so a scenario exploring the impact of removing biologic therapy is appropriate. This scenario resulted in an ICER of £12,553.

Complex scenario analyses are described in the following subsections.

Table 68: Parametric and structural scenario analysis results

Scenario description	Total costs			Total QALYs			ICER
	Darvadstrocel	Control	Difference	Darvadstrocel	Control	Difference	
Base case	[redacted]	[redacted]	**21,639**	[redacted]	[redacted]	**1.40**	**15,471**
0% discount rate for costs and QALYs	[redacted]	[redacted]	20,400	[redacted]	[redacted]	1.79	11,380
3.5% discount rate for costs and QALYs	[redacted]	[redacted]	21,639	[redacted]	[redacted]	1.05	20,591
10% annual proctectomy probability post defunctioning	[redacted]	[redacted]	22,024	[redacted]	[redacted]	1.39	15,890
50% annual stoma reversal probability from successful defunctioning state	[redacted]	[redacted]	21,186	[redacted]	[redacted]	1.39	15,281
Upper bound of annual stoma care costs (£2,682 per year)	[redacted]	[redacted]	20,944	[redacted]	[redacted]	1.40	14,974
Infusion costs halved (£142.25)	[redacted]	[redacted]	21,514	[redacted]	[redacted]	1.40	15,832
HSUVs based on CD patients vignette study set	[redacted]	[redacted]	21,639	[redacted]	[redacted]	1.31	16,542
Relapse HR for salvage therapy vs. control equal to 1.20	[redacted]	[redacted]	21,566	[redacted]	[redacted]	1.43	15,128
Time horizon: 20 years	[redacted]	[redacted]	21,846	[redacted]	[redacted]	0.92	23,761
Time horizon: 60 years	[redacted]	[redacted]	21,706	[redacted]	[redacted]	1.52	14,278
No inclusion of Biologic usage within salvage therapy (all other assumptions as per base case)	[redacted]	[redacted]	17,557	[redacted]	[redacted]	1.40	12,553

Abbreviations: CD, Crohn's disease; HR, hazard ratio; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

B.3.8.3.1 Alternative survival parametric models for description and extrapolation of clinical outcomes

Gompertz models are used for both time to CPC remission and time to CPC relapse in the base case. Alternative parametric models are explored to test the impact on the model outcomes of the parametric choices. In this scenario analysis, the non-Gompertz best fitting model is selected as an alternative parametric option. Goodness of fit is measured based on the AIC and BIC, reported in Table 32 and Table 38 for time to CPC remission and time to CPC relapse. The distributional parameters for the alternative curves are reported in Table 69 and Table 70 for time to CPC remission and time to CPC relapse, respectively.

In the alternative modelling approaches explored, the modelling approach and the HR for relative treatment effectiveness of salvage therapy compared to control are not varied from the base case values for both remission and relapse.

Table 69: Alternative generalised gamma model, time to CPC remission

Generalised gamma model	Coefficient (normal scale)	Coefficient (transformed scale)	Variance-covariance matrix			
			Mu	Sigma	Q	Darvadstrocel AF vs. Control
Mu		1.905	0.318282	0.107519	0.50496	-0.081683
Sigma		1.474	0.107519	0.042131	0.17493	-0.021714
Q		-2.599	0.504957	0.174931	0.88249	-0.101669
Darvadstrocel AF vs. Control	-0.637	0.502	-0.081683	-0.021714	-0.10167	0.055495

Abbreviations: AF, acceleration factor; CPC, clinical and patient-centric

Table 70: Alternative log-normal model, time to relapse from CPC remission

Log-normal model	Coefficient (normal scale)	Coefficient (transformed scale)	Variance-covariance matrix		
			Mean log	SD log	Darvadstrocel AF vs. Control
Mean log	2.709957	2.709957	0.090950	0.005748	-0.086482
SD log	0.585497	1.795883	0.005748	0.010341	0.002289
Darvadstrocel AF vs. Control	0.799256	2.223886	-0.086482	0.002289	0.156576

Abbreviations: AF, acceleration factor; CPC, clinical and patient-centric; log, logarithm (e.g. mean of the logarithm); SD, standard deviation.

The results of the scenario analyses are reported in Table 71. It should be noted that, although the log-normal parametric model resulted the second best-fitting model after the Gompertz curve for time to relapse from CPC remission, the associated extrapolations were not deemed plausible by clinical experts, as reported in Consultation 4 with two HEOR experts from England (13/12/17; Table 25).

Table 71: Scenario analysis results, alternative parametric modelling

Remission curve	Relapse curve	Total costs			Total QALYs			ICER
		Darvadstrocel	Control	Difference	Darvadstrocel	Control	Difference	
Gompertz (base case)	**Gompertz (base case)**	[redacted]	[redacted]	**21,639**	[redacted]	[redacted]	**1.40**	**15,471**
Generalised gamma	**Gompertz (base case)**	[redacted]	[redacted]	22,653	[redacted]	[redacted]	0.99	22,770
Gompertz (base case)	**Log-normal**	[redacted]	[redacted]	24,740	[redacted]	[redacted]	0.25	98,498
Generalised gamma	**Log-normal**	[redacted]	[redacted]	23,754	[redacted]	[redacted]	0.20	122,888

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

B.3.8.3.2 Use of different definitions of remission

The impact of alternative outcome definitions, i.e. clinical remission and combined remission is assessed in structural sensitivity analyses. More detail on the methodology for time to clinical remission is presented in Section B.3.3.1.2 and for combined remission is presented in Section B.3.3.1.3.

The results from the scenario analyses using alternative outcome definitions for remission are outlined in Table 72. Table 72 in scenario 1, the parametric model is adjusted by altering the outcome definition to clinical remission, which results in an ICER of £31,674. In scenario 2, the model is adjusted using the definition of CPC remission + MRI definition, resulting in an ICER of £16,121. In scenario 3, the model is adjusted using the definition of combined remission, resulting in an ICER of £29,990.

Table 72: Scenario analysis results, alternative outcome definitions for remission

	Total costs			Total QALYs			ICER
	Darvadstrocel	Control	Difference	Darvadstrocel	Control	Difference	
Base case: CPC remission	[redacted]	[redacted]	**21,639**	[redacted]	[redacted]	**1.40**	**15,471**
Scenario 1: Clinical remission	[redacted]	[redacted]	23,534	[redacted]	[redacted]	0.74	31,674
Scenario 2: CPC + MRI remission	[redacted]	[redacted]	21,755	[redacted]	[redacted]	1.35	16,121
Scenario 3: Combined remission	[redacted]	[redacted]	23,439	[redacted]	[redacted]	0.78	29,990

Abbreviations: CPC, Clinical and patient-centred; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

B.3.8.3.3 St Mark's retrospective data

A single-centre retrospective data analysis was carried out to provide additional information on the disease history and healthcare resource use associated to patients who would have been eligible for treatment with darvadstrocel. The analysis was conducted on a cohort of 78

consecutive CD patients with complex perianal fistulae considered eligible for treatment with darvadstrocel who visited the St Mark's Hospital from January, 1st 2008 to July, 1st 2017.

The results from the St Mark's data analysis are used as alternative inputs to populate different aspects of the model:

- The clinical course of the disease for patients in salvage therapy and last-resort surgery health states, applying a transition matrix calculated using a multistate model from the observed clinical outcomes of the retrospective cohort;
- Salvage therapy treatment mix, for patients in the chronic symptomatic fistulae (chronic symptomatic fistulae) health state with mild or severe symptoms;
- Maintenance and post-surgery treatment mixes, for patients in the remission, post-defunctioning and post-proctectomy health states;
- Healthcare resource utilisation, including healthcare professional visits, routine monitoring and testing.

Differently from the inputs elicited from clinical experts it was not possible to discriminate between resources being used specifically and only to manage and treat the underlying Crohn's disease or its associated symptoms, and therefore the dataset may include non-fistula related healthcare resources used by patients (in particular biologic usage).

The scenario results are reported in Table 73.

Table 73: Scenario analysis results, using St Mark's retrospective data analysis inputs

Scenario	Total costs			Total QALYs			ICER
	Darvadstrocel	Control	Difference	Darvadstrocel	Control	Difference	
Base case	[redacted]	[redacted]	**21,639**	[redacted]	[redacted]	**1.40**	**15,471**
St Mark's retrospective data set	[redacted]	[redacted]	26,201	[redacted]	[redacted]	1.51	17,405
Abbreviations: ICER, incremental cost-effectiveness ratio.							

B.3.9 Subgroup analyses

As presented in Section B.2.7, the trial was not powered for the subgroup analyses, with improvements for combined remission in all subgroups. Therefore, it is considered inappropriate to provide economic analyses for the subgroups. An additional limitation was that due to the small patient numbers, the number of patients who would relapse from CPC remission is even further reduced, and the economic model would be unstable.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

B.3.10.1.1 Electronic model validation

The Excel® electronic version underwent several rounds of interval quality assessment using both functional and glass box testing by different senior health economic modellers (from the UK), as well as validation from two external health economic modellers from the UK, and no major issues were identified from a structural and conceptual point of view or in the Excel® implementation. The model was also reviewed using the NICE PRIMA process (Consultation 5; 01/18-02/18). In brief, the model was thought to be of a high standard with minimal negative critique given. It was noted that the model has good quality documentation, clear graphics, as well as many other useful features. One small mathematical error was identified. Examining the 'HRQoL- Control' and 'HRQoL – Darvadstrocel' sheets revealed that the summing functions in row 3 are off by one row. The functions read as follows: =SUM(BE5:INDEX(BE5:BE785,timeHorizon*13)). The function should read =SUM(BE6:INDEX(BE6:AL786,timeHorizon*13)). Correcting this error fixed the discrepancy between QALYs and life years. Following the report, the error was corrected in the model.

B.3.10.1.2 External clinical validation

A number of external clinical experts from the St Mark's Hospital were involved throughout the model conceptualisation phase which culminated in a face to face model conceptualisation meeting, as described in Section B.3.2.1.

The early model framework, structure, assumptions and inputs were discussed in five separate one-to-one clinical interviews. The interviews were double-blinded with the experts blind to the technology under assessment and the interviewers blind to the expert name and institution of affiliation. The key points of discussion from the early model validation interviews are reported in Section B.3.2.1.

Following the consolidation of the model structure and analysis framework, two clinical advisory boards were conducted to validate the model structure, assumptions, inputs and predicted outputs. Six European clinical experts (including 2 from the UK) participated in the first ad board and provided *post hoc* feedback. Seven UK clinical experts validated the assumptions, inputs and predicted outputs during the second ad board which was used to populate resource use inputs such as treatment mix compositions and healthcare resource use. A detailed summary of the advisory board key points of discussions is reported in Appendix P.

B.3.10.1.3 External health economic validation

Three studies reporting cost outcomes deemed comparable to the economic analysis of darvadstrocel were identified in the systematic literature review: (Arseneau 2001, Lindsay 2008, Chaparro 2013). The studies are summarised below, with additional study details reported in the ancillary document detailing the systematic literature review.

- Chaparro *et al*. (2013) estimated the healthcare costs of complex perianal fistulae in CD. The study measured direct costs from visits, tests, hospitalisations, and treatment accrued by 97 patients from multiple centres across Spain, with a follow-up of 4.2 years. Costs were reported in 2009 euros.

- Lindsay *et al.* (2008) performed a cost-utility analysis of infliximab for the treatment of active luminal and fistulising CD compared to the control ACCENT trials based on a Markov model. Direct costs associated to hospital visits, treatment, and diagnostic procedures were included. Results were reported for a time horizon of 5 years. Costs were stated in 2006 GBP.
- Arseneau *et al.* (2001) reported a cost-utility of initial medical management with infliximab compared to 6-mercaptopurine and metronidazole for perianal fistulae in CD, over a 1-year time horizon. Direct costs for visits, treatment, and diagnostic procedures were included and reported in 1999 USD.

The cost comparison is performed by comparing the cost estimates associated to the control treatment model arm, with the results of the three economic data sources identified above and as reported in Table 74. Literature results were not adjusted for inflation of conversion.

Table 74: Comparison of model cost predictions and external data sources

Study comparison	Chaparro *et al.* (2013)	Lindsay *et al.* (2008)	Arseneau *et al.* (2001)
Comparison time horizon	1 year (annual global costs)	5 years (model time horizon)	1 year (model time horizon)
Direct costs	**€8,289 total costs**, of which: €6,242: treatment-related €1,027: hospitalisation and surgery €640: medical visits €30: emergency department visits	**£37,488 (infliximab arm)**	**$10,003 (infliximab arm)**
Base case model estimates	1-year control model costs: **£7,989 total costs**, of which: £6,441: treatment-related £1,289: visits and tests £259: last-resort surgery	5-year control model costs: **£37,493**	1-year control model costs: **£7,989**

The validation exercise highlighted that the economic model produces mid-term estimates aligned with the economic literature for the control arm. Differences might be due to different use of medical resources in different healthcare settings, in the comparison with the results by Chaparro (2013), and different costs of single resources across countries.

B.3.11 Interpretation and conclusions of economic evidence

A *de novo* economic model was performed to assess the incremental cost-effectiveness of darvadstrocel versus control treatment in CD patients with complex perianal fistula(e), in line with the final scope for this appraisal.

The results of the base case analysis demonstrate that darvadstrocel, at a total price of £xxxxxx per treatment, can provide significant quality of life benefits to CD patients with chronic perianal fistulae at an acceptable cost. The base case analysis projects that the per-patient QALYs increase by 1.40 if treated with darvadstrocel, equating to an extension of

about 17 months in perfect health compared to control. The QALY increase is mostly driven by the superior effectiveness of darvadstrocel compared to control treatment, bridging patients in sustained remission, avoiding repeated medical treatments, and reducing the number of last-resort surgeries such as colostomy and proctectomy. These surgeries are incredibly invasive and debilitating, resulting in significant, irreversible negative impact on daily activities, body image perception and patients' overall quality of life, whilst also requiring significant medical resources over the patients' lifetime.

The quality of life increase is associated to an additional upfront cost of treatment, partially offset by the cost savings due to the clinical benefits of darvadstrocel compared to control, in the mid- and long-term. When compared to standard control treatment options, darvadstrocel reduces the number of patients requiring continued active treatment with salvage therapy, decreases the number of last-resort surgical procedures performed on patients, and increases time spent in the remission health state which requires fewer healthcare resources. These cost reductions balance the acquisition cost of darvadstrocel to an investment threshold considered widely acceptable in England.

B.3.11.1 Relevance of the analysis to clinical practice in England.

Where possible, the analyses have used input values from literature sources, an English retrospective study and UK clinical expert opinion that have been considered generalisable to clinical practice in England. This includes the selection of cost inputs corresponding to the NHS and PSS perspective for patients with complex perianal fistula(e) as a complication of CD in England, where available, and the inclusion of HSU values derived from a vignette study using a UK general population.

B.3.11.2 Strengths and weaknesses

The key strengths of the analysis are shown below:

The model structure was developed through several rounds of blinded and unblinded clinical and economic validation, literature searching to understand the state of knowledge in the disease area. This resulted in a robust economic model structure and adherent to English clinical practice and has been extensively validated by key opinion leaders currently working in England.

The economic model was based on direct clinical trial data from the pivotal ADMIRE-CD trial, which compared darvadstrocel with control treatment. The control treatment arm is directly reflective of current English clinical practice, as demonstrated in a retrospective study from the St Mark's Hospital and validated by gastroenterologists and surgeons practicing in England.

The base case treatment effectiveness is CPC remission and relapse from CPC remission, based on *post-hoc* statistical analyses of the ADMIRE-CD trial data (Panes 2017a) (Section B.2.3.3). As described in Section B.2.3.3, the term CPC remission was created following discussion with clinical experts from St Mark's Hospital and Academic Institute (a specialised centre in gastrointestinal and bowel diseases based in London). This term was used to embody both clinical endpoints, and patient-centric remission (an endpoint which is more representative of routine clinical practice).

The key weaknesses of the analyses are sown below:

CPC remission was a *post hoc* analysis of the ADMIRE-CD trial. This limits external validation, however as stated above this definition was considered to be appropriate as it reflects both clinical endpoints and patient reported outcomes. The inclusion of CPC remission as the clinical relevant outcome was incorporated in the model structure, during the model development process. Therefore, the use of the definition was included *a priori* in the construction of the economic model.

The effectiveness associated to salvage therapy was based on clinical expert opinion in the base case scenario, under the assumption that re-treatments would not be effective. This assumption was confirmed by clinical experts, as they considered that given the limited treatment options, the effectiveness of salvage therapy would decline with the number of re-treatments. Clinical experts also considered that continuous treatment would have a palliative intent, rather than curative, thereby trying to manage and control the symptoms of the disease.

One issue related to the identification of healthcare resource utilisation that impacted the estimation of the total costs, could not be addressed conclusively in the economic analyses. Incontinence is widely considered to be a significant aggravation for complex perianal fistula(e) in CD patients, decreasing their QoL and requiring sustained and costly management. Events of incontinence are considered to be associated both to the clinical status of patients (i.e. health state) as well as being caused by repeated surgical procedures. Clinical experts stated that occurrence, frequency, and severity of incontinence are under-reported by patients due to the associated stigma, and that it was not possible to elicit an estimation of how many patients are affected by incontinence. However, all clinical experts interviewed were unanimous in identifying incontinence as a factor impacting severely the quality of life of patients carrying significant cost implications on the NHS. Given the preferable clinical profile of darvadstrocel and its sphincter sparring administration, it is expected that the inclusion of incontinence in the economic evaluation would have resulted in cost savings and an increased QALY gain when compared to control treatment.

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Appendices

Appendix C: Summary of Product Characteristics (SmPC) and European Public Assessment Report (EPAR)

- C.1 SmPC
- C.2 EPAR

Appendix D: Identification, selection, and synthesis of clinical evidence

- D.1 Identification and selection of relevant studies
- D.2 Participant flow in the relevant randomised control trials
- D.3 Quality assessment for each trial
- D.4 Methodology indirect and mixed treatment comparison

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

- J.1 Clinical outcomes from the model
- J.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

Appendix K: Checklist of confidential information

Appendix L: Perianal fistulae complexity and comparison of clinical guidance/ consensus documents

Appendix M: Protocol development for the ADMIRE-CD trial

Appendix N: Model conceptualisation and validation

Appendix O: Additional information on economic model

Appendix P: Summary of expert opinions

Appendix Q: St Mark's retrospective study

Appendix R: Vignette study

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Single Technology Appraisal (STA)

Darvadstrocel for treating complex perianal fistula in Crohn's disease [ID960]

Dear Glynn,

The Evidence Review Group, ScHARR-TAG, and the technical team at NICE have now had an opportunity to take a look at the submission received by Takeda on 18 April 2018. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **Thursday 24 May 2018.** Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Joanna Richardson, Technical Adviser Joanna.Richardson@nice.org.uk . Any procedural questions should be addressed to Marcia Miller and Thomas Feist, Project Manager TACommA@nice.org.uk in the first instance.

Yours sincerely

Joanna Richardson
Technical Adviser– Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

General

A1. PRIORITY QUESTION

The EPAR states: "While treatment with Alofisel is proposed for single dose administration, the need for repeated treatment in the clinical setting seems foreseeable in the targeted patient population. Therefore the prescriber is informed in section 4.2 of the SmPC about the limited experience of repeat administration of Alofisel. The supportive open-label study Cx601-0101 explored the issue of retreatment but included only few patients and the doses were lower than intended for marketing. Whether repeated administration could be associated with increased generation of DSA and/or in any way with increased risk of allo-immune response will also be further studied in a PASS as described in the RMP."[EPAR, page 79]

Is darvadstrocel intended to be given as a single course of treatment? If not, how many courses of the treatment are expected to be given? How frequently can they be given e.g. our clinical advisors suggest that if there is a relapse after a long period of remission following previously successful treatment with darvadstrocel (e.g. over a year) then they would consider using darvadstrocel again. Please clarify whether repeat treatment with darvadstrocel is expected following treatment failure or relapse after a period of remission?

A2. Please provide further details on the clinical pathway of care in England [company submission (CS), section B.1.3.4] in particular:

- Despite the lack of clinical consensus for classifying perianal fistula in CD into simple and complex variants [CS, page 15], please clarify how complex perianal fistula is diagnosed (including amount of variation) in the NHS, if possible.

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- Please clarify what is meant by conventional therapy in section B.1.1. In particular, does this refer to surgical management or the use of immunosuppressants?

- Please clarify how long setons remain in place and how this would vary according to the subsequent therapy given (as per the statement on pages 20-21 of the CS).

- In clinical practice, how rapidly is conventional treatment and/or biologic therapy escalated and how many immunosuppressants or biologic therapies would be used in sequence?

- Please clarify that the case for the cost-effectiveness of darvadstrocel is being made only for second-line use in patients who have shown an inadequate response to at least one conventional or biologic therapy and a case is not being made for darvadstrocel use in those who are contra-indicated to immunosuppressants and or biologics?

- The marketing authorisation [CS, Table 3] states that patients will need to have shown, 'inadequate response to at least one biologic or conventional therapy'. Please clarify how you expect this to be implemented in clinical practice?

- What treatment(s) would people be expected to receive following darvadstrocel in clinical practice?

A3. Please provide further details on how a more clinically appropriate outcome (i.e. revised definition of CPC remission) was derived (were patient perspectives considered?) and validated by clinical experts [CS, page 10]. Please clarify how this compares with the core outcome set for fistulising perianal Crohn's disease developed by the ENiGMA collaborators [Sahnan et al. Gut. 2018 Feb 3. pii: gutjnl-2017-315503. doi: 10.1136/gutjnl-2017-315503]?

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A4. Although a single course of treatment with darvadstrocel is expected to treat people with 2 or less internal openings, 3 or less external openings and only one tract. Please clarify what would be the procedure and course of treatment for a patient who has less than or more than three fistula openings? How would such patients be managed?

A5. The treatment procedure described in Panes et al [Lancet, 2016, 388: 1281-90] (and proposed in: CS, page 24, Figure 6,) suggests that 2 EUA procedures will be required. However, a professional organisation submission by the British Society of Gastroenterology states that 'Currently treatments do not involve 2 EUA procedures. The second EUA has to be coordinated with delivery of the stem cell treatment to the hospital as it has a short shelf-life of about 24-48 hrs'. Please clarify if 2 EUA procedures are standard in clinical practice?

A6. Please provide the rationale for the 24 mL dose of darvadstrocel containing 120 million cells distributed in 4 vials. Please clarify whether any dose-response studies were undertaken and could a lower dose be as effective as the licensed dose?

A7. Please clarify the definition of 'relapse' from CPC remission, e.g. either a re-opening appears only at a treated external opening (rather than an internal opening or another site) OR a score more than 0 is reported on PDAI domains after CPC remission has been achieved? Although PDAI is widely used in clinical trials, a professional organisation submission by the British Society of Gastroenterology and Gecse et al [J Crohns Colitis. 2016 Jul; 10(7):758-65; doi: 10.1093/ecco-jcc/jjw039] suggest that PDAI scores do not have good validation and there is no agreed score defined for either improvement or remission. Please provide further details on the strengths, robustness and limitations/criticisms of the PDAI scores.

A8. Faecal incontinence is noted as an important quality of life burden [CS, page 18], and is listed in the NICE scope, but has not been reported in the CS. Please explain why not?

Literature searching

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A9. Please clarify whether the aim of the searches was to identify studies on the clinical effectiveness of darvadstrocel or to identify a wider range of studies for a NMA. Please provide separate inclusion criteria for these two parts of the analysis.

A10. The searches described in Appendix D.1.1 (Table 3) use a series of concept combinations to identify relevant citations. Please clarify why line 11 does not also include the terms darvadstrocel and 6-MP? Why does the list of Interventions / Comparators in line 11 not correspond to the listed Interventions / Comparators in Table 7 (Appendix D.1.2)? In addition, the St Mark's study of current practice, commissioned by Takeda [CS, pages 21-25, Table 5], suggest that vedolizumab was used as a biologic therapy in 16.7% of patients considered to be eligible for darvadstrocel treatment. Please also clarify why none of the searches in Appendix D.1.1. included this intervention (and related terms)?

A11. Ileostomy, colostomy and stem cells are included as comparators in Table 7 of Appendix D1. However these terms do not appear to have been included in Appendix D1, Table 3 [statement 11]. Please provide reasons for the omission with implications?

A12. For completeness, please could the company provide brief details of any ongoing and or planned studies of darvadstrocel.

Systematic review process

A13. Please confirm if study selection, data extraction and quality assessment was undertaken independently by a minimum of two reviewers for each systematic review in the clinical and cost section. If not, please justify.

A14. Please confirm whether any potentially relevant non-English studies were excluded from the CS [see Appendix D.1.2, Table 7]? If so, what impact would these have had on the results, if any?

A15. Please amend/revise the PRISMA flow diagram and clarify why the numbers in Table 6 [Appendix D.1.1.] do not correspond with those on the study selection flowchart [Appendix D.1.2, Figure 1]. What was the source of the unpublished

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CSR? Please provide additional boxes at the end of the flowchart in Figure 1 to clarify the identity of the 19 included RCTs (37 publications), e.g. for clinical effectiveness review [n=1, the ADMIRE-CD]; for the SLR/NMA [n=6, Appendix D.1.3, Table 8, and D.4.5 Table 13]. Further details of 12 remaining RCTs are needed. In addition, please note a minor discrepancy in the numbers of citations 'After duplicates removed' in Figure 1, as it should read n=4864, not n=271.

A16. For clarity, of the 167 citations that were included [Appendix D.1.2, Figure 1], please could you provide brief details of the 19 RCTs (37 publications) that met the inclusion criteria of the company's systematic review including a full breakdown for the reasons for exclusion of the remaining articles (n=130) e.g. details of populations (including subgroups), interventions, comparisons and outcomes. Please also confirm that no subgroup data has been identified that could be used in a network meta-analysis

A17. Please clarify the statement regarding patients' baseline characteristics [CS, page 34], 'This may indicate that the patients randomised to darvadstrocel had more severe perianal fistulising disease in comparison to those randomised to the control treatment', given that the baseline figures for CDAI and IBDQ [CS, page 36, Table 9] indicate that the patients randomised to darvadstrocel had less severe disease and reported better quality of life?

Quality assessment, data synthesis, analysis

A18. PRIORITY QUESTION

Please explain in more detail how missing data were handled in the ITT and mITT analyses for categorical and continuous data. Does the following statement from Table 10, "A non-response or non-remission was imputed if an MRI scan or clinical assessment was not done after baseline by week 24 and if a rescue event took place before week 24", mean that patients with missing values were assumed to always have clinically negative binary outcomes i.e. non-response or non-resmission? If so, why do the figures in Table 12 for the ITT and sensitivity analysis 1 differ? Furthermore in Panes et al 2016 [Lancet, 2016, 388: 1281-90] please clarify what analyses were performed to assess the

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sensitivity of the results to methods other than last observation carried forward in the case of missing data?

A19. PRIORITY QUESTION

Please analyse the primary endpoint and the two key secondary endpoints adjusting for the stratification factors. Please also clarify why no attempt was made to account for the interval censoring in any analyses and in which events are attributed to assessment times; for example, using the Heller method [Lifetime Data Anal. 2011; 17: 373–385]?

A20. PRIORITY QUESTION

Please clarify in Table 19 [CS, page 51] why the 95% confidence interval for the hazard ratio includes one (95% CI: 0.89, 2.12), whereas the logrank test statistic corresponds to a p-value of 0.0262.

A21. Please provide justification for the quality assessment grading's in Appendix D.3 [Table 12] and Appendix D.4.5. [Table 13] giving reference to location (page, paragraph, and document) of source data. In particular, please provide the following additional information and likely impact on the risk of bias (for each outcome):

- Method of randomisation
- Process of concealment of allocation
- Unexpected imbalances in drop-outs between groups
- Were all the outcomes that were specified in the trial protocol reported in the company submission or final report? Were any additional outcomes reported?
- Methods used to account for missing data

A22. Please clarify why data on relapse at 24 and 52 weeks are not reported and why the definition of 'relapse' is different depending on follow-up (e.g. 24-week definition is 'reopening of any of the treated external openings with active drainage as clinically assessed, or development of a perianal collection > 2cm

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of the treated perianal fistulas confirmed by centrally blinded MRI assessment in patients with clinical remission at any previous visit' [Panes et al, 2016, Appendix Table, S4], compared with the CS reported, 'relapse' from CPC remission at 96 weeks: either a re-opening appears at a treated external opening OR a score more than 0 is reported on PDAI domains.

A23. Please provide further details and clarify the nature of the 'Serious TEAEs' noted in Table 22 [CS, page 58]. In addition, please define 'procedure emergent' and 'non-TEAEs' [CS, page 58, Table 23] and clarify how they differ from the TEAEs reported elsewhere.

A24. Please clarify why the number of control patients going into remission (n = 43, [CS, Table 18, page 50]) does not match the number at risk of relapse (n= 47, [CS, Table 19, page 51])?

A25. Please clarify why the study by Molendijk et al (2015), [Gastroenterology 149(4): 918-927.] which compared Mesenchymal Stromal Cells (MSC) to placebo, is included in Figure 14 [CS, page 53], but not mentioned elsewhere in the CS? Similarly, please clarify why the trials for interventions other than surgical or stem cell therapies (i.e. those linking the grey boxes) are included in Figure 14, but then are not discussed in CS [section B.2.9, pages 53-54]? Table 7 of Appendix D seems to imply that search terms related to non-surgical interventions were included in the searches only to identify health-related quality of life data. If this is the reason, then these studies should not be included in Figure 14 as they are not relevant to the network.

A26. The observed placebo rate in the Panes et al (2016) [Lancet, 2016, 388: 1281-90] is "probably higher [than the UK rate] due to the ligation and curetting of fistula tracts". Please clarify the extent to which the UK follows the process used in Panes et al (2016) and whether the UK could increase its response rate by following alternative processes? Furthermore, please clarify why there were no UK centres involved?

A27. Please clarify if there are any reasons to believe that race or other variables not used in the randomisation are a prognostic factors or treatment effect modifiers?

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A28. The CS [Page 38, Table 10] states that, "Time to clinical remission and response were analysed with Kaplan Meier estimates, supplemented with HRs from a stratified Cox-proportional model. Cox regression was done with adjustment for the randomisation stratum." Please present the results for the primary endpoint and the two key secondary endpoints from a stratified Cox proportional hazards including stratification factors used in the randomisation. In addition, please assess whether the stratification factors are treatment effect modifiers by fitting a Cox proportional hazards model with main effects for stratification factors and treatment, and the interactions between treatment and stratification factors.

A29. In the CS [page 45, Table 15], please clarify what is meant by the two sets of results in the cell in the hazard ratio column and the response/Kaplan-Meier estimates row.

A30. Please clarify why the results for PDAI scores in the CS [pages 45 – 47] are presented for the mITT population rather than the ITT population. Furthermore for Figure 10, please clarify:

- whether the treatment-specific means are sample means or estimated from the ANCOVA
- whether the ANCOVA is a repeated measures analysis or based on separate analyses at each assessment

A31. Please clarify that the median times to CPC remission in Table 18 [CS, page 50] correspond with Figure 11 [CS, page 50]

Section B: Clarification on cost-effectiveness data

Literature searching:

B1. Please clarify why a date limit was applied to the search strategy [Appendix G.1, Table 14 Embase® and MEDLINE® (statement 7), Table 15 Cochrane database (statement 12)], when the publication timeframe is 2000-2018 [Appendix G1, Table 18]? Please clarify if statements 12 and 13 of the MEDLINE search strategy

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[Appendix G.1, Table 14] are meant to be different given that they denote two different facets? Furthermore, please clarify whether stem cells are classed as other intervention?

Clinical parameters used in the model

B2. PRIORITY QUESTION

For all statistical models fitted to the relapse and remission data in the CS [pages 78 to 88], please clarify whether models were fitted independently to the data from each treatment group using the same statistical model structure each time or whether parameters for darvadstrocel are estimated relative to control.

B3. PRIORITY QUESTION

Standard log-cumulative hazard plots can be used to test the suitability of the Weibull and exponential distributions and variations on this approach can be used to test the suitability of the Gompertz, log normal and log-logistic distributions (see section 3.2 of NICE TSD 14 for more details). Please provide the relevant plots to assess whether the hazards behave as expected for all the fitted curves and for all endpoints included as either the base case or a scenario analysis in the economic model.

B4. PRIORITY QUESTION

Section B.3.3.2.4 of the CS [pages 87 to 89] describes the approach to modelling long-term relapse and states that it is assumed that patients have constant rate of relapse beyond 2 years based on the average relapse rate for the chosen curve between 2 and 3 years. Please clarify the following:

- What is the rationale behind the change in the relapse rates after two years? What is the clinical relevance of constant hazards for relapse after two years after remission and not before? In addition, what data supports this change in the hazards over time?

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- When deciding on the appropriate form of long-term extrapolation, why were only the Gompertz and Log-normal parametric models presented to the experts [CS, page 88] instead of all possible candidate curves?

- The clinical plausibility of the hazard function for all fitted curves?

B5. PRIORITY QUESTION

Given previous statements in the CS that darvadstrocel is better than control and the control is better than salvage therapy, please confirm if the data and headings are correct in table 44 [CS, page 90] (e.g. should the second column in table 44 instead be labelled salvage vs control)? Please also clarify where the HRs for Darvostrocel vs. control have been taken from and resolve any discrepancies. For example, a simple text search suggests that the number 1.674 for scenario 1 does not appear anywhere else in the submission document B, whilst the number 1.474 appears in Table 69 which relates the generalised gamma not the Gompertz.

B6. PRIORITY QUESTION

The CS states that the the probability of requiring a permanent defunctioning surgery was estimated using data in Mueller et al [World Journal of Gastroenterology, 21(5): 1394-1403]. :

- Please comment on the relevance of the Mueller study for estimating the risk of probability of requiring a permanent defunctioning surgery with particular reference to the comparability of current clinical practice to that used at the time of the Mueller study.

- Please provide: coefficents and covaraince matrices for all fitted models, graphical plots of all parametric curves against the Kaplan-Meier curve, AIC and BIC for all of the curves fitted to this data.

- Please provide the clinical rational supporting the use of a constant hazard model.

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- Please comment on the impact of using an exponential in the economic model, with reference to the previous two points.

B7. PRIORITY QUESTION

The CS presents base-case analyses using a non-reference case scenario with 1.5% discounting for benefits and 3.5% discounting for costs [CS, page 119, Table 64]. The justification given in the CS [pages 59 and 74] states/suggests to be that darvadstrocel is given with curative intent and that "darvadstrocel demonstrates long term healing potential in this population with a significant impact on QoL."[CS, page 74] The NICE methods guide (2013) states in section 6.2.19 that a discount rate of 1.5% for both cost and benefits may be considered by the Appraisal Committee "In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years)".

- Please provide evidence to support the fact that patients achieve near full health that is sustained over a very long period with particular reference to the lifetime probability of relapse of fistula disease and the impact of luminal disease on quality of life.

As it is the Appraisal Committee who decides whether or not the criteria in section 6.2.19 of the methods guide have been met, please provide all base-case and scenario analyses using: a) 3.5% discounting for BOTH costs and QALY as per the NICE reference case and; b) 1.5% discounting for BOTH costs and QALYs as per section 6.2.19 of the NICE methods guide (2013).

B8. Please clarify whether there is a clinical justification for the hazard of a CPC remission event being constant [CS, page 78] or if this was made simply as a modelling assumption.

B9. On pages 79 and 84 of the CS it describes how the remission events are structurally absent in the model during the first 4 weeks after treatment and relapse events are structurally absent in the model during the first 4 weeks after remission. It then describes that the curve fittings for time to remission and time to relapse are offset by 4 weeks to improve the fit to the observed outcomes. Please clarify why the curves are offset by 4 weeks and not 6 weeks given that

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the outcomes assessments from treatment to 36 weeks occurred at 6 weekly intervals and not 4 weekly intervals. Please also clarify whether the mismatch between the timing of outcomes assessment in the study and the model cycle length will lead to any systematic bias in the model.

B10. Please clarify and provide rationale for the assumption that perianal abscesses are resolved in an average of four weeks [CS, page 72]. Furthermore please clarify what uncertainty, if any, was placed around the four week resolution time.

B11. Please clarify why a 40 year time horizon [CS, Page 74] was selected for the base case, given that approximately 68% of the original model population are alive at this time point?

B12. Please provide further information regarding what is meant by the following statement: The trial design focussed on an attempt to heal the fistula tract rather than control symptoms, as is the case in clinical practice. Therefore, no changes over time where observed in the ADMIRE-CD trial, but changes are observed in the model to reflect clinical practice." [CS, Page 71]

B13. For completeness, please provide all of the candidate parametric curves fitted for Figures 19, 20, 21, and 22 (i.e. those in Table 32, Table 35, Table 38, and Table 41). [CS, pages 81-82, 84-85, 86-87]

B14. Please clarify, what evidence is available to support the assertion that "a simple average across all observations, irrespective of visit time and characteristics of the disease trajectory such as previous relapses, was a reasonable approach …" [CS, page 70] to estimate the proportion of mild and severe active chronic symptomatic fistula? Furthermore, please clarify the clinical rationale for the proportion of mild and severe chronic symptomatic fistulae being constant over time

B15. Please clarify the clinical rationale behind the following scenario analysis. "A scenario of interest was the exclusion of biologic usage within salvage therapy and keeping all other assumptions as per the base case. Biologics are used to treat luminal CD which is out of scope for this appraisal." [CS, Page 126]

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B16. Salvage therapy. The CS suggests that the hazard ratio of salvage therapy was elicted from clinical experts [CS, Pages 79-80, 89]. Please clarify the following points:

- Was a formal elicitation process followed to estimate this parameter?
- Why an eliciation protocol was not presented in the CS?
- Please clarify the scale on which the coefficient of variation is assumed and provide the mean and standard error. Please repeat the analyses with assumed coefficient of variations of 0.30 and 0.60
- Please clarify whether there is any reason to believe that the hazard for salvage therapy is truly proportional to the hazard for control.

B17. Please confirm any uncertainty associated with parameters representing probabilities and the distributions used to characterise the uncertainty. [CS, Page 117, Table 63].

Resource use & costs

B18. PRIORITY QUESTION

Due to the 24 to 48 hour shelf life of darvadstrocel, there were concerns by the British Society of Gastroenterology about wastage resulting from theatre cancelations in their professional organisation submission to NICE. Furthermore, the statement in EPAR “There is a potential risk on medication errors related to the surgical procedure such as the administration of the product…”[EPAR, page 71]:

- Please clarify, was there any wastage of darvadstrocel vials in the ADMIRE-CD study [Panes *et al.* Lancet, 2016, 388: 1281-90]?
- Please clarify why wastage of darvadstrocel was not included in the economic model?

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- Please conduct a scenario analysis in which wastage of darvadstrocel is included.

B19. Please clarify why an arbitrary standard error of 15% of the mean was assumed to be placed around NHS reference costs in the probabilistic sensitivity analysis, when the actual uncertainty in the NHS reference costs can be calculated in the following formulae:

Standard deviation = (upper quartile unit cost – lower quartile unit cost)/(2*NORM.INV(0.75,0,1))

Standard error = Standard deviation/SQRT(number of data submissions – 1)

Health utility

B20. Please clarify the following [CS, Appendix R, page 7]:

- How were potential external datasets for mapping identified?
- Which (if any) external datasets were identified?
- If any datasets were identified, why were they deemed to be inappropriate to estimate a mapping algorithm?

B21. Please clarify why the abscess state was not presented in Table 46 or Table 47 [CS, pages 99-100], when it was estimated directly in the vignette study?

B22. Please clarify what available evidence supports a disutility of 0 for people with proctalgia [CS, Page 100, Table 48]. Furthermore, please provide evidence/clinical rationale to support that this parameter has a fixed value.

Darvadstrocel for treating complex perianal fistula in Crohn's disease [ID960]

Response to clarification questions

Submitted by Takeda UK Ltd.

Single Technology Appraisal (STA)

National Institute for Health and Care Excellence

23rd May 2018

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List of Abbreviations

CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CPC	Clinical and patient-centric
CS	Company Submission
CSR	Clinical Study Report
eASC	Expanded stem cells extracted from adipose tissue
ERG	Evidence Review Group
EUA	Examination under anaesthesia
ITT	Intend to treat
PDAI	Perianal Disease Activity Index
RCT	Randomised Controlled Trial
SLR	Systematic Literature Review
TEAE	Treatment-emergent adverse event

1. Overview

This document contains the response to the clarification questions from the Evidence Review Group (ERG), ScHARR-TAG and the Technical Team at NICE sent to Takeda on Thursday 10th May 2018. We have attempted to address all questions as fully as possible within the timeframe permitted (deadline of 24th May 2018).

2. Response to clarification questions

Please find below responses by Takeda to each of the questions raised by The Evidence Review Group, ScHARR-TAG and the technical team at NICE.

Section A: Clarification on effectiveness data

General

A1. The EPAR states: "While treatment with Alofisel is proposed for single dose administration, the need for repeated treatment in the clinical setting seems foreseeable in the targeted patient population. Therefore the prescriber is informed in section 4.2 of the SmPC about the limited experience of repeat administration of Alofisel. The supportive open-label study Cx601-0101 explored the issue of retreatment but included only few patients and the doses were lower than intended for marketing. Whether repeated administration could be associated with increased generation of DSA and/or in any way with increased risk of allo-immune response will also be further studied in a PASS as described in the RMP."[EPAR, page 79]

Is darvadstrocel intended to be given as a single course of treatment? If not, how many courses of the treatment are expected to be given? How frequently can they be given e.g. our clinical advisors suggest that if there is a relapse after a long period of remission following previously successful treatment with darvadstrocel (e.g. over a year) then they would consider using darvadstrocel again. Please clarify whether repeat treatment with darvadstrocel is expected following treatment failure or relapse after a period of remission?

Response: Although some clinicians believe that Alofisel may be beneficial for retreatment in the following patient groups; (i) partial responders; (ii) responders who have relapsed, there is no current evidence to support this treatment approach.

Takeda UK are therefore unable to model the use of retreatment in a robust manner and have therefore elected to base the submission on single use only. Some patients who have responded to Alofisel treatment and achieved healing over a significant period of time may develop a new fistula tract (recurrence). We believe this should be considered as a new fistula and should therefore be treated as such.

A2. Please provide further details on the clinical pathway of care in England [company submission (CS), section B.1.3.4] in particular:

- Despite the lack of clinical consensus for classifying perianal fistula in CD into simple and complex variants [CS, page 15], please clarify how complex perianal fistula is diagnosed (including amount of variation) in the NHS, if possible.

Response: MRI or clinical examination under anaesthesia (EUA) is commonly used to define the tract of a patient's fistula. There is some variation in how fistulae are classified into simple and complex variants, reflecting differences between classification systems. Broadly,

where the entire fistula tract lies below the level of the anal sphincter, the fistula is classified as simple and may be suitable for potentially curative surgery, such as fistulotomy. Such fistulae would not be eligible for treatment with darvadstrocel. Fistula tracts that involve the anal sphincter are usually classified as complex. The precise definition of complex perianal fistulae in the ADMIRE-CD trial was the presence of one or more of the following: high inter-sphincteric, high trans-sphincteric, extra-sphincteric, or supra-sphincteric tract; at least two external openings; or associated collections.

- Please clarify what is meant by conventional therapy in section B.1.1. In particular, does this refer to surgical management or the use of immunosuppressants?

Response: Conventional therapy in this context relates to antibiotics and immunosuppressants as specified within the ADMIRE-CD trial.

- Please clarify how long setons remain in place and how this would vary according to the subsequent therapy given (as per the statement on pages 20-21 of the CS).

Response: Setons can remain in place permanently and this is common in UK clinical practice due to the poor healing potential of current treatment options observed. In this context, the objective is to keep the fistula tract open and draining in order to reduce the risk of infection or abscess formation.

Setons can also be kept in place for relatively short durations (2-4 months) in order to promote drainage where the ultimate objective is to achieve fistula healing once the seton is removed. This approach most commonly arises when initiating a biologic therapy. Before initiating biologic treatment any infection / abscess in the fistula tract has to be resolved and seton placement is used to drain any infection / abscess present.

Provided there are no ongoing signs of infection, the seton may be removed once the biologic has had time to take effect.

- In clinical practice, how rapidly is conventional treatment and/or biologic therapy escalated and how many immunosuppressants or biologic therapies would be used in sequence?

Response: Conventional therapy should be rapidly escalated in clinical practice, although a recent audit conducted in a tertiary referral centre in the UK (Lee 2018a) showed a median time from diagnosis of a perianal fistula in patients with CD to treatment with a biologic therapy was 204 days (IQR 113-453 days). It is difficult to separate the usage of biologic therapy for perianal disease as opposed to their usage in the treatment of luminal Crohn's Disease, however sequential use of biologic therapies for the treatment of perianal disease would not be expected in clinical practice. Infliximab is the only licenced therapy for fistulising Crohn's disease. Patients may be on other biologics to control luminal disease.

- Please clarify that the case for the cost-effectiveness of darvadstrocel is being made only for second-line use in patients who have shown an inadequate response to at least one conventional or biologic therapy and a case is not being

made for darvadstrocel use in those who are contra-indicated to immunosuppressants and or biologics?

Response: Darvadstrocel would generally be used after biologic therapy, however as specified in the CS (page 23) it may be used in patients where biologic therapy is contraindicated or unsuitable.

- The marketing authorisation [CS, Table 3] states that patients will need to have shown, 'inadequate response to at least one biologic or conventional therapy'. Please clarify how you expect this to be implemented in clinical practice?

Response: We would expect this to be implemented in clinical practice in a similar way to how this was specified in the ADMIRE-CD trial, i.e. patients had to be refractory to at least one of the following treatments: the antibiotics ciprofloxacin or metronidazole (refractory defined as no response after 1 month), the immunomodulators azathioprine, 6-mercaptopurine, or methotrexate (refractory defined as no response after 3 months), or induction or maintenance anti-TNF treatments. As per ECCO guidelines (ECCO 2014), anti-TNF and antibiotics are recommended for treatment of complex fistula, which is also observed in UK practice (Lee 2018b). Although not specified in the ADMIRE-CD trial, induction effectiveness would normally be assessed after 6 months of treatment, and refractory to maintenance treatment would generally be considered for patients currently on a biologic therapy for their luminal disease who develop a perianal fistula or relapse of a fistula that had been successfully treated with a biologic therapy.

- What treatment(s) would people be expected to receive following darvadstrocel in clinical practice?

Response: The most common treatment for perianal fistula in the UK is EUA +/- seton placement. Clinical opinion is that this would continue to be used after failure of darvadstrocel treatment. This treatment is the main therapy used in the salvage therapy treatment mix within the health economic model for patients who fail to respond or relapse on either standard of care or darvadstrocel treatment. Patients who experience significant symptoms of their perianal fistula (those who are in the Chronic Symptomatic Fistula (CSF) with Severe Symptoms health state) may require last resort surgery following treatment with Darvadstrocel (defunctioning or proctectomy). This is also included in the health economic model. The majority of patients with a complex perianal fistula would also receive background therapy which consists of immunosuppressants, biologics and antibiotics. The proportion of these treatments used in UK clinical practice was identified through a study examining 78 consecutive patients treated at St Mark's hospital and validated by UK clinicians; this data is presented in Appendix Q and table 53, page 106 of the CS.

A3. Please provide further details on how a more clinically appropriate outcome (i.e. revised definition of CPC remission) was derived (were patient perspectives considered?) and validated by clinical experts [CS, page 10]. Please clarify how this compares with the core outcome set for fistulising perianal Crohn's disease developed by the ENiGMA collaborators [Sahnan et al. Gut. 2018 Feb 3. pii: gutjnl-2017-315503. doi: 10.1136/gutjnl-2017-315503]?

Response: At the start of developing the economic model, the conceptual model structure was presented and discussed with a panel of experts from the St Mark's Hospital and Academic Institute, a specialised centre in gastrointestinal and bowel diseases. These experts included the authors from the paper by Sahnan et al 2018. A multidisciplinary team, including clinicians and surgeons with extensive experience provided their opinion and engaged in discussion to identify the best approach to the economic evaluation of darvadstrocel for the treatment of complex perianal fistulae in patients with CD.

The St Mark's experts advised using a different clinical endpoint than combined remission to define remission in patients with complex perianal fistulae. The expert panel were unanimous on the need to consider a patient-centric outcome according to their practice and experience. Figure 25 of the submission shows how the outcome of CPC remission was developed. The experts were asked what health states would be used to simulate the treatment of CPAF and how they would use the ADMIRE-CD data to assign patients to these health states.

The St Mark's expert consensus on the relevant outcome effectively used to represent the treatment algorithm as well as demarking the disease and remission state was that the endpoint should include a clinical assessment of the fistulae, identified in the definition of clinical remission, as well as an indication of the degree of pain and fistulae drainage experienced by patients. The experts stated that even in the event of achievement of clinical remission, but in the presence of pain, a patient would not be considered healed and thus in remission.

An agreement on the definition of remission which was agreed on by the St Mark's expert panel was:

- Achievement of clinical remission, defined as closure of all treated external openings that were draining at baseline defined as the absence of draining despite gentle finger compression, and
- No pain and no discharge as defined by a score of zero on the pain and discharge categories of the Perianal Disease Activity Index (PDAI).
- The St Mark's team was consulted on this topic due to their involvement with the development of the core outcomes set. Although the paper referred to in this question had not been published at this time and could not be shared with Takeda, the advice was given to be in line with the outcomes set being suggested.

This definition was then further verified by European clinical expert interviews and a UK advisory board which included clinical experts and health economists (Figure 25, CS).

A4. Although a single course of treatment with darvadstrocel is expected to treat people with 2 or less internal openings, 3 or less external openings and only one tract. Please clarify what would be the procedure and course of treatment for a patient who has less than or more than three fistula openings? How would such patients be managed?

Response: The SPC for darvadstrocel specifies that 4 vials must be administered for the treatment of up to two internal openings and up to three external openings. This means that

with a dose of 120 million cells it is possible to treat up to three fistula tracts that open to the perianal area. The number of tracts was not specified within the ADMIRE-CD trial, the only limitation being on the number of internal and external openings as discussed above. Patients with fewer than three fistula openings would therefore still receive the standard dose of 4 vials or 120 million cells (this will be supplied as a single treatment course). Without further data we cannot be certain that 120 million cells is sufficient to adequately treat disease that is characterised by a greater number of internal and external openings.

A5. The treatment procedure described in Panes et al [Lancet, 2016, 388: 1281-90] (and proposed in: CS, page 24, Figure 6,) suggests that 2 EUA procedures will be required. However, a professional organisation submission by the British Society of Gastroenterology states that 'Currently treatments do not involve 2 EUA procedures. The second EUA has to be coordinated with delivery of the stem cell treatment to the hospital as it has a short shelf-life of about 24-48 hrs'. Please clarify if 2 EUA procedures are standard in clinical practice?

Response: The use of two EUAs is not generally standard in clinical practice. EUAs are often associated with seton placement and there is concern around removal of the seton in the absence of a treatment with evidence of healing potential. The second EUA procedure would generally be used to remove the placed seton to allow healing of the fistula tract. This may be carried out where biologic therapy is administered, although as discussed in question A2 above the most appropriate timing of removal of the seton in this circumstance is not clear.

The SPC for darvadstrocel does not mandate the use of 2 EUA procedures although this was the procedure used in the ADMIRE-CD trial and may therefore be considered best practice.

A6. Please provide the rationale for the 24 mL dose of darvadstrocel containing 120 million cells distributed in 4 vials. Please clarify whether any dose-response studies were undertaken and could a lower dose be as effective as the licensed dose?

Response: Although there is no formal dose finding study, TiGenix tested two independent doses in the Phase I/IIa study (de la Portilla et al. 2013): 20 million cells and 40 million cells. In this study, fistula closure was defined as absence of suppuration of the fistula through the external orifice, spontaneously and by pressure, complete re-epithelization of the external orifice in the clinical evaluation and absence of collections > 2 cm, in three axes, directly related to the fistula tract treated.

Although this study focused primarily on safety, secondary efficacy measures showed that a percentage of patients not responding to 20 million cells could be healed with an additional higher dose of 40 million cells 12 weeks after the first dose of 20 million cells. A total of five (26.3%) patients in the per protocol population and six (28.6%) patients in the full analysis population increased the number of closed fistulas at 12 weeks according to blind investigator's assessment. At 24 weeks, five (35.7%) patients increased the number of closed fistulas in the per protocol population and six (40.0%) patients in the full analysis population (de la Portilla et al. 2013).

In contrast to this Phase I/IIa study (in which only one tract was treated), in ADMIRE-CD patients with up to 2-3 fistula tracts (typical of complex perianal fistulae in Crohn's patients) were included. By choosing 120 million (40 million cells x 3 doses), TiGenix ensured that all fistula tracts received at least the same dose (EMA 2017).

Therefore, a single dose of 120 million cells was proposed based on the following:

1. In order to achieve the therapeutic effect of the eASC, there is a need to treat all fistula tracts, especially as adjacent tracts can negatively influence the fistula closure.
2. As it is difficult to standardise the level of complexity of fistulae, a 120 million eASC dose was proposed in order to cover the most complex fistulae situations.
3. Re-opening of a partially closed fistula due to the need for a new surgical intervention (curettage) on a second administration (as seen in de la Portilla et al.) is avoided.

Overall, a single dose administration is considered an improvement for the patient in terms of clinical-surgical criteria: where closure is maintained, morbidity is minimised and the number of surgical procedures is kept at a minimum (Cellerix 2014, TiGenix 2016a).

A7. Please clarify the definition of ‘relapse’ from CPC remission, e.g. either a re-opening appears only at a treated external opening (rather than an internal opening or another site) OR a score more than 0 is reported on PDAI domains after CPC remission has been achieved? Although PDAI is widely used in clinical trials, a professional organisation submission by the British Society of Gastroenterology and Gecse et al [J Crohns Colitis. 2016 Jul; 10(7):758-65; doi: 10.1093/ecco-jcc/jjw039] suggest that PDAI scores do not have good validation and there is no agreed score defined for either improvement or remission. Please provide further details on the strengths, robustness and limitations/criticisms of the PDAI scores.

Response: Relapse from CPC remission is defined as either the presence of an external opening (this could be a new external opening or the re-opening of a previously treated external opening AND/OR a score more than zero is reported on either the pain or discharge component of the PDAI after CPC remission has been achieved. It is not possible to observe an internal opening outside of a surgical setting and this is therefore not normally part of a clinical assessment for a patient with stable disease.

Two components of the PDAI score are incorporated in the definition for CPC remission; pain and discharge. While the overall PDAI score may have limitations, the individual questions with regards to pain and discharge can be considered patient relevant. When comparing with the core outcome set for fistulising perianal CD as published by Sahnan et al (2018), pain and discharge are important outcomes to consider.

The change in definition was done *a priori*, during model development and therefore the incorporation of the pain and discharge sub-score should not have introduced bias.

Based on the clinical remission definition, remission is assessed only at the treated external opening. The PDAI, and specifically its pain and discharge elements, was considered the most appropriate and best available instrument to measure the symptomatic effects of the fistulae on patients, as other instruments (i.e. CDAI, IBDQ) were deemed not sufficient to capture the degree of the patient symptoms.

Post hoc analysis on the time to CPC remission yields very similar results to the combined remission results published for the ITT population in the ADMIRE-CD trials (see section B.2.6.4.1, CS), which provides some validation to this approach.

A8. Faecal incontinence is noted as an important quality of life burden [CS, page 18], and is listed in the NICE scope, but has not been reported in the CS. Please explain why not?

Response: Clinical experts were unable to identify adequately the required resource use, quality of life impact on patients and the clinical course of incontinence in fistulising disease. The lack of reliable estimates from either the ADMIRE-CD trial, clinical opinion or the literature meant faecal incontinence was unable to be included in the model. We believe it would likely have resulted in a lower ICER for darvadstrocel had it been included as both the presence of a fistula over time and repeated surgery are believed to increase the risk of incontinence in this patient group.

Literature searching

A9. Please clarify whether the aim of the searches was to identify studies on the clinical effectiveness of darvadstrocel or to identify a wider range of studies for a NMA. Please provide separate inclusion criteria for these two parts of the analysis.

Response: The aim of the searches was to assess efficacy, safety, and tolerability of various treatments used for the management of patients with perianal fistula in CD. The key inclusion/exclusion criteria have been detailed in Table 7 in Appendix D.1.2. A comprehensive systematic literature review (SLR) was conducted to identify and synthesise evidence from randomised controlled trials (RCTs) of intervention in the treatment of perianal fistula.

All the RCTs identified in the SLR were subjected to assessment for inclusion in an NMA by qualitatively assessing the similarities and differences between the trial populations (feasibility assessment).

A10. The searches described in Appendix D.1.1 (Table 3) use a series of concept combinations to identify relevant citations. Please clarify why line 11 does not also include the terms darvadstrocel and 6-MP? Why does the list of Interventions / Comparators in line 11 not correspond to the listed Interventions / Comparators in Table 7 (Appendix D.1.2)? In addition, the St Mark's study of current practice, commissioned by Takeda [CS, pages 21-25, Table 5], suggest that vedolizumab was used as a biologic therapy in 16.7% of patients considered to be eligible for darvadstrocel treatment. Please also clarify why none of the searches in Appendix D.1.1. included this intervention (and related terms)?

Response: Our response to questions A10 and A11 are detailed below

A11. Ileostomy, colostomy and stem cells are included as comparators in Table 7 of Appendix D1. However these terms do not appear to have been included in Appendix D1, Table 3 [statement 11]. Please provide reasons for the omission with implications?

Response: The initial search was conducted in November 2016. This search was broadly aligned with the draft NICE scope from May 2016. The search strategy was updated to reflect the change in scope and to extend the search beyond RCTs to include all potentially relevant evidence. The updated search strategies are presented in Tables 1-3 below.

Table 1: Search strategy for Embase® and MEDLINE® database

No.	Query	Facet
1	'crohn disease'/exp OR 'colon crohn disease'/syn OR (crohn* NEXT/2 (disease* OR ileitis OR enteritis OR ileocolitis OR colitis OR morbus)):ab,ti	Crohn's Disease
2	'rectum fistula'/exp OR 'anus fistula'/exp OR 'perianal fistula'/syn OR 'enterocutaneous fistula'/exp OR 'perianal abscess' OR fistul* OR fistul* NEAR/2 (perianal OR anal OR rectum OR rectal OR enterocutenous) OR 'anus disease' OR 'rectovaginal fistula' OR 'perianal lesions'	Perianal fistula
3	'complex anal' OR 'complex fistula' OR 'complex perianal' or 'complex perianal fistula'	Complex perianal fistula
4	#2 OR #3	Perianal fistula or complex perianal fistula
5	'clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR random* OR rct OR 'random allocation' OR 'random assignment' OR 'randomly allocated' OR 'randomly assigned' OR 'allocated randomly' OR 'assigned randomly' OR allocated NEAR/2 random OR assign* NEAR/2 random* OR (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) OR placebo* OR 'prospective study'/de	Study design (RCTs)
6	nrct OR 'n rct' OR n?rct OR 'controlled clinical trial'/exp OR 'intervention study'/exp OR (clinical NEXT/1 trial*):ab,ti OR 'major clinical study'/exp OR compar*:ab,ti OR group*:ab,ti OR 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR 'follow up'/exp OR 'open study'/exp OR 'clinical trial'/exp OR 'clinical article'/exp OR 'survival'/exp OR 'case control study'/exp	Study design (non-RCTs & observational studies)
7	non NEAR/2 random*	
8	cohort*:ab,ti OR (('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti	
9	(case* NEXT/1 control*):ab,ti	
10	#5 OR #6 OR #7 OR #8 OR #9	Combined study designs (RCTs + Observational studies)

No.	Query	Facet
11	'letter'/de OR 'abstract report'/de OR 'case report' OR 'case study'/de	Study designs not of interest
12	#10 NOT #11	Study design after excluding case studies/reports/letters
13	'ciprofloxacin'/syn OR 'metronidazole'/syn OR 'azathioprine'/syn OR '6-mercaptopurine'/syn OR 'cyclosporin'/syn OR 'tacrolimus'/syn OR 'methotrexate'/syn OR 'thalidomide'/syn OR 'tumor necrosis factor antibody'/de OR 'anti tumour necrosis factor' OR 'anti-tumor necrosis factor' OR 'anti tnf' OR 'anti-tnf' OR 'infliximab'/syn OR 'adalimumab'/syn OR 'certolizumab pegol'/syn OR 'cx601' OR 'stem cells' OR 'surgery'/exp OR 'surgical procedures' OR 'surgical procedure' OR 'fibrin glue'/syn OR 'advancement flap' OR 'surgical flap' OR 'surgical flaps' OR lift OR 'diverting stoma' OR 'protectomy' OR 'colectomy' OR 'colon surgery' OR (ligation NEAR/1 'intersphincteric fistula') OR fistula Near/2 plug OR 'fistulotomy' OR seton OR eua OR exam* NEXT/2 (anaesthesia OR anesthesia)	Interventions including surgery
14	VAAFT OR 'vaaft' OR 'video-assisted anal fistula treatment' OR 'video assisted anal fistula treatment' OR 'filac' OR 'fistula-tract laser closure' OR 'fistula tract laser closure'	New interventions
15	'proctectomy' OR 'ileostomy' OR 'colostomy' OR 'stoma'	Additional key words
16	#14 OR #15	Combined string for additional terms
17	#1 AND #4 AND #12 AND #13	PF/CPF+ CD + study design + previous review interventions
18	#17 AND [1-11-2016]/sd NOT [28-7-2017]/sd	Latest evidence (from 1st November to present)
19	#1 AND #4 AND #12 AND #16	PF + CD+ study design + new keywords for interventions
20	#13 OR #14 OR #15	All included interventions
21	#3 AND #12 AND #20	CPF + SD + Interventions
22	#18 OR #19 OR #21	Combined evidence for current update

Table 2: Search strategy for Cochrane database

#	Search string	Facet
1	[Crohn Disease] explode all trees	Crohn's Disease

#	Search string	Facet
2	"Crohn Disease" or "Crohns Disease"	
3	(Crohn or Crohns) next/2 (disease or ileitis or enteritis or ileocolitis or colitis or morbus)	
4	#1 OR #2 OR #3	
5	[Rectal Fistula] explode all trees	Perianal fistula/complex perianal fistulae
6	[Fistula] explode all trees	
7	"rectum fistula" OR "anus fistula" OR "perianal fistula" OR "enterocutaneous fistula" OR "perianal abscess" OR fistula OR "anus disease" OR "rectovaginal fistula" OR "perianal lesions"	
8	Fistula NEAR/2 (perianal OR anal OR rectum OR rectal OR enterocutenous)	
9	"complex anal" OR "complex fistula" OR "complex perianal" or "complex perianal fistula"	
10	#5 or #6 or #7 or #8 or #9	
11	#4 AND #10	PF/CPF+ CD
12	#11 Publication Year from 2016 to 2017, in Trials (Word variations have been searched)	Latest evidence in PF/CPF+ CD
13	#9 in Trials (Word variations have been searched)	Evidence for CPF
14	#12 OR #13	Combined evidence for current update

Table 3: Search strategy for MEDLINE® In-Process searched via PubMed® platform

#	Search string	Facet
1	Search "Crohn Disease"	Crohn's Disease
2	Search "Crohns Disease"	
3	Search ((Crohn or Crohns) next/2 (disease or ileitis or enteritis or ileocolitis or colitis or morbus))	
4	Search (#1 OR #2 OR #3)	
5	Search "Rectal Fistula"	Perianal fistula/Complex perianal fistula
6	Search Fistula	
7	Search ("rectum fistula" OR "anus fistula" OR "perianal fistula" OR "enterocutaneous fistula" OR "perianal abscess" OR fistula OR "anus disease" OR "complex anal" OR "rectovaginal fistula" OR "perianal lesions" OR "complex fistula")	
8	Search fistula near/2 (perianal OR anal OR rectum OR rectal OR enterocutaneous	

#	Search string	Facet
9	Search ('complex anal' OR 'complex fistula' OR 'complex perianal' or 'complex perianal fistula')	
10	Search (#5 OR #6 OR #7 OR #8 OR #9)	
11	#4 AND #10	PF/CPF + CD
12	Search (#11 AND (inprocess[sb] OR pubstatusaheadofprint))	Latest evidence (articles ahead of publication_
13	Search (#9 AND (inprocess[sb] OR pubstatusaheadofprint))	Evidence for CPF
14	#12 OR #13	Combined evidence for current update

In summary, the searches includes '6-mercaptopurine'/syn, which covers all the synonyms of the interventions including any study indexed with '6-MP'. At the time of performing the search, darvadstrocel was not yet indexed in the database. However, the search strategy included Cx601, the former identifier for darvadstrocel.

When the updated search criteria are compared with the interventions/comparators they are all aligned. As can be observed in the search strategy, in the updated search ileostomy, colostomy and stem cells were included in the search strategy (see line 14 of the Embase and Medline search).

Of note, vedolizumab was not an intervention of interest in the initial or updated search strategy, since it was not considered an appropriate comparator in the Final NICE scope. However, a preliminary search was conducted (until 22nd Jan 2018) to identify if any RCTs assess vedolizumab in patients with perianal fistula in CD. One trial was identified (Gemini 2) and assessed whether subgroup data was reported for perianal fistulae in patients with CD. However, only 74% of patients were with fistula located in the perianal area and therefore this study would be excluded from the search. One of the exclusion criteria was that at least 80% of the study population needed to qualify for the disease criteria.

A12. For completeness, please could the company provide brief details of any ongoing and or planned studies of darvadstrocel.

Response: The ADMIRE-CD-II study (ClinicalTrials.gov Identifier: NCT03279081) is currently recruiting. This is a similar study to the ADMIRE-CD study but is being conducted to include patients from the US and to satisfy FDA requirements. This study is expected to complete in October 2021. No other studies are currently planned.

Systematic review process

A13. Please confirm if study selection, data extraction and quality assessment was undertaken independently by a minimum of two reviewers for each systematic review in the clinical and cost section. If not, please justify

Response: Study selection, data extraction and quality assessment was undertaken by two independent reviewers and any discrepancies were reconciled by a third independent reviewer.

A14. Please confirm whether any potentially relevant non-English studies were excluded from the CS [see Appendix D.1.2, Table 7]? If so, what impact would these have had on the results, if any?

Response: There were no potentially relevant non-English studies excluded from the search. The non-English studies were identified and evaluated to assess whether they contained any relevant information.

A15. Please amend/revise the PRISMA flow diagram and clarify why the numbers in Table 6 [Appendix D.1.1.] do not correspond with those on the study selection flowchart [Appendix D.1.2, Figure 1]. What was the source of the unpublished CSR? Please provide additional boxes at the end of the flowchart in Figure 1 to clarify the identity of the 19 included RCTs (37 publications), e.g. for clinical effectiveness review [n=1, the ADMIRE-CD]; for the SLR/NMA [n=6, Appendix D.1.3, Table 8, and D.4.5 Table 13]. Further details of 12 remaining RCTs are needed. In addition, please note a minor discrepancy in the numbers of citations 'After duplicates removed' in Figure 1, as it should read n=4864, not n=271.

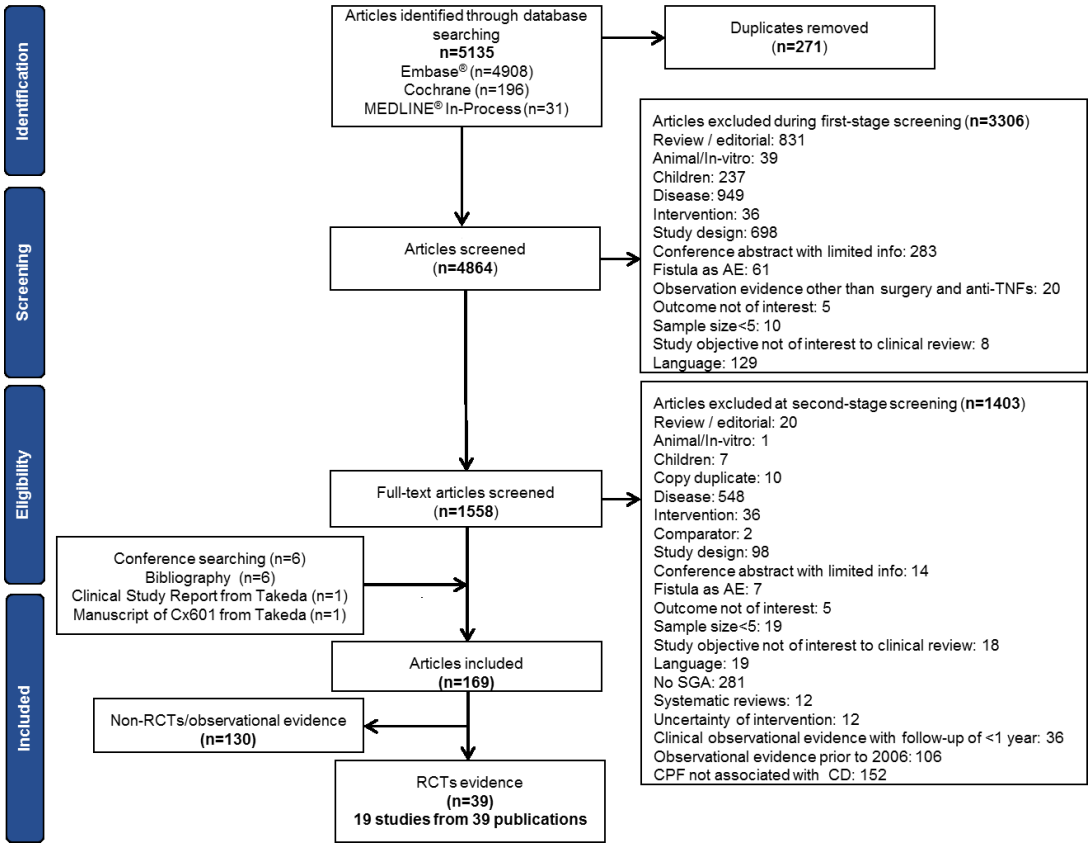
Response: In error, Table 6 in Appendix D.1.1 reflected the numbers in the original search. The search was updated in January 2018 and the final numbers are reflected in Table 4: Total number of citations retrieved for clinical review from all databasesbelow.

Table 4: Total number of citations retrieved for clinical review from all databases

Database	Numbers retrieved
Embase® and MEDLINE®	4908
Cochrane	196
MEDLINE® In-Process	31
Total	5135

The CSR for darvadstrocel (ADMIRE-CD) was retrieved from Takeda's internal database. The updated PRISMA flow chart is presented in Figure 1: Flow of studies through the systematic review processbelow and incorporates the suggested changes, i.e. duplicates are clearly identified, inclusion of the CSR and indicating the difference between the articles included and the RCT evidence (per Question A.16).

Figure 1: Flow of studies through the systematic review process



A16. For clarity, of the 167 citations that were included [Appendix D.1.2, Figure 1], please could you provide brief details of the 19 RCTs (37 publications) that met the inclusion criteria of the company's systematic review including a full breakdown for the reasons for exclusion of the remaining articles (n=130) e.g. details of populations (including subgroups), interventions, comparisons and outcomes. Please also confirm that no subgroup data has been identified that could be used in a network meta-analysis

Response: The draft scope pre-referral (May 2016) included the following potential comparators:

- Infliximab
- Adalimumab (does not currently have a marketing authorisation for this indication),
- Surgical treatment (such as use of a seton, fistulotomy, advancement flap procedures or insertion of biosynthetic plugs),
- Fibrin glue
- Best supportive care

Therefore, the search was inclusive of all potential treatments for complex perianal fistulae, regardless of line of therapy.

The search was not restricted to randomised controlled trials to be inclusive. This broader search was performed to include observational evidence of anti-TNFs and surgical therapies in perianal fistula in patients with CD. Such studies were assessed as proxy data in case of limited evidence from RCTs. The search identified 167 citations, of which 130 citations related to non-randomised studies. The PRISMA flowchart has been updated to reflect this (see Question A15.). The details of the remaining 19 RCTs are provided in Table 5: The 19 RCTs identified in the systematic literature review; reason for exclusion and Table 6: Summary of key efficacy outcomes reported across the included studies below. The reason why 13 of the RCTs were excluded was that they did not include a surgical intervention as one of the treatment arms.

No subgroup could be considered for feasibility analysis, as there was considerable variability in reporting, patient characteristics, prior therapy across the studies in comparison to population included in the ADMIRE-CD trial.

Table 5: The 19 RCTs identified in the systematic literature review; reason for exclusion

Study name	Treatment arms	Sample size	Patient population	Inclusion/exclusion reason
Complex fistula				
ADMIRE-CD trial (Panes 2016)	Darvadstrocel	107	Adults with active CD, if they had complex perianal fistulas with a maximum of two internal and three external openings, which had been draining for at least six weeks. Patients were refractory to antibiotics, immunosuppressant and/or anti-TNF therapies	Include
	Placebo	105		
(Wiese 2015)	CONTROL group: EUA + adalimumab + seton; guided by physical exam	11	Adults with CD and known complex perianal fistulas with a willingness to start ADA	Include in feasibility assessment for NMA
	EUS group: EUA + adalimumab + seton; guided by EUS	9		
(Schwartz 2015)	Seton therapy + certolizumab pegol	21	Patients with both simple and complex perianal fistulas. All pts received azathioprine, 6-MP or MTX at therapeutic doses (unless intolerant or contraindicated), and either metronidazole or ciprofloxacin. Baseline PDAI = 7. 84% of the included patients were of complex fistula	Include in feasibility assessment for NMA
	Certolizumab pegol			
Mixed: complex and simple perianal fistula				
(Senejoux 2016)*	Anal fistula plug after seton removal	54	Adults with a CDAI ≤250 and at least one active ano-perineal fistula track for at least 2 months with seton drainage for at least 1 month. Treatments with azathioprine, 6-MP, MTX, thalidomide, or anti-TNF were permitted providing the dose was stable for >3 months and stable dose of amino-salicylates for >1 month. 26.4% patients presented with complex perineal fistula.	Include in feasibility assessment for NMA
	Control group (observation after seton removal)	52		
	Fibrin glue + Cx401	25		

Study name	Treatment arms	Sample size	Patient population	Inclusion/exclusion reason
(Garcia-Olmo 2009)	Fibrin glue alone	25	Adults with complex anal fistula in CD; of which 28% were with perianal fistula. Patients had received at least one complete course of antibiotics with a seton placement or conventional surgery (advancement flap or fistulectomy). In addition, patients had received at least one complete induction course of infliximab, unless anti-TNF-α was contraindicated	Include in feasibility assessment for NMA
(Molendijk 2015)	Group 1: 1 x 10^7 mesenchymal stromal cells	5	Adults with actively draining perianal fistulising CD refractory to conventional therapies (anti-TNF s and, in addition, antibiotics, steroids, thiopurines, MTX, surgery, or combinations). Patients with CDAI ≤250, 1-2 internal openings and 1-3 fistula tracts and stable dose of current drugs. Patients were not allowed to use antibiotics after inclusion in the trial. Approximately, 66.7% were with complex perianal fistula	Exclude, not a relevant comparator
	Group 2: 3 x 10^7 mesenchymal stromal cells	5		
	Group 3: 9 x 10^7 mesenchymal stromal cells	5		
	Placebo group	6		
(Grimaud 2010)*	Fibrin glue injection	36	Adults with a CDAI ≤250 and at least one perianal fistula that drained for more than 2 months. If the patients had setons, they should have been inserted for at least 2 months and were removed at the time of inclusion. Treatments with AZA, 6-MP, MTX, or thalidomide were permitted providing the dose was stable for ≥3 months, and a stable dose of amino-salicylates for >1 month. Approximately, ~49% were with complex perianal fistula	Include in feasibility assessment for NMA
	Observation group	41		
Perianal fistula				
(Present 1999)	Placebo	31	Adults with draining fistulas for ≥3 months as a complication of CD. Around 90% of the study population was having perianal fistulas.	Exclude, not a relevant comparator
	Infliximab (5 mg/kg)	31		

Study name	Treatment arms	Sample size	Patient population	Inclusion/exclusion reason
	Infliximab (10 mg/kg)	32	Patients could receive concomitant therapy. Treatments with azathioprine, 6-MP, MTX, or antibiotics were permitted providing the dose was stable for ≥3 months, and stable dose of amino-salicylates for >1 month	
(West 2004)	Ciprofloxacin + infliximab	11	Adults with CD complicated by perianal fistula. Concomitant therapy could be used at a stable dose. Patients who were included from January 2003 onwards received hydrocortisone intravenously immediately prior to the infliximab infusions if they were not on concomitant immunosuppressive therapy	Exclude, not a relevant comparator
	Placebo + infliximab	13		
(Colombel 2009)	Placebo	47	Adults with moderate to severely active CD (CD AI: 220-450) for >4 months, who had draining fistulas at baseline. Of the included population, 96.5% were with perianal fistulas. Enrolment with a history of INF treatment was permissible only if infliximab had been discontinued at least 12 weeks before the screening visit and the patient had experienced an initial response to the agent. Around 62% patients had prior exposure to anti-TNFs	Exclude, not a relevant comparator
	Adalimumab every other week	30		
	Adalimumab weekly	40		
(Dewint 2014)	Adalimumab + ciprofloxacin	37	Adults with active perianal fistulising CD. Previous treatment with infliximab was permitted if infliximab had been discontinued at least 12 weeks before the screening visit and the patient had initially experienced response to the agent. Concomitant use of thiopurine derivatives, MTX and 5-ASA was allowed provided the dose was stable for at least 12 weeks	Exclude, not a relevant comparator
	Adalimumab + placebo	39		
(Schreiber 2011)	Placebo maintenance	30	Adults with 3-month history of active CD, defined as CDAI of 220-450, having open draining fistulas at Week 0. Around 95% of patients were with perianal fistula. Permitted concomitant therapies for CD were stable doses of 5-aminosalicylates, prednisolone, azathioprine, 6-MP, MTX, and antibiotics.	Exclude, not a relevant comparator
	Certolizumab pegol maintenance	28		
(Thia 2009)	Ciprofloxacin 500 mg	10		Exclude, not a relevant comparator
	Metronidazole 500 mg	7		

Study name	Treatment arms	Sample size	Patient population	Inclusion/exclusion reason
	Placebo	8	Patient (≥16 years) with a confirmed diagnosis of CD for at least 1 month, stable concomitant medications, and 1 or more open actively draining perianal fistulas	
(Maeda 2010)	Metronidazole	33	Adults having CD with perianal involvement, PDAI score ≥5 at baseline, and receiving a stable dose of concomitant medication (amino-salicylates, oral corticosteroids, MTX, antibiotics, cyclosporine) for at least 4 weeks. In the case of INF, subjects must have received their initial dose 3 months, and their most recent and last dose at least 8 weeks, before starting study medication and not had a further infusion during the study period. Patients with setons must have had them in place for at least 4 weeks before screening	Exclude, not a relevant comparator
	Placebo	41		
(Sandborn 2003)	Tacrolimus	22	Patients (≥12 years) with CD and ≥1 open draining enterocutaneous fistulas (perianal or abdominal wall) that had not closed despite previous treatment with at least 1 antibiotic	Exclude, not a relevant comparator
	Placebo	26		
(Hart 2007)	Tacrolimus	6	Adults with CD and single or multiple draining perianal fistulas of ≥1 month duration. Concurrent therapies permitted were oral 5-ASA or oral corticosteroids, MTX, AZA, or 6-MP, and antibiotics. Any therapy with infliximab had to have been discontinued for 8 weeks	Exclude, not a relevant comparator
	Placebo	6		
(Sands 2004)	Induction responders: with infliximab maintenance	96	Adults with CD and single or multiple draining fistulas, including perianal fistulas and enterocutaneous fistulas for at least three months. Setons were permitted at screening but were required to be removed by Week 2. Concurrent therapies for CD, including stable doses of 5-ASA, oral corticosteroids, AZA, 6-MP, mycophenolate mofetil, MTX, and antibiotics, were permitted	Exclude, not a relevant comparator
	Induction responders: with placebo maintenance	99		
	Induction non-responders: with infliximab maintenance	43		

Study name	Treatment arms	Sample size	Patient population	Inclusion/exclusion reason
	Induction non-responders: with placebo maintenance	44		
(Steenholdt 2014)	Infliximab dose intensification (5 mg/kg every 4 weeks)	6	Adults with a previous beneficial clinical response to standard IFX maintenance therapy with regular infusions of 5 mg/kg. all patients had secondary IFX treatment failure on IFX maintenance therapy defined as recurrence of active disease with a CDAI ≥220 and/or a minimum of one draining perianal fistula	Exclude, not a relevant comparator
	Infliximab algorithm (based upon serum IFX and antibody concentration)	8		
(Ardizzone 2003)	Methotrexate	6	Adult patients with fistulising disease not requiring surgery, All patients presented chronic active CD defined as CDAI of ≥200. Immunosuppressant could have been used in the past in addition to steroids but the patient had to have been off immunosuppressive drugs for at least 3 months at the time of enrolment in the study	Exclude, not a relevant comparator
	Azathioprine	4		

*Studies reported subgroup results for complex perianal fistula in CD; CDAI: Crohn's Disease Activity Index; IBDQ: Inflammatory Disease Activity Index; PDAI: Perianal Disease Activity Index

Table 6: Summary of key efficacy outcomes reported across the included studies

Study name	Clinical remission	Response defined as ≥50% improvement	Combined remission	Relapse / recurrence rate	No response/ failure	Mortality	PDAI score	Time to response	Time to relapse	Safety	Tolerability
Complex perianal fistula in CD											
(Panes 2016)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
(Wiese 2015)	✓	-	-	-	-	-	✓	✓	-	✓	-
(Schwartz 2015)	-	-	-	-	-	-	✓	-	-	-	✓

Study name	Clinical remission	Response defined as ≥50% improvement	Combined remission	Relapse / recurrence rate	No response/ failure	Mortality	PDAI score	Time to response	Time to relapse	Safety	Tolerability
Mixed (complex + simple) perianal fistula in CD											
(Senejoux 2016)*	✓	✓	-	-	✓	-	✓	-	-	✓	✓
(Garcia-Olmo 2009)	✓	-	-	-	-	-	-	-	-	-	-
(Molendijk 2015)	✓	-	-	-	-	-	✓	-	-	✓	-
(Grimaud 2010)*	✓	-	-	-	✓	-	-	-	-	✓	✓
Perianal fistula in CD											
(Present 1999)	✓	✓	-	-	-	-	✓	✓	-	✓	✓
(West 2004)	-	✓	-	-	-	-	✓	-	-	✓	✓
(Colombel 2009)	✓	-	-	-	-	✓	-	-	-	✓	✓
(Dewint 2014)	✓	✓	-	-	-	-	✓	-	-	✓	✓
(Schreiber 2011)	✓	✓	-	-	-	-	-	✓	-	✓	✓
(Thia 2009)	✓	✓	-	-	-	-	✓	-	-	✓	✓
(Maeda 2010)	-	-	-	-	-	-	✓	-	-	✓	✓
(Sandborn 2003)	✓	✓	-	-	-	-	-	-	-	✓	✓
(Hart 2007)	✓	✓	-	-	-	-	✓	-	-	✓	✓
(Sands 2004)	✓	✓	-	-	✓	✓	-	-	-	✓	✓
(Steenholdt 2014)	-	-	-	-	-	-	✓	-	-	-	-
(Ardizzone 2003)	✓	-	-	-	-	-	-	-	-	-	-

*Studies reported subgroup results for complex perianal fistula in CD; CDAI: Crohn's Disease Activity Index; IBDQ: Inflammatory Disease Activity Index; PDAI: Perianal Disease Activity Index

A17. Please clarify the statement regarding patients' baseline characteristics [CS, page 34], 'This may indicate that the patients randomised to darvadstrocel had more severe perianal fistulising disease in comparison to those randomised to the control treatment', given that the baseline figures for CDAI and IBDQ [CS, page 36, Table 9] indicate that the patients randomised to darvadstrocel had less severe disease and reported better quality of life?

Response: The CDAI focuses on luminal CD severity, and therefore any differences in CDAI score do not necessarily reflect perianal disease activity. All patients had a CDAI<150, indicating patients were in remission from their luminal disease, therefore there is no clinically significant difference in CDAI between treatment groups.

The only patient-reported outcome instrument included was the IBDQ; however the IBDQ does not focus on perianal fistulising disease, rather on systemic bowel disease (e.g. luminal CD).

The difference in baseline in IBDQ total score between treatment groups is 4.1 (Table 17, section B.2.6.3.3, CS). An increase in IBDQ score of 16 to 32 points constitutes the upper and lower bounds of the clinically meaningful improvement in HRQL using IBDQ in patients with Crohn's disease (Irvine 1994), which would suggest a clinical difference was not observed.

The proportion of patients with more than one draining external fistula opening was slightly higher for patients randomised to darvadstrocel compared with control treatment (Section B.2.3.4 and Table 9 CS). A similar pattern was observed for internal openings; patients randomised to darvadstrocel were more likely to have two internal openings, compared with patients randomised to control treatment.

Any differences in CDAI and IBDQ do not reflect differences in perianal disease severity, while differences in the number of openings may indicate more severe disease, which according to clinical opinion is harder to treat.

Quality assessment, data synthesis, analysis

A18. Please explain in more detail how missing data were handled in the ITT and mITT analyses for categorical and continuous data. Does the following statement from Table 10, "A non-response or non-remission was imputed if an MRI scan or clinical assessment was not done after baseline by week 24 and if a rescue event took place before week 24", mean that patients with missing values were assumed to always have clinically negative binary outcomes i.e. non-response or non-resmission? If so, why do the figures in Table 12 for the ITT and sensitivity analysis 1 differ? Furthermore in Panes et al 2016 [Lancet, 2016, 388: 1281-90] please clarify what analyses were performed to assess the sensitivity of the results to methods other than last observation carried forward in the case of missing data?

Response: In the primary analyses of the primary and key secondary outcomes (binary), non-response was imputed after rescue medication. In addition if data was missing non-response after the LOCF rule was applied.

In sensitivity analysis 1, the description as provided in Panes et al 2016 may have been slightly misleading. The correct description is that for missing data non-response after LOCF was applied. The data as recorded after rescue therapy was used (see Table 2, p51 of the 24-week CSR) as compared to a non-response being imputed for patients who received rescue therapy in the primary analyses.

For time to event analyses, missing data was censored at the date of last clinical fistula assessment. For all continuous data, missing data was imputed using LOCF methods.

A19. Please analyse the primary endpoint and the two key secondary endpoints adjusting for the stratification factors. Please also clarify why no attempt was made to account for the interval censoring in any analyses and in which events are attributed to assessment times; for example, using the Heller method [Lifetime Data Anal. 2011; 17: 373–385]?

Response: The analyses of the primary and key secondary endpoints (combined remission, clinical remission and response) were adjusted by stratification factors (see description in Table 10 in the CS); outcomes are presented in Table 12, Table 14 and Figure 8 in the CS. These endpoints are the proportion of patients with the event (event rates) at specific time points and, as such, are not evaluated in a time-to-event framework; consequently interval-censoring was not considered for these endpoints. Observations for which no information was available (e.g. loss to follow-up) were considered as not in remission in these analyses. The number of patients not in remission based on data and imputed due to lack of data is presented in the respective summary tables for these endpoints (e.g., CSR table 14.1.2.1.1 for combined remission at week 24).

Times to the events analyses (combined remission, clinical remission and response) were only considered secondary endpoints. For the time to combined remission, there was a high proportion of censoring observed at week-24 (50% for darvadstrocel and 65.7% for placebo). Therefore, methods to adjust for the interval gap would have limited data to inform estimation of the “true” underlying value. For the time to clinical remission and response, these endpoints were assessed at each visit (every 6 weeks). Therefore, the bias introduced from large intervals is reduced.

The time-to-event analyses presented in Section B.3.3 of the CS did not consider interval censoring. The use of CPC remission in the base case analysis addresses the potential bias introduced from lack of interval censoring, as this is derived from PDAI measurements which are measured every 6 weeks. This reduces the interval and increases the number of measurements compared with combined remission and clinical remission outcomes, minimising the potential for interval bias.

A20. Please clarify in Table 19 [CS, page 51] why the 95% confidence interval for the hazard ratio includes one (95% CI: 0.89, 2.12), whereas the logrank test statistic corresponds to a p-value of 0.0262.

Response: The hazard ratio (HR) is estimated based on the treatment effect under a Gompertz model, and therefore the associated point and interval estimates differ from the

HR and CI derived from a non-parametric analysis, in this case the log-rank Mantel-Haenszel test.

A21. Please provide justification for the quality assessment grading's in Appendix D.3 [Table 12] and Appendix D.4.5. [Table 13] giving reference to location (page, paragraph, and document) of source data. In particular, please provide the following additional information and likely impact on the risk of bias (for each outcome):

- Method of randomisation
- Process of concealment of allocation
- Unexpected imbalances in drop-outs between groups
- Were all the outcomes that were specified in the trial protocol reported in the company submission or final report? Were any additional outcomes reported?
- Methods used to account for missing data

Response: Tables 12 and 13 in Appendix D.4.5 have been updated to incorporate additional information and the likely impact on the risk of bias and are presented below in Table 7: Quality assessment results for parallel group RCTs and Table 8: Quality assessment results for parallel group RCTs. The source of this information was the methods section of the relevant publications.

Table 7: Quality assessment results for parallel group RCTs

	ADMIRE-CD
Was randomisation carried out appropriately?	Yes; the randomisation and allocation concealment was carried out appropriately using centrally located computer-generated randomisation list and treatments were assigned using a pre-established randomisation list generated by the Department of Biostatistics, Linical (Madrid, Spain). Method of allocation concealment was adequate. (see Panes 2016, pages 2-3)
Was concealment of treatment allocation adequate?	Yes; due to the distinct appearance of a cell suspension it was difficult to blind the administration of darvadstrocel. Therefore, the double-blind trial design was maintained by administering the treatment by an unmasked surgeon, and using a masked gastroenterologist and radiologist to carry out all therapeutic assessments. Surgeons were not permitted to share information about the treatment used in the surgical procedure with the gastroenterologist or radiologists, and were also not allowed to participate in any clinical assessment of the fistula during the study. The radiologists (who centrally read MRI scans) were provided with figures to identify the treated fistulae, but were masked to patient data, order of examinations, and treatment received. (Panes 2016, page 3)
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes; this was a double-blind study; gastroenterologist and radiologist were blinded. Masking of treatments was not possible.
Were there any unexpected imbalances in drop-outs between groups?	No, see Table 11, p39 of the company submission
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No, the authors have measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT01541579). There is no evidence to suggest that there are any outcomes measured that were not specified.
Did the analysis include an intention-to-treat analysis? **If so, was this appropriate and were appropriate methods used to account for missing data?**	Yes Yes, see Section B.2.4 of the company submission
How closely do the RCT(s) reflects routine clinical practice*	The control arm consisted of EUA +/- seton placement which accounts for at least 90% of all treatments for perianal disease in UK clinical practice. Also the background therapy received in the trial (antibiotics/immunosuppressants and biologics) is also consistent with treatments used in UK clinical practice, although biologic usage may be higher in clinical practice than that observed in the trial.
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination) Abbreviations: RCT, Randomised controlled trial	

Table 8: Quality assessment results for parallel group RCTs

Study name	(Panes 2016)	(Wiese 2015)	(Schwartz 2015)	(Senejoux 2016)	(Garcia-Olmo 2009)	(Grimaud 2010)
Allocation concealment grade	A	B	B	A	A	A
Randomisation and allocation concealment	Low risk; The randomisation and allocation concealment was carried out appropriately using centrally located computer-generated randomisation list and treatments were assigned using a pre-established randomisation list generated by the Department of Biostatistics, Linical (Madrid, Spain). Method of allocation concealment was adequate.	Not clear; This was a randomised trial but the method of randomisation was not reported. Allocation concealment was unclear	Not Clear; The study was a randomised study but method of randomisation not reported. Allocation concealment was also not reported	Low risk; The randomisation was adequate. Randomisation was carried out centrally using permutations tables. Allocation concealment was also adequate	Low risk; The study was a randomised study. A centralized randomization procedure was used in this study; Method of allocation concealment was also adequate	Low risk; The randomisation was adequate. Randomisation was carried out centrally using permutations tables. Allocation concealment was also adequate but method was unclear
Baseline characteristics	Low risk; There was no significant difference in the baseline characteristics reported between the two groups	Low risk; There was no significant difference in the baseline characteristics reported between the two groups	Low risk; There was no significant difference in the baseline characteristics reported between the two groups	Low risk; There was no significant difference in the baseline characteristics reported between the two groups	Low risk; There was no significant difference in the baseline characteristics reported between the two groups	Low risk; There was no significant difference in the baseline characteristics reported between the two groups
Blinding	Low risk; This was a double-blind study; gastroenterologist and radiologist both assessing the therapeutic effects were blinded. Masking of treatments to the treating surgeon was not possible because the cell suspension was clearly	High risk; This was an open label study	Not clear; Details regarding blinding were not reported	High risk; This was an open- label study	High risk; This was an open-label study	High risk; This was an open- label study

Study name	(Panes 2016)	(Wiese 2015)	(Schwartz 2015)	(Senejoux 2016)	(Garcia-Olmo 2009)	(Grimaud 2010)
	different to saline solution (i.e., placebo)					
Withdrawals	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported	Not clear; Withdrawals and reasons for withdrawals were not reported	Low Risk; Withdrawals and reasons for withdrawals were reported	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported
Outcomes selection and reporting	Low risk; Author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT01541579). No additional outcomes were measured which were not included in the protocol	Not clear; There was no evidence to conclude whether all outcomes assessed were reported or not	Not clear; There was no evidence to conclude whether all outcomes assessed were reported or not	Not clear; There was no evidence to conclude whether all outcomes assessed were reported or not	Not clear; There was no evidence to conclude whether all outcomes assessed were reported or not	Low risk; Author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT00723047)
Statistical analysis	Low risk; The safety and efficacy analysis were done using both ITT/mITT population	Low risk; The safety and efficacy analysis was done using ITT population	Low Risk; The safety and efficacy analysis were done using mITT population. LOCF was used to account for missing data	Low risk; The safety and efficacy analysis were done using both ITT population	Low risk; The safety and efficacy analysis were done using both mITT population	Low risk; The safety and efficacy analysis were done using both ITT population

Abbreviations: ITT, intend to treat; LOCF, last one carried forward; mITT, modified intend to treat

A22. Please clarify why data on relapse at 24 and 52 weeks are not reported and why the definition of 'relapse' is different depending on follow-up (e.g. 24-week definition is 'reopening of any of the treated external openings with active drainage as clinically assessed, or development of a perianal collection > 2cm of the treated perianal fistulas confirmed by centrally blinded MRI assessment in patients with clinical remission at any previous visit' [Panes et al, 2016, Appendix Table, S4], compared with the CS reported, 'relapse' from CPC remission at 96 weeks: either a re-opening appears at a treated external opening OR a score more than 0 is reported on PDAI domains.

Response: Relapse, using the definition presented in the CSR, was not presented in the company submission. The rationale was that the definition used in the CSR changed for the different time points as presented below. Within the 52-week CSR, two different definitions of relapse are presented:

- Week 24: Since no MRI data are available before week 24, relapse is considered in those patients who had achieved clinical remission at some point during the 24 week follow-up. Relapse was then defined, using the definition of not achieving combined remission
- Week 52: For week 52, the assessment of relapse related to those patients who had achieved combined remission by week 24. Again the definition of relapse related to those patients who did not have combined remission anymore.

The results for the two definitions are presented in Table 9: Time to relapse from clinical remission, ITT populationbelow.

Table 9: Time to relapse from clinical remission, ITT population

	Darvadstrocel (N=107)	Control (N=105)	Difference (95% CI)
Week 24			
Patients at risk (i.e. clinical remission at some point before week 24)	N=79	N=56	
Relapse, n (%) *	30 (38.0%)	28 (50.0%)	-12.0% (-28.9%, 4.9%)
Relapse by Week 52 in patients with combined remission at week 24			
Patients at risk (i.e. combined remission at week 24)	N=52	N=34	
Relapse, n (%) $	13 (25.0%)	15 (44.1%)	-19.1% (-39.5%, 1.3%)

Source: *Post hoc* analyses of ADMIRE-CD, data on file

Abbreviations: CI, Confidence interval; CPC, Clinical and patient-centric; NA, Not available

* Relapse is defined as reopening of any of the treated external openings with active drainage as clinically assessed, or development of a perianal collection > 2cm of the treated perianal fistulas confirmed by centrally blinded MRI assessment in patients with clinical remission at any previous visit

$ Defined as in patients with combined remission at Week 24 (no LOCF) as reopening of any of the treated external openings with active drainage as clinically assessed, or the development of a perianal collection > 2 cm of the treated perianal fistulas confirmed by centrally blinded MRI assessment at Week 52

Within the company submission, the focus has been on CPC remission. Therefore, the definition of relapse related to relapse from CPC remission. A similar approach was applied for relapse from clinical remission (see Section B.3.3.2.2, CS).

Time to relapse from combined remission could not be calculated, due to the limited time points reported in the ADMIRE-CD trial for combined remission. Therefore the economic model used time to relapse from clinical remission as a proxy (see Section B.3.3.2.3).

A23. Please provide further details and clarify the nature of the 'Serious TEAEs' noted in Table 22 [CS, page 58]. In addition, please define 'procedure emergent' and 'non-TEAEs' [CS, page 58, Table 23] and clarify how they differ from the TEAEs reported elsewhere.

Response: Table 22 (CS) detailed the longer-term safety from ADMIRE-CD, safety population, with a focus on the 52 week data. Table 21 of the submission provides greater details of the nature of the 'Serious TEAEs' as seen at 24 weeks within the ADMIRE-CD study.

At 52 weeks, a numerically greater proportion of patients (24.3%; 31 serious TEAEs) in the darvadstrocel group experienced a serious TEAE compared with the placebo group (20.6%; 26 Serious TEAE; TiGenix 2016b)

A similar portion of patients (5.8%; 6 serious TEAEs) in the darvadstrocel group were withdrawn due to a serious TEAE compared with the placebo group (6.9%; 7 serious TEAEs).

The proportion of patients in both treatment groups who experienced serious TEAEs considered to be of moderate intensity, (15.5% of patients, 18 serious TEAEs in the darvadstrocel group, 12.7%, 14 serious TEAEs in the placebo group), or severe intensity (6.8%, 8 serious TEAEs in the darvadstrocel, 5.9%, 8 serious TEAEs in the placebo group) were similar.

In patients in the darvadstrocel group who experienced serious TEAEs, a greater proportion (18.4%) of patients experienced serious TEAEs considered not related to study treatment compared with the placebo group (15.7%). The number of patients who experienced serious TEAEs considered related to treatment was similar across the groups, 6.8% for darvadstrocel and 6.9% in the placebo group.

The majority of patients with serious TEAEs in both treatment groups were considered to have recovered without sequelae (18.4% Cx601; 14.7% placebo).

Further information on treatment-emergent SAEs occurring up to the Week 52 visit in the Safety Population are summarised in Table 10: Summary of Treatment-Emergent serious adverse events up to Week 52below.

Table 10: Summary of Treatment-Emergent serious adverse events up to Week 52

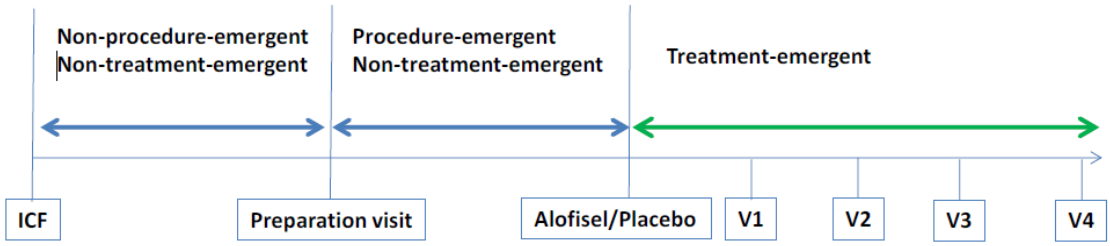
	Darvadstrocel (N=103)		Placebo (N=102)	
	n (%)	**events**	**n (%)**	**events**
Number of patients with TESAEs	25 (24.3)	31	21 (20.6)	26
Number of patients withdrawn due to a TESAE	6 (5.8)	6	7 (6.9)	7
Intensity				
Mild	3 (2.9)	4	2 (2)	2
Moderate	16 (15.5)	18	13 (12.7)	14
Severe	7 (6.8)	8	6 (5.9)	8
Missing	1 (<1.0)	1	2 (2)	2
Relationship to Study Drug				
Related	7 (6.8)	7	7 (6.9)	9
Not Related	19 (18.4)	24	16 (15.7)	17
Outcome				
Death	0	0	0	0
Not recovered	0	0	2 (2)	2
Recovered with sequelae	9 (8.7)	11	3 (2.9)	4
Recovered without sequelae	19 (18.4)	20	15 (14.7)	19
Changed intensity	0	0	0	0
Unknown	0	0	1 (<1.0)	1
Missing	0	0	0	0
Concomitant medication given				
Yes	19 (18.4)	23	13 (12.7)	16
No	7 (6.8)	7	10 (9.8)	10
Missing	1 (<1.0)	1	0	0

Abbreviations: TESAE, treatment-emergent serious adverse event

In ADMIRE-CD, non-treatment-emergent AEs (TEAEs) were also collected. Non-TEAEs were further defined as procedure-emergent or non-procedure emergent.

Procedure-emergent Non-TEAEs started prior to study treatment but after the first (preparatory) curettage procedure that was performed 2 to 3 weeks prior to the day of study treatment administration; non-treatment nor procedure-emergent AEs started prior to the curettage procedure (see Figure 2 below).

Figure 2: Schematic of Non-Procedure-Emergent and Procedure-Emergent, Non-Treatment-Emergent Adverse events



Overall, 15.1% of patients who underwent the preparatory surgery (curettage, and seton placement as necessary) prior to receiving study treatment with either darvadstrocel or placebo experienced an AE between the time of the preparatory surgery and the day of study treatment administration (a total of 48 procedure emergent non-TEAEs). Since none of the patients had yet received study treatment, the focus is on the overall frequency of procedure-emergent (non-treatment emergent) AEs that occurred prior to study treatment administration.

Individual procedure emergent non-TEAEs were uncommon, with the majority occurring in only 1 patient. The most common procedure emergent non-TEAEs overall were procedural pain (2.4% of patients) and nausea and pyrexia (both in 2.0% of patients; TiGenix 2016a).

It should be noted that the most common serious TEAE was abscess formation; this was considered serious as it requires surgical drainage of the abscess which requires hospitalisation.

A24. Please clarify why the number of control patients going into remission (n = 43, [CS, Table 18, page 50]) does not match the number at risk of relapse (n= 47, [CS, Table 19, page 51])?

Response: This is the effect of the restriction to week 52 of the time to CPC remission data. There were four patients who achieved CPC remission between week 52 and 54 in the control arm. These four patients were censored for the CPC remission as presented in the CS Table 18; however they were included in the analysis for time to relapse from CPC remission.

A25. Please clarify why the study by Molendijk et al (2015), [Gastroenterology 149(4): 918-927.] which compared Mesenchymal Stromal Cells (MSC) to placebo, is included in Figure 14 [CS, page 53], but not mentioned elsewhere in the CS? Similarly, please clarify why the trials for interventions other than surgical or stem cell therapies (i.e. those linking the grey boxes) are included in Figure 14, but then are not discussed in CS [section B.2.9, pages 53-54]? Table 7 of Appendix D seems to imply that search terms related to non-surgical interventions were included in the searches only to identify health-related quality of life data. If this is the reason, then these studies should not be included in Figure 14 as they are not relevant to the network.

Response: As presented in reply to Question A16., RCTs which did not include the intervention or the comparator as per the final NICE scope were not further considered, but

are listed in the response to Question A16. In Figure 14 of the company submission, all RCTs for the treatment of perianal fistulae in patients with CD were included. This included RCTs with antibiotics, immunosuppressants, biologics and mesenchymal stromal cells. These were then not further considered, as they are outside of the final NICE scope.

A26. The observed placebo rate in the Panes et al (2016) [Lancet, 2016, 388: 1281-90] is "probably higher [than the UK rate] due to the ligation and curetting of fistula tracts". Please clarify the extent to which the UK follows the process used in Panes et al (2016) and whether the UK could increase its response rate by following alternative processes? Furthermore, please clarify why there were no UK centres involved?

Response: EUA +/- seton placement is commonly used in UK clinical practice as a palliative treatment, that is, a loose seton is placed and left in situ to promote drainage of the fistula tract. Practice is variable in the UK as there is some concern with removing setons due to the low healing rate observed in clinical practice, and the risk of abscess formation due to resulting collections in the fistula tract caused by a non-draining fistula.

Although the placebo rate observed in the Panes trial was higher than anticipated by clinical experts, there is no evidence provided by the Panes study that would support a change in the use of EUA in clinical practice. The Panes study does demonstrate that darvadstrocel is an improvement over the gold standard of care.

As the Panes study was conducted by TiGenix we cannot comment on why no UK centres where included in the study.

A27. Please clarify if there are any reasons to believe that race or other variables not used in the randomisation are a prognostic factors or treatment effect modifiers?

Response: In a review by Braithwaite et al (2017), prognostic factors affecting outcomes of perianal disease were examined. This review identified some studies showing significant prognostic factors, yet these were considered insignificant in other identified studies. The heterogeneity observed across the identified studies limits the ability to draw robust conclusions about prognostic markers in this population.

Candidate prognostic factors reported across multiple identified studies included; NOD2/CARD15, duration of fistulising disease, distribution of CD, and fistulae anatomy. These prognostic factors could not be explored in more detail using data from the ADMIRE-CD trail; the trial did not capture data on NOD2/CARD15 or duration of fistulising disease and excluded patients with proctitis (believed to be the main factor linked to distribution of CD). The ADMIRE-CD study did capture some aspects of fistulae anatomy (number of internal and external openings). However, other variables are important when considering fistulae anatomy, e.g. the presence of horseshoe collections in the fistula tract(s), which was not collected as part of this trial.

As the ADMIRE-CD trial was not powered to examine data on these subgroups, no test for prognostic indicators was performed.

Feedback from UK clinical experts (n=2) corroborated the conclusions of the Braithwaite review. It was considered that there is no clear evidence for prognostic factors in perianal

disease other than the presence of proctitis and fulminant disease (often characterised by the presence of anal strictures). Due to the immunomodulatory effect of MSCs, the clinical experts stated that these may work well in this group of patients for whom other interventions are ineffective.

A28. The CS [Page 38, Table 10] states that, "Time to clinical remission and response were analysed with Kaplan Meier estimates, supplemented with HRs from a stratified Cox-proportional model. Cox regression was done with adjustment for the randomisation stratum." Please present the results for the primary endpoint and the two key secondary endpoints from a stratified Cox proportional hazards including stratification factors used in the randomisation. In addition, please assess whether the stratification factors are treatment effect modifiers by fitting a Cox proportional hazards model with main effects for stratification factors and treatment, and the interactions between treatment and stratification factors.

Response: As stated in the protocol, the primary and key secondary endpoints were to be analysed at week 24 and not as time to event. The stratification factor was always included in the main analysis model, comparing the percentage of patients with combined, clinical remission, or clinical response at week 24.

For the primary endpoint, the interaction between treatment and the stratification factor was tested by use of the Breslow-Day test for homogeneity of odds ratio, resulting in a p-value of 0.639. Similarly, the interaction was tested for the key secondary endpoint, clinical remission, and resulted in a p value of p=0.728. The treatment by stratum interaction for response, the other key secondary endpoint, was not tested, although the response rate was similar to the clinical remission, and would not be significant either. In addition and as reported by Panes et al. (2016), no difference in treatment effect in the proportion of patients achieving combined remission at week 24 was identified across randomisation strata (p=0.47).

The results for the primary endpoint and the two key secondary endpoints based on a stratified Cox proportional hazards model with stratification factor are considered secondary and can be found in Tables 14.1.4.3.1, 14.1.4.4.1 and 14.1.4.5.1 of the Week 24 CSR (TiGenix 2016a). As there is no evidence of non-homogeneity in the treatment effect across strata and the trial was not powered to detect differences in treatment effect between these randomisation strata, these analyses were not included in the CS.

A29. In the CS [page 45, Table 15], please clarify what is meant by the two sets of results in the cell in the hazard ratio column and the response/Kaplan-Meier estimates row.

Response: The time to response was presented using both 24 and 52 week follow-up. The values at 52 week follow-up were derived from the 52-week CSR. A table note is added to reflect this. The Kaplan-Meier estimates were measuring time to event as measured in ADMIRE-CD. Please note this was not used in the model as the model uses CPC remission as discussed in question A19 above.

Table 11: Time to combined remission, clinical remission and response of perianal fistula by Week 24, ITT population

	Darvadstrocel (N=107)	Control (N=105)	Hazard Ratio (95% CI)
Combined remission			
Combined remission, n (%) *	[redacted]	[redacted]	
Censored cases, n (%)	[redacted]	[redacted]	
Kaplan-Meier Estimates, Median (95% CI), weeks	25.0 (24.7, 26.1)	28.1 (24.7, 36.0)	0.74 (0.48, 1.14)
Clinical remission			
Clinical remission, n (%)*	[redacted]	[redacted]	
Censored cases, n (%)	[redacted]	[redacted]	
Kaplan-Meier Estimates, Median (95% CI), weeks	6.7 (6.4, 11.9)	14.6 (11.9, 22.9)	0.57 (0.41, 0.79)
Response			
Response, n (%)*	[redacted]	[redacted]	
Censored cases, n (%)	18 (16.8%)	30 (28.6%)	
Kaplan-Meier Estimates, Median (95% CI), weeks	6.3 (6.0, 6.6)	11.7 (6.7, 12.9)	0.59 (0.43, 0.81) [redacted]

Figures have been rounded to 1 decimal place
Source: (Panes 2016), and Table 23 and pages 92-94 of (Tigenix 2016a)
Abbreviations: CI, Confidence interval; ITT, Intention-to-treat
* Achieved at least once during the 24-week follow-up
^ derived from the 52 week follow-up data presented in the CSR (Tigenix, 2016b)

A30. Please clarify why the results for PDAI scores in the CS [pages 45 – 47] are presented for the mITT population rather than the ITT population. Furthermore for Figure 10, please clarify:

- whether the treatment-specific means are sample means or estimated from the ANCOVA
- whether the ANCOVA is a repeated measures analysis or based on separate analyses at each assessment

Response: The analyses were presented for the mITT population, since Panes et al (2016) presented the results in the mITT population and Takeda considered it most appropriate to present the data which are in the public domain. For calculating the CPC remission, the ITT population was used. The results of the PDAI subscore for the ITT population are presented in

Table 12:.

The PDAI scores were presented as summaries of absolute values as well as changes from baseline by visit and by treatment group for the total score and the 5 domain scores. The 95% CI for between-group difference was derived from an analysis of covariance (ANCOVA) model with treatment group and stratum as factors and baseline value as covariate.

Table 12: Individual domain scores of the PDAI over time in ADMIRE-CD, ITT population

	Darvadstrocel		Control		Treatment difference (95% CI)
	N	mean (SD)	N	mean (SD)	
Discharge					
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	
6 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain					
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	
6 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Restriction of sexual activity					
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	
6 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type of perianal disease					
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	
6 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Degree of induration					
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	
6 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 14.1.4.9.1.1 of CSR

Abbreviations: CI, Confidence interval; ITT, Intention-to-treat; SD, Standard deviation

Bold is significant difference, p-value ≤0.05

A31. Please clarify that the median times to CPC remission in Table 18 [CS, page 50] correspond with Figure 11 [CS, page 50]

Response: The values in the Table 18 (page 50 of the company submission) inadvertently presented the mean rather than the median time to CPC remission. Table 13 below presents the correct median values**.**

Table 13: Time to CPC remission, ITT population

	Darvadstrocel (N=107)	Control (N=105)	Hazard Ratio (95% CI)
CPC remission, n (%)	59 (55.1%)	43 (41.0%)	
Kaplan-Meier Estimates, Median (95% CI), weeks*	NA (24.4, NA)	22.6 (17.7, 37.0)	0.61 (0.42, 0.91)
Log-rank test			X_1^2=6.0, p=0.014

Source: *Post hoc* analyses of ADMIRE-CD, data on file
Abbreviations: CI, Confidence interval; CPC, Clinical and patient-centric; NA, Not applicable
* Restricted mean with upper limit of 52 weeks

Section B: Clarification on cost-effectiveness data

Literature searching:

B1. Please clarify why a date limit was applied to the search strategy [Appendix G.1, Table 14 Embase® and MEDLINE® (statement 7), Table 15 Cochrane database (statement 12)], when the publication timeframe is 2000-2018 [Appendix G1, Table 18]? Please clarify if statements 12 and 13 of the MEDLINE search strategy [Appendix G.1, Table 14] are meant to be different given that they denote two different facets? Furthermore, please clarify whether stem cells are classed as other intervention?

Response: The SLR was conducted in two phases. The original review was undertaken in November 2016, with searches conducted on 1st November 2016. Subsequently, an update of original review was conducted in July 2017 and later the searches were updated on 22nd January 2018 prior to submission. The initial search and the updated search strategies are presented in Tables 14-20 below.

Two small errors were detected in the search strategies presented in Appendix G.1.

Inadvertently, statement 13 in Table 17 of the company submission was an error it should be Search *(#9 AND (inprocess[sb] OR pubstatusaheadofprint))*, this string was used to include data of complex perianal fistula, irrespective of disease background. This could be used as proxy data, in case of data paucity. The typographical errors did not have an impact on the search and results.

Table 14: Search Strategy: Embase® and MEDLINE® database (searched via Embase.com on 1st November 2016)

#	Search string	Number of hits
1	'crohn disease'/exp OR 'colon crohn disease'/syn OR (crohn* NEXT/2 (disease* OR ileitis OR enteritis OR ileocolitis OR colitis OR morbus)):ab,ti	78358
2	'rectum fistula'/exp OR 'anus fistula'/exp OR 'perianal fistula'/syn OR 'enterocutaneous fistula'/exp OR 'perianal abscess' OR fistul* OR fistul* NEAR/2 (perianal OR anal OR rectum OR rectal OR enterocutenous) OR 'anus disease' OR 'complex anal' OR 'rectovaginal fistula' OR 'perianal lesions' OR 'complex fistula'	150561
3	'economics'/de OR 'economic aspect'/de OR 'cost'/de OR 'health care cost'/de OR 'drug cost'/de OR 'hospital cost'/de OR 'socioeconomics'/de OR 'health economics'/de OR 'pharmacoeconomics'/de OR 'fee'/exp OR 'budget'/exp OR 'hospital finance'/de OR 'financial management'/de OR 'health care financing'/de OR 'low cost' OR 'high cost' OR health*care NEXT/1 cost* OR 'health care' NEXT/1 cost* OR fiscal OR funding OR financial OR finance OR cost NEXT/1 estimate* OR 'cost variable' OR unit NEXT/1 cost* OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti OR health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization) OR resource NEXT/1 (utilisation OR utilization OR use) OR (cost* NEAR/3 (treat* OR therap*)):ab,ti OR ((direct OR indirect) NEAR/2 cost*):ab,ti OR 'cost effectiveness analysis'/syn OR 'cost benefit analysis'/syn OR 'cost utility analysis'/syn OR 'cost minimization analysis'/syn OR 'economic evaluation'/syn OR (economic OR 'cost-benefit' OR 'cost-effectiveness' OR 'cost-utility') NEXT/1 (evaluation* OR analys* OR model* OR intervention*) OR ('cost minimization' OR 'cost minimisation') NEXT/1 (analys* OR model*) OR economic NEXT/1 (evaluation* OR model)	1220408
4	1 AND #2 AND #3	280
5	**#4 AND [2000-2016]/py**	**273**

Table 15: Search strategy for Embase® and MEDLINE® database for economic burden review platform (searched on 28th July 2017)

#	Search string	Number of hits
1	'crohn disease'/exp OR 'colon crohn disease'/syn OR (crohn* NEXT/2 (disease* OR ileitis OR enteritis OR ileocolitis OR colitis OR morbus)):ab,ti	82,151
2	'rectum fistula'/exp OR 'anus fistula'/exp OR 'perianal fistula'/syn OR 'enterocutaneous fistula'/exp OR 'perianal abscess' OR fistul* OR fistul* NEAR/2 (perianal OR anal OR rectum OR rectal OR enterocutenous) OR 'anus disease' OR 'rectovaginal fistula' OR 'perianal lesions'	157,540
3	'complex anal' OR 'complex fistula' OR 'complex perianal' or 'complex perianal fistula'	638
4	#2 OR #3	157,553

#	Search string	Number of hits
5	'economics'/de OR 'economic aspect'/de OR 'cost'/de OR 'health care cost'/de OR 'drug cost'/de OR 'hospital cost'/de OR 'socioeconomics'/de OR 'health economics'/de OR 'pharmacoeconomics'/de OR 'fee'/exp OR 'budget'/exp OR 'hospital finance'/de OR 'financial management'/de OR 'health care financing'/de OR 'low cost' OR 'high cost' OR health*care NEXT/1 cost* OR 'health care' NEXT/1 cost* OR fiscal OR funding OR financial OR finance OR cost NEXT/1 estimate* OR 'cost variable' OR unit NEXT/1 cost* OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti OR health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization) OR resource NEXT/1 (utilisation OR utilization OR use) OR (cost* NEAR/3 (treat* OR therap*)):ab,ti OR ((direct OR indirect) NEAR/2 cost*):ab,ti OR 'cost effectiveness analysis'/syn OR 'cost benefit analysis'/syn OR 'cost utility analysis'/syn OR 'cost minimization analysis'/syn OR 'economic evaluation'/syn OR (economic OR 'cost-benefit' OR 'cost-effectiveness' OR 'cost-utility') NEXT/1 (evaluation* OR analys* OR model* OR intervention*) OR ('cost minimization' OR 'cost minimisation') NEXT/1 (analys* OR model*) OR economic NEXT/1 (evaluation* OR model)	1,291,082
6	#1 AND #4 AND #5	300
7	#6 AND [1-11-2016]/sd NOT [28-7-2017]/sd	21
8	#3 AND #5	31
9	#7 OR #8	49
	#9 AND [28-7-2017]/sd NOT [22-1-2018]/sd*	**23**

The above search strategy was rerun on 22nd January 2018 to include the updated evidence. Additional 23 hits from 28th July 2017 to 22nd January 2018 were retrieved.

Table 16: Search strategy for Cochrane database (searched on 1st November 2016)

#	Search string	Number of hits
1	[Crohn Disease] explode all trees	1107
2	"Crohn Disease" or "Crohns Disease"	1809
3	(Crohn or Crohns) next/2 (disease or ileitis or enteritis or ileocolitis or colitis or morbus)	2386
4	#1 OR #2 OR #3	2386
5	[Rectal Fistula] explode all trees	121
6	[Fistula] explode all trees	485
7	"rectum fistula" OR "anus fistula" OR "perianal fistula" OR "enterocutaneous fistula" OR "perianal abscess" OR fistula OR "anus disease" OR "complex anal" OR "rectovaginal fistula" OR "perianal lesions" OR "complex fistula"	2301
8	Fistula NEAR/2 (perianal OR anal OR rectum OR rectal OR enterocutenous)	204

#	Search string	Number of hits
9	#5 or #6 or #7 or #8	2301
10	**#4 AND #9**	**175**
11	**#10 in Economic Evaluations**	**3**

Table 17: Search strategy for Cochrane database (searched on 28th July 2017)

#	Search string	Number of hits
1	[Crohn Disease] explode all trees	1146
2	"Crohn Disease" or "Crohns Disease"	2178
3	(Crohn or Crohns) next/2 (disease or ileitis or enteritis or ileocolitis or colitis or morbus)	2862
4	#1 OR #2 OR #3	2862
5	[Rectal Fistula] explode all trees	131
6	[Fistula] explode all trees	511
7	"rectum fistula" OR "anus fistula" OR "perianal fistula" OR "enterocutaneous fistula" OR "perianal abscess" OR fistula OR "anus disease" OR "rectovaginal fistula" OR "perianal lesions"	2842
8	Fistula NEAR/2 (perianal OR anal OR rectum OR rectal OR enterocutenous)	239
9	"complex anal" OR "complex fistula" OR "complex perianal" or "complex perianal fistula"	32
10	#5 or #6 or #7 or #8 or #9	2843
11	#4 AND #10	217
12	**#11 Year from 2016 to 2017, in Technology Assessments and Economic Evaluations (Word variations have been searched)**	**2**
13	#9 in in Technology Assessments and Economic Evaluations (Word variations have been searched)	2
14	#12 OR #13	2
	#4 AND #10 Year from 2017 to 2018, in Technology Assessments and Economic Evaluations (Word variations have been searched)	**0**

The above search strategy was rerun on 22nd January to include the updated evidence. No additional evidence from 28th July 2017 to 22nd January 2018 were retrieved

Table 18: Search strategy for MEDLINE® In-Process searched via PubMed® platform (searched on 1st November 2016)

#	Search string	Number of hits
1	Search "Crohn Disease"	34283
2	Search "Crohns Disease"	150
3	Search ((Crohn or Crohns) next/2 (disease or ileitis or enteritis or ileocolitis or colitis or morbus))	76
4	Search (#1 OR #2 OR #3)	34352
5	Search "Rectal Fistula"	3964
6	Search Fistula	91492
7	Search ("rectum fistula" OR "anus fistula" OR "perianal fistula" OR "enterocutaneous fistula" OR "perianal abscess" OR fistula OR "anus disease" OR "complex anal" OR "rectovaginal fistula" OR "perianal lesions" OR "complex fistula")	102999
8	Search fistula near/2 (perianal OR anal OR rectum OR rectal OR enterocutaneous	19
9	Search (#5 OR #6 OR #7 OR #8)	102999
10	#4 AND #9	2468
11	**Search (#10 AND (inprocess[sb] OR pubstatusaheadofprint))**	**11**

Table 19: Search strategy for MEDLINE® In-Process searched via PubMed® platform (searched on 28th July 2017)

#	Search string	Number of hits
1	Search "Crohn Disease"	**35,474**
2	Search "Crohns Disease"	170
3	Search ((Crohn or Crohns) next/2 (disease or ileitis or enteritis or ileocolitis or colitis or morbus))	83
4	Search (#1 OR #2 OR #3)	35,551
5	Search "Rectal Fistula"	4,081
6	Search Fistula	94,319
7	Search ("rectum fistula" OR "anus fistula" OR "perianal fistula" OR "enterocutaneous fistula" OR "perianal abscess" OR fistula OR "anus disease" OR "complex anal" OR "rectovaginal fistula" OR "perianal lesions" OR "complex fistula")	94,670
8	Search fistula near/2 (perianal OR anal OR rectum OR rectal OR enterocutaneous	19

#	Search string	Number of hits
9	Search ('complex anal' OR 'complex fistula' OR 'complex perianal' or 'complex perianal fistula')	30
10	Search (#5 OR #6 OR #7 OR #8 OR #9)	94,672
11	#4 AND #10	2,523
12	Search (#11 AND (inprocess[sb] OR pubstatusaheadofprint))	9
13	Search (#9 AND (inprocess[sb] OR pubstatusaheadofprint))	1
14	**#12 OR #13**	**10**
	#4 AND #10 (AND (inprocess[sb] OR pubstatusaheadofprint))*	**10**

The above search strategy was rerun on 22nd January to include the updated evidence and an additional 10 hits were retrieved.

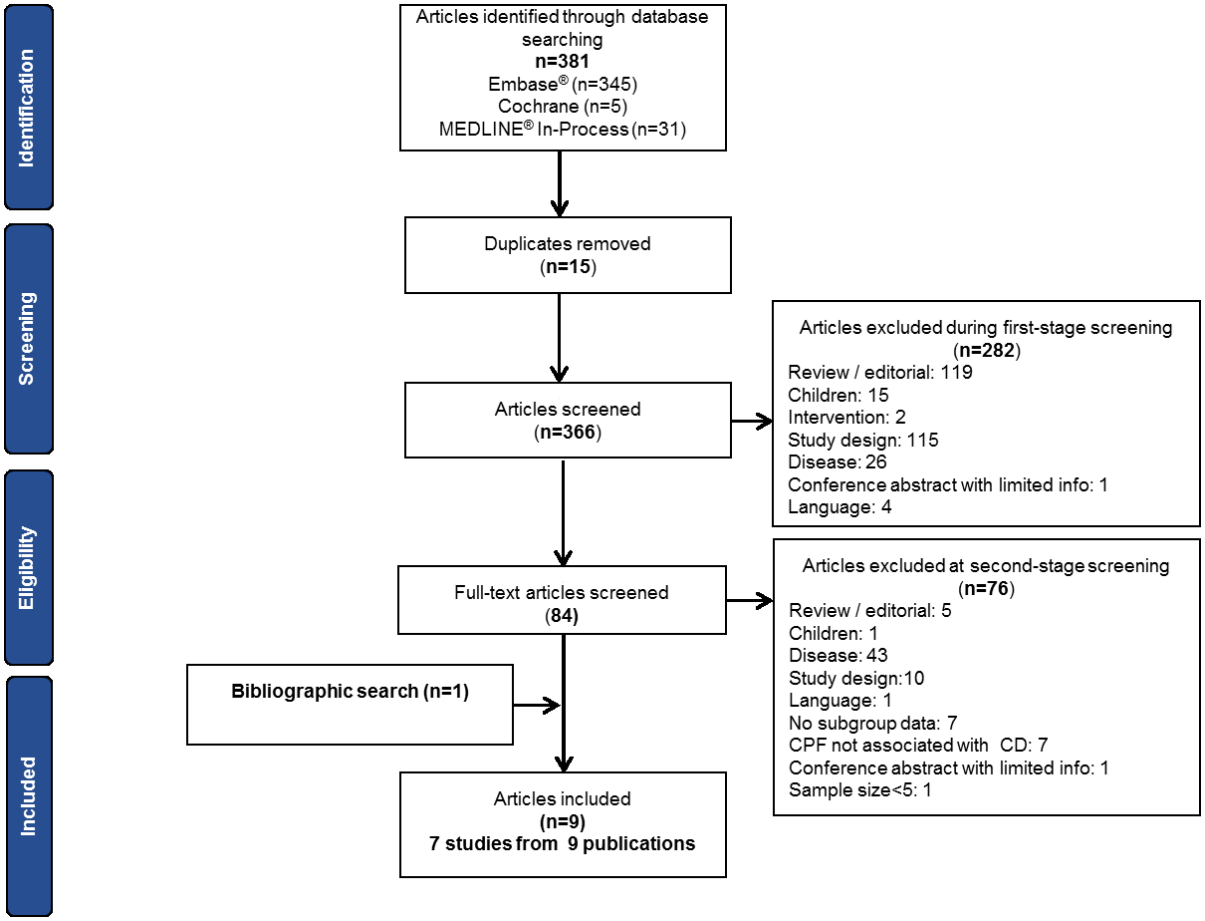
Table 20: Total number of citations retrieved for economic review from all databases (01-01-2000 to 22nd January 2018)

Database	2000 to 1st Nov-2016	1st Nov-2016 to 28th July 2017	28th July 2017 to 22nd January 2018
Embase® and MEDLINE®	273	49	23
CENTRAL	3	2	0
MEDLINE® In-Process	11	10	10
Total	287	61	33
Overall search hits	381		

The flow chart for the economic literature review is presented in the figure below.

Figure 3: **PRISMA flow diagram, economic studies**shows the flow of studies through the systematic review process. The search of the literature databases yielded 381 references. Due to the overlap of coverage between the databases, 15 of the abstracts were found to be duplicates. Following the first-stage screening, 282 references were excluded. Following a detailed examination of the 84 references, eight references were included, while 76 references were excluded. Additionally, one study each was retrieved through bibliographic searching. Across these nine publications, multiple reports of the same study were linked together, and data from these were extracted into the same data extraction grids. After linking of related citations, seven primary studies were included.

Figure 3: PRISMA flow diagram, economic studies



Clinical parameters used in the model

B2. For all statistical models fitted to the relapse and remission data in the CS [pages 78 to 88], please clarify whether models were fitted independently to the data from each treatment group using the same statistical model structure each time or whether parameters for darvadstrocel are estimated relative to control.

Response: Singular cox regression models were fit to the relapse and remission data (pages 78 to 88 of the CS) with a treatment effect included to capture the impact of darvadstrocel relative to placebo. This method was validated using the Grambsch-Therneau test (presented in the CS), the Schoenfeld residuals plot (presented as response to B3) and the log-cumulative hazard plot (presented as response to B3).

B3. Standard log-cumulative hazard plots can be used to test the suitability of the Weibull and exponential distributions and variations on this approach can be used to test the suitability of the Gompertz, log normal and log-logistic distributions (see section 3.2 of NICE TSD 14 for more details). Please provide the relevant plots to assess

whether the hazards behave as expected for all the fitted curves and for all endpoints included as either the base case or a scenario analysis in the economic model.

Response:

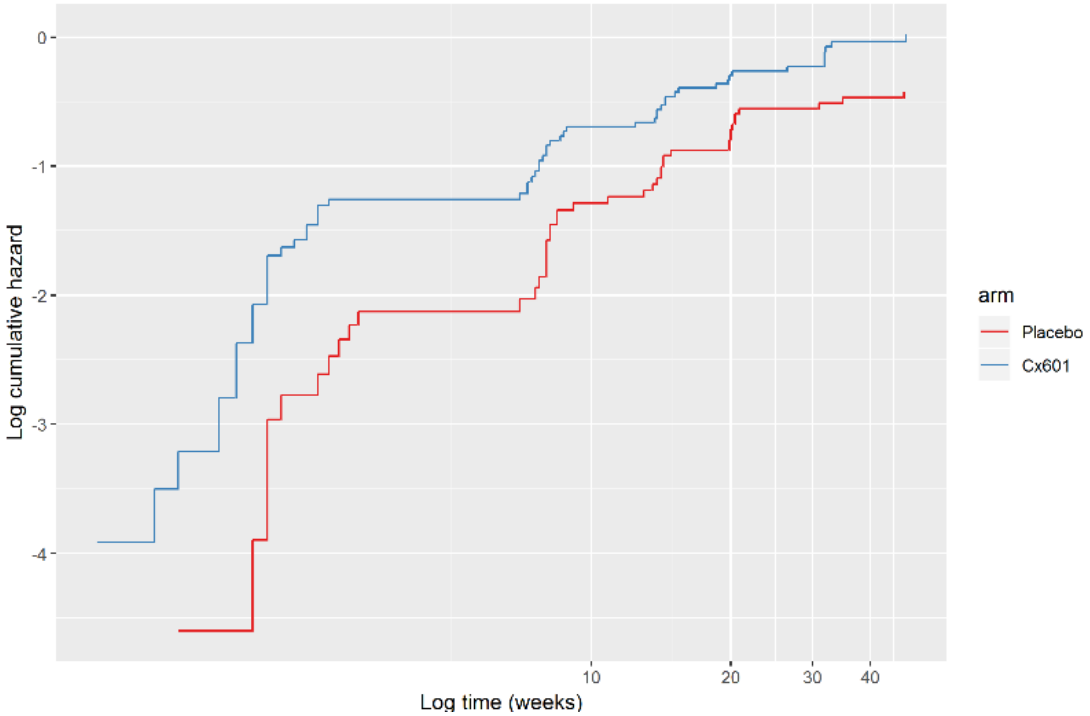
Time to remission

Time to CPC remission (base case)

The log-cumulative hazard plot (LCHP) and the Schoenfeld residuals plot are presented based on the CPC remission data in Figure 4**: Log-cumulative hazard plot (LCHP) for CPC remission data** and

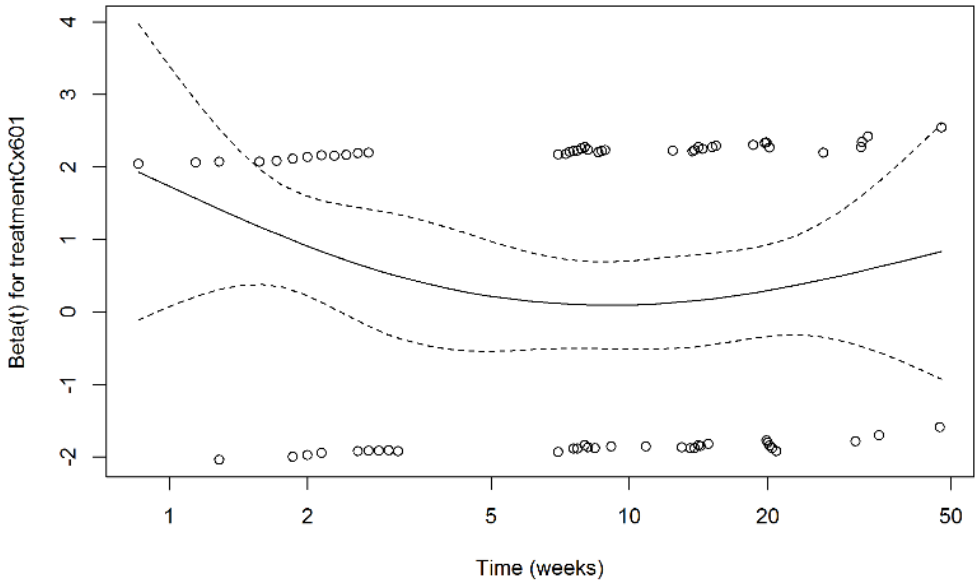
Figure 5, respectively. These plots support the assumption of proportional hazards as the curves in the LCHP prove to be approximately parallel and the Schoenfeld residual plot indicates equally spread residuals without distinct patterns.

Figure 4: Log-cumulative hazard plot (LCHP) for CPC remission data



Abbreviations: CPC, Clinical and Patient Centred; LCHP, log-cumulative hazards plot

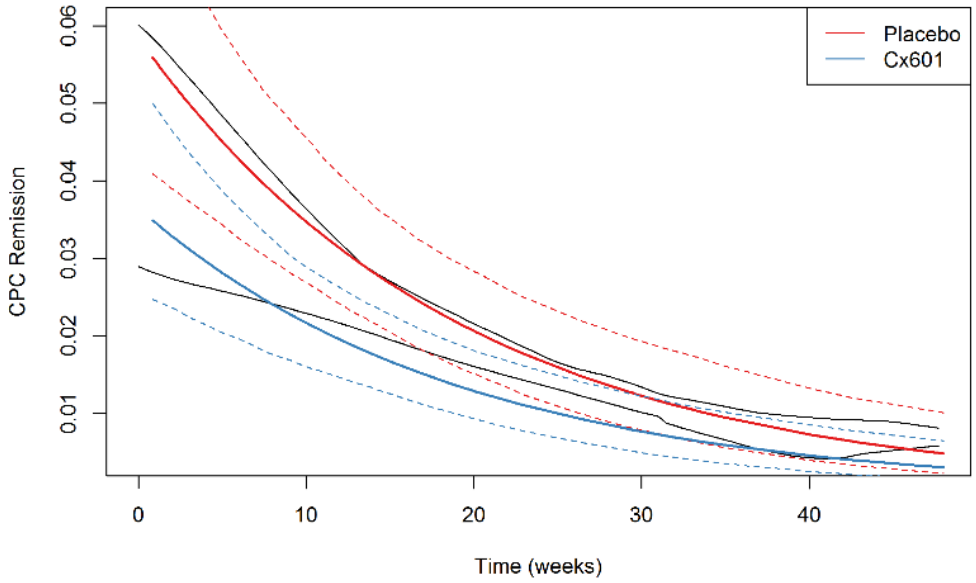
Figure 5: Schoenfeld residuals plot for CPC remission data



Abbreviations: CPC, Clinical and Patient Centred

In the base case, the Gompertz curve is selected based on both internal and external validity. The shape of the predicted Gompertz hazards are shown to approximate the shape of the observed hazards over time, see Figure 6:, indicating that the Gompertz provides a good statistical fit to the data.

Figure 6: Empirical hazard plot vs. predicted Gompertz hazards for CPC remission outcome (base case)

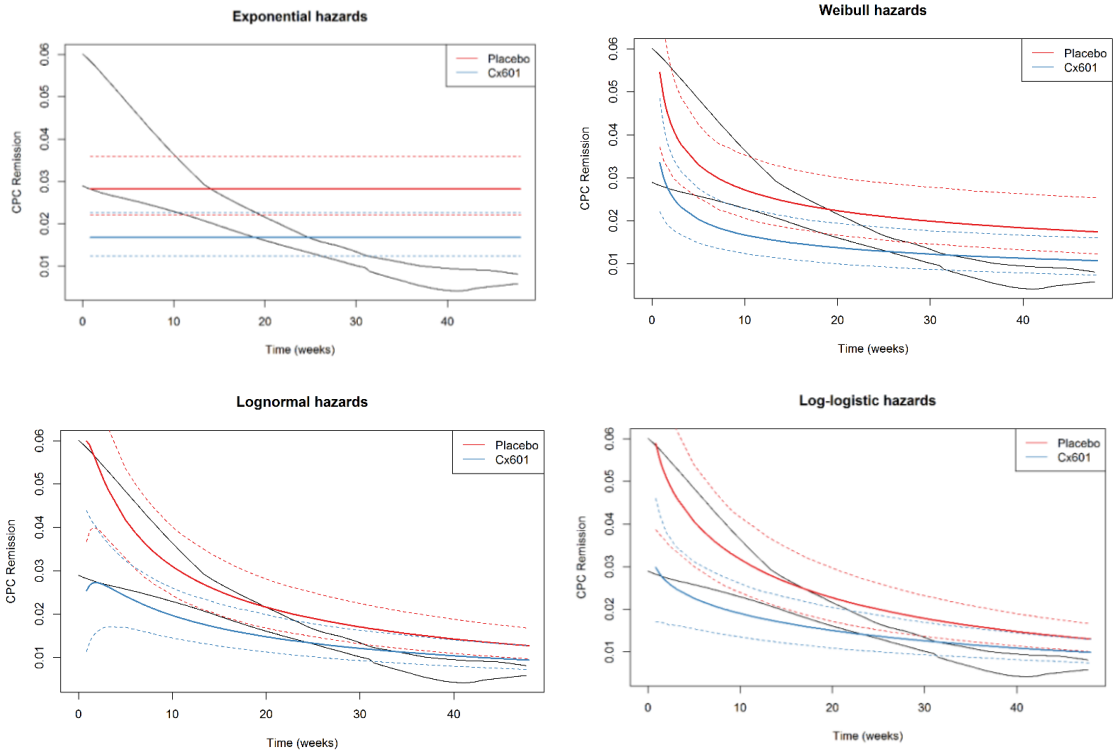


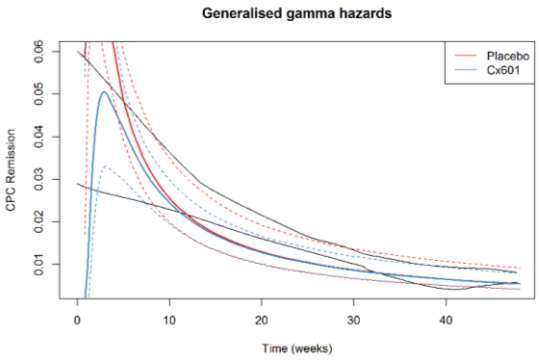
Abbreviations: CPC, Clinical and Patient Centred

Notes: the black lines present the empirical hazards from the observed data.

Figure 7 presents the empirical hazard plot compared with the predicted hazards based on the other parametric curves included in the model.

Figure 7: Empirical hazard plot vs. predicted hazards for CPC remission outcome (scenario analyses)





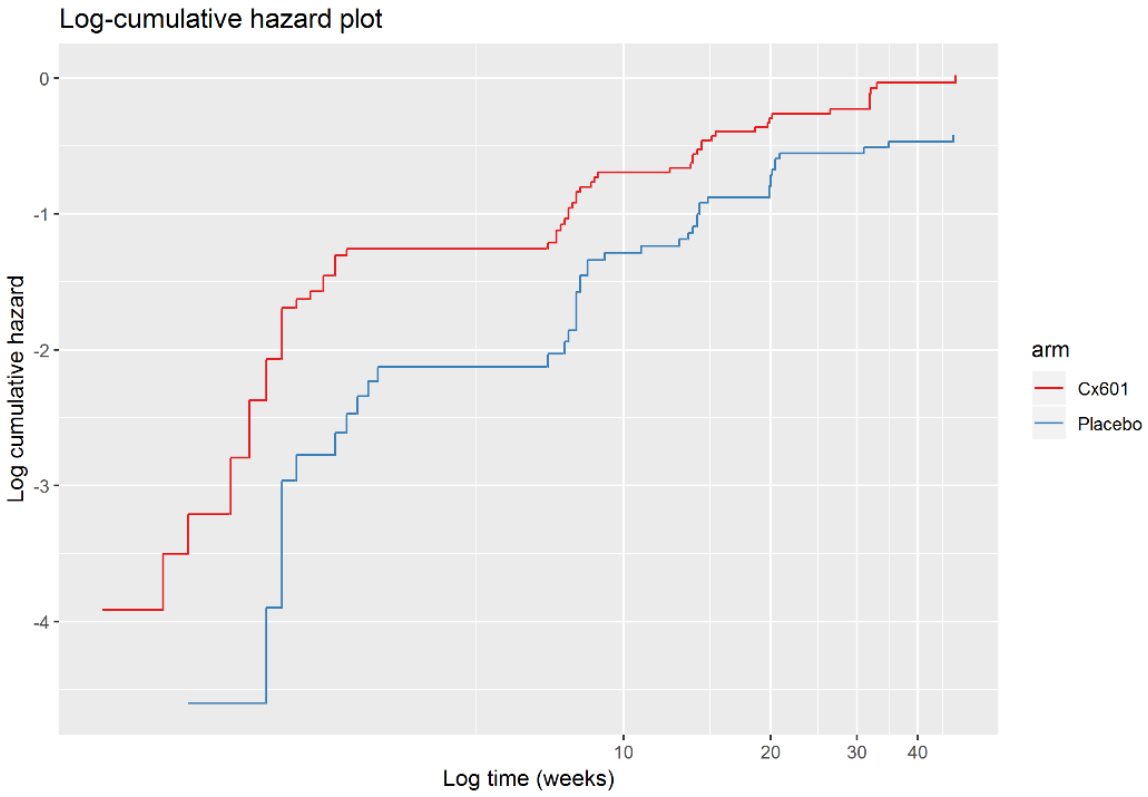
Abbreviations: CPC, Clinical and Patient Centred

Time to clinical remission

The LCHP and the Schoenfeld residuals plot are presented based on the clinical remission data in Figure 8 and **Abbreviations:** LCHP, log-cumulative hazards plot

Figure 9, respectively. These plots support the assumption of proportional hazards as the curves in the LCHP prove to be approximately parallel and the Schoenfeld residual plot indicates equally spread residuals without distinct patterns.

Figure 8 Log-cumulative hazard plot (LCHP) for clinical remission data



Abbreviations: LCHP, log-cumulative hazards plot

Figure 9: Schoenfeld residuals plot for clinical remission data

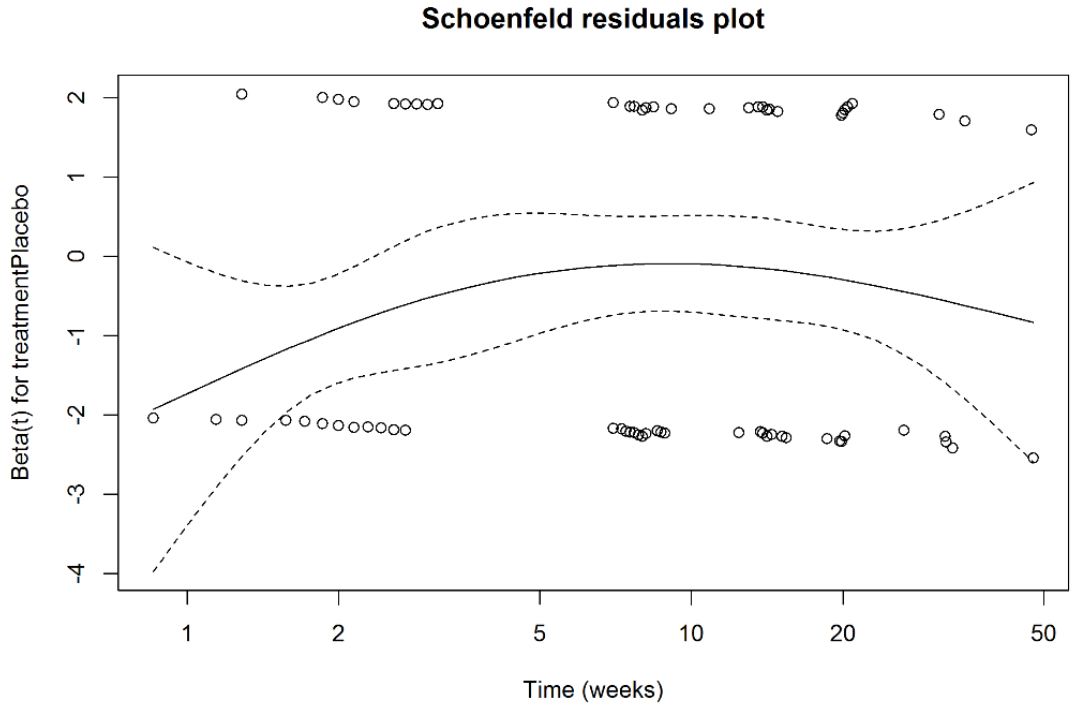
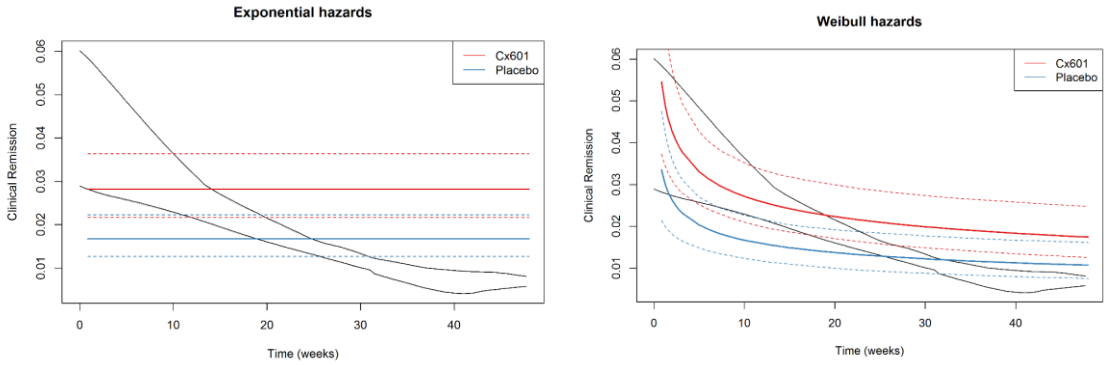
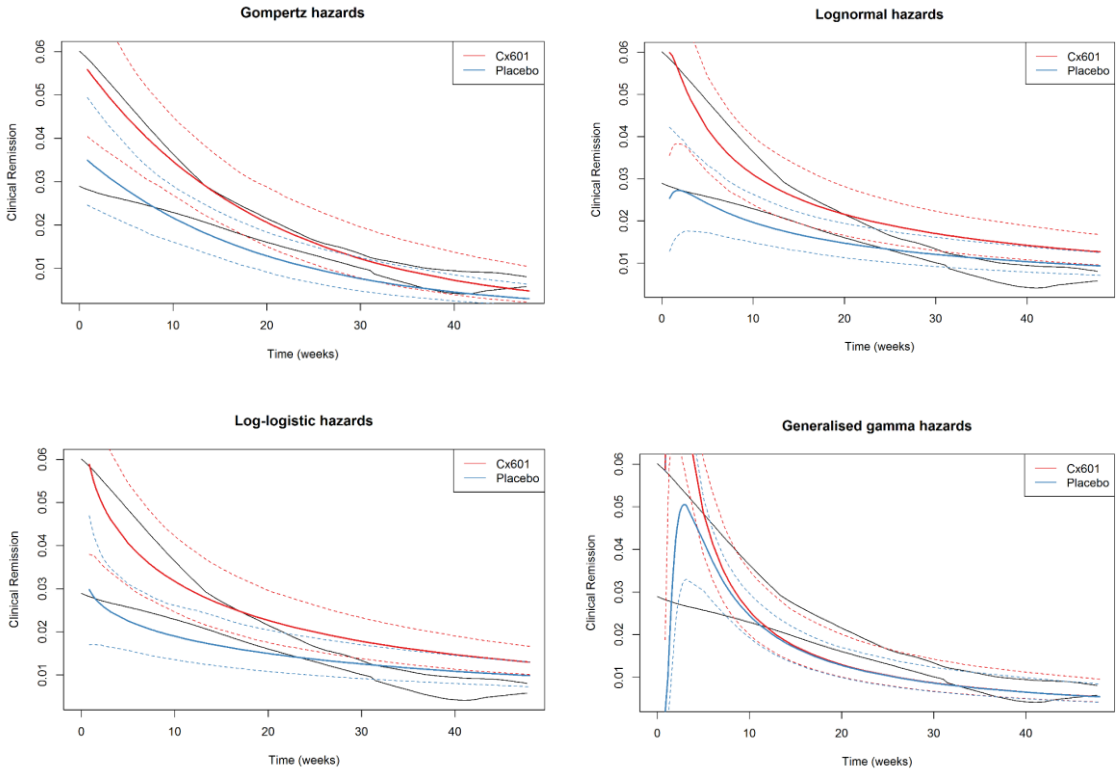


Figure 10 presents the shape of the predicted hazards vs. the observed hazards for all parametric curves

Figure 10: Empirical hazard plot vs. predicted Gompertz hazards for clinical remission outcome





Time to CPC and MRI remission and time to combined remission

No separate curves are provided for time to CPC + MRI remission and time to combined remission. As presented in the company submission, a HR-based approach was adopted in order to estimate the time to remission rates for both CPC remission and clinical remission to CPC remission + MRI and combined remission respectively.

The number of patients with CPC remission but not CPC + MRI remission was not greater than three patients per arm at either visit. For both remission definitions, the rate ratio of non-MRI to MRI remissions results are lower for control than darvadstrocel at week 24, and vice versa at week 52. The confidence interval associated to the rate ratio did not indicate any significant difference between the arms. Therefore, no differential effect due to the addition of MRI as an additional criterion to achieve remission is included in the analysis.

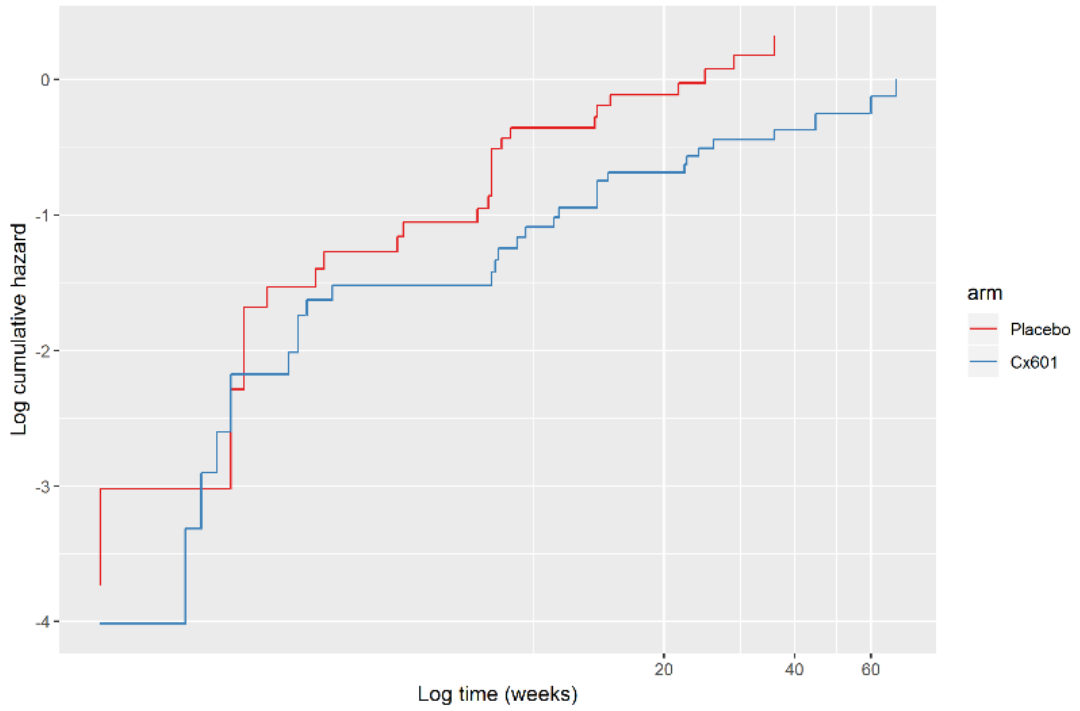
Time to relapse

Time to relapse from CPC remission (base case)

The LCHP and the Schoenfeld residuals plot are presented based on relapse from CPC remission data in Figure 11 and

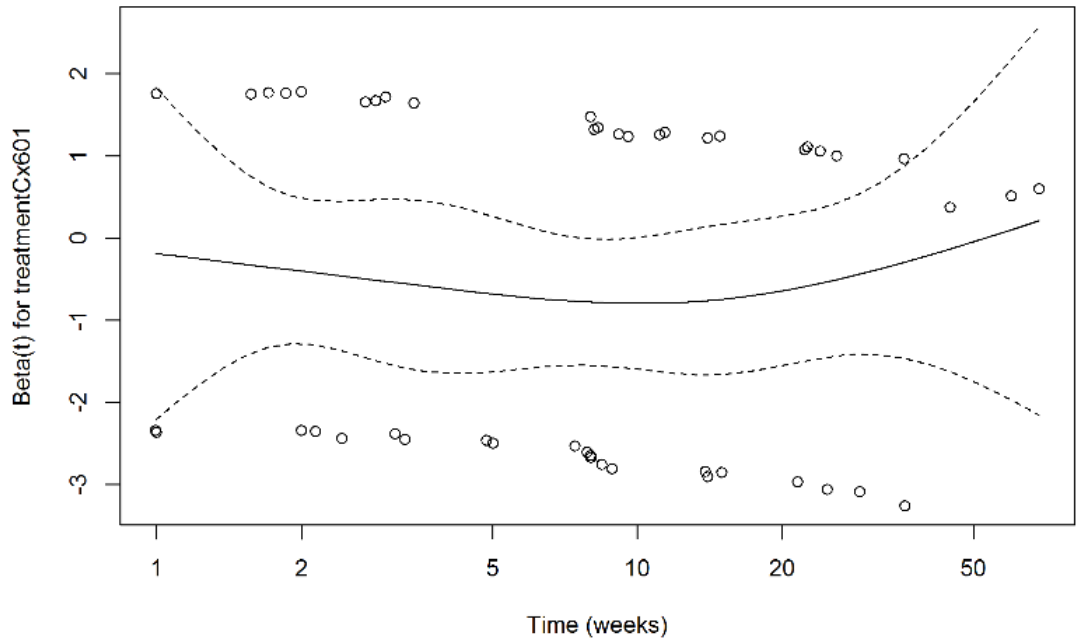
Figure 12, respectively. The LCHP shows the curves initially crossing in the short term and then approximating parallelism between the medium to long term. This supports the assumption of proportional hazards based on the medium to long term data, further supported by the Schoenfeld residual plot which indicates equally spread residuals without distinct patterns.

Figure 11: Log-cumulative hazard plot (LCHP) for relapse from CPC remission data



Abbreviations: CPC, Clinical and Patient Centred; LCHP, log-cumulative hazards plot

Figure 12: Schoenfeld residuals plot for relapse from CPC remission data

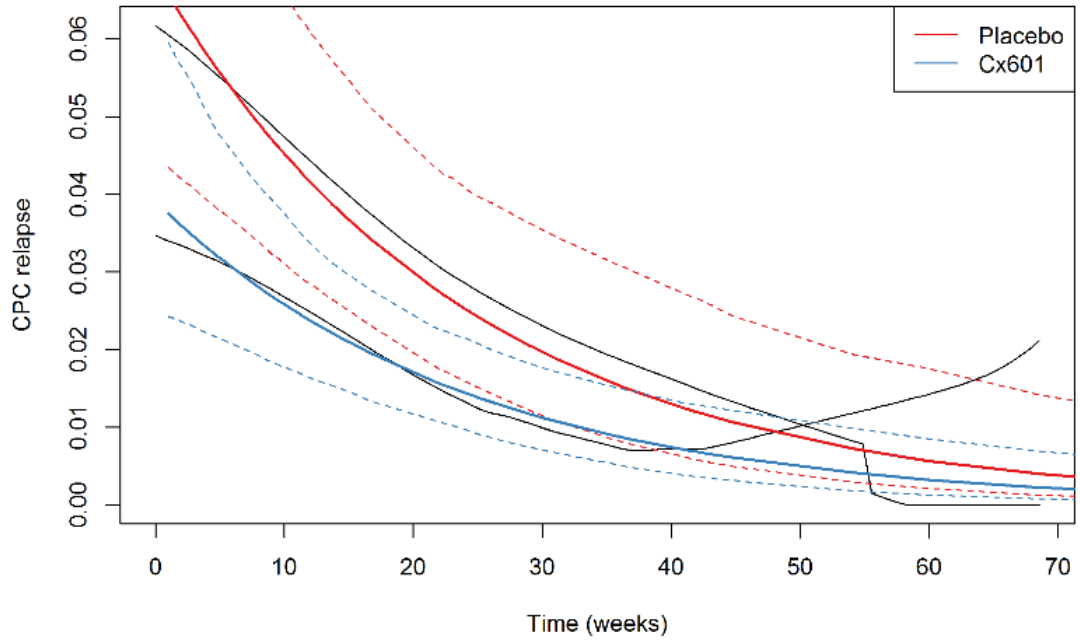


Abbreviations: CPC, Clinical and Patient Centred

In the base case, the Gompertz curve is selected for the short-term relapse from CPC remission based on both internal and external validity. The shape of the predicted Gompertz hazards are shown to approximate the shape of the observed hazards over time, see

Figure 13, indicating that the Gompertz provides a good statistical fit to the data.

Figure 13: Empirical hazard plot vs. predicted Gompertz hazards for relapse from CPC remission outcome (base case)

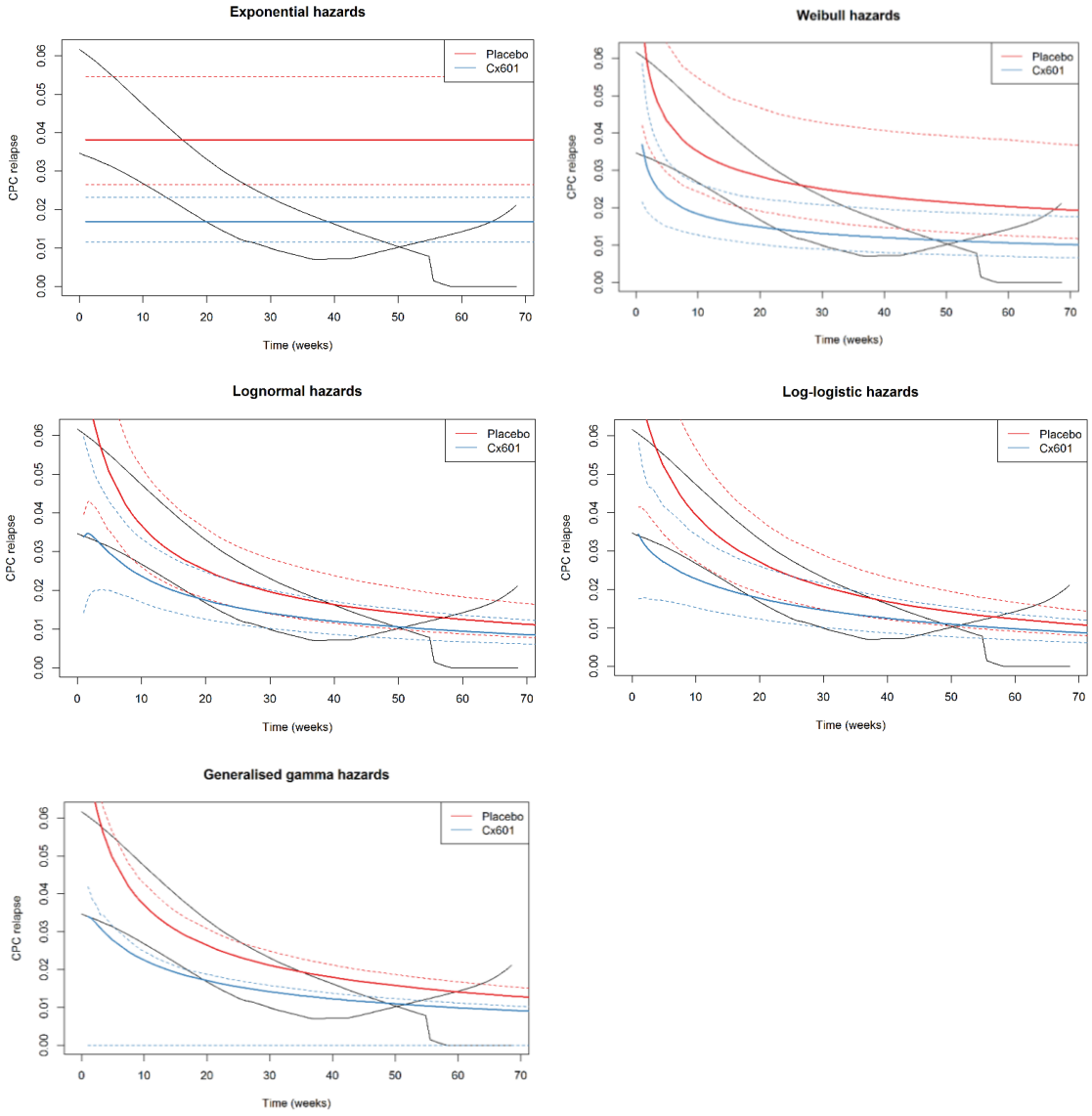


Abbreviations: CPC, Clinical and Patient Centred

Note: the black lines present the empirical hazards from the observed data.

Figure 14 presents the empirical hazard plot compared with the predicted hazards for the short-term relapse from CPC remission data based on the other parametric curves included in the model.

Figure 14: Empirical hazard plot vs. predicted hazards for CPC remission outcome (scenario analyses)

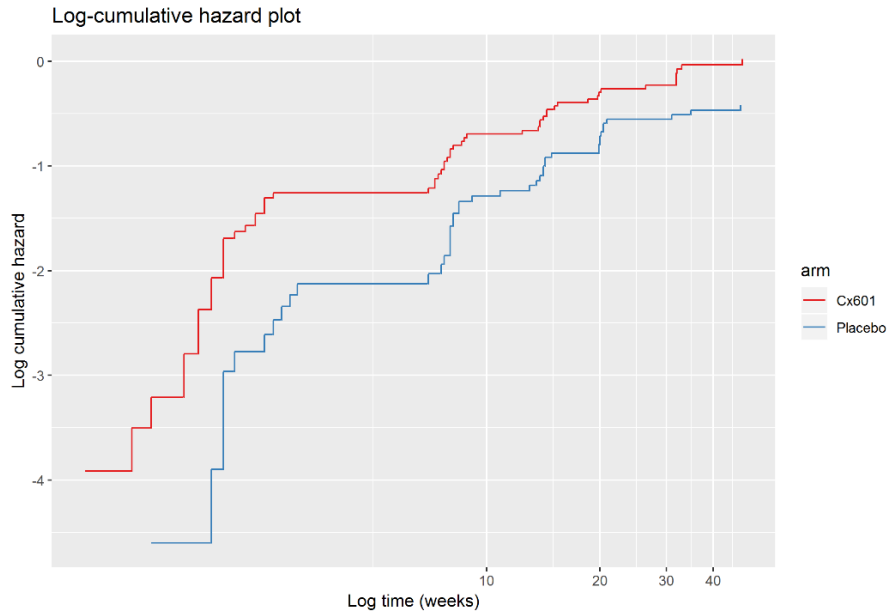


Abbreviations: CPC, Clinical and Patient Centred

Time to relapse from clinical remission

The LCHP and the Schoenfeld residuals plot are presented based on relapse from CPC remission data in Figure 15 and Figure 16, respectively. The LCHP indicate the proportional hazards assumption may not be relevant for this outcome.

Figure 15 Log-cumulative hazard plot (LCHP) for relapse from clinical remission data



Abbreviations: LCHP, log-cumulative hazards plot

Figure 16 Schoenfeld residuals plot for relapse from clinical remission data

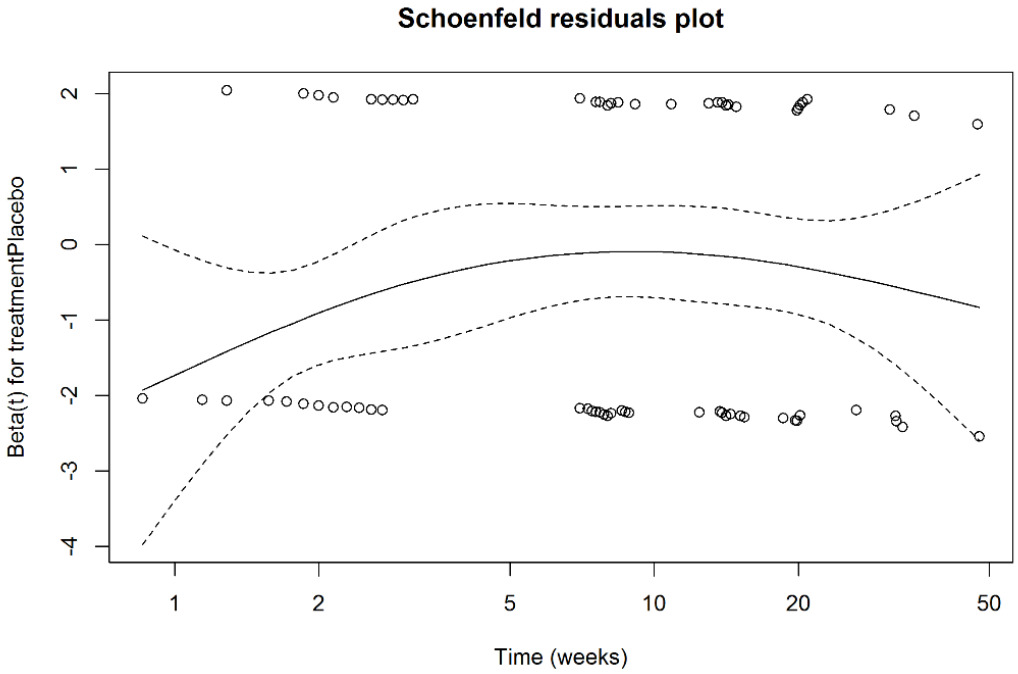
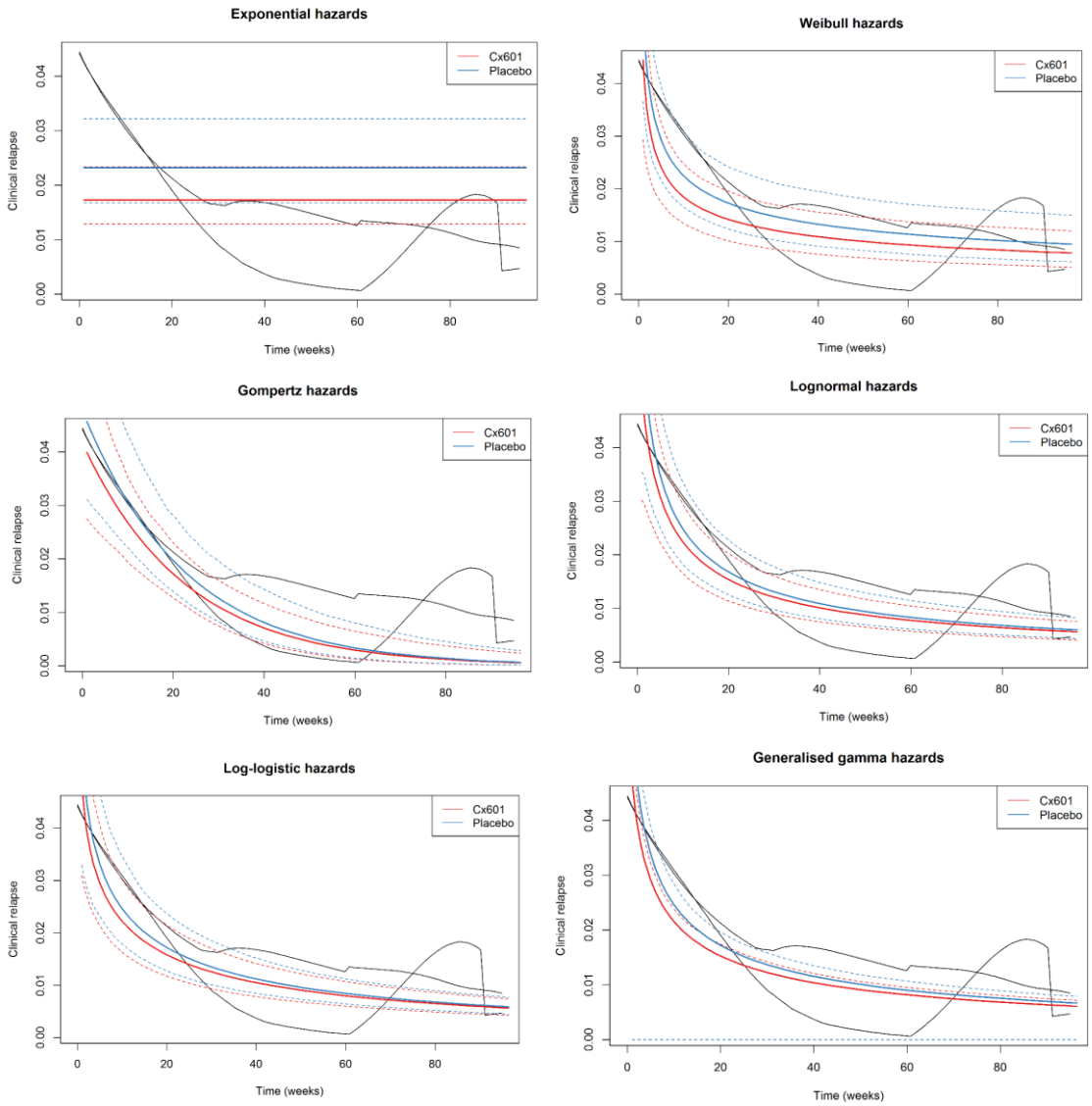


Figure 17 presents the shape of the predicted hazards vs. the observed hazards for all parametric curves

Figure 17: Empirical hazard plot vs. predicted hazards for relapse from clinical remission outcome (scenario analyses)



Time to relapse from CPC and MRI or combined remission

Time to relapse from CPC + MRI or combined remission could not be calculated, due to the limited time points that combined remission was reported in the ADMIRE-CD trial. Therefore, the time to relapse from CPC remission and clinical remission, respectively were used as proxies.

The response to B4 provides the rationale for the long-term relapse assumptions and the response to B6 provides the relevant hazard information associated with the time to permanent stoma data used to estimate the probability of defunctioning surgery.

B4. Section B.3.3.2.4 of the CS [pages 87 to 89] describes the approach to modelling long-term relapse and states that it is assumed that patients have constant rate of relapse beyond 2 years based on the average relapse rate for the chosen curve between 2 and 3 years. Please clarify the following:

- What is the rationale behind the change in the relapse rates after two years? What is the clinical relevance of constant hazards for relapse after two years after remission and not before? In addition, what data supports this change in the hazards over time?

- When deciding on the appropriate form of long-term extrapolation, why were only the Gompertz and Log-normal parametric models presented to the experts [CS, page 88] instead of all possible candidate curves?

- The clinical plausibility of the hazard function for all fitted curves?

Response: Data were available for time to CPC relapse from the ADMIRE-CD trial up to 2-years; see Figure 12 of the CS. The Gompertz curve provided the best fit to the observed data, based on the AIC and BIC statistics; see Table 38 of the CS.

Feedback from 10 clinical experts indicated that the risk of relapse for patients who have been in remission a long time would decrease, aligning with the Gompertz hazard function. However, clinicians stated that in clinical practice you would not expect the risk of relapse to reduce to zero, as predicted by the Gompertz hazard function. Instead, it would be expected that a small constant probability of relapse would be relevant to each patient throughout their lifetime. Therefore, the best fit curve to the observed data was used up to 2-years (where the observed data ends), and then clinician feedback informed the estimation of a constant annual rate of relapse applied for the duration of the model time horizon. There exists no long-term data on the risk of relapse in this population for validation. Therefore, these data were presented to clinicians (n=7) at an advisory board who agreed with the methods taken, and the resultant predicted risk of relapse modelled.

The consultants suggested a lifetime risk of relapse after 2 years to be 5% if patients had achieved radiological proven healing and 25% if patients had achieved clinically defined remission. The predicted lifetime risk of relapse for a patient who achieved relapse at 2 years using this modelling approach was later calculated to be 39.0%. This is a conservative method as applying the Gompertz distribution across the whole model time horizon or using the values suggested by clinicians would shift the results in favour of darvadstrocel.

Prior to presenting the parametric curves to clinical experts it was concluded to best reflect clinical practice the model should use the curve best fitting the observed data up to 2-years followed by a constant annual rate, based on the clinical rationale explained above. Given that in this scenario, we were only interested in the fit to the observed data, the Gompertz and the log-normal curves were selected as the two curves providing the best fit to these observed data based on the AIC and BIC statistics. Other parametric curves were not presented as these provided a worse fit to the observed data.

The response to question B3 provides detail associated with the hazard function for all the fitted curves for CPC relapse outcomes. The trial data provides information on these hazard functions up until 2-years, from which point we relied on clinical expert opinion due to lack of published long-term data. The shape of the predicted Gompertz hazards is shown to approximate the shape of the observed hazards across the trial time horizon, see Figure 8, indicating that the Gompertz provides a good statistical fit to the data.

B5. Given previous statements in the CS that darvadstrocel is better than control and the control is better than salvage therapy, please confirm if the data and headings are correct in table 44 [CS, page 90] (e.g. should the second column in table 44 instead be labelled salvage vs control)? Please also clarify where the HRs for darvostrocel vs. control have been taken from and resolve any discrepancies. For example, a simple text search suggests that the number 1.674 for scenario 1 does not appear anywhere else in the submission document B, whilst the number 1.474 appears in Table 69 which relates the generalised gamma not the Gompertz.

Response: The table was incorrectly labelled and inadvertently the incorrect hazard ratios were presented for time to CPC remission and time to clinical remission. The corrected table is presented below.

Table 21: Treatment effectiveness for darvadstrocel vs. control and control vs. salvage

Gompertz model HR	Time to remission		Time to relapse from remission	
	Darvadstrocel vs. Control	Salvage vs. control *	Darvadstrocel vs. Control	Salvage vs. control
Base case – CPC	2.121	0.600	0.571	1.00
Scenario 1 – Clinical	1.9295	0.600	0.874	1.00
Scenario 2 – CPC + MRI	0.922 * CPC	0.600	0.571**	1.00
Scenario 3 – Combined	0.896 * clinical	0.600	0.874**	1.00

Abbreviations: CPC, Clinical and patient-centred; HR, hazard ratio

Notes: * For salvage therapy, the time to remission rate was only applied to the first treatment. It is assumed that patients do not respond to re-treatment with salvage therapy

** Due to the lack of MRI data available for time to relapse from CPC + MRI remission and time to relapse from combined remission, the hazard ratio for time to CPC remission and clinical remission was applied, respectively

B6. The CS states that the probability of requiring a permanent defunctioning surgery was estimated using data in Mueller et al [World Journal of Gastroenterology, 21(5): 1394-1403]. :

- Please comment on the relevance of the Mueller study for estimating the risk of probability of requiring a permanent defunctioning surgery with particular reference to the comparability of current clinical practice to that used at the time of the Mueller study.
- Please provide: coefficents and covariance matrices for all fitted models, graphical plots of all parametric curves against the Kaplan-Meier curve, AIC and BIC for all of the curves fitted to this data.
- Please provide the clinical rational supporting the use of a constant hazard model.

- Please comment on the impact of using an exponential in the economic model, with reference to the previous two points

Response: There are limited data associated with permanent defunctioning surgery in patients with complex perianal fistulae available from the literature and this was not an outcome captured in the ADMIRE-CD clinical trial.

Although there is heterogeneity between the ADMIRE-CD trial and the Mueller study (Mueller 2007) in terms of population, the Mueller study provides informative Kaplan-Meier data on the time to permanent stoma in a population which approximates the ADMIRE-CD trial population. These data are available for 46 patients and provided up to 30-years, in a disease area where long-term data are not often available.

The application of these data within the economic model has been validated using expert advice from clinicians currently practicing in the UK. Feedback from these experts advised that patients will only transition to last resort surgery from the chronic symptomatic fistulae severe health state. Therefore, this is the only transition allowed in the model. Applying the probability of defunctioning from the Mueller study to this population results in an estimate of 39% requiring last resort surgery within the model, aligning with clinical expert opinion (25% of patients eligible for darvadstrocel are likely to require last resort defunctioning surgery). As defunctioning is commonly used in UK clinical practice as an intermediary step prior to proctectomy, comparison to last resort surgery (defunctioning or proctectomy) was felt to be a more robust test of validity.

Therefore, we believe that the data presented in the Mueller paper is of relevance to our decision problem and addresses an important data gap associated with defunctioning surgery in the perianal fistulae in CD population.

In response to this clarification question, six parametric distributions (exponential, Weibull, Gompertz, generalised gamma, log-normal and log-logistic) have been fit to the digitised Kaplan-Meier data for the complex perianal fistulae in CD population from the Mueller study. Note in the CS only the exponential distribution was fit to these data based on the assumption of a constant hazard rate associated with the probability of requiring defunctioning surgery. This was an assumption required for simplification of the model structure, but one which is explored in more detail in this response.

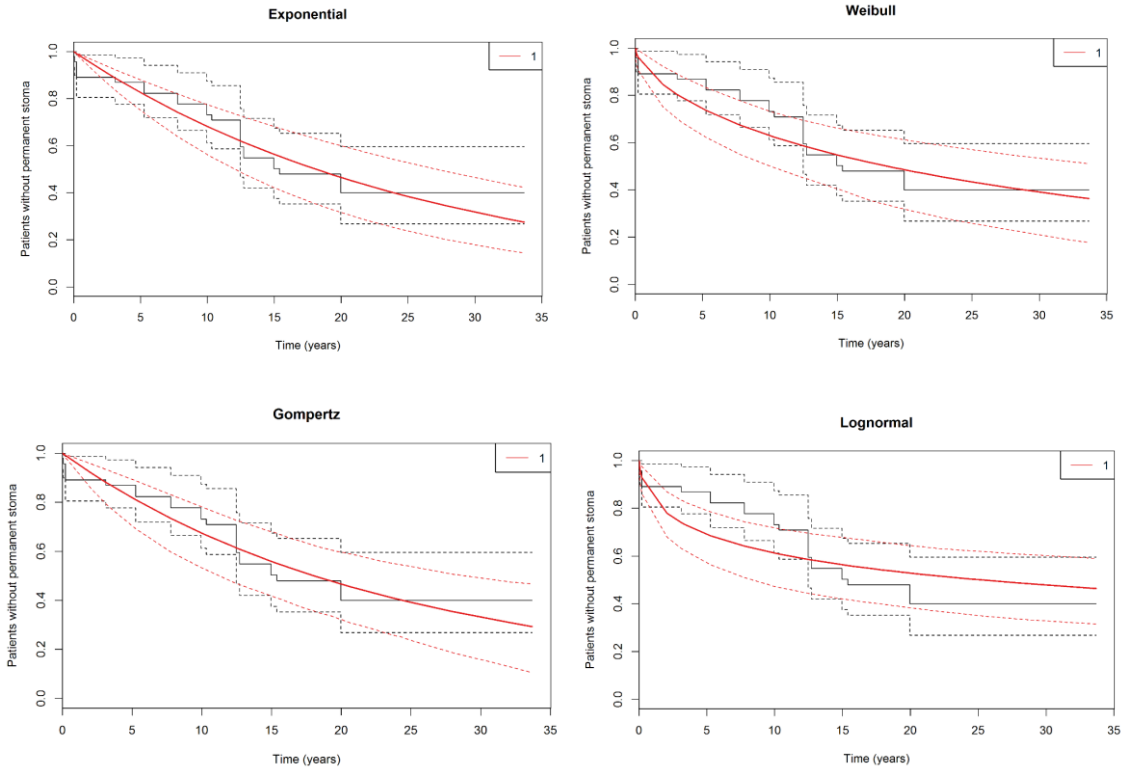
Table 22: Goodness of fit measures, parametric models for time to permanent stoma presents the AIC and BIC values for each parametric survival distributions. The statistical goodness-of-fit indicates that the generalised gamma and Weibull provide the best fit to the observed data. All the models, except for the log-normal, are shown to fit the data reasonable well; the AIC values are less than 8 points between these models

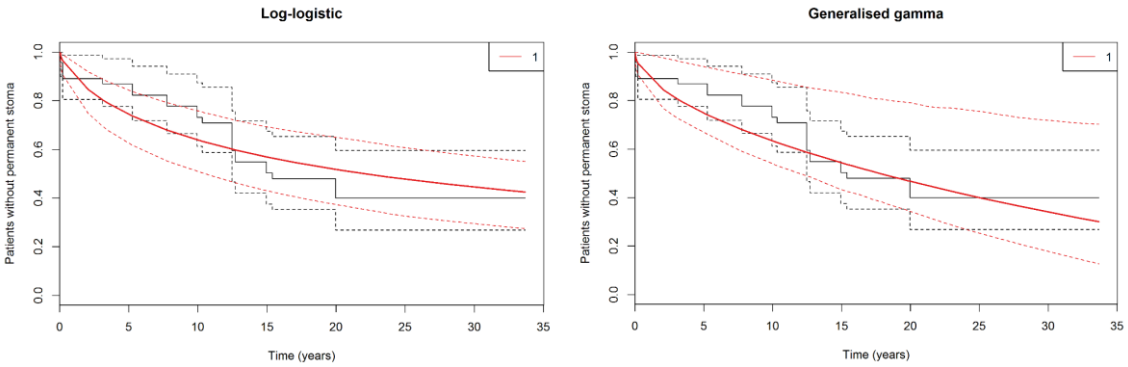
Table 22: Goodness of fit measures, parametric models for time to permanent stoma

Parametric model	AIC	BIC
Generalised gamma	209.5852	215.0711
Weibull	210.6724	214.3297
Log-logistic	214.5136	218.1709
Exponential	215.1842	217.0129
Gompertz	217.1266	220.7839
Lognormal	222.7323	226.3896
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.		

The digitised Kaplan-Meier curve and fitted parametric distributions are presented in Figure 18: Parametric models fit to time permanent stoma data. The visual inspection of the fitted curves suggests that the exponential and the Gompertz curves provide the best fit to the first 10-years of data.

Figure 18: Parametric models fit to time permanent stoma data





In the CS, it was assumed that the rate of defunctioning surgery could be predicted using a constant probability derived from the exponential distribution. This assumption enabled us to maintain a simple model structure without the need for tunnel states accounting for differential probability of defunctioning surgery based on time spent in the chronic symptomatic fistulae health state. The assumption was validated based on the visual inspection of the exponential curve fit to the digitised Kaplan-Meier data, shown in Figure 3

Full parametric analysis, presented in this response, indicates that the exponential is also a reasonable fit to these data relative to other parametric curve choices (less than six points between the AIC-ranked top four curves). Therefore, the statistical validity of the exponential curve is validated.

Furthermore, it was considered in the absence of more robust data a constant probability of defunctioning surgery was a conservative assumption as in clinical practice it may be expected that the longer you spend in the chronic symptomatic fistulae health state the higher the probability of requiring defunctioning surgery. Modelling an increasing risk would favour darvadstrocel as patients treated with darvadstrocel spend relatively less time in the chronic symptomatic fistulae health state compared with the control arm

B7. The CS presents base-case analyses using a non-reference case scenario with 1.5% discounting for benefits and 3.5% discounting for costs [CS, page 119, Table 64]. The justification given in the CS [pages 59 and 74] states/suggests to be that darvadstrocel is given with curative intent and that "darvadstrocel demonstrates long term healing potential in this population with a significant impact on QoL."[CS, page 74] The NICE methods guide (2013) states in section 6.2.19 that a discount rate of 1.5% for both cost and benefits may be considered by the Appraisal Committee "In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years)".

- Please provide evidence to support the fact that patients achieve near full health that is sustained over a very long period with particular reference to the lifetime probability of relapse of fistula disease and the impact of luminal disease on quality of life.

As it is the Appraisal Committee who decides whether or not the criteria in section 6.2.19 of the methods guide have been met, please provide all base-case and scenario analyses using: a) 3.5% discounting for BOTH costs and QALY as per the

NICE reference case and; b) 1.5% discounting for BOTH costs and QALYs as per section 6.2.19 of the NICE methods guide (2013).

Response: As stated in the CS, "darvadstrocel demonstrates long term healing potential in this population with a significant impact on QoL. Darvadstrocel is an important and much needed intervention in the treatment of complex perianal fistula(e) in patients with CD, a disease that has a high unmet need. Additionally, the disease complex perianal fistula(e) often affects young people and has with a median age of onset of 15-30 years, and so the benefit of an effective treatment in this young population is likely to provide long term health benefits (>30 years) and that would be life-changing. As darvadstrocel is administered as a single course of treatment and complex perianal fistula(e) is an orphan disease this is unlikely to commit the NHS to significant irrecoverable costs."

With respect to the long term relapse rate of fistula disease, >60% of patients treated with darvadstrocel maintain remission for 40 years in the base case analysis which represents a significant benefit.

The vignettes eliciting utility values, described within the CS, take account of the baseline luminal disease in the initial description of Crohn's disease. However, darvadstrocel is not considered as a treatment for luminal disease, nor is it expected to impact the course of the disease. Therefore, the impact of evolving luminal disease on quality of life across the model time horizon is not captured. This is considered an unrelated morbidity outside the scope of this appraisal. The elicited utilities do reflect the impact of treatment with darvadstrocel in the population of interest.

As requested, the results are presented using both 3.5% discount for costs and effects and 1.5% for costs and effects.

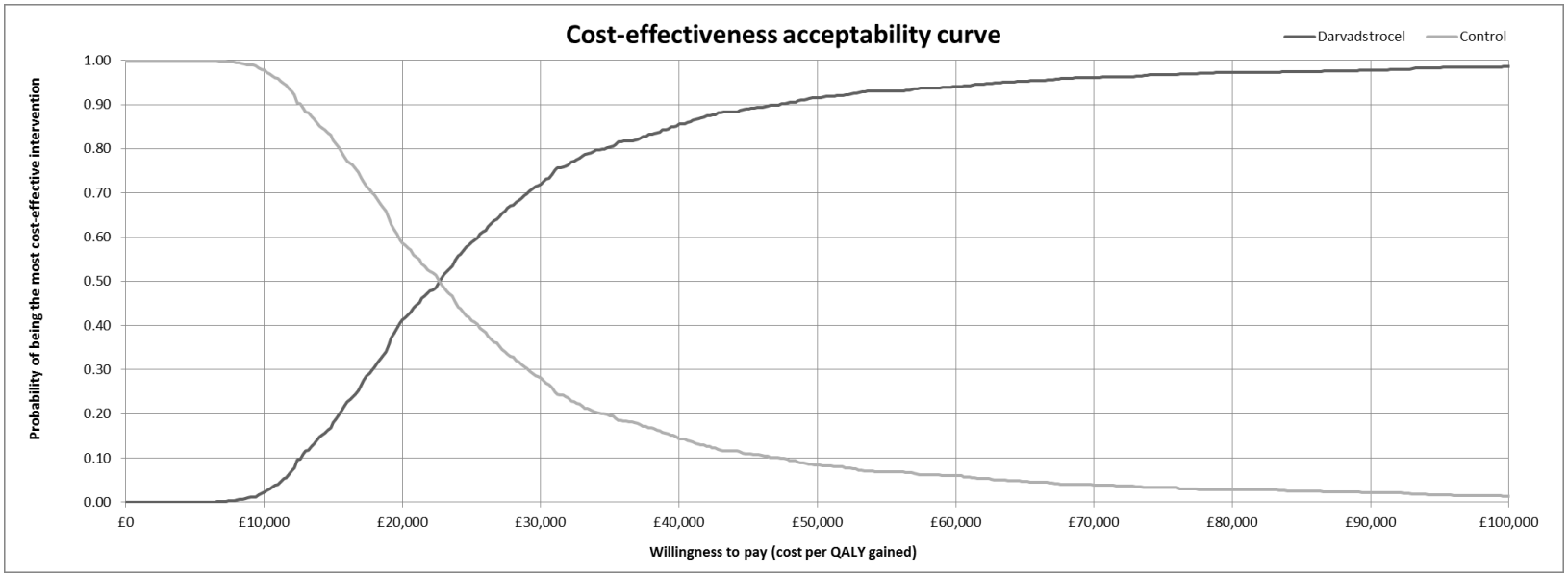
Results using 3.5% discount for costs and effects

Table 23: Base-case results, 3.5% discount for costs and effects

Treatment	Total costs (£) With PAS applied	Total LYG	Total QALYs	Incr cost with PAS applied	Incr LYG	ICER (cost / LYG)	Incr QALYs	ICER (cost / QALY)
Control	[redacted]	36.65	[redacted]					
Darvadstrocel	[redacted]	36.65	[redacted]	21,639	0.00	N/A	1.05	20,591

Abbreviations: ICER, incremental cost-effectiveness ratio; incr, Incremental; LYG, life years gained; N/A, Not applicable; QALYs, quality-adjusted life years.

Figure 19: Cost-effectiveness acceptability curve, probabilistic base case

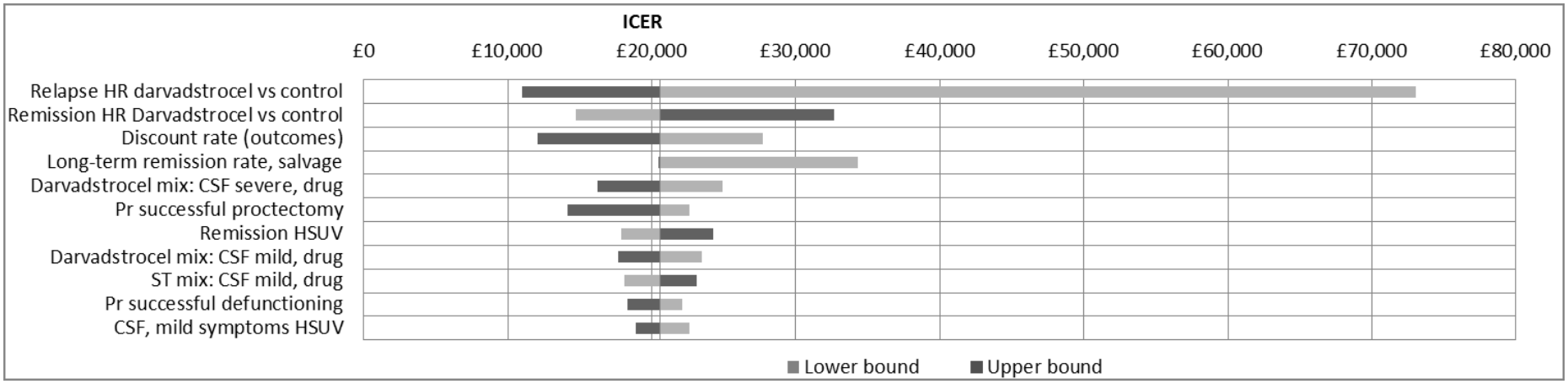


Abbreviations: QALY, quality-adjusted life year.

Table 24: Probabilistic results

Treatment	Costs Mean	QALY Mean	Incremental cost, mean (95% CrI)	Incremental QALY mean (95% CrI)	Probabilistic ICER	Probability cost effective at £20,000	Probability cost effective at £30,000
Control	[redacted]	[redacted]					
darvadstrocel	[redacted]	[redacted]	21,811 (18,423, 24,394)	1.01 (0.29, 1.90)	21,685	0.41	0.72
Abbreviations: QALYs, quality-adjusted life years; CrI, Credible interval							

Figure 20: One-way sensitivity analysis tornado plot, ICER



Abbreviations: CSF, chronic symptomatic fistulae; HR, hazard ratio; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; Pr, probability

Table 25: Parametric and structural scenario analysis results

Scenario description	Total costs			Total QALYs			ICER
	Darvadstrocel	Control	Difference	Darvadstrocel	Control	Difference	
Base case, 3.5% discount for costs and QALYs	[redacted]	[redacted]	21,639	[redacted]	[redacted]	1.05	20,591
0% discount rate for costs and QALYs	[redacted]	[redacted]	20,400	[redacted]	[redacted]	1.79	11,380
6% discount rate for costs and QALYs	[redacted]	[redacted]	22,233	[redacted]	[redacted]	0.78	28,438
10% annual proctectomy probability post defunctioning	[redacted]	[redacted]	22,024	[redacted]	[redacted]	1.04	21,124
50% annual stoma reversal probability from successful defunctioning state	[redacted]	[redacted]	21,186	[redacted]	[redacted]	1.04	20,312
Upper bound of annual stoma care costs (£2,682 per year)	[redacted]	[redacted]	20,944	[redacted]	[redacted]	1.05	19,930
Infusion costs halved (£142.25)	[redacted]	[redacted]	21,514	[redacted]	[redacted]	1.05	20,472
HSUVs based on CD patients vignette study set	[redacted]	[redacted]	21,639	[redacted]	[redacted]	0.98	22,095
Relapse HR for salvage therapy vs. control equal to 1.20	[redacted]	[redacted]	21,566	[redacted]	[redacted]	1.07	20,131
Time horizon: 20 years	[redacted]	[redacted]	21,846	[redacted]	[redacted]	0.78	28,181
Time horizon: 60 years	[redacted]	[redacted]	21,706	[redacted]	[redacted]	1.10	19,719
No inclusion of Biologic usage within salvage therapy (all other assumptions as per base case)	[redacted]	[redacted]	17,557	[redacted]	[redacted]	1.05	16,707
Wastage assumed to result in 5% additional cost for darvadstrocel	[redacted]	[redacted]	22,889	[redacted]	[redacted]	1.05	21,781

Abbreviations: CD, Crohn's disease; HR, hazard ratio; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 26: Scenario analysis results, alternative parametric modelling

Remission curve	Relapse curve	Total costs			Total QALYs			ICER
		Darvadstrocel	Control	Difference	Darvadstrocel	Control	Difference	
Gompertz (base case)	**Gompertz (base case)**	[redacted]	[redacted]	21,639	[redacted]	[redacted]	1.05	20,591
Generalised gamma	**Gompertz (base case)**	[redacted]	[redacted]	22,653	[redacted]	[redacted]	0.75	30,064
Gompertz (base case)	**Log-normal**	[redacted]	[redacted]	24,740	[redacted]	[redacted]	0.24	104,398
Generalised gamma	**Log-normal**	[redacted]	[redacted]	24,754	[redacted]	[redacted]	0.19	133,311
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.								

Table 27: Scenario analysis results, alternative outcome definitions for remission

	Total costs			Total QALYs			ICER
	Darvadstrocel	Control	Difference	Darvadstrocel	Control	Difference	
Base case: CPC remission	[redacted]	[redacted]	21,639	[redacted]	[redacted]	1.05	20,591
Scenario 1: Clinical remission	[redacted]	[redacted]	23,343	[redacted]	[redacted]	0.68	34,177
Scenario 2: CPC + MRI remission	[redacted]	[redacted]	21,755	[redacted]	[redacted]	1.01	21,446
Scenario 3: Combined remission	[redacted]	[redacted]	23,367	[redacted]	[redacted]	0.68	34,295
Abbreviations: CPC, Clinical and patient-centred; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year							

Table 28: Scenario analysis results, using St Mark's retrospective data analysis inputs

Scenario	Total costs			Total QALYs			ICER
	Darvadstrocel	Control	Difference	Darvadstrocel	Control	Difference	
Base case	[redacted]	[redacted]	21,639	[redacted]	[redacted]	1.05	20,591
St Mark's retrospective data set	[redacted]	[redacted]	26,201	[redacted]	[redacted]	1.11	23,524
Abbreviations: ICER, incremental cost-effectiveness ratio.							

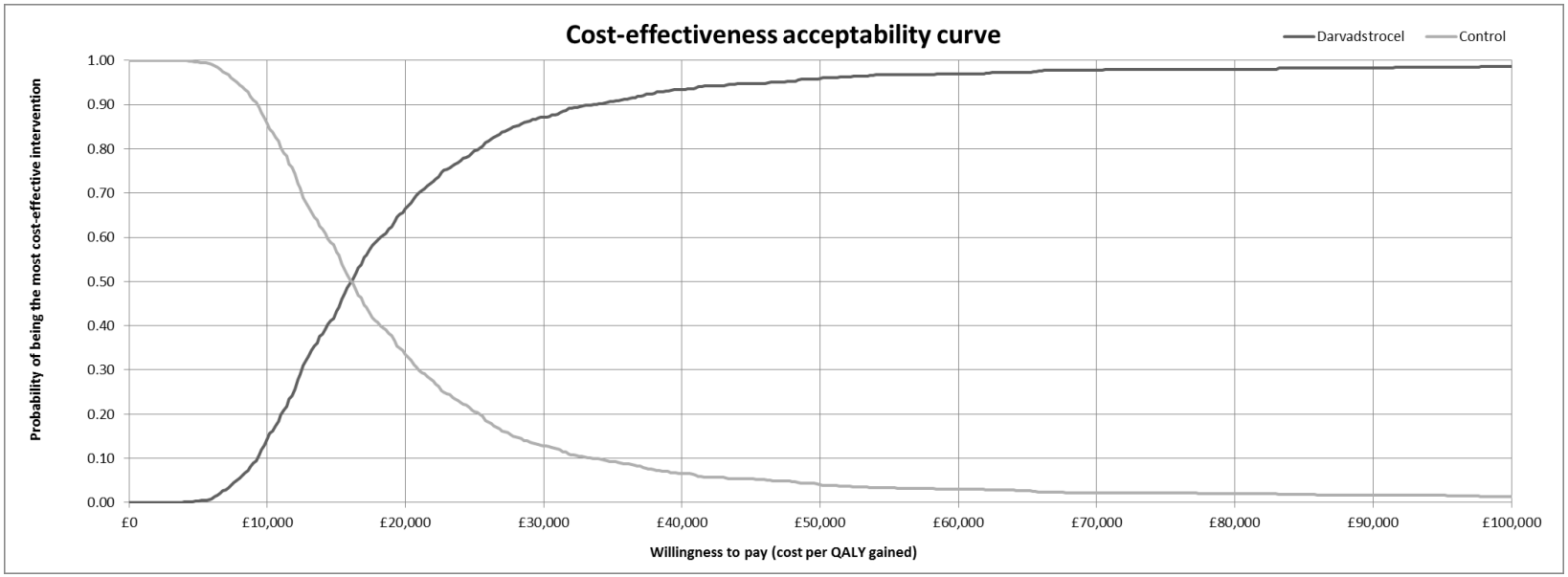
Results using 1.5% discount for costs and effects

Table 29: Base-case results, 1.5% discount for costs and QALYs

Treatment	Total costs (£) With PAS applied	Total LYG	Total QALYs	Incr cost with PAS applied	Incr LYG	ICER (cost / LYG)	Incr QALYs	ICER (cost / QALY)
Control	[redacted]	36.65	[redacted]					
Darvadstrocel	[redacted]	36.65	[redacted]	21,004	0.00	N/A	1.40	15,017

Abbreviations: ICER, incremental cost-effectiveness ratio; incr, Incremental; LYG, life years gained; N/A, Not applicable; QALYs, quality-adjusted life years.

Figure 21: Cost-effectiveness acceptability curve, probabilistic base case

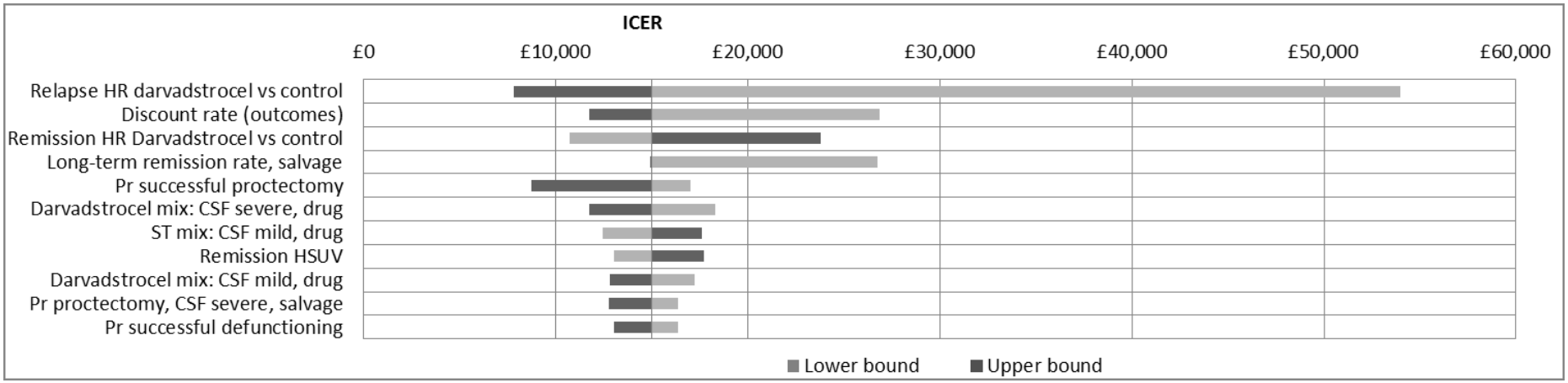


Abbreviations: QALY, quality-adjusted life year

Table 30: Probabilistic results

Treatment	Costs Mean	QALY Mean	Incremental cost, mean (95% CrI)	Incremental QALY mean (95% CrI)	Probabilistic ICER	Probability cost effective at £20,000	Probability cost effective at £30,000
Control	[redacted]	[redacted]					
Darvadstrocel	[redacted]	[redacted]	21,161 (16,533, 24,335)	1.35 (0.37, 2.53)	15,649	0.66	0.87
Abbreviations: QALYs, quality-adjusted life years; CrI, Credible interval							

Figure 22: One-way sensitivity analysis tornado plot, ICER



Abbreviations: CSF, chronic symptomatic fistulae; HR, hazard ratio; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; Pr, probability

Table 31: Parametric and structural scenario analysis results

Scenario description	Total costs			Total QALYs			ICER
	Darvadstrocel	Control	Difference	Darvadstrocel	Control	Difference	
Base case	[redacted]	[redacted]	21,004	[redacted]	[redacted]	1.40	15,017
10% annual proctectomy probability post defunctioning	[redacted]	[redacted]	21,625	[redacted]	[redacted]	1.39	15,603
50% annual stoma reversal probability from successful defunctioning state	[redacted]	[redacted]	20,313	[redacted]	[redacted]	1.39	14,651
Upper bound of annual stoma care costs (£2,682 per year)	[redacted]	[redacted]	19,972	[redacted]	[redacted]	1.40	14,280
Infusion costs halved (£142.25)	[redacted]	[redacted]	20,809	[redacted]	[redacted]	1.40	14,878
HSUVs based on CD patients vignette study set	[redacted]	[redacted]	21,004	[redacted]	[redacted]	1.31	16,057
Relapse HR for salvage therapy vs. control equal to 1.20	[redacted]	[redacted]	20,922	[redacted]	[redacted]	1.43	14,676
Time horizon: 20 years	[redacted]	[redacted]	21,323	[redacted]	[redacted]	0.92	23,191
Time horizon: 60 years	[redacted]	[redacted]	21,172	[redacted]	[redacted]	1.52	13,926
No inclusion of Biologic usage within salvage therapy (all other assumptions as per base case)	[redacted]	[redacted]	15,297	[redacted]	[redacted]	1.40	10,937
Wastage assumed to result in 5% additional cost for darvadstrocel	[redacted]	[redacted]	22,254	[redacted]	[redacted]	1.40	15,911

Abbreviations: CD, Crohn's disease; HR, hazard ratio; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 32: Scenario analysis results, alternative parametric modelling

Remission curve	Relapse curve	Total costs			Total QALYs			ICER
		Darvadstrocel	Control	Difference	Darvadstrocel	Control	Difference	
Gompertz (base case)	**Gompertz (base case)**	[redacted]	[redacted]	21,004	[redacted]	[redacted]	1.40	15,017
Generalised gamma	**Gompertz (base case)**	[redacted]	[redacted]	22,316	[redacted]	[redacted]	0.99	22,432
Gompertz (base case)	**Log-normal**	[redacted]	[redacted]	24,952	[redacted]	[redacted]	0.25	99,339
Generalised gamma	**Log-normal**	[redacted]	[redacted]	24,924	[redacted]	[redacted]	0.20	123,732
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.								

Table 33: Scenario analysis results, alternative outcome definitions for remission

	Total costs			Total QALYs			ICER
	Darvadstrocel	Control	Difference	Darvadstrocel	Control	Difference	
Base case: CPC remission	[redacted]	[redacted]	21,004	[redacted]	[redacted]	1.40	15,017
Scenario 1: Clinical remission	[redacted]	[redacted]	23,550	[redacted]	[redacted]	0.81	29,061
Scenario 2: CPC + MRI remission	[redacted]	[redacted]	21,145	[redacted]	[redacted]	1.35	15,669
Scenario 3: Combined remission	[redacted]	[redacted]	23,597	[redacted]	[redacted]	0.80	29,359
Abbreviations: CPC, Clinical and patient-centred; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year							

Table 34: Scenario analysis results, using St Mark's retrospective data analysis inputs

Scenario	Total costs			Total QALYs			ICER
	Darvadstrocel	Control	Difference	Darvadstrocel	Control	Difference	
Base case	[redacted]	[redacted]	21,004	[redacted]	[redacted]	1.40	15,017
St Mark's retrospective data set	[redacted]	[redacted]	27,893	[redacted]	[redacted]	1.51	18,529
Abbreviations: ICER, incremental cost-effectiveness ratio.							

B8. Please clarify whether there is a clinical justification for the hazard of a CPC remission event being constant [CS, page 78] or if this was made simply as a modelling assumption.

Response: The paragraph in the CS on page 78 refers to the model conceptualisation phase. The exponential model was assumed *a priori* as a statistical model candidate. As the constant hazard event assumption was found to be inappropriate, a more complex economic model structure was required to describe the pattern of observed events of remission over time.

B9. On pages 79 and 84 of the CS it describes how the remission events are structurally absent in the model during the first 4 weeks after treatment and relapse events are structurally absent in the model during the first 4 weeks after remission. It then describes that the curve fittings for time to remission and time to relapse are offset by 4 weeks to improve the fit to the observed outcomes. Please clarify why the curves are offset by 4 weeks and not 6 weeks given that the outcomes assessments from treatment to 36 weeks occurred at 6 weekly intervals and not 4 weekly intervals. Please also clarify whether the mismatch between the timing of outcomes assessment in the study and the model cycle length will lead to any systematic bias in the model.

Response: As per the trial protocol, the first visit could occur in the first 6 ± 2 weeks. The minimum time to the first assessment was chosen as no events could occur (and none occurred) prior to 4 weeks, and thus the curves are offset by 4 weeks. This mismatch between the timings of outcomes assessment in the study and model cycle length will not lead to any systematic bias in the model, and was considered the most suitable approach.

B10. Please clarify and provide rationale for the assumption that perianal abscesses are resolved in an average of four weeks [CS, page 72]. Furthermore please clarify what uncertainty, if any, was placed around the four week resolution time.

Response: The four-week resolution time was a modelling decision deemed appropriate by the interviewed clinical experts. While it was mentioned that some events might take longer (i.e. 8 weeks), not including a longer time duration, and therefore the associated additional costs and quality of life decrements compared to 4-week events, is a conservative assumption as fewer events are expected with darvadstrocel than with the current standard of care.

B11. Please clarify why a 40 year time horizon [CS, Page 74] was selected for the base case, given that approximately 68% of the original model population are alive at this time point?

Response: Due to uncertainty in the extrapolations and in the long-term effectiveness of salvage therapy, a shorter 40-year time horizon was selected in the base case to limit the impact of the forecasts with scenarios exploring 20- and 60-year time horizons to present the range of potential ICERs.

The effects of treatment with darvadstrocel are expected to accumulate over time, with a lifetime horizon showing the full benefits in the patients' quality of life. Applying an annual discount of 1.5% to costs **and** QALYs results in an ICER of £15,017 across a 40-year time

horizon (base case). Time horizons of 20- and 60-years result in ICERs of £23,191 and £13,926 respectively.

B12. Please provide further information regarding what is meant by the following statement: The trial design focussed on an attempt to heal the fistula tract rather than control symptoms, as is the case in clinical practice. Therefore, no changes over time where observed in the ADMIRE-CD trial, but changes are observed in the model to reflect clinical practice." [CS, Page 71]

Response: In clinical practice, setons are often left in place for a long period of time in order to keep a fistula open and draining and to maintain patients in a more mild health state (i.e. CSF mild rather than CSF severe). This would result in movement between these two health states in clinical practice. The ADMIRE-CD trial was focussed on an attempt to heal the fistula tract, hence any setons placed during the preparation visit were removed. Despite the proportion of patients in CSF mild compared to CSF severe in the trial remaining fairly constant, the model shows a tendency towards the CSF mild health state. Although this is due to patients transitioning from the CSF severe health state to last resort surgery, this was also felt to better represent clinical practice.

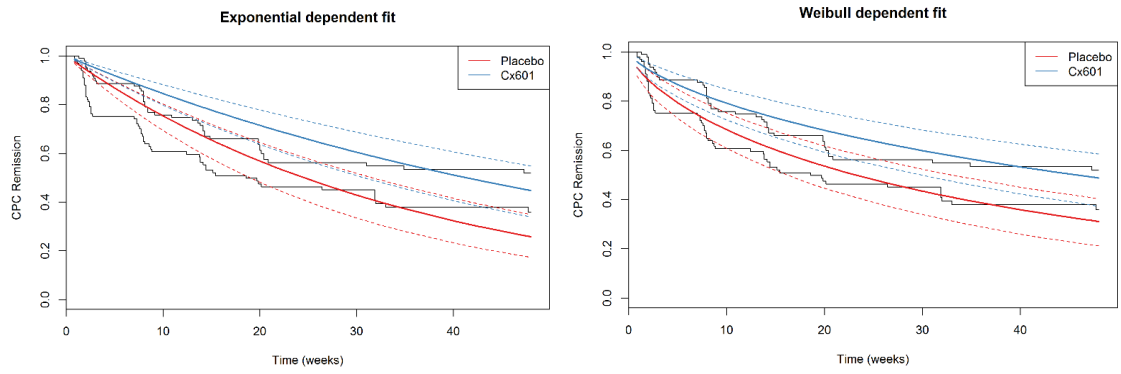
B13. For completeness, please provide all of the candidate parametric curves fitted for Figures 19, 20, 21, and 22 (i.e. those in Table 32, Table 35, Table 38, and Table 41). [CS, pages 81-82, 84-85, 86-87]

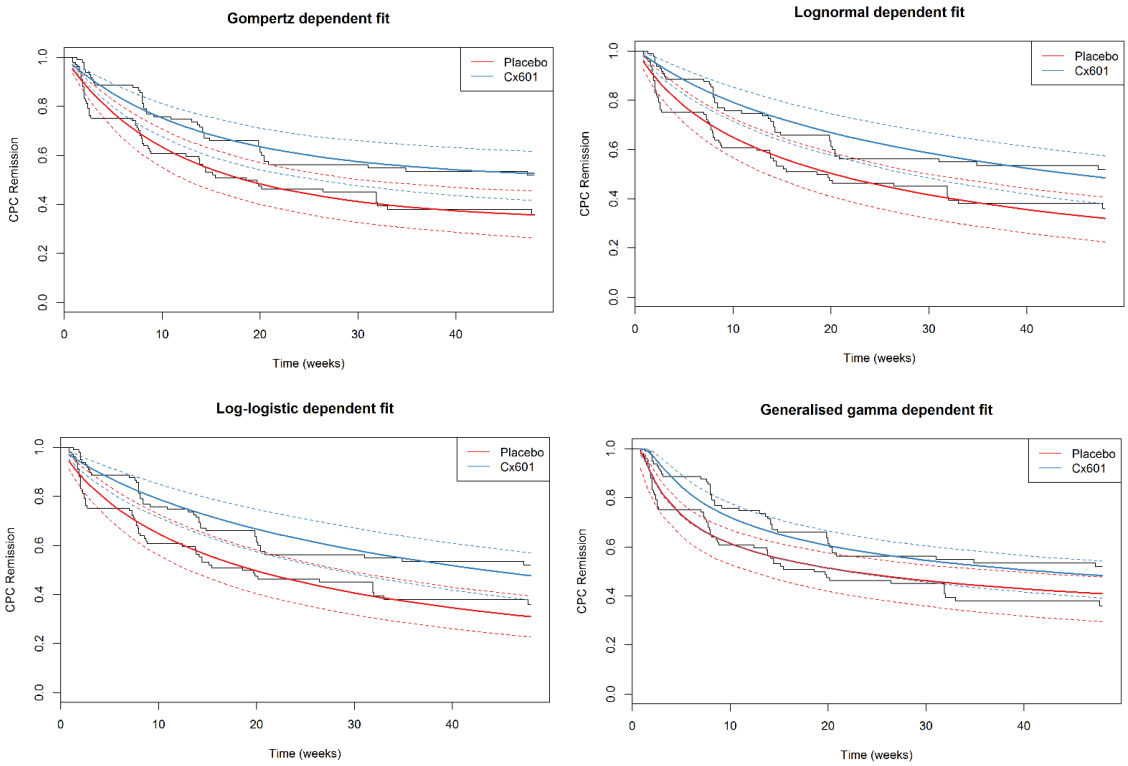
Response:

Time to CPC remission

The candidate parametric curves fit for Figure 19 and Table 32 from the CS are presented in Figure 23.

Figure 23: Parametric curves fit to the CPC remission data



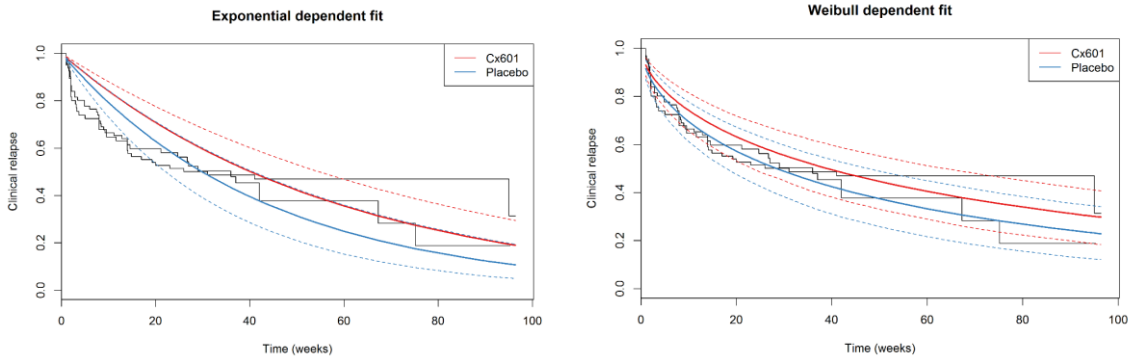


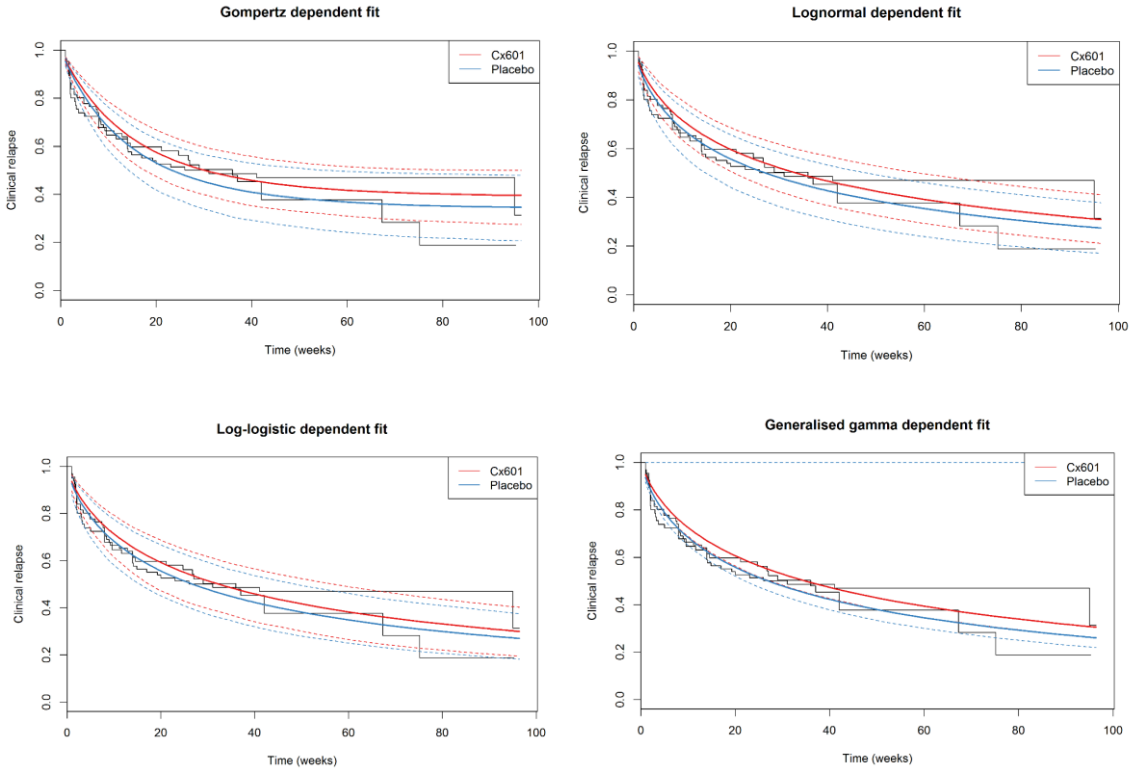
Abbreviations: CPC, Clinical and Patient Centred

Time to clinical remission

The candidate parametric curves fit for Figure 20 and Table 35 from the CS are presented in Figure 24:.

Figure 24: Parametric curves fit to clinical remission data

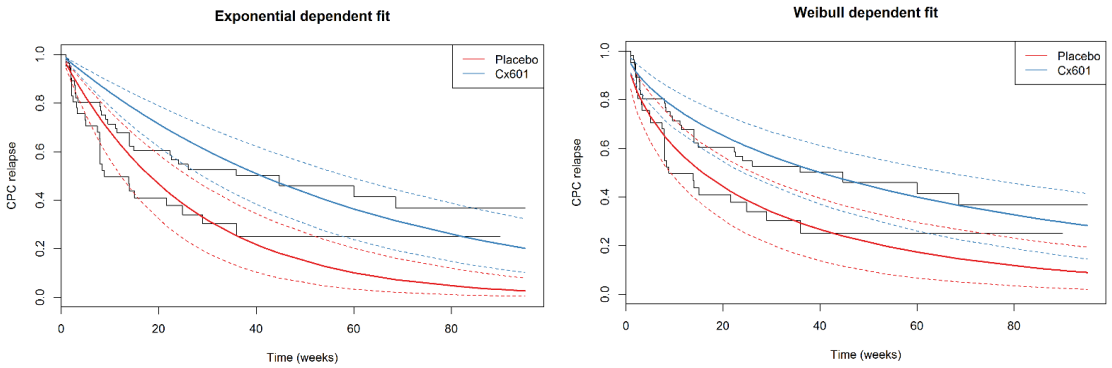


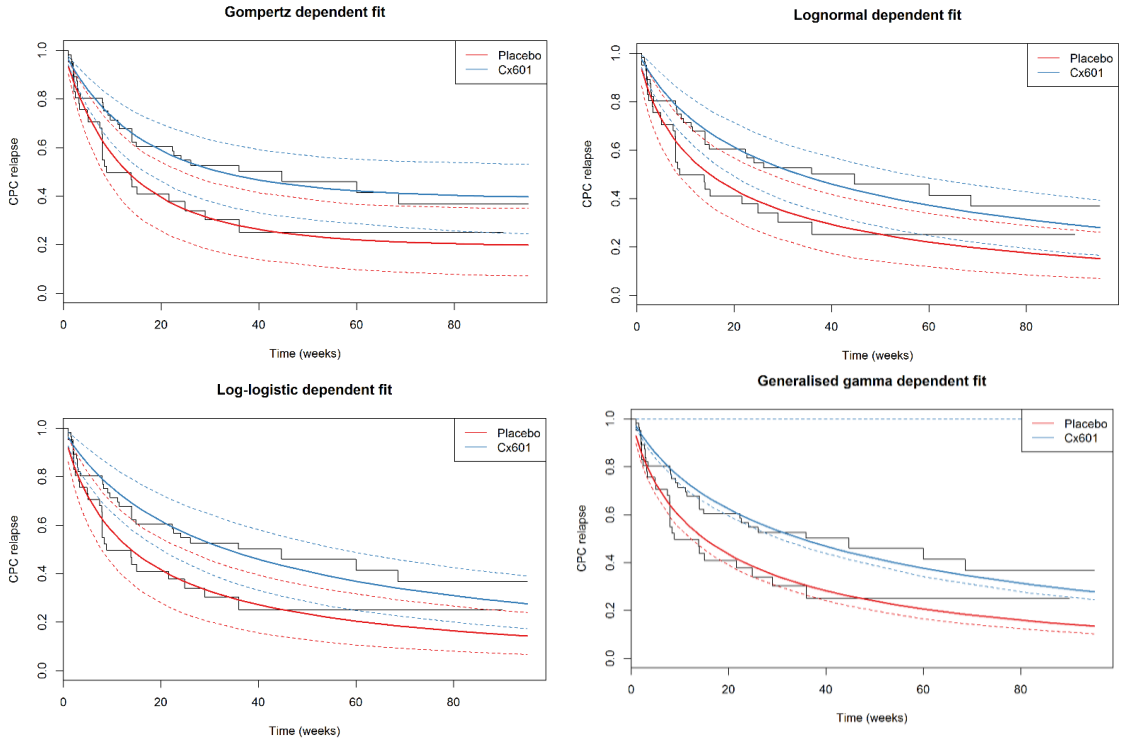


Time to relapse from CPC remission

The candidate parametric curves fit for Figure 21 and Table 38 from the CS are presented in Figure 25.

Figure 25: Parametric curves fit to relapse from CPC remission data



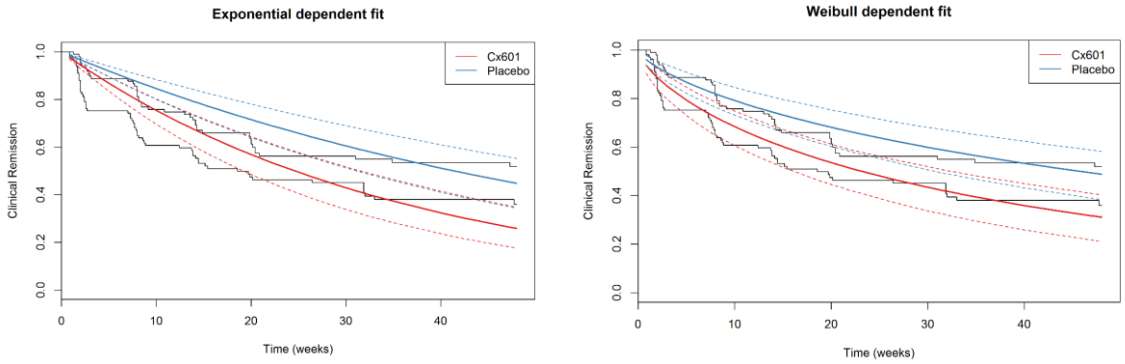


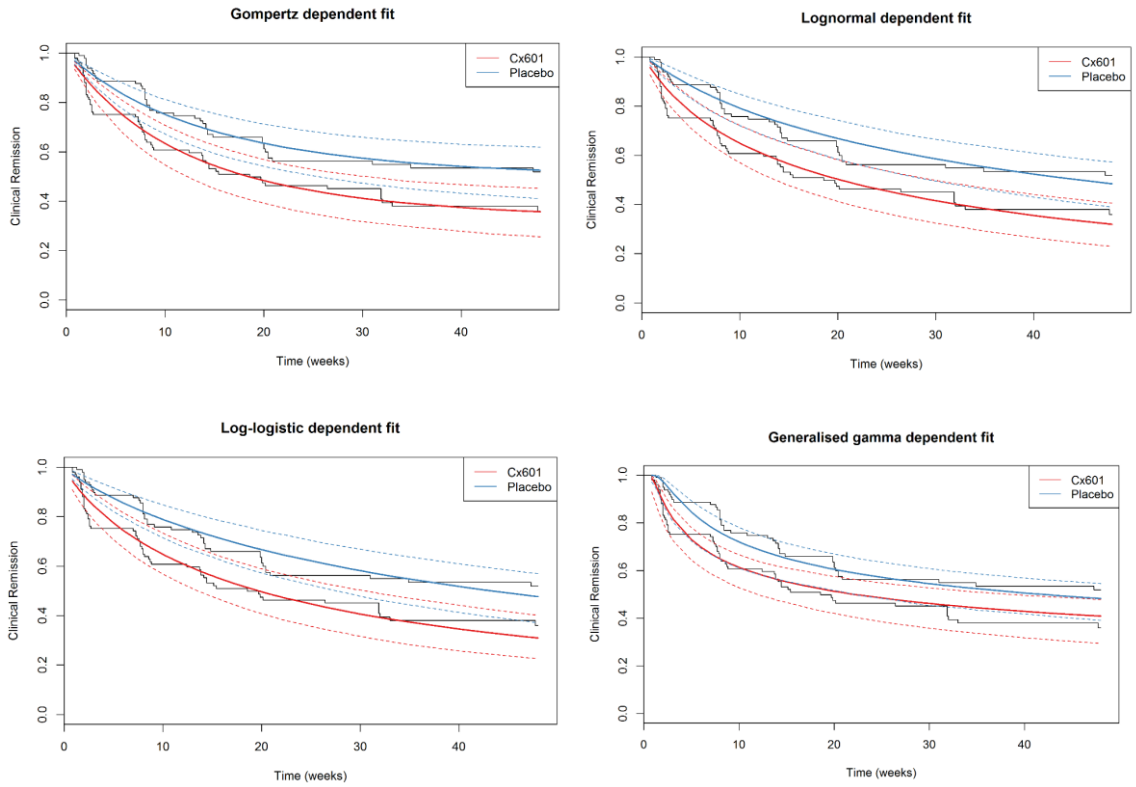
Abbreviations: CPC, Clinical and Patient Centred

Time to relapse from clinical remission

The candidate parametric curves fit for Figure 22 and Table 41 from the CS are presented in Figure 26:.

Figure 26: Parametric curves fit to relapse from clinical remission data



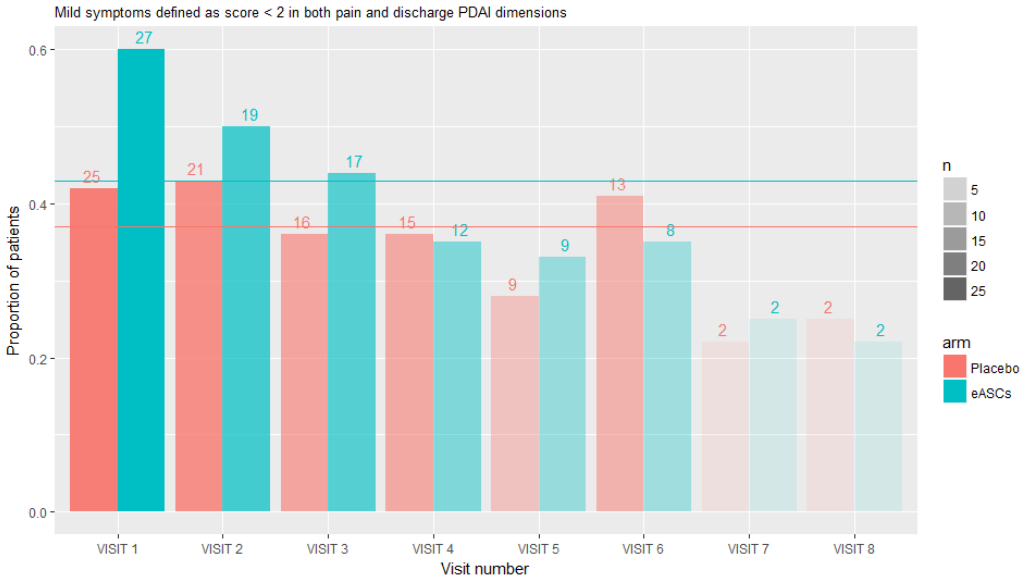


B14. Please clarify, what evidence is available to support the assertion that “a simple average across all observations, irrespective of visit time and characteristics of the disease trajectory such as previous relapses, was a reasonable approach …” [CS, page 70] to estimate the proportion of mild and severe active chronic symptomatic fistula? Furthermore, please clarify the clinical rationale for the proportion of mild and severe chronic symptomatic fistulae being constant over time

Response:

Figure 27: Proportion of CSF patients with mild symptoms at each visit by treatment armpresents the proportion of CSF patients with mild symptoms at each visit by treatment arm. A weak trend to a greater severe proportion seems to be present in the trial data however; patients in the CSF health state of the model would have a mix of different times since initiation of therapy. It is therefore deemed reasonable that an approximate equilibrium around the average over the re-treatment period timeframe would be achieved. Furthermore, the assumption of non-worsening disease severity over time is conservative, as patients treated with darvadstrocel spend less time in the CSF health state. Modelling a decreasing trend in symptoms would therefore increase the QALY difference between darvadstrocel and control. As discussed in B12, an increasing proportion of patients in the model are in the CSF mild vs the CSF severe health state which was felt to better represent the palliative nature of salvage therapy in clinical practice.

Figure 27: Proportion of CSF patients with mild symptoms at each visit by treatment arm



B15. Please clarify the clinical rationale behind the following scenario analysis. “A scenario of interest was the exclusion of biologic usage within salvage therapy and keeping all other assumptions as per the base case. Biologics are used to treat luminal CD which is out of scope for this appraisal.” [CS, Page 126]

Response: During consultations with clinical experts, it was difficult to determine the amount of biologic usage for fistulising disease as opposed to that used to treat luminal disease. As darvadstrocel is not indicated for the treatment of luminal disease, the potential inclusion of biologic usage for this condition could affect the resulting ICER and a scenario excluding biologic usage was therefore included to explore this.

B16. Salvage therapy. The CS suggests that the hazard ratio of salvage therapy was elicited from clinical experts [CS, Pages 79-80, 89]. Please clarify the following points:

- Was a formal elicitation process followed to estimate this parameter?
- Why an elicitation protocol was not presented in the CS?
- Please clarify the scale on which the coefficient of variation is assumed and provide the mean and standard error. Please repeat the analyses with assumed coefficient of variations of 0.30 and 0.60
- Please clarify whether there is any reason to believe that the hazard for salvage therapy is truly proportional to the hazard for control

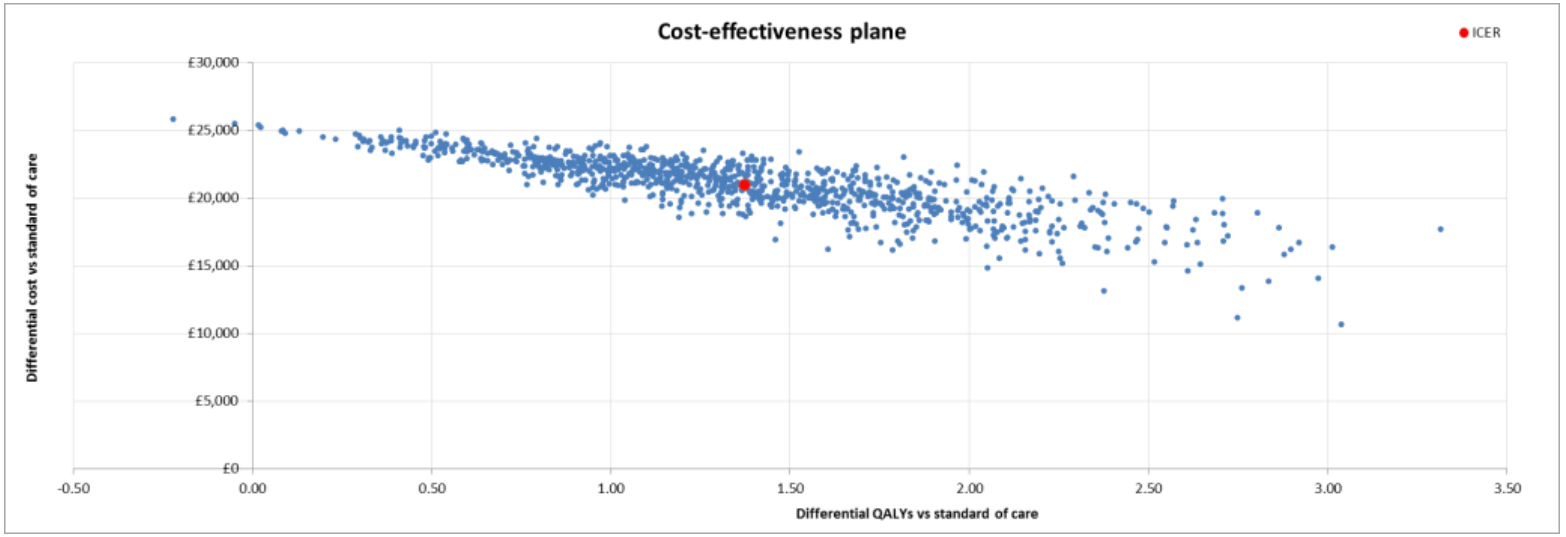
Response: A formal elicitation process was not followed. Six clinical experts from across the European Union, including three from the UK, were presented with alternative scenarios representing the effectiveness of salvage therapy relative to control and were asked to identify the scenario best reflecting their clinical experience.

The PSA has been rerun for 1000 simulations (based on the assumption of a 1.5% discount rate applied to costs **and** QALYs) with assumed coefficient of variations of 0.30 and 0.60. As can be noted from the table and graphs below, changing the coefficient of variation did not result in substantive differences as compared with the base case results presented under Question B.12.

The hazard for salvage therapy being proportional to the hazard for control was an assumption which was validated by clinical experts in Europe and the UK. This assumption was originally based on the fact that both control and salvage therapy broadly consisted of the same interventions, those being EUA +/- seton placement with background therapy consisting of antibiotics, immunosuppressants and biologic therapy.

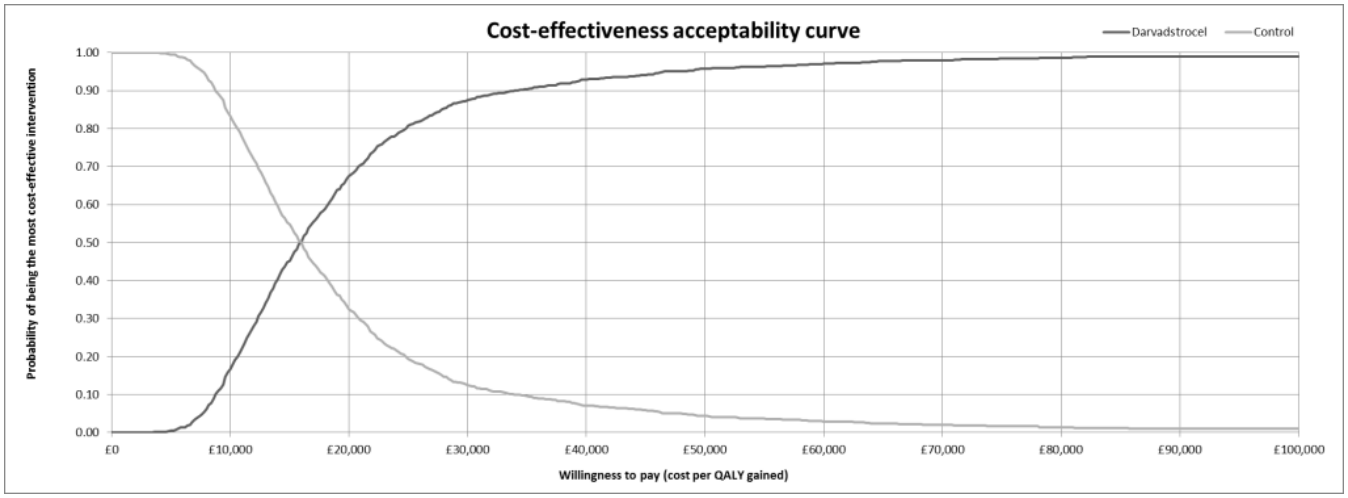
1.5% discount cost/efficacy; 0.30 coefficient of variance for HR salvage vs. control

Figure 28: Cost-effectiveness plane, coefficient of variance 0.30 for HR salvage therapy



Abbreviations: HR, Hazard ratio

Figure 29: Cost-effectiveness acceptability curve, coefficient of variance 0.30 for HR salvage therapy



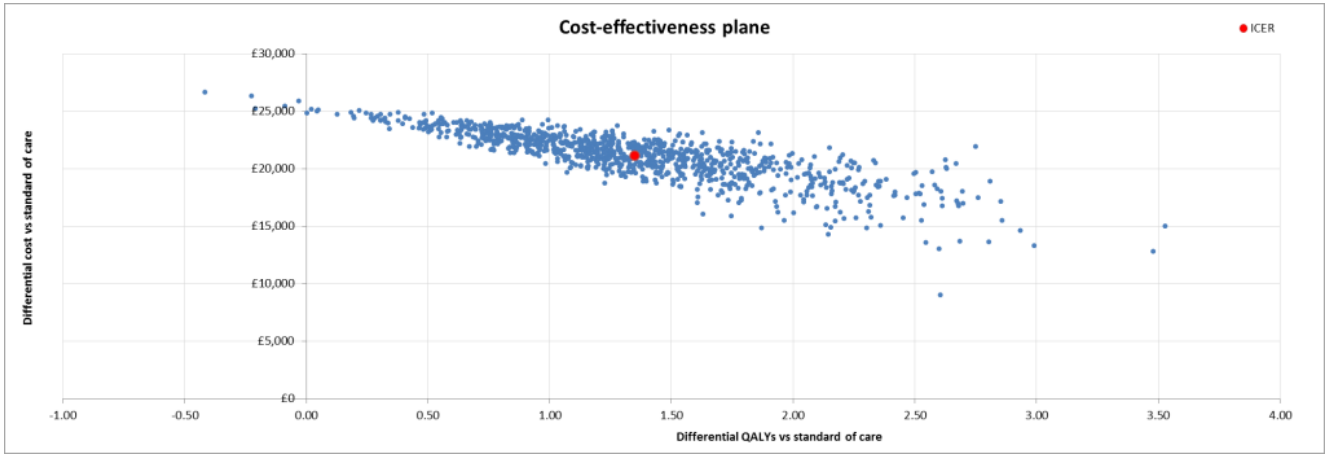
Abbreviations: QALY, quality-adjusted life year

Table 35: Probabilistic results, coefficient of variance 0.30 for HR salvage therapy

Treatment	Costs Mean	QALY Mean	Incremental cost, mean (95% CrI)	Incremental QALY mean (95% CrI)	Probabilistic ICER	Probability cost effective at £20,000	Probability cost effective at £30,000
Control	[redacted]	[redacted]					
Darvadstrocel	[redacted]	[redacted]	21,011 (16,455, 24,308)	1.35 (0.38, 2.57)	15,311	0.67	0.88
Abbreviations: QALYs, quality-adjusted life years; CrI, Credible interval							

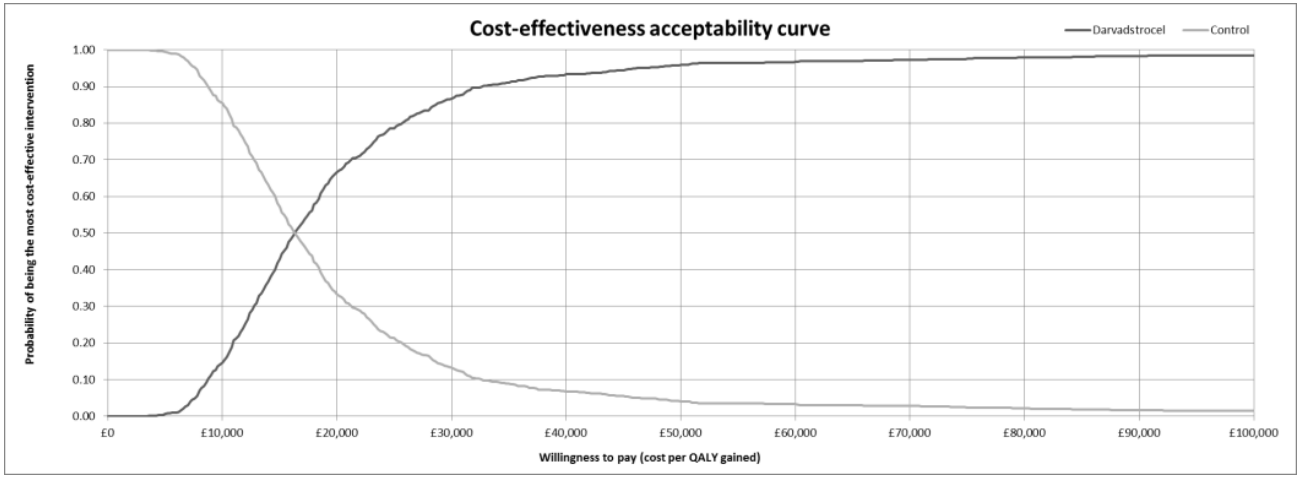
1.5% discount cost/efficacy; 0.60 coefficient of variance for HR salvage vs. control

Figure 30: Cost-effectiveness plane, coefficient of variance 0.60 for HR salvage therapy



Abbreviations: QALY, quality-adjusted life year

Figure 31: Cost-effectiveness acceptability curve, coefficient of variance 0.60 for HR salvage therapy



Abbreviations: QALY, quality-adjusted life year

Table 36: Probabilistic results, coefficient of variance 0.60 for HR salvage therapy

Treatment	Costs Mean	QALY Mean	Incremental cost, mean (95% CrI)	Incremental QALY mean (95% CrI)	Probabilistic ICER	Probability cost effective at £20,000	Probability cost effective at £30,000
Control	[redacted]	[redacted]					
Darvadstrocel	[redacted]	[redacted]	21,140 (16,144, 24,402)	1.02 (0.33, 2.59)	15,666	0.67	0.87
Abbreviations: QALYs, quality-adjusted life years; CrI, Credible interval							

B17. Please confirm any uncertainty associated with parameters representing probabilities and the distributions used to characterise the uncertainty. [CS, Page 117, Table 63].

Response: The probabilities were associated with beta distributions to bootstrap the associated values used in the PSA simulations. When information was available on the numbers at risk n and observed number of events np (i.e. annual probability of abscess for control arm from the 52-week trial follow-up) the associated variances were obtained by assuming binomial distributions and calculating the variance as $\mathbb{V}[X] = np(1-p)$. When this was not possible, the associated standard deviation was assumed relative to the control arm standard deviation (e.g. probability of abscess for salvage therapy), or an arbitrarily coefficient of variation considered sufficiently large (15%) was assumed around the average parameter value.

Note – when running the PSA cell I8 should be set to TRUE to save the sampled parameters, these can be then imported on BCEAweb (https://egon.stats.ucl.ac.uk/projects/BCEAweb/)

Table 37: Probabilistic sensitivity analysis inputs below presents the uncertainty associated with parameters representing probabilities and the distributions, as presented in the Excel model.

Table 37: Probabilistic sensitivity analysis inputs

Model parameter		Parameter value	Variation	SD or % variation	95% CI or approximated bounds		Distribution	Parameters	
					Lower bound	Upper bound		α	β
Efficacy									
Remission rate									
Darvadstrocel	**first 6 cycles**	0.12	SE	0.0164	0.085	0.149	Lognormal	-2.16	0.14
	6 to 12 cycles	0.04	SE	0.0138	0.012	0.066	Lognormal	-3.30	0.34
Control	**first 6 cycles**	0.07	SE	0.0122	0.049	0.097	Lognormal	-2.63	0.17
	6 to 12 cycles	0.03	SE	0.0098	0.007	0.045	Lognormal	-3.72	0.37
Salvage therapy		0.03	SE	0.0010	0.031	0.035	Lognormal	-3.40	0.03
Gompertz model	**Shape**	-0.05	Covariance matrix	'Data Store - Clinical'!R16C15: R19C18	-0.071	-0.033	Multinormal	-0.05207529; -3.31108003; 0.47134516;	0.00009319051; -0.001060872; 0.00006778169; -0.001060872; 0.03533722; -0.024031983; 0.00006778169; -0.024031983; 0.04026077;
	Rate	-3.31			-3.680	-2.943			
	Darvadstrocel	0.47			0.078	0.865			
HR salvage therapy vs control		0.60	SE	0.0900	0.424	0.776	Lognormal	-0.52	0.15
HR MRI inclusion		1.00	SE	0.0100	0.981	1.020	None	0.00	0.01
Long-term remission rate, salvage		0.0003	SE	0.0000	0.0002	0.0004	Lognormal	-8.18	0.15

Model parameter		Parameter value	Variation	SD or % variation	95% CI or approximated bounds		Distribution	Parameters	
					Lower bound	Upper bound		α	β
Relapse rate									
Darvadstrocel	**first 6 cycles**	0.08	SE	0.0173	0.047	0.115	Lognormal	-2.53	0.21
	6 to 12 cycles	0.03	SE	0.0118	0.010	0.057	Lognormal	-3.46	0.34
Control	**first 6 cycles**	0.15	SE	0.0298	0.088	0.204	Lognormal	-1.95	0.20
	6 to 12 cycles	0.06	SE	0.0319	0.001	0.126	Lognormal	-2.86	0.47
Salvage therapy		0.12	SE	0.0082	0.107	0.139	Lognormal	-2.10	0.07
Gompertz model	**Shape**	-0.04	Covariance matrix	'Data Store - Clinical'!R155C15 :R158C18	-0.062	-0.021	Multinormal	-0.04154549;-2.68117432;-0.56045644;	0.0001096271; -0.0011263858; -0.0004236341; -0.0011263858; 0.048610303; -0.032684311; -0.0004236341; -0.032684311; 0.0720074137;
	Rate	-2.68			-3.113	-2.249			
	Darvadstrocel	-0.56			-1.086	-0.035			
HR salvage therapy vs control		1.00	SE	0.1500	0.706	1.294	Lognormal	-0.01	0.15
Long-term relapse rate									
Darvadstrocel		0.0010	SE	0.0001	0.0007	0.0013	None	0.0000	0.0000
Control		0.0018	SE	0.0003	0.0012	0.0023	Lognormal	-6.3586	0.1492
Salvage		0.0018	SE	0.0003	0.0012	0.0023	None	0.0000	0.0000
Probability defunctioning									

Model parameter	Parameter value	Variation	SD or % variation	95% CI or approximated bounds		Distribution	Parameters	
				Lower bound	Upper bound		α	β
CSF mild	0.00	SE	0.0000	0.000	0.000	Beta	0.00	0.01
CSF severe	0.04	SE	0.0056	0.026	0.049	Beta	42.74	1097.00
Successful	0.62	SE	0.0930	0.438	0.802	Beta	16.27	9.97
Probability proctectomy								
CSF mild	0.00	SE	0.0000	0.000	0.000	Beta	0.00	0.01
CSF severe	0.04	SE	0.0058	0.027	0.050	Beta	42.69	1066.26
Defunctioning	0.04	SE	0.0058	0.027	0.050	Beta	42.69	1065.50
Successful	0.80	SE	0.1200	0.565	1.035	Beta	8.09	2.02
Population								
Average body weight	72.57	SE	1.0340	70.547	74.600	Lognormal	4.28	0.01
Average age	38.27	SE	0.9000	36.510	40.038	Lognormal	3.64	0.02
% male patients	54.72%	SE	0.0342	0.480	0.614	Beta	115.45	95.55
Relapsers with mild symptoms (%)	40.12%	SE	0.0220	0.358	0.444	Beta	198.60	296.40
HSUV								
Remission	0.87	SE	0.0299	0.806	0.924	Beta	111.86	17.46
CSF, mild symptoms	0.58	SE	0.0454	0.489	0.667	Beta	67.79	49.49
CSF, severe symptoms	0.38	SE	0.0301	0.324	0.442	Beta	99.57	160.41
Undergoing	0.38	SE	0.0301	0.324	0.442	Beta	99.57	160.41

Model parameter		Parameter value	Variation	SD or % variation	95% CI or approximated bounds		Distribution	Parameters	
					Lower bound	Upper bound		α	β
Defunctioning	Successful	0.57	SE	0.0445	0.480	0.654	Beta	69.58	53.14
	Unsuccessful	0.19	SE	0.0152	0.163	0.223	Beta	130.54	545.84
Proctectomy	Undergoing	0.38	SE	0.0301	0.324	0.442	Beta	99.57	160.41
	Successful	0.56	SE	0.0443	0.477	0.651	Beta	70.07	54.17
	Unsuccessful	0.20	SE	0.0159	0.171	0.233	Beta	129.07	509.91
Disutility									
Abscess		0.16	SE	0.0260	0.109	0.211	Beta	31.65	166.17
Proctalgia		0.00	SE	0.0000	0.000	0.000	Beta	0.00	0.01
Abscess, annual probability									
Darvadstrocel		7.77%	SE	0.0264	0.026	0.129	Beta	7.92	94.08
Control		8.82%	SE	0.0281	0.033	0.143	Beta	8.91	92.09
Salvage		12.00%	SE	0.0382	0.045	0.195	Beta	8.57	62.82
Proctalgia, annual probability									
Darvadstrocel		4.85%	SE	0.0212	0.007	0.090	Beta	4.95	97.05
Control		7.84%	SE	0.0266	0.026	0.131	Beta	7.92	93.08
Salvage		14.50%	SE	0.0492	0.049	0.241	Beta	7.28	42.91
Costs									
Defunctioning cost		5034.24	SE	755.1360	3554.201	6514.279	Gamma	44.44	113.27
Proctectomy cost		11925.05	SE	1788.7574	8419.149	15430.949	Gamma	44.44	268.31

Model parameter		Parameter value	Variation	SD or % variation	95% CI or approximated bounds		Distribution	Parameters	
					Lower bound	Upper bound		α	β
HS costs									
Remission		31.70	SE	4.7547	22.379	41.017	Gamma	44.44	0.71
CSF mild		52.04	SE	7.8059	36.740	67.339	Gamma	44.44	1.17
CSF severe		99.35	SE	14.9030	70.144	128.563	Gamma	44.44	2.24
Defunctioning	**Undergoing**	746.38	SE	111.9566	526.947	965.808	Gamma	44.44	16.79
	Successful	39.21	SE	5.8812	27.681	50.735	Gamma	44.44	0.88
	Unsuccessful	117.66	SE	17.6486	83.067	152.248	Gamma	44.44	2.65
Proctectomy	**Undergoing**	924.62	SE	138.6926	652.785	1196.450	Gamma	44.44	20.80
	Successful	48.06	SE	7.2095	33.933	62.194	Gamma	44.44	1.08
	Unsuccessful	154.34	SE	23.1512	108.966	199.717	Gamma	44.44	3.47
AE cost: Abscess		2303.00	SE	345.4500	1625.930	2980.070	Gamma	44.44	51.82
AE cost: Proctalgia		50.00	SE	7.5000	35.300	64.700	Gamma	44.44	1.13

Resource use & costs

B18. Due to the 24 to 48 hour shelf life of darvadstrocel, there were concerns by the British Society of Gastroenterology about wastage resulting from theatre cancelations in their professional organisation submission to NICE. Furthermore, the statement in EPAR "There is a potential risk on medication errors related to the surgical procedure such as the administration of the product…"[EPAR, page 71]:

- Please clarify, was there any wastage of darvadstrocel vials in the ADMIRE-CD study [Panes et al. Lancet, 2016, 388: 1281-90]?
- Please clarify why wastage of darvadstrocel was not included in the economic model?
- Please conduct a scenario analysis in which wastage of darvadstrocel is included.

Response: There were no no-shows and no cancellations during the ADMIRE-CD trial meaning no wastage was observed for the 107 patients assigned to darvadstrocel.

Takeda UK recognise the potential issue of wastage with darvadstrocel and have been working with UK centres of excellence to ensure that appropriate systems can be set up to avoid this in clinical practice. Although some NHS trusts do have high surgical cancellation rates there are a number of specialist centres where this is very rare, these trusts have also stated that as the surgical procedure associated with the administration of darvadstrocel is short (no more than 1 hour) that they could avoid cancellations. We therefore believe that by working closely with NHS specialist centres to deliver darvadstrocel that wastage should be avoided, and have therefore not included wastage in the model.

Including 5% wastage in the model, which is achieved by increasing the cost of darvadstrocel by 5%, results in an ICER of £15,911 (assuming a 1.5% discount rate applied to costs **and** QALYs) compared to an ICER of £15,017 excluding wastage.

B19. Please clarify why an arbitrary standard error of 15% of the mean was assumed to be placed around NHS reference costs in the probabilistic sensitivity analysis, when the actual uncertainty in the NHS reference costs can be calculated in the following formulae:

> Standard deviation = (upper quartile unit cost – lower quartile unit cost)/(2*NORM.INV(0.75,0,1))
>
> Standard error = Standard deviation/SQRT(number of data submissions – 1)

Response: While we agree that the methodology using the formulae presented by the ERG provides the actual uncertainty around a point estimate of the NHS reference cost, we decided against using this approach. This method does not incorporate the uncertainty encompassed outside of the specific DRG code, for example the varying number of complications associated with some procedures. Therefore, a universal method was selected exploring 15% variation of the mean.

Health utility

B20. Please clarify the following [CS, Appendix R, page 7]:
- How were potential external datasets for mapping identified?
- Which (if any) external datasets were identified?
- If any datasets were identified, why were they deemed to be inappropriate to estimate a mapping algorithm?

Response: No potential datasets for mapping were identified.

In order to develop a mapping algorithm it is necessary to have a valid predictor of EQ-5D (or similar measure) in the ADMIRE-CD trial for CD patients with perianal fistulising disease. Data from the Perianal Disease Activity Index (PDAI) were collected in the ADMIRE-CD trial; however this a measure of disease activity and its conceptual overlap (necessary for the development of a reliable mapping algorithm) with generic preference-based measures (GPBMs), such as EQ-5D and SF-6D, is limited.

A review of the literature reporting utility values was conducted. This included specific search terms for GPBMs such as those relating to EQ-5D, SF-6D and the Health Utilities Index (HUI) instruments. None of the identified studies reporting standardised GPBMs also reported data from the PDAI, and therefore could not have been used for generating a mapping algorithm. To our knowledge, none of the routinely available datasets that include instruments such as EQ-5D and SF-6D also includes PDAI (e.g. Health Survey for England, Department of Health PROMs datasets).

Other measures included in the trial (e.g. CDAI and IBDQ) were not appropriate to map from, as these instruments have not been developed to measure perianal fistulising disease.

B21. Please clarify why the abscess state was not presented in Table 46 or Table 47 [CS, pages 99-100], when it was estimated directly in the vignette study?

Response: As described in Section B.3.4.5 of the company submission, the results of the vignette study were adapted to estimate the disutility associated with perianal abscess events. This was because in the economic model abscess were considered as events occurring while patients were in the chronic symptomatic fistulae health state and not as a separate health state. To estimate the disutility associated to abscesses, it was conservatively assumed that this would be equal to the difference between the HSUV associated to severe chronic symptomatic fistulae and the active perianal abscess utility.

B22. Please clarify what available evidence supports a disutility of 0 for people with proctalgia [CS, Page 100, Table 48]. Furthermore, please provide evidence/clinical rationale to support that this parameter has a fixed value.

Response: Proctalgia, i.e. anal pain, is by definition included in some degree in the CSF health state, as a necessary condition to achieve remission is for patients to have minimal pain according to the CPC definition of remission. Therefore the quality of life impact of proctalgia is not accounted separately to avoid double-counting the detrimental effects of

pain on CSF patients. The associated uncertainty is also considered to be captured by the health state utility value for CSF.

The disutility value associated to proctalgia was conservatively assumed to be null, as by definition of chronic symptomatic fistulae the patients could experience pain, and was therefore considered to be already accounted for by the chronic symptomatic fistulae HSUVs.

The vignettes for the chronic symptomatic health states are presented below:

Health State 2: Chronic Symptomatic Fistulae with mild symptoms

You have a condition that causes inflammation of the gastrointestinal tract. This inflammation can occur within your intestines, anywhere from near your mouth to your anus. People with this condition can experience stomach cramps and a need to go to the toilet urgently. Because of the condition, you also experience fistulae, which are small holes or openings, near the anus. These sometimes cause you mild discomfort and a small amount of mucous sometimes leaks from the fistulae opening. You have no or slight restrictions on your daily activities. You have slight physical restrictions on your sexual activity.

Health State 3: Chronic Symptomatic Fistulae with severe symptoms

You have a condition that causes inflammation of the gastrointestinal tract. This inflammation can occur within your intestines, anywhere from near your mouth to your anus. People with this condition can experience stomach cramps and a need to go to the toilet urgently. Because of the condition, you also experience fistulae, which are small holes or openings, near the anus. These sometimes cause you moderate or marked discomfort. You experience moderate or substantial discharge from the fistulae openings, which contains mucous, pus and/or poo. Your daily activities are moderately to markedly restricted as a result of the fistulae. You have moderate or marked physical restrictions on your sexual activity.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Darvadstrocel for treating complex perianal fistula in Crohn's disease [ID960]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	Crohn's and Colitis UK

3. Job title or position	Health Policy & Public Affairs Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Crohn's and Colitis UK is the leading charity dedicated to improving the lives of everyone affected by Crohn's Disease, Ulcerative Colitis and other forms of Inflammatory Bowel Disease (IBD). Founded as a patient's organisation in 1979, we now have over 35,000 members and 50 local networks. Working together, we provide information and support, campaign to improve services and healthcare, and fund vital research. We are funded through membership subscriptions and a wide range of fundraising activities, including events, grants, legacies and corporate partnerships. Full details are available in our annual accounts: https://www.crohnsandcolitis.org.uk/about-us/annual-accounts
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	Through our day-to-day work providing information and support, we are in contact with thousands of people affected by IBD, who share their experiences through our helplines, online forum and at events. We also regularly conduct surveys and hold focus groups exploring issues that are relevant to people with Ulcerative Colitis and Crohn's Disease and fund and support qualitative and quantitative research. In relation to this submission, we put out a call for evidence through social media channels and healthcare professionals and researchers. We have heard directly from patients and carers who have personal experience of living with or caring for someone living with perianal fistulising Crohn's disease, including those we have nominated as patient experts for this appraisal.
Living with the condition	
6. What is it like to live with the	For those living with perianal fistula in Crohn's, day-to-day life can be extremely debilitating, as illustrated by the quotes used throughout this submission from patients who contacted us about this.

condition experience when caring for someone with the condition? What do carers	*"It is very hard, it's on my mind all the time, it affects pretty much everything I do. I have to plan my work days, activities, trips away meticulously. Looking after the fistula is a full time occupation. I don't recall a time when I didn't have to worry about the effects of my fistula on my life, or the way I live my life".* The first sign of a fistula can be a tender swelling or lump in the area round the anus. Symptoms include skin irritation around the anus, pain, abscess formation, and passing of blood or pus when having a bowel movement[i]. In patients with longstanding chronic active perianal disease, faecal incontinence may occur. Between 23%-38%of people with Crohn's disease will develop a fistula[ii] with perianal fistulas being the most common type[iii]. Of this group, 30% of these people have recurrent fistulas. Longstanding remission of complex fistulas occurs only in about one third of patients[iv]. Population-based studies indicate that longer disease duration increases the cumulative incidence of perianal fistulas.[v] There is an associated risk of septicaemia[vi]. There is limited research into the impact of fistula on patients' quality of life and Patient Report Outcome Measures are not used routinely as part of condition management. A 2017 survey of gastroenterologists found that the clinical management of fistula varies in practice and there is a 'lack of consensus among physicians for the optimal medical management of perianal Crohn's disease'.[vii] Patients and carers report that living with or caring for someone with perianal fistula can have a dramatic and detrimental impact on their physical and mental health, placing restrictions not only on their ability to undertake or participate in everyday activities but also on life outcomes (e.g. employment, family life and emotional wellbeing). A recent qualitative exploration into the experiences of people with fistulising perianal Crohn's disease found that the experience was encompassed by several themes in three key areas: burden of symptoms; burden of treatment; and negative impact on emotional, physical, social well-being within developed coping strategies[viii]. Within these categories, the following themes emerged: Limited mobility; Restriction of activities; Feelings of loss of confidence/altered body image; Emotional and psychological impact; Anxieties relating to treatment and Fear and uncertainty about the future. On a day to day basis, managing a fistula is an involved activity. Patients are required to keep the wound open and therefore careful wound management and skin care is essential. Daily management will involve changing dressings as often as is needed, keeping the wound clean and protecting the skin, sometimes with the support of a loved one, carer or health professional. This can be challenging given that the wound can often be contaminated by faecal matter

	because of its location and discharge involved. This means patients may take frequent showers/bathe regularly, and may require clothing changes during the day and/or bedding changes at night. Patients often need to carry around a dressing kit or change of clothes Those affected regularly attend specialist reviews and medical appointments. "*Living with fistulas is not easy…If they are leaking I need to have tissue paper to soak up the liquid (pus or blood) as well as a pad inside my underwear for the escaped bits. If they're not leaking and have temporarily sealed up it can become like toothache in my bottom. This doesn't happen often now as there is more of them but when it does the only relief is strong painkillers until they burst. I get more infections because of the open wound, usually resulting in cold like symptoms, the shivers and aching all over, again paracetamol reduces my temp and an early night is called for. This is not too bad if I am at home but I work away from home where an early night is not an option. Sitting down is sometimes uncomfortable so I end up sitting on one side or the other or laying flat out."* *"Living with perianal fistulas is a chronic debilitating condition affecting most of my day. Leakage 24 hours a day, soreness, swelling, pain when you move. Discomfort when bathing (and) showering. Clothes are uncomfortable. I wear very large continence pads to deal with my seton drainage. Just wiping your bottom can make you cry, catching a seton string can be agony. I've 3 setons fistulas at present and a RV fistula - my quality of life is very poor…going for a wee can make them burn and pooing can hurt too."* *"I need the support of my mum and partner on a daily basis to help me dress the fistula and keep a check on it."* Patients report that living with a fistula can restrict activities such as sport and socialising as well as ability to work or study. Intimacy can also be challenging, with those affected reporting that sexual relations can be painful. Perianal disease is associated with fewer pregnancies.[ix] *"I used to be a keen runner and cyclist but since developing a complex perianal fistula I have had to give them up due to the several surgeries required to treat the symptoms and the daily pain and discomfort in the area. The disabling aspect of the condition has affected my whole life; I've required months off work, it's made me bed bound, socially isolated and become an increasing burden to my family."* *"I have recently got married, however my condition is currently preventing me and my husband from starting a family as intercourse is too painful".*

	"I quit my job in February as I am unable to do my work. I am exhausted with fatigue and cannot rest enough. Since the fourth operation, I have been unable to maintain an erection, causing frustration between me and my girlfriend." As a result, the psychological impact and effect on self-esteem and social relationships can be profound. "*The pain from the acidic stool is bad enough on a bottom that is healthy and doesn't have open sores, but the pain onto an open fistula is like something nobody can imagine unless they have experienced it. It has left me at time contemplating suicide to make it stop."* *"They change how you feel about yourself they make you feel unclean all the time, like you smell always uncomfortable."* *"I have never told my girlfriends I have had one to date, due to the shame and worry - and I am not sure I ever could, which makes me worry about my future life with a partner. My close family know, and one of my closest friends (who I then went on to find out two years later had a fistula and seton too!) It is still something that embarrasses me, and I don't know if I will ever overcome that".*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	*"The continuous mental battle of trying new treatments, going through surgery after surgery, without getting more positive results is very challenging".* Effective treatment options for perianal fistula are limited and suboptimal. There are no quick fixes and consequently patients can live with fistula for many years. While a limited range of drug treatment options are available for treating perianal fistula in Crohn's Disease, they do not work for everyone and a substantial number of patients experience lack of response (primary or secondary) and/or adverse reactions. Up to one third of people with Crohn's Disease who have perianal fistulas will require surgery at some stage[x]. Surgery does not offer a definitive cure. For many patients, the prospect of surgery is one they face with considerable anxiety and it can bring with it a range of potential complications, which may require further treatment and ongoing management. Complications from surgery can include faecal incontinence, infection, damage to the anal sphincter muscles and reoccurrence of the fistula. There can also be an associated profound psychological and social impact,

	for example, in terms of body image and self-esteem. For those who are facing this at an age when they have just begun to form relationships and do not yet have a family, this can be especially difficult, as it can for those of some religious faiths and cultures. *"So far I've had 6 surgeries in the past 10 months and all these are doing are treating the symptom of the abscesses when they appear by draining them and helping them to drain further with setons"* *"There needs to be some form of document across the country so care is the same across the board. Even how setons are fitted - I've had a seton that was very comfortable and others that are like living with a piece of glass or barbed wire in your bottom. Just appalling."* *"Surgeons not really appreciative of the debilitating aspect of the condition especially for patients with Crohn's, a long term chronic illness, they just see the abscess to drain and once that's done ship you out without much care in terms of the support you will require to recover or manager the wound/seton."* **The formation of a stoma does not guarantee that fistulas will not reoccur or further surgery is prevented.** *"I was diagnosed with extensive, complex pelvic and perianal fistulae last year after an abscess was discovered. It was decided that I would need a temporary ileostomy to allow the infection to be drained and bowel to heal before starting on the immunosuppressant therapies which would hopefully heal the fistula tracts. Due to the nature of the fistulae/abscess, I required daily packing and dressing changes for 3 months, all of which were quite tough emotionally. Having to undergo this and other examinations was made much easier with my stoma. However, I have since had 2 further abscesses and infections despite being on medication for my Crohn's, which have also required an operation and then around 2-3 months of aftercare again.* *"I have two perianal fistulas, recurring abscesses and an anal fissure. It's all got so bad they have had to give me a colostomy as passing stool was agony back there. I have two setons back there to keep the fistulas open and drain. I have an old style one and a new style one. One is held together with stitches which I always describe as barbed wire. The other is just a knotted string which is much better. I was climbing the walls in pain. It's still painful to sit and sometimes the only way around this is to lay on my back. But then I still get a niggling pricking pain."* **Many individuals wish to avoid surgical options, for example to have a family.**

	"Thankfully my consultant put a stop to the operations just in time and put me on Humira instead. I have had Crohn's Disease for 13 years now and a stoma bag is still a huge fear for me. In the near future my only option will be a permanent stoma and extension reconstructive surgery on my tail end due to the damage caused by the fistulating Crohn's Disease. It feels like a ticking time bomb. I have been told they will try not to do the reconstructive surgery until I have completed my family, as it is highly likely the operation will affect my fertility. At this moment in time I appear to be in remission but I live every day in fear that my time to have a family has run out and surgery has to happen." **Supporting care** *"There is very little supporting care for fistulas. GP and clinic nurses also do not appear to have much knowledge or experience in dealing with perianal fistulas."* *"I think the packing of perianal abscesses in this day and age is absolutely shocking and barbaric, surely a lesser painful way of treating an abscess drain is out there?"* *"I think there needs to be significantly more support with patient's mental health when dealing with these conditions. When I've tried to explain to doctors the difficulties of this previously, I've not really had any support, and in some cases, made to feel like I was being dramatic."*
8. Is there an unmet need for patients with this condition?	For some patients, acceptable treatment options run out and the impact of this can be profound. For others, a more limited quality of life can be normalised due to inadequate response. *"It's scary, I think what's going to happen if this never gets under control, I'm fed up of being in pain, I'm a mum to a toddler and I want to enjoy life with her not have to get her to stand in a toilet with me for 20 mins whilst I dress a fistula."* *"There are so many unmet needs for us with perianal fistulas, lack of knowledgeable nurses, pain management and pads available for us instead of people having to spend £100s each month to deal with leakage ".*

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	This is a highly innovative technology, in the context of current suboptimal treatments for this particularly difficult and debilitating complication of Crohn's Disease, and has the potential to represent a step-change in its management. This therapy has the potential to Increase treatment options available to patients, especially for those who cannot tolerate or have found current drug treatments ineffective or *"If I was eligible for the new treatment, then it would give me another option for them to try before the surgery is the only option. Infliximab is not healing the fistulas so there will be surgery in my near future and the likelihood of the fistulas flaring up is probably very high once the day comes that infliximab no longer works."* The management of treatment such as infusion therapy and drug monitoring for immunosuppressants such as azathioprine can impact significantly on patient's lives and work requiring regular attendance at hospital and additional travel and parking costs. Some patients find the prospect of subcutaneous injection unacceptable, or at least unpleasant, home delivery has to be managed and the need to store these drugs at an appropriate temperature can impact on travel plans.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Some patients may object to the use of stem cells and, if only available in limited centres, this might restrict access for some patients that could benefit. However, the potential for a successful one-off treatment would be very much welcomed by those who currently have no other acceptable treatment options for their perianal fistula.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others?	Patients who have had little or no success with currently available medical treatment options, and wish to avoid or delay surgery, are likely to benefit in particular. This would include young people wishing to complete studies or start a family and those for whom surgery would be considered unacceptable due to cultural or religious factors.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There are particular implications for women of child-bearing age, due to potential reduction in fertility associated with pelvic surgery and obstetric complications. The need for frequent wound cleaning and dressing may also impact on those following particular religious practices.
Other issues	
13. Are there any other issues that you would like the committee to consider?	This is a highly innovative technology, in the context of current suboptimal treatments for this particularly difficult and debilitating complication of Crohn's Disease, and has the potential to represent a step-change in its management.

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • Patients and carers report that living with or caring for someone with perianal fistula can have a profound and detrimental impact on their physical, emotional and social wellbeing, placing restrictions not only on their ability to undertake or participate in everyday activities but also on employment and family and social relationships. • Effective treatment options for perianal fistula are limited and suboptimal. • This therapy has the potential to Increase treatment options available to patients, especially for those who cannot tolerate or have found current drug treatments ineffective or wish to delay or avoid surgery. • This is a highly innovative technology, in the context of current suboptimal treatments for this particularly difficult and debilitating complication of Crohn's Disease, and has the potential to represent a step-change in its management.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

[i] Living with a Fistula (2016) Crohn's and Colitis UK. St Albans
[ii] Management of perianal fistulas in Crohn's Disease: An up to date review (2015) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4316082/
[iii] Fistulizing Crohn's Disease (2017) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5539341/
[iv] Fistulizing Crohn's Disease (2017) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5539341/
[v] Fistulizing Crohn's Disease (2017) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5539341/
[vi] Management of perianal fistulas in Crohn's Disease: An up to date review (2015) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4316082/
[vii] Frontline Gastroenterol. 2018 Jan;9(1):16-22. doi: 10.1136/flgastro-2017-100866. Epub 2017 Sep 23.
[viii] A qualitative exploration into the experiences of people living with Crohn's Anal Fistula (2018) Kings College London and St Marks Hospital
[ix] Perianal disease results in fewer pregnancies https://www.ncbi.nlm.nih.gov/pubmed/26342947
[x] Fistulizing Crohn's Disease (2017) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5539341/

NICE National Institute for Health and Care Excellence

Professional organisation submission

Darvadstrocel for treating complex perianal fistula in Crohn's disease [ID960]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Society of Gastroenterology (BSG)**

3. Job title or position	**Consultant Gastroenterologist. Chairman of the Inflammatory Bowel Disease section committee of the BSG**
4. Are you (please tick all that apply):	☐ ✓ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ ✓ a specialist in the treatment of people with this condition? ☐ ✓ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Society of Gastroenterology is an organisation focused on the promotion of gastroenterology within the United Kingdom. It has over three thousand members drawn from the ranks of physicians, surgeons, pathologists, radiologists, scientists, nurses, dietitians, and others interested in the field. Founded in 1937 it has grown from a club to be a major force in British medicine, with representation within the British Royal Colleges and consequently the Department of Health and Government. Internationally it is represented at World and European level. The BSG is a registered charity.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Perianal fistulae are epithelialised tracts connecting the anal canal to the perianal skin. They cause symptoms due to faeculent discharge onto perianal skin, and through development of abscesses when the

or prevent progression or disability.)	tract becomes blocked and infected material cannot discharge to the skin, with pain, fever and the need for surgical drainage. The aim of the treatment is to enable healing of the fistula tract, preventing discharge and abscess formation. An effective treatment would also prevent recurrence which occurs when the same tract opens up, or when new tracts form.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	There is considerable debate about appropriate end-points for trials of perianal fistula trials. The most widely used end-points currently are:- 1) Cessation of fistula drainage reported by a) clinical examination – no discharge when the fistula track is 'milked' by digital pressure; and b) patient-reported cessation of drainage. This should be reported for each external fistula opening 2) Cessation of abscess formation as documented by reports of admission for abscess drainage, and MRI scan of pelvis confirming no abscess collection greater than 1-2cm 3) Other clinically significant end-points could include: absence of pain, incontinence, or PDAI scores, but PDAI scores do not have good validation, and no agreed score defined for either improvement or remission. 4) The Fistula Drainage Assessment (Present, NEJM 1999;340:1398) defines Improvement as "Closure of individual fistulas defined as no fistula drainage despite gentle finger compression. Improvement defined as a decrease from baseline in the number of open draining fistulas of 50% or more for at least 4 weeks". Remission is defined as "Closure of all fistulas (no fistula drainage despite gentle finger compression) that were draining at baseline for at least 4 weeks." 5) From a patient perspective the most important end-point is the long-term remission rate (ie at 1 year or longer)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The unmet need is enormous. Most perianal fistulizing disease can be controlled by continuing drug therapy, but only a small % are permanently healed. Rates of about 30% healing after 3 years are reported (Tozer IBD 2012;18:1825). Surgical treatment of complex perianal fistulae has a recurrence rate of 25-50% (Yassin, APT 2014;40:741). Many patients need to have long-term seton placement, and a significant proportion will required proctectomy and permanent ileostomy. Most of the data comes from the pre-biologics era with reported proctectomy rates of 38% (Michelassi, Surgery 2000;128:597), with little reliable outcomes data from the last decade although proctectomy rates likely to be lower than this, but at the price of long-term biologics therapy.

What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ECCO Crohn's disease Guidelines 2016. Part 2 (Surgery etc)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Basic pathway of assessment and treatment is well-defined. Disagreement about the details (eg how rapidly treatment should be escalated; how long setons should remain in place)
• What impact would the technology have on the current pathway of care?	The treatment is recommended for patients failing conventional therapy (abscess drainage, seton insertion, medical therapy with immunosuppressive and anti-TNF therapy), so it will affect 2nd-line treatment options for those who fail anti-TNF therapy, and are often offered alternative biologics, surgical repair, or even proctectomy
10. Will the technology be used (or is it already used) in	This is a novel treatment, not currently used in the UK (except in clinical trials?)

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The treatment as described in the Panes study (Lancet 2016) requires a specific surgical treatment under anaesthetic to curette the fistulae tracts, and insert setons. A second anaesthetic is required at least 2 weeks later to ligate the internal fistulae opening and inject the stem cells. This requires expertise from the surgeon. Currently treatments do not involve 2 EUA procedures. The second EUA has to be coordinated with delivery of the stem cell treatment to the hospital as it has a short shelf-life of about 24-48 hrs
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist hospital clinics with surgical and medical experience of treating perianal Crohn's
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training of colorectal surgeons to deliver the treatment at EUA
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Higher remission rates
• Do you expect the technology to increase	No. Death from perianal fistulising Crohn's is rare

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. This would be the major benefit
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The treatment may be less effective in those with active proctitis (as are all current therapies). There may be much more difficulty in achieving ligation of the internal fistula opening in these patients, but there may also be a lower likelihood of treatment response generally
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	See section 10 above. The delivery of the stem cells has to be coordinated with the examination under anaesthetic procedure, due to the very short shelf-life of the product. If theatre lists are cancelled unexpectedly then the treatment may be wasted, at great cost.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The treatment is a single event, and repeat treatment in the event of failure or recurrence, has no current evidence base. The issue would be duration of concomitant anti-TNF therapy, which would follow current NICE guidelines regarding stopping.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	QALY data on perianal fistulising disease is relatively limited
16. Do you consider the technology to be innovative in	Yes. Innovative and could result in significantly higher long-term healing rates

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Potentially yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes. See above
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No obvious risks, and the trial reported proctalgia and anal abscess as the main serious adverse event, and these also occurred in the placebo group. If the treatment reduces requirement for long-term biologic therapy then this may reduce long-term adverse events although no data as yet to show this.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, apart from the standardised EUA procedure which should be introduced along with the stem cell treatment (as the placebo group response rate was probably higher due to the ligation and curetting of fistula tracts)
• If not, how could the results be extrapolated to the UK setting?	See above
• What, in your view, are the most important outcomes, and were they measured in the trials?	Remission at 6 months (closure of fistula and no significant abscesses) is an important end-point, as measured in the Panes study
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Little data as yet on longer-term outcomes (1 year follow-up only to date) and impact on long-term biologics therapy
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	Lower remission rates for standard therapy currently compared to the placebo group in the Panes study
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No, other than availability in non-tertiary centres if sufficient expertise not available to administer treatment
21b. Consider whether these issues are different from issues with current care and why.	No
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Novel therapy
- Safe
- May increase remission rates significantly in difficult patient group
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Darvadstrocel for treating complex perianal fistula in Crohn's disease [ID960]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Tariq Iqbal**
2. Name of organisation	**Queen Elizabeth Hospital Birmingham**

3. Job title or position	**Consultant Gastroenterologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x** other (they didn't submit one, I don't know if they submitted one etc.) I don't know if they submitted one
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve the healing of perianal fistulae in Crohn's disease
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Healing of more than 50% fistulae with cessation of discharge
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	A combination of surgery, antibiotics and immune suppression
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	None specifically for this topic but guidance as part of more generalised Crohn's disease management exists (ECCO Crohns consensus 2016 part 2)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No. The components of management are the same but vary from practice to practice and between different MDTs across the UK
• What impact would the technology have on the current pathway of care?	This is a novel approach designed exclusively for the management of perianal fistulae. Adoption of this technology would provide a therapeutic endpoint and would enable the development of a focused, more uniform approach than that currently taken
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology would be part of the current management algorithm

• How does healthcare resource use differ between the technology and current care?	Current care usually involves antibiotics + surgery to resolve sepsis and then immune-suppression to promote healing. I would envisage that the proposed technology would slot in after the initiation of immune-suppression in the case of incomplete efficacy
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care-initiated and overseen by IBD MDTs
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Surgical training would be needed
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	No

• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with extensive disease and undrain-able pelvic collections, patients with ongoing un resolved rectal inflammation
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	More difficult in that it will require the involvement of specialised colorectal surgeons who are trained in the deployment of this technology. Monitoring will not need new equipment or practices and I don t see a problem with patient acceptability in this condition which is not well managed currently

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting will be proscribed by a management algorithm and will be overseen by IBD MDTs in a consensual manner. Stopping (ie how many treatments in the event of primary non-response) would be more tricky; I suspect there is little evidence to support this
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes-there is a pressing need to help patients with complex peri-anal fistulising disease. We don't do well currently
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes. This is the first approach to use technology specifically designed to heal Crohns fistulae. I am not sure about medium to long term outcomes as data is pretty sparse.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes-a good proportion of patients end us with radical surgery which should be the last resort. If this can be avoided and patient's QOL maintained that would go a long way to meeting a need.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No evidence; the technology seems well tolerated
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	Not applicable
• What, in your view, are the most important outcomes, and were they measured in the trials?	There was a significant improvement in clinical remission in the active arm compared to placebo at 24 weeks in the phase III RCT. Long term efficacy was not addressed in this trial
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No
22. How do data on real-world experience compare with the trial data?	I don't know
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as “Is comparator X [excluded from company submission] considered to be established clinical practice in	

the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • Unmet need • Novel treatment approach to complement current treatment • Needs surgical training • Seems well tolerated • Benefit seems small and long term outcome uncertain	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Darvadstrocel for treating complex perianal fistula in Crohn's disease [ID960]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Janindra Warusavitarne**
2. Name of organisation	**LNWUH NHS Trust St Mark's Hospital**

3. Job title or position	
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.) **I have not seen it**
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To heal fistulas To improve quality of life
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Closure of fistula tracts Improvement in quality of life
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	yes
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Medical treatment with biological agents and surgery as an adjunct to optimise patient for medical treatment
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The guidelines by Gecse et al are the closest guidelines but these are not universally used as far as I understand
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are differences in opinions and approach across the NHS
• What impact would the technology have on the current pathway of care?	It would add to the current treatment armamentarium in this disease where no standard treatment exists and many patients become treatment refractory. Other options are always needed in this situation and this would be a suitable alternative
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not currently used

• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training and pharmacy resources
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	yes
• Do you expect the technology to increase length of life more than current care?	no

• Do you expect the technology to increase health-related quality of life more than current care?	yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Less effective probably in those with severe proctitis but this group tends to be more refractory to most treatments More effective in those with multiple openings where standard surgical approaches such as LIFT may not be suitable
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Needs to be used in a timely manner and thus planning of theatre lists are paramount Training I do not anticipate any extra clinic visits

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not that I am aware of
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	no
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes In those patients where standard treatment does not offer relief this has the potential to offer good outcomes

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	yes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Not aware of any to date
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	no
• If not, how could the results be extrapolated to the UK setting?	Current UK management is fairly non uniform. On this basis it would be useful to restrict the use to high volume specialised centres with an IBD MDT where potential usage should be discussed
• What, in your view, are the most important outcomes, and were they measured in the trials?	Fistula closure QOL
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
20. Are you aware of any relevant evidence that might	no

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	no
22. How do data on real-world experience compare with the trial data?	Real world data are not available yet but I suspect with that real world data may reflect the trial data but once experience is gained the indications could potentially be extended. This would certainly be the case once the effects of scaffolds in influencing healing would be evaluated such as currently being done at the Mayo Clinic in the USA.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Potentially religious groups

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in	

the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Novel and new treatment for complex perianal Crohn's disease
- Has the potential to improve quality of life
- Indications need re evaluation
- Technology in evolution with promise
- Should be used in speciliased centres to ensure appropriate expertise and after discussion in MDT

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Darvadstrocel for treating complex perianal fistula in Crohn's disease [ID960]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Paula Carr**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Crohns & Colitis UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with perianal fistulas is such a chronic debilitating condition for me affecting most parts of my day. I was diagnosed with Crohn's 24 years ago and had 34 surgeries, with 17 for fistula problems. I suffer leakage 24 hours a day, soreness, swelling and pain when I move and discomfort when bathing, showering, during sexual activity and life In general. Clothes can be so uncomfortable. I personally wear very large continence pads to deal with drainage. This problem is so invisible and I feel that living with perianal fistulas changes how you feel about yourself, mentally and physically - they make you feel unclean all the time. The daily impact on my life is so untold and people looking at me would never know the battle I endure underneath my clothes and in my head.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	As a long term patient with Crohn's, I personally feel I'm near exhausting what's available. I've been under care for 24 years and have had a total of 34 surgeries from a total colectomy to J-Pouch formation, hernia repairs, lots of change of seton strings and insertion of new setons into fistulas. 17 of the surgeries have concentrated totally on perianal fistulas and trying to repair rectovaginal fistula. These surgeries entail having seton strings inserted into fistulas which are so very painful, uncomfortable and embarrassing - you don't share in everyday conversation that you've had surgical bows put in your bottom as you are leaking poo. Having a seton changed in surgery can need doing regularly as they become pungent and sore. It's not a complex surgery but is a painful recovery. I've had to return after these changes due to infection on several occasions. Having so many surgeries is very daunting. My latest was an emergency surgery due to an infection from a prior surgery 12 days earlier for new seton strings as a day patient. I had an allergic reaction to suxamethonian which has led to me now having fibromyalgia due to the reaction. Mentally it is very tiring trying all the biological medicines, always wondering will this be my last chance before another surgery, which won't necessarily cure me of the fistulas. In terms of medicine, I was on azathioprine, which failed, then more recently infliximab and methotrexate for 5 years, which has also stopped working and caused me to develop drug-induced lupus, so was withdrawn. I'm now trying a new medicine called Stelara which isn't working as well as expected and surgery is looming for me. With all this medical care and time at hospital having treatments for Crohn's and all its complications, I spend lots of time at clinics, it's impacted on my work life and sadly it's cost me good jobs I've loved.
10. Is there an unmet need for patients with this condition?	There are so many unmet needs for those of us with perianal fistulas, including lack of knowledge from nurses, pain management and availability of incontinence pads, on which I spend £100s each month to deal with leakage. After care is virtually zero

	Named nurses - maybe like stoma nurses, - a plan to be in place for follow up for uncomfortable setons and fistulas and a system where all fistulas are treated in a similar way, just from the type of surgical strings or wires that are inserted, could have a dramatic impact on quality of life.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	This treatment feels like it would be my last chance before removal of my J-Pouch and rectum and a permanent stoma. It gives me another hope or avenue that may improve my quality of life as infliximab has already failed for me and looks like the new drug I'm on, Stelera, is failing too,
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	I personally cannot see any disadvantages for myself.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	I personally feel this would have huge benefits for younger females of childbearing age

Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Patients that have had failed attempts at biological medicines maybe should be considered first
Other issues	
15. Are there any other issues that you would like the committee to consider?	This treatment could potentially change so many Crohn's patient's lives and surely save millions in surgery costs and stoma appliances
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • • • • • •	

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Darvadstrocel for treating complex perianal fistula in Crohn's disease [ID960]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Damian McCluskey**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Crohns' s Colitis UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with fistulising Crohn's prompts immediate thoughts of pain, fatigue, frustration and embarrassment, not to mention the social and psychological impacts that come with living with the disease. Perianal fistula adversely impacts my quality of life, it restricts ability to work, socialise and includes much thought and planning on a daily basis. For work, I now have 'reasonable adjustments' in place meaning I can occasionally work from home. The pain from the fistula means sitting at my desk for long periods is extremely painful and uncomfortable. Working from home allows me to work from my laptop, lying on my stomach/my front and changing positions frequently to help alleviate the pain of having to sit in the same position and fidget endlessly at

	work. But more often than not I have to be at work which causes me distress and having to put on a brave face as if all was ok. Over the last 10 years I have had at least one surgery per year which has resulted in a minimum of 8-10 weeks off work per episode/surgery. I am lucky to have an understanding employer but because of the desire to be in work I often force myself in when I know I shouldn't be there. Also, it's embarrassing to honestly answer the questions from colleagues regarding my absence so, whilst I appreciate their concern, I tend not to answer honestly to avoid having to explain the experience and associated embarrassment. Socially, from time to time, I am able to play sport with work colleagues. However, I have to take pain relief before and after to enable this. The group will then go to the pub after showering, but I always have to make excuses purely because I am too embarrassed to get into the shower because of the scarring, dressing and seton that is visible. So I continue to make excuses which is really embarrassing for me, and frustrating because it would be really nice to go along. Family time, I have 3 children and my ability to be able to be an active dad is curtailed because of the pain associated with the fistulising Crohns, they love swimming but again it's extremely painful to swim because of pain associated with the movement/stretching of the affected area. Similarly, they love getting on their bikes but I am unable to ride because I simply can't tolerate sitting on a saddle for any length of time. So I have to walk whilst they cycle. The condition has impacted the ability for me to care for my 3 children over the last 14 years, not being able to do the normal things a parent would, because of the chronic, sustained pain, and not forgetting that the extreme guilt that comes with this does not go away. Generally, it can and has been an extremely painful condition to endure, with frequent bouts of infection, fever, drug treatment more often than not leading to surgery. Post surgery, though the acute infection may have been dealt with, the pain and healing process is long and arduous. The healing process of the wound adversely impacts on ability to lead a life without having to plan and cancel activities until fully recovered. Once fully recovered, it's then not unusual to go through the same cycle quite soon afterwards. It affects what would be deemed to be normal things in life, like being able to sit comfortably, being able to socialise without planning/being aware of where the nearest toilet is so you can change dressings that get

	saturated from the constant discharge, that if not dealt with then stain your clothes which causes further upset. It's also the constant cycle of drug therapy and pain relief and the adverse side effects that come with taking immune suppressive therapy and high strength pain relief for a very long period of time. I have taken immunosuppressant therapy for 30 years, anti TNF's for 10 years, anti-inflammatory for 35 years, steroids intermittently and high strength pain relief (opiates/Codeine based drugs) for prolonged periods. I have now ceased immunosuppressant therapy due to the adverse side effects (see Q9 below).
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	The current treatments, especially the biological anti TNF therapies, have had a significant, positive impact on my quality of life. Whilst appreciating they are expensive treatments, the benefits are huge and assume costs may be offset by less surgical interventions and general hospitalisation I have had. Drug treatment, previously i have had periods of high dose oral and enema based steroids (prednisolone) which has come with side effects (moon face) which brings ridicule from 'friends'. Long term treatment has led to issues with thinning of the skin and more recently problems with my joints. And then I have experienced the continual cycle of reducing dose, experiencing flare-ups, then back to a high dose. Immunosuppressive therapy is useful (Azathioprine for example) in conjunction with the biologicals, but still not sufficient to prevent reoccurring fistula/abscess on their own. Antibiotic therapy, in particular Metronidazole, comes with unpleasant the side effects. Whilst long term treatment (up to 3 months) does help, again, like Azathioprine, cannot always be relied on when taken in isolation, to prevent surgical intervention. So whilst the introduction of Biologicals has improved my quality of life, the long team side effects are not truly known. More recently, using Biologicals in conjunction with immunotherapy has adversely impacted my health leading to frequent infection/virus and more recently numerous skin cancers (Basal/Squamous Cell Carcinomas) meaning I have had to cease immunotherapy treatment for a period of time because of the increased risk of taking this therapy with skin cancers and lymphomas.

	I am unable to mitigate the risk/likelihood of having a fistulising Crohns flare up as there are no other medical alternatives.
10. Is there an unmet need for patients with this condition?	I think greater education how to cope post operatively would be advantageous. So in terms of wound healing, someone to manage expectations and healing times, review of medication (as it can be unclear of what to do next as often you're sent home 24 hours after surgery without seeing a Gastro Consultant). A greater number of surgical interventions to be carried out by a Colorectal surgeon as opposed to 'general' surgeons who don't always appreciate the complexity of the fistula or that you even have fistulising Crohns. Psychological support to be offered as the norm – especially for newly diagnosed patients. Unmet need, as a patient, for me what I would want to see is a drive on preventative medicine as opposed to continually going through the cycle of drugs/pain/surgery/wound management. So treatments that are truly effective with minimal or no side effects and that achieve a quality of life I once had pre fistulising Crohns.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Another alternative for patients who have exhausted all their options and are not responding to conventional treatments. Success of any new treatment would positively impact a patient's life, less drug therapy and side effects, less hospital admission and impact on daily life, and an overall improvement in the quality of life for sufferers.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	N/k
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**N/K**

Other issues	
15. Are there any other issues that you would like the committee to consider?	No

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Fistulising Crohns has had a profound, negative impact on the quality of my life
- Drug therapies for the condition can be useful but do not cure nor take away the need for hospitalisation and/or surgery
- There are physical, psychological and social impacts of living with the condition
- The side effects of conventional therapies for fistulising Crohns are unpleasant and can be more serious and as a consequence can lead to further surgery/hospitalisation
- Any new therapy that would limit the disease, with few side effects, would be hugely welcome.

Thank you for your time.

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Darvadstrocel for treating complex perianal fistula in Crohn's disease: A Single Technology Appraisal

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Date completed	Date completed 21/06/2018

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Declared competing interests of the authors

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Abdullah Pandor and Chris Carroll summarised and critiqued the clinical effectiveness data reported within the company's submission. John Stevens critiqued the statistical analyses undertaken by the company. Daniel Pollard and Sarah Davis critiqued the health economic analysis submitted by the company. Ruth Wong critiqued the company's search strategy. Charmian Banks, Janindra Warusavitarne and Baljit Singh provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AE	Adverse event
AIC	Akaike information criterion
BIC	Bayesian information criterion
CD	Crohn's disease
CI	confidence interval
CPC	clinical and patient centric
CS	Company's submission
CSF	Chronic symptomatic fistula
Darv	darvadstrocel
ERG	Evidence Review Group
eASCs	expanded adipose-derived allogeneic mesenchymal stem cells
HR	hazard ratio
HRQoL	Health-related quality of life
HSUV	health state utility value
ICER	Incremental cost-effectiveness ratio
ITT	intention-to-treat
ln	natural logarithm
mITT	modified intention-to-treat
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
QALY	Quality-adjusted life year
QALYs	quality-adjusted life years
RCT	Randomised controlled trial
SE	standard error
STA	Single Technology Appraisal
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's submission (CS) assesses the clinical effectiveness and cost-effectiveness of darvadstrocel (Alofisel®) within its marketing authorisation for the treatment of complex perianal fistulas in adult patients with non-active / mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy. The company's description of complex perianal fistulae in adults with Crohn's disease is broadly appropriate. The decision problem addressed by the CS is partly in line with the final scope issued by the National Institute for Health and Care Excellence (NICE). The submitted evidence is limited to people with fistulas which have up to two internal openings and up to three external openings. Whilst this restriction is consistent with the information in the summary of product characteristics (SmPC) on the number of internal and external openings that can be treated with a single administration of Darvadstrocel, it is not clear whether patients with more openings can have a subset of their fistula treated (i.e. partial treatment) or if they can have all of their fistula treated by using multiple courses of darvadstrocel. Therefore, it is uncertain whether the population missing from the CS may be able to receive treatment under the marketing authorisation for darvadstrocel. With respect to the population of patients included in the CS, the evidence for darvadstrocel is limited to a single treatment administration; the SmPC advises that "there is currently limited experience with the efficacy or safety of repeat administration."

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS includes a systematic review of clinical effectiveness evidence. The ADMIRE-CD study, which forms the main supporting evidence for the intervention, was a Phase III, industry-sponsored, randomised, double-blind, placebo-controlled, multicentre trial (49 sites across eight countries, excluding the UK). ADMIRE-CD was designed to evaluate the efficacy and safety of a single intralesional injection of darvadstrocel (an allogeneic preparation of adipose-tissue-derived mesenchymal stem cells) added on to standard of care in patients (aged ≥18 years) with non-active or mildly active luminal Crohn's disease (defined by a Crohn's Disease Activity Index [CDAI] of ≤220) who had complex perianal fistulas (maximum of 2 internal and 3 external openings that had been draining for at least 6 weeks) that was refractory to conventional therapy. Conventional therapy was defined to consist of at least one of: no therapeutic effect of an antibiotic (recommended treatments were ciprofloxacin and metronidazole) after one month; no response to an immunosuppressant (azathioprine [2-2.5 mg/kg] or 6-mercaptopurine [1-1.5 mg/kg]) after three months, or; no response to an anti-tumour necrosis factor (TNF) inhibitor either 12 weeks after initiation of induction treatment or loss of response after 12 weeks of maintenance treatment under a stable dose.

Prior to randomisation, a pelvic magnetic resonance imaging (MRI) scan was administered (screening visit) and patients' fistula were examined under anaesthesia, curetted and, if indicated, setons were placed during this procedure (preparation visit). If a seton was placed, this was subsequently removed immediately prior to the administration of darvadstrocel. Thereafter, patients were randomly allocated to receive darvadstrocel (24mL containing 120 million expanded allogeneic adipose-derived stem cells) and standard of care (n=107) or placebo sham (saline) and standard of care (n=105) in a 1:1 ratio, with risk stratification based upon previously received therapy (immunomodulators, anti-TNF therapy, both, or neither). After receiving darvadstrocel, patients could be treated with antibiotics for no more than four weeks. Immunomodulators and anti-TNF drugs were maintained at stable doses throughout the study. Initiation or dose increases of these drugs were not allowed. A steroid course was permitted to treat occurrences of luminal disease during the study, with a starting dose of 40mg tapered over a maximum of 12 weeks.

The primary endpoint of the ADMIRE-CD study was combined remission (both clinical and radiologic improvement) at week 24 after study treatment and was defined as the clinical assessment of closure of all treated external openings that were draining at baseline, and the absence of collections >2 cm within the perianal fistula in at least two of three dimensions, confirmed by blinded central MRI. The clinical assessment of closure was defined as the absence of draining despite gentle finger compression. The key secondary endpoints were defined as clinical remission (closure of all treated external openings that were draining at baseline despite gentle finger compression) and response (clinical closure of at least 50% of all treated external openings that were draining at baseline) at week 24. The company also presented two additional *post hoc* analyses - time to clinical and patient centric (CPC) remission and time to relapse from CPC remission. These outcomes were the ones used in the economic model as they were considered by UK clinical experts to be the most relevant way to measure remission and relapse in a population who were refractory to at least one conventional (i.e. antibiotics, immunosuppressants) and/or biological therapy. In addition, following a series of protocol amendments, long-term follow-up was extended to week 52 and then to week 104; however, the efficacy data beyond 52 weeks were limited (only 40/212 [18.9%] patients entered into the 104 week follow-up) as a number of patients had already finished the 52 week trial period. The main efficacy analyses were conducted using the intention-to-treat (ITT) approach (which included all randomly assigned patients, n=212) and the modified ITT (mITT) approach (which included all randomly assigned patients who received study treatment and had at least one efficacy assessment after baseline, n=204). The population used to assess safety was all randomly assigned patients who received study treatment (n= 205).

In the primary ITT population (n=212), a significantly greater proportion of patients in the darvadstrocel group achieved the primary endpoint of combined remission at week 24 compared with the control group (49.5% versus 34.3%, respectively; difference of 15.2%; 97.5% confidence interval [CI] 0.2% to

30.3%; p=0.024). With longer follow-up (52 weeks), the beneficial effect of darvadstrocel was maintained in the ITT population with 54.2% of patients achieving combined remission compared with 37.1% in the control group (difference of 17.1%; 97.5% CI: not reported; p=0.012). Similar results were observed in the mITT population (p=0.021 at week 24 and p=0.010 at week 52).

A range of secondary endpoints were evaluated in the ADMIRE-CD study. In general, darvadstrocel demonstrated greater improvements in clinical remission (week 24, p=0.064 in ITT population; week 52, p=0.013 in mITT population [data not reported for ITT population]) and response (week 24, p=0.054 in ITT population; week 52, p=0.128 in mITT population [data not reported for ITT population]); however, no significant differences (p>0.05 in mITT population) were observed in total Perianal Disease Activity Index, Crohn's Disease Activity Index, Inflammatory Bowel Disease Questionnaire and Van Assche scores (p=not reported) at week 24 or week 52.

Adverse events (AEs) were common and were reported by approximately two-thirds of patients receiving darvadstrocel at 24 weeks in the ADMIRE-CD trial. The most common treatment-emergent AEs (TEAEs) were proctalgia (12.6% of patients in the darvadstrocel arm versus 11.8% in the control arm), anal abscess (11.7% versus 12.7%), nasopharyngitis (9.7% versus 4.9%) and diarrhoea (6.8% versus 2.9%). The percentages of patients experiencing the principal TEAEs and severe TEAEs (TESAEs) were generally similar across the darvadstrocel and control arms at 24 weeks. The ERG noted that proctalgia, anal abscess and anal fistulae are symptomatic of the indication in this appraisal and therefore might represent treatment failure, i.e. a lack of efficacy, rather than an AE related to the treatment. Safety data were also available for 52 weeks from the ADMIRE-CD trial. The percentages of TEAEs, treatment-related TEAEs, severe TEAEs (TESAEs), and withdrawals due to treatment-related TEAEs among patients in the darvadstrocel arm were all higher at 52 weeks than at 24 weeks. It was also the case that the percentages of patients experiencing key TEAEs, previously similar between arms at 24 weeks, had by 52 weeks become noticeably higher in the darvadstrocel arm than the control arm: anal abscess (19.4% of patients in the treatment arm versus 13.7% in the control arm, of which 13.6% versus 7.8% were TESAEs); anal fistula (10.7% versus 7.8%) and nasopharyngitis (10.7% versus 4.9%). The ERG also noted that the frequency of treatment-related TEAEs among patients at 24 weeks was higher in the earlier Phase I/II trial than the later ADMIRE-CD trial. This might be explained by the considerably lower dose of darvadstrocel in the earlier trial (<60 million expanded adipose-derived allogeneic mesenchymal stem cells [eASCs] versus 120 million eASC) and the issue that some TEAEs and treatment-related TEAEs might represent a lack of efficacy rather than AEs.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic review process followed by the company was reasonably comprehensive. Despite minor limitations in the company's search strategy, the ERG is reasonably confident that all relevant published studies of darvadstrocel were included in the CS, including data from ongoing studies. The specified inclusion and exclusion criteria were mostly appropriate and generally reflected the scope. The validity assessment tool used to appraise the ADMIRE-CD was considered appropriate by the ERG.

Although the efficacy (assessed in terms of combined remission and CPC remission) in the ADMIRE-CD study appears favourable, and the safety appears acceptable, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation.

A key limitation of the efficacy and safety data for darvadstrocel relates to the *post hoc* analyses of CPC remission (an outcome used in the economic model) and CPC relapse. These endpoints were not designed or powered to test formal hypotheses. As a result, these results should be treated with caution. It should be noted that the CPC definition of remission was considered by the ERG's and the company's clinical experts to be the most relevant way to measure remission and relapse in a population with complex perianal fistula and non-active / mildly active luminal Crohn's disease who were refractory to at least one conventional and/or biological therapy. Another issue is the lack of a confirmatory study. The effect size in the ADMIRE-CD trial was considered to be modest and less than the 25 percentage difference that it was designed to detect but was considered clinically meaningful given that other treatment options for fistulas had failed. A post-authorisation efficacy and safety trial, ADMIRE-CD-II is expected to help address this concern. However, this study not expected to be complete until October 2021.

The key uncertainties in the clinical evidence for darvadstrocel relate to repeated administration, optimal dosing and long-term efficacy and safety.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's *de novo* state transition model assesses the cost-effectiveness of darvadstrocel versus standard care (based on the ADMIRE-CD trial) in adults with complex perianal fistula with non-active/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy. Incremental health gains, costs and cost-effectiveness of darvadstrocel are evaluated over a 40-year time horizon from the perspective of the National Health Service (NHS) and Personal Social Services (PSS). The company's model is comprised of eight health states: (1) mild chronic symptomatic complex perianal fistulae (CSF); (2) severe CSF; (3) remission; (4) defunctioning surgery (cycle 1); (5) defunctioning surgery (subsequent cycles); (6) proctectomy (cycle 1); (7) proctectomy (subsequent cycles) and (8) death. The transitions between the remission and

the two CSF health states were generated from analyses of time-to-event data (CPC remission and CPC relapse) from the ADMIRE-CD study. CPC remission and CPC relapse are both modelled using a Gompertz distribution with the differences between the two arms being estimated using a treatment effect covariate (a hazard ratio). A retrospective study at St Marks hospital (a national referral centre for intestinal and colorectal diseases) in the UK was used to determine: the proportion of CSFs which are mild; the proportion of defunctioning surgeries which are successful, and; the proportion of proctectomies which are successful. The annual probability of receiving a defunctioning surgery and the annual probability of receiving a proctectomy were estimated from the literature. Health-related quality of life (HRQoL) is principally determined by the time spent in the different model health states and the incidence of treatment related adverse events; these estimates are informed by a vignette study. Resource use estimates and costs were based on data collected in the ADMIRE-CD trial, clinical expert opinion and routine cost sources. The company states that they believe that Section 6.2.19 of the NICE Methods Guide applies when considering the cost-effectiveness of darvadstrocel and consequently darvadstrocel should be assessed using a discount rate of 1.5% for and quality adjusted life years (QALYs) and 3.5% for costs. The company's rationale is that: (1) as darvadstrocel demonstrates long term healing potential in this population with a significant impact on QoL and the condition often affects young people and has a median age of onset of 15-30 years, and so the benefit of an effective treatment in this young population is likely to provide long term health benefits (>30 years), and; (2) darvadstrocel is unlikely to commit the NHS to significant irrecoverable costs.

Based on the probabilistic version of the model (assuming a 3.5% discount rate for both costs and QALYs), darvadstrocel is expected to generate 1.02 additional QALYs at an additional cost of £21,773 per patient; this corresponds to an incremental cost-effectiveness ratio (ICER) for darvadstrocel versus standard care of £21,417 per QALY gained. The deterministic version of the company's model produces a similar ICER of £20,591 per QALY gained. Assuming a maximum acceptable ICER (MAICER) of £20,000 and £30,000 per QALY gained, the company's model suggests that the probability that darvadstrocel produces more net benefit than standard care is 0.421 and 0.736, respectively.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG critically appraised the company's economic analysis and double programmed the deterministic version of their model. The ERG's critical appraisal identified eleven issues relating the company's economic analysis and the evidence used to inform it. These include: (1) exclusion of relevant patient groups from the economic analysis; (2) possibility of repeat administrations of darvadstrocel; (3) whether costs and QALYs should be discounted at 1.5% by applying Section 6.2.19 of the NICE Methods Guide, is justified; (4) wastage of darvadstrocel; (5) the company's selection of time to relapse and time to remission time to event functions; (6) the company's expert elicitation exercise to estimate the time to relapse and remission for people on third or later line therapies; (7) the

data used to populate the transitions to the defunctioning and proctectomy health states; (8) missing transitions within the model structure; (9) the company's approach to identifying HRQoL data from the literature; (10) the estimates of utilities from a vignette study; (11) adoption of a 40-year time horizon.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company undertook a reasonably comprehensive systematic review of darvadstrocel for the treatment of complex perianal fistulae in patients with Crohn's disease. No major limitations were noted with the review. The ADMIRE-CD study was a well-reported and conducted randomised controlled trial (RCT) and measured a range of clinically relevant outcomes.

1.6.2 Weaknesses and areas of uncertainty

Although darvadstrocel offers a novel treatment option with curative intent there are a number of uncertainties in the evidence base: (1) there is no robust supporting data beyond 52 weeks follow-up; (2) there is no evidence on the repeated use of darvadstrocel (licensed dose) when new fistulas open; (3) it is unclear whether patients who have not achieved complete closure with one treatment course would benefit from an additional treatment course, and; (4) whether stem cell therapy would be effective in patients with very complicated perianal fistulising disease who may have more than two internal and/or three external openings.

No evidence was submitted on the cost-effectiveness of darvadstrocel for the treatment of: (1) people who have more than two internal openings or more than three external openings of their complex perianal fistula, or (2) people who receive darvadstrocel as a repeat treatment. The ICER for darvadstrocel versus standard care cannot be estimated in either of these populations and may be substantially different from the ICER for the population considered in the CS. It is unclear whether the ICER would be lower or higher than the base case ICER in these populations.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook eight sets of exploratory analyses using the deterministic version of the company's model. The ERG's preferred model uses a discount rate of 3.5% for both costs and QALYs and produces a deterministic ICER for darvadstrocel of £23,176 per QALY gained. This model includes: the correction of several minor errors; calibration of the health state occupancy of the defunctioning surgery and proctectomy health states to their data sources; estimating the long term event rates for the salvage therapy arm using the time to event functions for salvage therapy, and; setting the time horizon to 60 years. The ERG undertook a number of further analyses to explore the sensitivity of the ICER to; the inclusion of transitions that were not included in the company's base case model; the impact of under predicting utility values for the CSF mild, successful defunctioning surgery and the successful

proctectomy health states; the impact of using alternative time to event functions; and to assess whether darvadstrocel meets the criteria in Section 6.2.19 of the NICE methods guide. The ERG considers that the exploratory analysis on whether darvadstrocel meets the criteria in Section 6.2.19 of the NICE methods guide indicates that these criteria are not met. Consequently, the ERG considers that both costs and QALYs should be discounted at a rate of 3.5%. The other exploratory analyses suggest that the ICER is sensitive to the time to event functions and any under prediction of the utility values for the CSF mild, successful defunctioning surgery, and/or the successful proctectomy surgery health states. Including additional transitions within the company's model structure has only a minor impact on the ICER.

2 BACKGROUND

This report provides a review of the evidence submitted by the company (Takeda) in support of darvadstrocel for treating complex perianal fistulae in people with Crohn's disease. It considers both the company's submission (CS) received on 20th April 2018 and a subsequent response to clarification questions supplied by the company on 24th May 2018.[1, 2]

2.1 Critique of company's description of underlying health problem

The CS (pages 14-25) provided a reasonable description of the underlying health problem.[1] The health problem is summarised briefly below.

A perianal fistula is an abnormal passage or tract between the bowel and the perianal region. A complex perianal fistula is difficult to define, but perianal fistulae are usually considered complex if (i) their origin is high enough in the bowel to result in the tract having sphincter involvement or (ii) there are multiple branches with more than one internal or external opening. Information on the aetiology is limited, but in people with Crohn's disease, inflammation of the bowel can lead to repeated abscesses and the development of a perianal fistula and the inflammation of the bowel wall inhibits healing of the fistula.

No direct evidence exists on the incidence of complex perianal fistulae in people with non-active / mildly active Crohn's disease in the UK. In the CS, the company combines evidence on the incidence of Crohn's disease in the UK and data from the Netherlands on the incidence of perianal fistulae to estimate that 7,473 people in the England will have a perianal fistulae and Crohn's disease. The incidence of complex perianal fistulae in people with non-active/mildly active Crohn's disease will be a subset of this population.

Complex perianal fistulae are not associated with mortality, however the available evidence suggests that there is a high morbidity and significant impairment in quality of life (QoL). Symptoms of a perianal fistula include: persistent anal and/or abdominal pain, perianal inflammation, pain during defaecation, continuous malodorous drainage (pus, blood, and faecal material), incontinence, and skin irritation around the anus.[3, 4] As complex perianal fistulae can lead to the development of repeated abscesses, additional effects on QoL include fevers related to an abscess, severe pain, and the abscess itself will require surgical drainage.

2.2 Critique of company's overview of current service provision

In general, the CS provides a reasonable overview of current service provision for people with complex perianal fistula and Crohn's disease.[1] The company's description of the treatment pathway is briefly summarised in this section.

First-line treatment for people with Crohn's disease who are diagnosed with a complex perianal fistula consists of examination under anaesthesia (EUA), abscess drainage and loose seton placement. Seton placement involves placing a piece of silicone string into the fistula tract to ensure that the fistula remains open so that it can drain and heal adequately from the middle of the fistula towards the openings. The timing of the seton removal will depend on any other treatments which are given. If the patient has active luminal Crohn's disease, this will be treated in conjunction with the surgical management of the fistula. Immunosuppresants and/or biologics are treatment options to manage any luminal disease that is present in people with complex perianal fistulae who also have mildly luminal Crohn's disease.

Second-line treatment for people who are refractory to first-line treatments is poorly defined and care varies widely across sites even within the UK. Medical decision teams will typically make choices based on their own experience. Data from St Mark's hospital (a UK national referral centre for intestinal and colorectal diseases) indicates that care varies greatly for people in second-line treatment and beyond. Typically, a new seton will be placed and a different medical treatment (from the previous line treatments) will be used. This was also indicated to be the case by the advisors to the ERG. After several lines of failed therapy, patients may go on to receive defunctioning surgery (potentially temporary) or proctectomy (permanent). Defunctioning surgery involves a temporary diversion of the bowel, so that the fistula can heal. A proctectomy involves a permanent removal of the bowel to bypass the perianal fistula.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

3.1 Population

The population defined in the final NICE scope relates to adults with non-active/mildly active luminal Crohn's disease, with complex perianal fistulas which have shown an inadequate response to at least one conventional or biologic therapy.[5]

The population in the CS differs from this population, as it includes only those people with non-active/mildly active luminal Crohn's disease, with complex perianal fistulas which have shown an inadequate response to at least one conventional or biologic therapy who also: (i) have two or less internal openings and three or less external openings of their complex perianal fistula, and; (ii) are naïve to darvadstrocel treatment.

The Summary of Product Characteristics (SmPC) for darvadstrocel, specifies that the full content of four vials must be administered to treat no more than two internal openings or three external openings. It is unclear from the SmPC whether darvadstrocel is licenced to be given more than once; this has two implications.

Firstly, it is unclear from the SmPC whether two procedures could be administered to people who have more than two internal openings or more than thee external openings. The clinical advisors to the ERG stated that care does not currently differ according to the number of external or internal openings of a patient's complex perianal fistula. As such, it is ambiguous whether the population with more than two internal openings or three external openings could be treated with darvadstrocel given the current licence. Therefore, caution may be warranted in interpreting the evidence in this submission for this excluded population, as under the marketing authorisation they may be eligible to receive darvadstrocel.

Secondly, the SmPC does not specify that darvadstrocel can only be administered once per patient, therefore the current licence may allow repeated administration of darvadstrocel. The population included in the final CS does not include any evidence for those people who receive multiple darvadstrocel administrations. As stated in the company's clarification response to question A1, the company have "… *elected to base the submission on single use only….*".[2]

3.2 Intervention

The intervention under appraisal is darvadstrocel (24mL dose). Four vials of darvadstrocel are required for a single treatment course. Each vial contains a suspension of 30 million expanded adipose stem cells in a 6mL solution, giving a total dose of 120 million cells per treatment. Darvadstrocel currently holds

an European Union (EU) marketing authorisation for the treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy.[6]

The list price of darvadstrocel stated in the CS (page 12, Table 3) is £13,500 per vial, which corresponds to a total drug cost of £54,000 for one course of treatment. A Patient Access Scheme has been approved by the Department of Health involving a simple price discount. Including the discount, the price of darvadstrocel is [redacted] per vial and a total course of treatment costs [redacted].

Contraindications for darvadstrocel include hypersensitivity to: Dulbecco's Modified Eagle´s Medium, human albumin, or bovine serum.

3.3 Comparators

The final NICE scope identified surgical management without darvadstrocel as the only relevant comparator.[5]

The company's review of clinical effectiveness (see Section 0) identified two studies which included direct head-to-head comparisons of darvadstrocel versus surgical management without darvadstrocel. Only the ADMIRE-CD study had a dosing schedule (120 million cells, 4 vials multiplied by 30 million cells per vial) which is in line with the European Medicines Agency (EMA) licence for darvadstrocel.[7] In the other study by de la Portilla *et al*., a dosing schedule of 20 million cells were administered at baseline and in the event of incomplete closure at 12 weeks a further 20 million cells were administered.[8] The clinical evidence which is used to estimate the differences in costs and QALYs between darvadstrocel and surgical management without darvadstrocel in the health economic model is largely based on the ADMIRE-CD study.[7, 9]

3.4 Outcomes

The final NICE scope lists the following outcomes[5]:

- Closure of fistula
- Recurrence of fistula
- Continence
- Mortality
- Adverse effects of treatment
- Health-related quality of life (HRQoL)

The CS reports on all of these outcomes, except continence, for patients receiving darvadstrocel or standard care within the ADMIRE-CD study. The ERG's clinical advisors believed that continence was

an important outcome measure, however they thought it was unlikely that incontinence would differ between the darvadstrocel and control arms of ADMIRE-CD.

However, the definition of closure and recurrence of the fistula used in the cost-effectiveness model is defined using a *post hoc* composite outcome, which the company calls clinical and patient-centric (CPC) remission. CPC remission is defined as the closure of external openings as per clinical assessment (not draining when gently compressed with fingers) and the patient does not experience any pain or discharge (defined as a patient scoring 0 in both the pain and discharge sections of the Perianal Disease Activity Index [PDAI] scale). This outcome measure, whilst not pre-specified in the scope, was deemed to be the most relevant outcome by the ERG's clinical advisors for second-line treatment of complex perianal fistulae in people with Crohn's disease.

Fistula recurrence was defined as the lack of continued CPC remission. The ERG's clinical advisors considered that a clinical diagnosis of recurrence of a complex perianal fistula would be made based on clinical factors such as pain, discharge and whether the fistula was adequately draining. However, a successful outcome would not require the fistula to be completely healed.

Mortality was reported in the CS as an adverse event, rather than a primary or secondary outcome in the efficacy analysis.[1] However, this was deemed to be appropriate as there were no deaths in the ADMIRE-CD trial.

HRQoL was captured in the ADMIRE-CD study using the inflammatory bowel disease questionnaire (IBDQ), which is a disease specific measure focused on systemic bowel disease (i.e. luminal Crohn's disease) rather than perianal fistulising disease. The source of utility values for the economic valuation was a separate vignette study (CS,[1] Appendix Q).

3.5 Other relevant factors

The CS (page 25) states that there are no equality considerations relevant for the use of darvadstrocel in the treatment of complex perianal fistulae in patients with Crohn's disease.

The company claims that darvadstrocel meets criteria set out in Section 6.2.19 in the NICE Methods Guide (CS, page 64), QALYs should be discounted at 1.5% in the base case.[1, 10] These criteria require that: darvadstrocel restores people to full health for a long period of time (normally at least 30 years); that people receiving standard care have a severely impaired quality of life or would otherwise die, and; that darvadstrocel would not commit the NHS to significant irrecoverable costs. The ERG believes that darvadstrocel does not meet these criteria and, as such, both costs and QALYs should be discounted at 3.5% (see Sections 5.3.4.3 and 5.4).

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company performed a single clinical effectiveness search to identify all studies of darvadstrocel and its comparators (broadly called surgical interventions, antibiotics, immunosuppressants, biologics and stem cells) for patients with complex perianal fistula in Crohn's disease.

For the searches, three electronic bibliographic databases including MEDLINE [via Embase.com], MEDLINE in Process [via PubMed], EMBASE [via Embase.com], Cochrane Central Register of Controlled Trials [via Wiley Online Library]) were searched covering the period from inception of the database until January 2018. Several conference proceedings websites (ECC, UEG, AGA/DDW, ESCP, WCG, AIBD, ISPOR) were searched in January 2018 covering the period from 2014 until 2017. The CS did not appear to have searched any clinical trials registers such as clinicaltrials.gov or WHO International Clinical Trials Registry Platform nor did the company report carrying out supplementary searching such as citation searching of included studies. The company's clarification response (question A12) gave details of one ongoing study of darvadstrocel.[2]

In the CS (Appendix D), the company reported the full literature search strategies of the databases searched.[1] The scope of the searches took into account the potential need to make simultaneous comparisons between all interventions (e.g. infliximab, adalimumab, surgical treatment and best supportive care) in the draft NICE scope (the ERG notes that the final scope issued by NICE limited the comparators to surgical management without darvadstrocel only).[5, 11] The search strategy was designed to identify RCTs and systematic reviews of the relevant intervention, darvadstrocel, as well as studies reporting on any comparators relevant to the scope for patients with complex perianal fistula in Crohn's disease (clarification response[2], question A9). Given the broad range of possible comparators, the searches consisted only of terms for 'Crohn disease' or 'fistula' combined/not combined with terms for the comparators and search filters for the relevant study types. However, the strategies did not include all free-text terms for darvadstrocel. At the time of the company searches, darvadstrocel was not indexed in the database (clarification response[2], question A11). The company's amended search, which included keywords for ileostomy, colostomy and new interventions such as stem cells, was provided in the company's clarification response (question A11).[2]

Despite the noted limitations, the ERG considers all the search strategies to be sufficiently comprehensive to retrieve all important and eligible studies of which the ERG and its clinical advisors are aware. However, as no search details/strategies were provided in the CS, it is unclear whether any relevant AE studies have been missed.

4.1.2 Inclusion criteria

The CS describes appropriate methods of identifying and screening references for inclusion in the systematic reviews of clinical effectiveness. Two independent reviewers applied pre-specified inclusion and exclusion criteria (via a two-stage sifting process) to citations identified by the searches. Any differences in selection process were resolved through consultation with a third reviewer, if required (CS, Appendix D.1.2). A summary of the inclusion and exclusion criteria is presented in Table 1.

Table 1: Inclusion/exclusion criteria used select studies of patients with complex perianal fistula and Crohn's disease (adapted from CS,[1] Appendix D, Table 7)

Clinical effectiveness	Inclusion criteria		Exclusion criteria	Rationale
Population	Patients with perianal fistula in Crohn's disease, irrespective of the age, race, or ethnicity		Studies which enrolled a mixed population of perianal fistula in Crohn's disease, ulcerative colitis and inflammatory bowel disease of undetermined origin were only included if there was subgroup data for the disease of interest or 80% of the study population met the eligibility criteria of the review	The review is not limited to patients with any particular age group, and does not restrict to any specific gender or race
Intervention	• 'Cx601' (darvadstrocel)			
Comparators	Surgical interventions • Fibrin glue • advancement flap, • LIFT, • diverting stoma, • proctectomy, • colectomy, • fistula plugs, • fistulotomy, • exam under anaesthesia, • multiple seton placement, • ileostomy, • colostomy, • VAAFT and • Filac	Antibiotics • Ciprofloxacin* • Metronidazole* • Azathioprine* Immunosuppressants • Cyclosporine* • Tacrolimus* • Methotrexate* • Thalidomide* • 6-MP* Biologics • Infliximab* • Adalimumab* • Certolizumab* Other interventions • stem cells*		Surgical interventions are included in the NICE scope. Antibiotics, immunosuppressants, biologics and other stem cell preparations were included in the search for HRQoL

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Rationale
Outcomes	• Remission rate • Relapse rate • Definitions of outcomes • No response/failure rate • Fistula closure and partial closure as defined by clinical exam • Fistula internal closure as demonstrated by MRI • Relapse or recurrence rate • Time to remission/relapse • Proportion of patients with draining fistula • Stoma closure • Seton removal time • Mortality • Safety (any adverse events, serious adverse events, specific adverse events) and tolerability (discontinuations due to any reason or due to any adverse event) • HRQoL measures, either disease specific or generic • Perianal Disease Activity Index (PDAI) • Crohn's Disease Activity Index (CDAI) • Inflammatory Bowel Disease Questionnaire (IBDQ) • Short Form 36 Item (SF-36) • EuroQoL-5D (EQ-5D) • Incontinence scores		
Study design	• RCT - parallel group • RCT - crossover • Non-randomized controlled clinical trials • Controlled cohort studies (retrospective) • Controlled cohort studies (prospective) • Case-control studies • Cross-sectional studies • Analysis of hospital records/database/chart/claims database • Single arm studies (uncontrolled trials) • For the UK/NICE perspective, only RCTs will be considered for extraction in the clinical review		
Language restrictions	English		

• CD, Crohn's disease; HRQoL; health related quality of life; MRI, magnetic resonance imaging; RCT, randomised controlled trial

The specified inclusion and exclusion criteria were mostly appropriate and generally reflected the decision problem. It is noteworthy that the CS[1] (page 25) initially considered a wider remit to capture the entire evidence base as part of the inclusion criteria for the review (i.e. all treatments used for the

management of complex perianal fistulae in patients with Crohn's disease) but then restricted the systematic review only to those studies which are directly relevant to the decision problem (i.e. darvadstrocel treatment only [see CS,[1] Section B.2.2]). Despite a request from the ERG to provide separate inclusion and exclusion criteria for two parts of the review, this was not provided by company (clarification response[2], question A9). Ideally, systematic reviews should have clearly focused research questions and inclusion/exclusion criteria at the outset.

The company's systematic review excluded studies which were reported only as abstracts (CS,[1] Appendix D.1.2, Figure 1); however, limited justification for this exclusion was provided. In order to avoid publication bias, a systematic review should aim to include all relevant studies, regardless of publication status. Although differences often occur between data reported in conference abstracts and their corresponding full reports, differences in results are usually not very large.[12] However, the ERG notes that it can be difficult to appraise study quality from limited details provided in an abstract. As a result, sensitivity analyses may be carried out to examine the effect of including data from conference abstracts.[13]

Finally, the reporting of clinical harms is often inadequate in controlled clinical trial publications because they exclude patients at high (or even medium) risk from harms,[12, 14] they may be too short to identify long-term or delayed harms, or they may have insufficient sample sizes to detect rare events.[12, 15] Supplementary sources of evidence may provide additional supporting information concerning safety considerations.[16] The SmPC (pages 11 and 12) suggests that the marketing authorisation was granted with a number of conditions and included the following: periodic safety update reports, adherence to the agreed risk management plan, additional risk minimisation errors (i.e. provide educational material for healthcare professionals on how to give the medicine correctly and on the possibility of passing on an infection to the patient), and conducting a post-authorisation efficacy and safety study - ADMIRE-CD-II (expected to complete in October 2021 [clarification response[2], question A9]).

4.1.3 Critique of data extraction

The data extracted and presented in the clinical section of the CS appear appropriate and comprehensive. Although details of the data extraction process were lacking in the CS, the company's clarification response (question A13) suggests that data extraction was undertaken by two independent reviewers and disagreements were resolved through consultation with a third reviewer.

4.1.4 Quality assessment

The validity assessment tool used to appraise the included studies in the CS[1] (Appendix D.3, p22-23) was based on the minimum criteria for assessment of risk of bias in RCTs, as suggested by the Centre for Reviews and Dissemination.[12] As noted in the company's clarification response (question A13)

methodological quality assessment of included studies was performed by two independent reviewers and disagreements were resolved through consultation with a third reviewer.[2] The ERG acknowledges that the validity assessment tool used in the CS was appropriate.[1]

4.1.5 Evidence synthesis

The company did not undertake a formal meta-analysis as only one darvadstrocel RCT study was considered relevant to the submission. As a result, the company undertook a narrative synthesis of the evidence for darvadstrocel. However, no explicit details were provided in the CS[1] on how this approach was undertaken. Ideally, a narrative synthesis approach should be justified, rigorous (i.e. describe results without being selective or emphasising some findings over others) and transparent to reduce potential bias.[12, 15] Despite the lack of transparency regarding the methods adopted, the ERG acknowledges that the narrative synthesis approach undertaken by the company was acceptable.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Studies included in/excluded from the submission

The company's Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram relating to the literature searches does not conform exactly to the PRISMA statement flow diagram (http://www.prisma-statement.org/). Despite this, the revised diagram and accompanying narrative provided in the company's clarification response (questions A15 and A16) appear to be a reasonable record of the literature searching and screening process for the systematic literature review of treatments used for the management of complex perianal fistulae in patients with Crohn's disease.[2] Moreover, although the CS initially failed to provide a full and explicit breakdown of the reasons why each citation was rejected (especially after full text papers were retrieved for detailed evaluation), further details were provided by the company in their clarification response (questions A14 and A16).[1, 2]

The company's systematic review of darvadstrocel for the treatment of complex perianal fistulae in patients with Crohn's disease identified two potentially relevant studies (a Phase I/IIa study[8] and a Phase III study).[7, 9] However, as suggested in the CS[1] (p24) and the European Public Assessment Report (EPAR),[17] the design and context of the Phase I /IIa study[8] was not considered to be entirely relevant to the recommended dosing or the licenced indication in the approved product label for darvadstrocel (further details of this study are briefly provided in Section 4.2.4.2). As such, evidence from the Phase III ADMIRE-CD study[7, 9] forms the main pivotal evidence in the CS.[1] Further details of this study are provided in this section.

The company's broader systematic review of all RCTs for complex perianal fistulae in patients with Crohn's disease (which was conducted to assess the feasibility of performing a network meta analysis (NMA) against other treatment options, such as: surgical interventions and medical treatments [i.e. antibiotics, immunosuppressants and biologics; however, these were not included in the final scope issued by NICE])[5] initially identified six potential studies (clarification response,[2] question A15 and A16). Of these, no additional studies to the ADMIRE-CD trial[7, 9] were considered relevant to the decision problem. The company stated that "… *an NMA could not be conducted due to a lack of comparable RCTs and considerable heterogeneity in the studies identified by the systematic review. The assessment found a high level of variability in the comparators, outcomes, patient populations, and sample size across studies.*" (CS,[1] page 53).

- Main evidence (pivotal study: ADMIRE-CD)[7, 9]

The ADMIRE-CD study[7, 9] was a Phase III, company-sponsored, randomised, double-blind, placebo-controlled, multicentre trial designed to assess the efficacy and safety of a single intralesional injection of darvadstrocel (an allogeneic preparation of adipose-tissue-derived mesenchymal stem cells) and standard of care in 212 patients (54.7% male, 92.5% Caucasian) with non-active or mildly active luminal Crohn's disease (defined by a Crohn's Disease Activity Index [CDAI] of ≤220) who had complex perianal fistulae that was refractory to conventional (i.e. antibiotics, immunosuppressants) and/or biological therapy. There is some uncertainty about the repeat use of darvadstrocel in clinical practice, it should be noted that the company states that "*Although some clinicians believe that Alofisel [darvadstrocel] may be beneficial for retreatment in the following patient groups; (i) partial responders; (ii) responders who have relapsed, there is no current evidence to support this treatment approach… therefore elected to base the submission on single use only*" (clarification response[2], question A1). A summary of the study design and population characteristics is provided in Table 2.

The study included patients from 49 hospitals across seven European Union countries (Austria, Belgium, France, Germany, Italy, the Netherlands, and Spain) and Israel. Eligible patients were enrolled between July 2012 to July 2015 and were required to be: (i) ≥18 years old (mean age, 38 years; >65 years, n=7)[17]; (ii) diagnosed with Crohn's disease at least 6 months earlier (in accordance with accepted clinical, endoscopic, histological and/or radiologic criteria); (iii) had complex perianal fistulas with a maximum of 2 internal and 3 external openings (assessed by clinical assessment and MRI) that had been draining for at least 6 weeks (a complex perianal fistula was defined as one or more of the following during its evolution: high intersphincteric, high trans-sphincteric, extra-sphincteric, or supra-sphincteric origin; at least two external openings (tracts); or associated collections); (iv) refractory to antibiotics (ciprofloxacin or metronidazole with lack of response after one month of treatment), immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate with no response after 3 months), or induction or maintenance therapy with anti-TNF therapies. The key exclusion criteria were: (1) a

history of rectovaginal fistulas; (2) rectal and/or anal stenosis and/or active severe proctitis; (3) diverting stomas, an abscess (collection >2 cm) that was not properly drained at the fistula preparation visit; (4) received corticosteroids within the previous 4 weeks; (5) if they had not received previous treatment for perianal fistulising Crohn's disease including antibiotics, and those who underwent previous surgery for the active fistula other than drainage or seton placement.

Table 2: Characteristics of the ADMIRE-CD study[7, 9]

Study	Location (sites)	Design	Population	Intervention	Comparator	Primary outcome measures	Duration
ADMIRE-CD (NCT01541579; Cx601-0302)[7, 9] Funded by: TiGenix	49 sites in 8 countries (Austria, Belgium, France, Germany, Italy, the Netherlands, Spain and Israel)	Phase III, randomised, double-blind, parallel group, placebo controlled trial (n=212)	Patients (aged ≥ 18 years) with complex perianal fistulising Crohn´s disease who are refractory to conventional (antibiotics, immunosuppressants) or biological treatment strategies	Darvadstrocel (24 mL containing 120 million expanded allogeneic adipose-derived stem cells) given as a single intralesional injection[a] and standard of care (n=107)	Placebo (24 mL saline solution) given as a single intralesional injection and standard of care (n=105)	Combined remission (clinical and MRI) at 24 weeks[b]	Active treatment consists of one administration of darvadstrocel, follow-up extended from 24 weeks to 52 weeks and then to 104 weeks[c]

MRI, magnetic resonance imaging

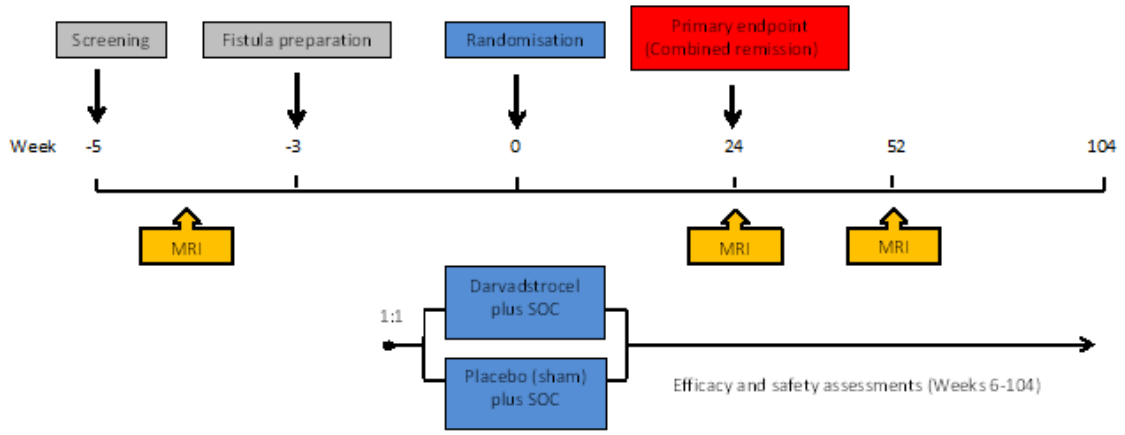
[a] The administration procedure involved the injection of darvadstrocel (or placebo) into the tissues surrounding the tract. Four vials (6mL each) containing approximately 30 million cells were shipped to the hospital for use by the surgeon on the day they were received. The content of two vials (60 million cells) was injected into the fistula walls along the length of the fistula tract and two vials (60 million cells) injected around the internal opening during an Examination Under Anaesthesia. This procedure was done by specialist physicians experienced in the diagnosis and treatment of conditions for which darvadstrocel is indicated.

[b] Defined as the clinical assessment of closure of all treated external openings that were draining at baseline, and the absence of collections > 2 cm of the treated perianal fistula in at least two of three dimensions, confirmed by masked central magnetic resonance imaging. Clinical assessment of closure was defined as the absence of draining despite gentle finger compression.

[c] Following a series of protocol amendments, the follow-up period was extended to 52 weeks (October 2012) and then to 104 weeks (December 2014)[17]

Prior to randomisation, a pelvic MRI was administered (screening visit) and patients' fistulae were examined under anaesthesia, curetted and, if indicated, setons were placed during this procedure (preparation visit). If a seton was placed, this was subsequently removed immediately prior to the administration of darvadstrocel Subsequently, patients were randomly allocated to receive darvadstrocel and standard of care (n=107) or placebo sham (saline) and standard of care (n=105) in a 1:1 ratio, with risk stratification based upon previously received therapy (immunomodulators, anti-TNF therapy, both, or neither). A summary of the ADMIRE-CD trial[7, 9] schema is presented in Figure 1.

Figure 1: ADMIRE-CD trial schema (adapted from CS,[1] Figure 7)



MRI, magnetic resonance imaging; SOC, standard of care

After darvadstrocel administration, patients could be treated with antibiotics for no more than four weeks. Immunomodulators and anti-TNF drugs were maintained at stable doses throughout the study. Initiation or dose increases of these drugs were not allowed. A steroid course was permitted to treat occurrences of luminal disease during the study, with a starting dose of 40 mg tapered over a maximum of 12 weeks. Fistula closure was clinically assessed at weeks 6, 12, 18, and 24, 36 and 52; assessing for spontaneous drainage after gentle finger compression was applied to treat external openings. Fistula-associated collections were also radiologically assessed at weeks 24 and 52 by blinded, centrally read pelvic MRI scans. The study protocol was amended five times (CS,[1] page 31), the ERG considers that the most notable change included extending the trial duration from 24 weeks to 104 weeks to allow assessment of long-term efficacy and clinical and immunological safety of darvadstrocel treatment.

The primary endpoint was combined remission (both clinical and radiologic improvement) at week 24 after study treatment and was defined as the clinical assessment of closure of all treated external openings that were draining at baseline, and the absence of collections >2 cm within the perianal fistula in at least two of three dimensions, confirmed by blinded central MRI. The clinical assessment of closure was defined as the absence of draining despite gentle finger compression. The key secondary

endpoints were defined as clinical remission (closure of all treated external openings that were draining at baseline despite gentle finger compression) and response (clinical closure of at least 50% of all treated external openings that were draining at baseline) at week 24. In addition, long term follow-up was conducted up to week 52 and 104 (CS,[1] page 39). As noted in the CS[1] (page 64) *'...the efficacy data available beyond 52 weeks was limited. This is due to the changes in the protocol whereby the trial duration was extended beyond 104 weeks, which occurred when various patients had already finished the 52 week trial period. This resulted in a low level of patient data, and so generalisation of results beyond 52 weeks is difficult and should be approached with care'*. Other endpoints included safety, time to clinical remission, time to response, relapse, time to relapse and various disease severity measures such as (CS,[1] page 32): Perianal Disease Activity Index (PDAI) and the Van Assche scores (both focus on local perianal fistulising disease activity); Crohn's Disease Activity Index (which focuses on luminal Crohn's disease severity [CDAI]) and the Inflammatory Bowel Disease Questionnaire (a quality of life measure that focuses on systemic bowel disease e.g. luminal Crohn's disease [IBDQ]).

- *Ongoing studies of darvadstrocel for treating complex perianal fistula in non-active or mildly active luminal Crohn's disease*

Although there are no ongoing studies of darvadstrocel that will provide additional evidence in the next 12 months (CS,[1] page 59), the ADMIRE-CD-II study[18] (ClinicalTrials.gov Identifier: NCT03279081; Cx601-0303) is currently recruiting. The company's clarification response to question A12[2] suggests that this is a similar study to the ADMIRE-CD study[7, 9] but is being conducted to include patients from the USA and to satisfy Food and Drug Administration (FDA) requirements (Table 3). This study is expected to complete in October 2021. No other studies are currently planned (see company's clarification response,[2] question A9).

Table 3: Summary of key ongoing studies

Criteria	ADMIRE-CD-II study[18]
Title (official)	Phase-III randomised, double-blind, parallel-group, placebo-controlled, multicentre study to assess efficacy and safety of Cx601, allogeneic expanded adipose-derived stem cells for complex perianal fistula(s) in Crohn's disease - ADMIRE-CD-II
Study ID number	Clincinaltrials.gov: NCT03279081 Other: Cx601-0303; 2017-000725-12 (EudraCT Number)
Primary objective	To evaluate the efficacy and safety of darvadstrocel compared to placebo for the treatment of complex perianal fistula(s) in patients with Crohn's disease at week 24 with a follow-up period up to 52 weeks.
Study design	Phase III, randomised, double-blind, placebo controlled trial
Study location	>120 sites in EU/Israel and Canada/ USA (~60% of all sites)
Study population	• Target enrolment: 326 patients to be randomised (>436 to be screened) • Patients (aged 18-75 years) with complex perianal fistulising (maximum of 2 internal openings and a maximum of 3 external openings) Crohn´s disease who are refractory to conventional (antibiotics, immunosuppressants) or biological treatment strategies
Intervention/ comparator	• Darvadstrocel (24mL containing 120 million expanded allogeneic adipose-derived stem cells) given as a single intralesional injection and standard of care • Placebo solution given as a single intralesional injection and standard of care
Primary endpoint	• Combined remission at week 24 with $\alpha<0.05$ for all treated fistulas
Key secondary endpoints at week 24 and relevant at week 52	• Clinical remission at week 24 • Response at week 24 • Combined remission, clinical remission/response at week 52 • Time to clinical remission / response at week 24, week 52 • Safety and tolerability up to week 52 • Electronic patient-reported outcomes and quality of life assessments
Expected completion date	October 2021

4.2.2 Details of relevant studies not included in the submission

The ERG is confident that all relevant studies have been included in the CS[1] and that details of all ongoing trials that are likely to be reporting additional evidence within 12 months were reported.

4.2.3 Summary and critique of the company's analysis of validity assessment

The company provided a formal appraisal of the validity of the included darvadstrocel RCT[7, 9] using standard and appropriate criteria (an adaptation for the Centre for Reviews and Dissemination's guidance for undertaking reviews in healthcare[12]). However, the ERG is unclear as to why the company undertook quality assessments of the potentially relevant studies identified in the broader systematic review of all RCTs for complex perianal fistulae in patients with Crohn's disease (CS,[1] Appendix D.4.5), as none of these studies were included or considered relevant to the decision problem (clarification response[2], question A16 and A25). The completed validity assessment tool for the ADMIRE-CD trial, as reported in the CS,[1] is reproduced (with minor changes) in Table 4.

Table 4: Quality assessment results for the ADMIRE-CD study, as assessed by the company (adapted from CS,[1] Appendix D3, Table 2)

Quality assessment criteria	ADMIRE-CD[7, 9]	
	Company's assessment	ERG's assessment
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

In general, the ERG considered the ADMIRE-CD trial[7, 9] to be a well-reported and conducted study; however, some further discussion around specific points is required.

In the ADMIRE-CD trial,[7, 9] randomisation was performed using a computer generated randomisation list (stratified according to previously received therapy i.e. immunomodulators, anti-TNF therapy, both, or neither) and allocation concealment was done centrally by a third party. Whilst masking of treatments was not possible due to the visual differences between the darvadstrocel cell suspension and saline solution (i.e. placebo), the double-blind design of the study was maintained by a blinded gastroenterologist and blinded radiologist independently evaluating the clinical and radiological responses, respectively. Unmasked surgeons who administered the treatment were not permitted to share information about the treatment used in the surgical procedure with the gastroenterologist or radiologists, and were also not allowed to participate in any clinical assessment of the fistula during the study. The ERG acknowledges that adequate methods of randomisation, allocation concealment and blinding were used in the conduct of the included trial.

The ADMIRE-CD trial,[7, 9] stratified randomisation according to previously received therapy and did not specify any other relevant prognostic factors. The company's clarification response (question A27) states, "*In a review by Braithwaite et al.(2017), prognostic factors affecting outcomes of perianal disease were examined. This review identified some studies showing significant prognostic factors, yet these were considered insignificant in other identified studies. The heterogeneity observed across the identified studies limits the ability to draw robust conclusions about prognostic markers in this*

population."[2] Prognostic factors should be accounted for in statistical analyses whether or not there is baseline balance between treatments. Nevertheless, the CS[1] (Table 9, pages 34 to 36) suggests that there were slight imbalances in the following key baseline disease characteristics (≥5% difference between the two treatment groups). In the darvadstrocel group 48/107 patients (45%) compared with 31/105 patients (30%) in the control group had more than one fistula tract. The proportion of patients with more than one draining external fistula opening was slightly higher for patients randomised to darvadstrocel (56%, 36%, and 8%, for 1, 2 or >2 draining external openings, respectively [safety population, n=103]) compared with control treatment (72%, 25%, and 4%, respectively [safety population, n=102]). A similar pattern was observed for internal openings, and patients randomised to darvadstrocel were more likely to have two internal openings (0%, 80% and 20% for 0, 1, 2 respectively [safety population, n=103]), compared with patients randomised to control treatment (1%, 88%, 11% respectively [safety population, n=102]). In addition, the majority of patients were receiving concomitant Crohn's disease medication at baseline, although approximately 24 % of patients in the darvadstrocel group and 18 % of the control group did not receive concomitant treatment with either immunosuppressants and/or anti-TNF. The primary endpoint was analysed using a stratified Cochran-Mantel-Haenszel test adjusted for the randomisation strata. PDAI score was analysed using analysis of covariance adjusting for the randomisation strata and baseline response. An imbalance in a variable that is not prognostic is not important. Overall, it is not clear how these baseline differences and ignoring observed variables that may be prognostic may have affected the results.

The CS (Table 11, page 40) showed that during the study period of the ADMIRE-CD study,[7] 19/107 patients (17.8%) in darvadstrocel group and 22/105 patients (21.0%) in the control group did not complete the study protocol due to substantial clinical deterioration, adverse events (AEs) or patient decision/withdrawal of consent.[1] In general, the robustness of an analysis may be threatened if attrition is more than 20%, depending on the method of analysis.[19] In the ADMIRE-CD trial,[7] all patients were accounted for and the key efficacy analyses were conducted using the intention-to-treat (ITT) approach (which included all randomly assigned patients, n=212) or the modified ITT (mITT) approach (which included all randomly assigned patients who received study treatment and had at least one efficacy assessment after baseline, n=204). Therefore, attrition bias should be low in the ADMIRE-CD study.[7, 9]

Although there was no evidence to suggest that the ADMIRE-CD[7, 9] authors measured more outcomes than they reported, based on feedback from clinical experts, the company (CS,[1] page 34 and clarification response[2], question A3) performed and presented two additional *post hoc* analyses - time to clinical and patient-centric [CPC] remission and time to relapse from CPC remission.[1] As noted in the CS (page 10), whilst the key outcomes from the ADMIRE-CD study were combined remission and clinical remission, gastroenterologists and surgeons from the St Mark's Hospital (UK) advised that a more

clinically appropriate outcome of relevance to Crohn's disease patients with perianal fistulae should include a component of pain and discharge in addition to clinical remission. [1] The CS (page 34) considered a patient '*...to achieve CPC remission from complex perianal fistulae when: all the external openings are closed as per clinical assessment, i.e. not draining despite gentle finger compression (i.e. the clinical remission definition of ADMIRE-CD); AND the patient does not experience any pain or discharge, as determined by a score equal to 0 in both the pain and discharge dimensions of the PDAI... The time to CPC remission was the outcome used in the economic model, because expert clinical opinion indicated that this outcome represented more accurately the decision algorithm used in clinical practice*.'[1] The clinical advisors to the ERG also considered CPC remission to be the most clinically relevant outcome to Crohn's disease patients with perianal fistulae. However, the ERG notes that the ADMIRE-CD study was not designed to test hypothesis about these exploratory analyses, as such; the results of these outcomes should be treated with caution.

The ADMIRE-CD trial[7, 9] was performed across several EU countries and Israel; however, no UK sites were included. Based on the findings of a retrospective cohort study of 78 patients, treated by St Mark's Hospital in London (a specialist centre for intestinal and colorectal disorders), the CS[1] (page 63, Appendix Q) and clarification response[2] (questions A21 and A26) suggest that surgical treatments such as an examination under anaesthesia plus/minus seton placement are the most common treatments (approximately 90%) in UK clinical practice for adults with Crohn's disease who have a complex perianal fistula that is refractory to conventional or biologic therapy. In addition, the background therapy received in the trial (antibiotics/immunosuppressants and biologics) was similar to that used in clinical practice. As a result, the CS[1] considered the ADMIRE-CD trial[7, 9] to be reflective of UK practice. Clinical advisors to the ERG agreed with this view.

4.2.4 Summary and critique of results

This section presents the main results from the ADMIRE-CD trial, based on information reported in the CS[1] and trial publications,[7, 9] for the efficacy and safety of darvadstrocel in the treatment of non-active/mildly active luminal Crohn's disease, with complex perianal fistulas which have shown an inadequate response to at least one conventional or biologic therapy. Additional information, not reported in the CS,[1] was provided by the company in the company's clarification response.[2]

4.2.4.1 Efficacy

- Primary outcome (CS,[1] Table 12 and 13, page 42)

In the primary ITT population (n=212), a significantly greater proportion of patients in the darvadstrocel group achieved the primary endpoint of combined remission at week 24 compared with the control group (49.5% versus 34.3%, respectively; difference 15.2%, 97.5% confidence interval [CI]: 0.2 to 30.3; p=0.024). Similar results were observed in the mITT (n=204) population (51.5% versus 35.6%;

difference 15.8%, 97.5% CI: 0.5 to 31.2; p=0.021) and across all sensitivity analyses (p<0.05) used to assess the effects of the imputation conventions for missing data and the impact of use of rescue medication. With longer follow-up (52 weeks), the beneficial effect of darvadstrocel was maintained in the ITT population with 54.2% of patients achieving combined remission compared with 37.1% in the control group (difference 17.1%, 97.5% CI: NR; p=0.012).[20] Similar results were observed in the mITT population (56.3% versus 38.6%; 17.7%, 95% CI: 4.2 to 31.2; p=0·010). A summary of the key results is presented in Table 5 and Table 6.

Table 5: Summary of key results from the ADMIRE-CD trial[7, 9] - combined remission, clinical remission and response (adapted from CS[1] Tables 12, 13 and 14)

Outcomes	Darvadstrocel n/total N (%)	Control n/total N (%)	Difference (%)	95 % CI (unless otherwise stated)	*p*-value
Analyses at week 24					
Combined remission					
ITT population[a]	53/107 (49.5%)	36/105 (34.3%)	15.2%	97.5% CI: 0.2, 30.3	0.024
mITT population	53/103 (51.5%)	36/101 (35.6%)	15.8%	97.5% CI: 0.5, 31.2	0.021
Sensitivity 1[b]	52/107 (48.6%)	34/105 (32.4%)	16.2%	97.5% CI: 1.3, 31.1	0.014
Sensitivity 2[c]	53/107 (49.5%)	36/105 (34.3%)	15.2%	97.5% CI: 0.2, 30.3	0.024
Sensitivity 3[d]	53/107 (49.5%)	36/105 (34.3%)	NA	NA	0.017
Clinical remission					
ITT population	57/107 (53.3%)	43/105 (41.0%)	12.3%	-1.0, 25.7	0.064
Response					
ITT population	71/107 (66.4%)	56/105 (53.3%)	13.0%	-0.1, 26.1	0.054
Analyses at week 52					
Combined remission					
ITT population[20]	58/107 (54.2%)	39/105 (37.1%)	17.1%	NR	0.012
mITT population	58/103 (56.3%)	39/101 (38.6%)	17.7%	4.2, 31.2	0.010
Clinical remission					
mITT population	61/103 (59.2%)	42/101 (41.6%)	17.6%	4.1, 31.1	0.013
Response					
mITT population	68/103 (66.0%)	56/101 (55.4%)	10.6%	-2.8, 23.9	0.128

CI, Confidence interval; LOCF, Last observation carried forward; (m)ITT, (modified) intention-to-treat; NA, not applicable; NR, not reported

[a] Primary analysis of the ADMIRE-CD trial[7]

[b] Sensitivity analysis 1: ITT, non-response/non-remission imputed for all missing data and after rescue therapy (no LOCF) (rescue therapy was defined as corticosteroids at 40 mg prednisone equivalent for ≥12 weeks; new anti-TNF compared with baseline therapy for ≥8 weeks; new immunosuppressant compared with baseline therapy for ≥12 weeks; or surgical intervention for the treated fistula)

[c] Sensitivity analysis 2: ITT, missing = non-response/non-remission after LOCF applied. Rescue medication not considered as failure

[d] Sensitivity analysis 3: ITT, missing = non-response/non-remission after LOCF applied. Logistic analysis including stratification factor and number of baseline external openings as factors

Table 6: Time to combined remission, clinical remission and response of perianal fistula by week 24, ITT Population (adapted from CS,[1] Table 15)

	Darvadstrocel (N=107)	Control (N=105)	Hazard ratio (95% CI)
Combined remission			
Combined remission, n (%) [a]	53 (49.5%)	36 (34.3%)	
Censored cases, n (%)	[redacted]	[redacted]	
Kaplan-Meier estimates, Median (95% CI), weeks	25.0 (24.7, 26.1)	28.1 (24.7, 36.0)	0.74 (0.48, 1.14)
Clinical remission			
Clinical remission, n (%) [a]	[redacted]	[redacted]	
Censored cases, n (%)	[redacted]	[redacted]	
Kaplan-Meier estimates, Median (95% CI), weeks	6.7 (6.4, 11.9)	14.6 (11.9, 22.9)	0.57 (0.41, 0.79)
Response			
Response, n (%) [a]	[redacted]	[redacted]	
Censored cases, n (%)	18 (16.8%)	30 (28.6%)	
Kaplan-Meier estimates, Median (95% CI), weeks	6.3 (6.0, 6.6)	11.7 (6.7, 12.9)	0.59 (0.43, 0.81)

CI, Confidence interval; ITT, Intention-to-treat
[a] Achieved at least once during the 24-week follow-up

- Secondary and other outcomes (CS,[1] p42-49)

A range of secondary endpoints were evaluated in the ADMIRE-CD study. A summary of the results is presented in Table 5 and Table 6. The key secondary endpoints were clinical remission and clinical response at week 24.

In the ITT population, 53.3% of the patients treated with darvadstrocel achieved clinical remission compared with 41.0% of the control patients (difference 12.3%; *p*=0.064) at week 24. Similar results were observed in the mITT population (55% and 43%, respectively; difference 12.8%; *p*=0.057).[9] The time to achieve clinical remission was significantly faster by 7.9 weeks for the darvadstrocel group compared with the control group (6.7 versus 14.6 weeks, respectively; hazard ratio [HR]: 0.57, 95% CI: 0.41 to 0.79; *p* = not reported [NR]). With longer follow-up (52 weeks), clinical remission in the mITT population (data not reported for ITT population) was 59.2% in the darvadstrocel group and 41.6% in the control group with a difference of 17.6% (*p*=0.013).

In the ITT population, response was achieved in 66.4% of the patients treated with darvadstrocel compared with 53.3% of the control patients (difference 13.0%; *p*=0.054) at week 24. Similar results were observed in the mITT population (69% and 55%, respectively; difference 13.5%; *p*=0.045).[9] The time to response was significantly faster by 5.4 weeks with darvadstrocel compared with the control group (6.3 versus. 11.7 weeks, respectively; HR: 0.59, 95% CI: 0.43 to 0.81; *p* = NR;). At week 52, response in the mITT population (data not reported for ITT population]) was achieved in 66.0% in the darvadstrocel group and 55.4% in the control group with a difference of 10.6% (*p*=0.128).

The ERG notes that the times to clinical remission and clinical response are interval censored such that events could have occurred at any time between assessments; this may result in exaggerated estimates of treatment effect. According to the CS, time to clinical remission and response were analysed using Cox regressions adjusted for the randomisation stratum, although HRs from this model are not presented in the CS. The company's clarification response[2] (question A28) states that the results of the Cox regression could be found in Tables 14.1.4.3.1, 14.1.4.4.1 and 14.1.4.5.1 of the week 24 CSR, although the ERG could not find these. Furthermore, the company clarification response stated, "*As there is no evidence of non-homogeneity in the treatment effect across strata and the trial was not powered to detect differences in treatment effect between these randomisation strata, these analyses were not included in the CS*." (clarification response, [2] A28)

Various other disease severity outcomes measures (PDAI, CDAI and Van Assche score) and quality of life (IBDQ) were assessed in the ADMIRE-CD trial. Detailed results for these outcomes are presented in the CS (pages 45-49) and in Panes *et al*.[9] Briefly, total PDAI scores in the mITT population decreased in both treatment groups at all visits (week 6, 12 and 18) and at week 24 (treatment difference, -0.8; 95% CI: -1.8 to 0.2; *p*=0.101) and week 52 (treatment difference, -0.7; 95% CI: -1.7 to 0.3; *p*=0.186),[9] with the improvement (i.e. decrease) being greater in the darvadstrocel group compared with the control group. However, the differences between treatments did not reach statistical significance ($p > 0.05$). Similarly, in the mITT population, there were no significant differences ($p>0.05$ for all) between the groups at weeks 24 or 52 for total and subdomain IBDQ, CDAI and Van Assche scores. The CS (page 48) stated that '*...darvadstrocel did not have an effect on instruments designed primarily to assess the impact of luminal CD, such as the CDAI or IBDQ…. Since patients with active luminal disease were excluded from the study, CDAI scores were low and IBDQ scores were high throughout as expected'*.[1] A summary of these results is presented in

Table 7.

Table 7: Other secondary outcomes - PDAI, CDAI, IBDQ and Van Assche score, mITT population (adapted from CS[1] Table 17)

Outcome	Darvadstrocel (N=103)	Control (N=101)	Treatment difference (95% CI)	*p*-value
PDAI, mean (SD) [a]				
Baseline	6.7 (2.5)	6.5 (2.8)	NR	
Week 24	4.4 (3.6)	5.1 (3.9)	NR	
Change from baseline	-2.3 (3.8)	-1.3 (3.5)	-0.8 (-1.8 to 0.2)	0.101
Week 52	4.4 (3.8)	5.0 (4.0)	NR	
Change from baseline	-2.3 (4.1)	-1.4 (3.7)	-0.7 (-1.7 to 0.3)	0.186
IBDQ [b] ***mean (SD)***				
Baseline	173.5 (31.6)	169.4 (36.1)	NR	NR
Week 24	178.3 (34.6)	174.7 (36.2)	NR	NR
Change from baseline	3.8 (25.5)	4.0 (25.6)	0.3 (-6.6, 7.3)	0.923
Week 52	176.1 (38.1)	172.7 (40.6)	NR	NR
Change from baseline	2.1 (27.4)	1.7 (25.0)	0.7 (-6.7, 8.2)	0.849
CDAI [c] ***mean (SD)***				
Baseline	87.8 (48.3)	93.3 (55.0)	NR	NR
Week 24	92.5 (66.5)	94.1 (76.1)	NR	NR
Change from baseline	5.7 (62.2)	2.2 (65.5)	1.8 (-16.0, 19.7)	0.839
Week 52	97.4 (82.7)	99.2 (77.8)	NR	NR
Change from baseline	11.1 (80.5)	7.6 (67.3)	-1.3 (-19.6, 22.1)	0.906
Van Assche Score [d]				
Baseline	9.0	9.4	NR	NR
Week 24	8.6	9.0	0.004 (-0.686, 0.694)	NR
Change from baseline	NR	NR	NR	NR
Week 52	[redacted]	[redacted]	[redacted]	NR
Change from baseline	NR	NR	NR	NR

CDAI, Crohn's Disease Activity Index; CI, Confidence interval; IBDQ, Inflammatory Bowel Disease Questionnaire; mITT, Modified intention-to-treat; PDAI, Perianal Disease Activity Index; SD, Standard deviation

[a] Data from Panes *et al.*[9]
[b] IBDQ score ranges from 32 to 224, whereby a higher score indicates a better quality of life
[c] CDAI score ranges from 0 to 600, whereby a higher score indicates that the disease is more active / severe
[d] Van Assche score ranges from 0-22, whereby a higher score indicates more severe disease

In the mITT population, a subgroup analysis across four randomisation strata (i.e. Crohn's disease treatment being received at the time of randomisation) found that the effect of darvadstrocel on combined remission was proportionally greater than control with the difference between groups being greatest in patients receiving neither (difference 33.1%, 95% CI: 6.0 to 60.2; *p*=NR) or both anti-TNF and immunosuppressant treatments (20.0%, 95% CI: –5.2 to 45.2; *p*=NR) at week 24; however, the difference in the treatment effect between the four stratification groups was not significant (*p*=0.47).

The CS[1] (page 52) notes that *'…The trial was not powered for the subgroup analyses due to the small patient numbers in these subgroups… Due to low patient numbers during the 52 week follow up, it is not possible to analyse the relapse rates within these subgroups'.*

- *Post hoc* analyses (CS,[1] pages 49-51)

The company presented two additional *post hoc* analyses: (i) time to CPC remission (used in the economic model, because expert clinical opinion to the company indicated that this outcome represented more accurately the decision algorithm used in UK clinical practice), and (ii) time to relapse from CPC remission (as these outcomes were considered by clinical experts to the most relevant outcome). The time to CPC remission in the ITT population, improved by 14.1% in the darvadstrocel group as compared with control treatment (55.1% versus 41.0%, respectively), and the median time to CPC remission was 6.5 weeks faster (28.7 versus 35.2 weeks, HR 0.61; 95% CI: 0.42 to 0.91; *p*=NR). The CS[1] (page 50) noted that *'…this analysis yields very similar results to the combined remission results…'*. Moreover, fewer patients relapsed with darvadstrocel as compared with control treatment (50.8% versus 59.6%, respectively). The time to loss of CPC remission was extended with darvadstrocel compared with control (48.7 versus. 12.9 weeks; HR: 1.38; 95% CI: 0.89 to 2.12; *p*=NR). A summary of these data, adapted by the ERG, is presented in Table 8. However, the company's clarification response[2] (question A20) stated that the HR and 95% confidence interval for CPC relapse is from a Gompertz model. The HR under this model suggests that the effect of darvadstrocel on CPC relapse is worse than control, although the sample data suggest otherwise. It is unclear whether a Gompertz model was also used to estimate the HR for CPC remission.

Table 8: *Post hoc* analyses - time to CPC remission and time to relapse from CPC remission (adapted from CS[1] Tables 18 and 19)

	Darvadstrocel	**Control**	**Hazard ratio (95% CI)**
CPC remission			
Patients at risk	N=107	N=105	
CPC remission, n (%)	59 (55.1%)	43 (41.0%)	
Kaplan-Meier estimates, Median (95% CI), weeks[a]	28.7 (17.7, 37.0)	35.2 (24.4, NA)	0.61 (0.42, 0.91)
Log-rank test			X_1^2=6.0, p=0.014
CPC relapse			
Patients at risk	N=59	N=47	
CPC relapse, n (%)	30 (50.8%)	28 (59.6%)	
Kaplan-Meier estimates, Median (95% CI), weeks	48.7 (18.9, NA)	12.9 (12.0, 33.0)	1.38 (0.89, 2.12)
Log-rank test			X_1^2=4.9, p=0.0262

CI, Confidence interval; CPC, Clinical and patient-centric
[a] Restricted mean with upper limit of 52 weeks

4.2.4.2 Safety and tolerability

This section provides the main safety evidence, as reported by the company, for all patients who received study treatment within the ADMIRE-CD trial (safety population). Additional safety data were also reported from a Phase I/IIa study.[8]

The CS[1] (page 54) states that darvadstrocel is well tolerated, with an AE profile similar to control treatment (CS,[1] Tables 20, 21 and 22), although no test was performed to determine whether there was a statistically significant difference between trial arms for any specific AE. The majority of the data were for AEs up to week 24 of the ADMIRE-CD trial,[7] although some longer-term, 52-week safety data were also provided.[9] The CS,[1] published papers[7, 9] and clinical study reports[21, 22] reported treatment-emergent AEs (TEAEs), defined as any AE reported during the trial; treatment-related TEAEs, defined as '*events with relationship certain, probable or possible with the study treatment …*';[21] serious AEs (TESAEs), defined as '*events that threaten patient life or functions*';[21] and severe TEAEs, defined as an event that '*causes a significant interference with function*'.[21]

In the ADMIRE-CD trial at 24 weeks, TEAEs were common (66.0% of patients in the darvadstrocel arm compared with 64.7% in the control arm, see Table 9). The most common treatment-related TEAEs were proctalgia (12.6% of patients in the darvadstrocel arm versus 11.8% in the control arm), anal abscess (11.7% versus 12.7%) and nasopharyngitis (9.7% versus 4.9%), respectively. Diarrhoea was also more frequent in the darvadstrocel arm (6.8%) compared with the control arm (2.9%). The reported frequency of most TEAEs in patients was similar between the darvadstrocel and control arms of the ADMIRE-CD trial at 24 weeks. In many instances, the reported frequency of AEs was higher in the placebo arm than the treatment arm. This is because, as acknowledged in the CS[1] and reported in the EPAR,[17] some AEs, including anal abscess and proctalgia, are associated with the indication and might represent treatment failure, i.e. a lack of efficacy, rather than an AE related to the treatment (CS,[1] page 54). This explains why, for example, after 24 weeks, fewer patients treated with darvadstrocel compared with control experienced treatment-related TEAEs (17.5% of patients receiving darvadstrocel versus 29.4% receiving control, see Table 9), and why the reported frequency of withdrawal from the trial to due TEAEs was similar between arms (4.9% of patients receiving darvadstrocel versus 5.9% receiving control). Clinical advice received by the ERG indicated that such outcomes should have been treated as efficacy outcomes rather than AEs.

The CS[1] (Table 23, page 58) also reported so-called procedure-emergent, non-treatment emergent events (PENTE) for ≥2 patients up to week 24 in the ADMIRE-CD trial. These events are defined as AEs 'starting prior to administration of study treatment, but after [the] curettage procedure'.[21] None of these specific events were reported to affect more than [redacted] in any treatment arm, and only [redacted]

[redacted] were more frequent in the darvadstrocel arm compared with the control arm.

Table 9: TEAEs, treatment-related TEAEs (≥10 patients), severe TEAEs and TESAEs up to week 24 in ≥2 patients in either treatment group, of ADMIRE-CD, safety population (adapted from CS,[1] Table 21)

Number patients (%)	TEAE		Treatment related TEAE		Severe TEAE		TESAE	
	Darvadstrocel N=103	Control N=102	Darvadstrocel N=103	Control N=102	Darvadstrocel N=103	Control N=102	Darvadstrocel N=103	Control N=102
Number of patients	68 (66%)	66 (64.7%)	18 (17.5%)	30 (29.4%)	[redacted]	[redacted]	18 (17.5%)	14 (13.7%)
Withdrawals due to AE	5 (4.9%)	6 (5.9%)					[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proctalgia	13 (12.6%)	11 (10.8%)	5 (4.9%)	9 (8.8%)	[redacted]	[redacted]		
Anal fistula	3 (3%)[c]	6 (6%)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and Infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anal abscess	12 (11.7%)	13 (12.7%)	6 (5.8%)	9 (8.8%)	[redacted]	[redacted]	9 (8.7%)[d]	7 (6.9%)[d]
Nasopharyngitis	10 (9.7%)	5 (4.9%)						
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]				

CSR, Clinical study report; TEAE, Treatment-emergent adverse event; TESAE, Treatment-emergent serious adverse event

[redacted] b-[redacted] d-Treatment-related TESAEs: 5% in both arms (Panes *et al.*)[7] and [redacted] ‡

[redacted] (see Table 10). The latter increased to [redacted] arm at 52 weeks.[22] There were no deaths recorded due to AEs or during the trial. The outcomes from TEAEs and TESAEs were similar across trial arms, although there was [redacted], where there was recovery, there was a [redacted] (see Table 10).

Table 10: Summary of treatment-emergent adverse events and treatment-emergent serious adverse events up to week 24 in ADMIRE-CD, safety population[7, 21] (reproduced from CS,[1] Table 20)

	TEAE		TESAEs	
	Darvadstrocel N=103	**Control N=102**	**Darvadstrocel N=103**	**Control N=102**
	n (%)	**n (%)**	**n (%)**	**n (%)**
TEAEs/TESAEs	68 (66.0%)	66 (64.7%)	18 (17.5%)	14 (13.7%)
Intensity of TEAEs				
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Outcome of TEAEs/TESAEs				
Death	[redacted]	[redacted]	[redacted]	[redacted]
Not recovered	[redacted]	[redacted]	[redacted]	[redacted]
Recovered with sequelae	[redacted]	[redacted]	[redacted]	[redacted]
Recovered without sequelae	[redacted]	[redacted]	[redacted]	[redacted]
Changed intensity	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]

TEAE, Treatment-emergent adverse event; TESAE, Treatment-emergent serious adverse event

Safety data for 52 weeks follow-up have been published[9] and are reported in the CS[1] (Table 22, page 58). As with the 24-week data, the frequency of patients with some TEAEs was similar across the treatment and control arms, but the trend changed at 52 weeks for key AEs such as anal abscess (19.4% of patients in the treatment arm versus 13.7% in the control arm) and anal fistula (10.7% versus 7.8%) and nasopharyngitis (10.7% versus 4.9%), with higher frequencies of patients affected in the darvadstrocel arm than the control arm (see Table 11). This trend was the same for the TESAEs of anal abscess (13.6% of patients in the treatment arm versus 7.8% in the control arm) and anal fistula (3.9% versus <1.0%).

For the 52-week data, compared with the 24-week data, there were higher frequencies of patients with TEAEs, treatment-related TEAEs and TESAEs. For example, for darvadstrocel 76.7% of patients experienced a TEAE by week 52 compared to 66.0% of people experiencing a TEAE by week 24. Equivalently for standard care, 72.5% of patients experienced a TEAE by week 52 compared to 64.7% for week 24. The withdrawals due to TEAEs also increased over time (darvadstrocel. 8.7% of patients for week 52 versus 4.9% for week 24; standard care 8.8% versus 5.9%). The ERG noted that there was a sizeable increase in the frequency of patients with TESAEs at 52 weeks across arms compared with week 24 (24.3% at week 52 versus 17.5% at week 24 for darvadstrocel, and 20.6% at week 52 versus 13.7% at week 24 for control). The CS[1] (page 59) also reported that there were no immune reactions or TEAEs associated with the development of donor-specific antibodies, and no association between positivity for donor-specific antibodies and therapeutic response.

Table 11: Longer-term safety from ADMIRE-CD, safety population, ≥4 patients, (adapted from CS,[1] Table 22, with data from Panes et al,[7, 9] and TiGenix Clinical Study Reports[21, 22])

Number patients (%)	Week 24		Week 52[22]	
	Darvadstrocel N=103	Control N=102	Darvadstrocel N=103	Control N=102
TEAEs	68 (66.0%)	66 (64.7%)	79 (76.7%)	74 (72.5%)
Proctalgia	13 (12.6%)	11 (10.8%)	15 (14.6%)	12 (11.8%)
Anal abscess	12 (11.7%)	13 (12.7%)	20 (19.4%)[a]	14 (13.7%)[a]
Anal fistula	3 (3%)	6 (6%)	11 (10.7%)[a]	8 (7.8%)[a]
Nasopharyngitis	10 (9.7%)	5 (4.9%)	11 (10.7%)	5 (4.9%)
Treatment-related TEAEs	18 (17.5%)	30 (29.4%)	21 (20.4%)	27 (26.5%)
Withdrawn due to AEs	5 (4.9%)	6 (5.9%)	9 (8.7%)	9 (8.8%)
Treatment-related AEs in ≥5% of patients				
Anal abscess	6 (5.8%)	9 (8.8%)	[redacted][b]	[redacted][b]
Anal fistula	[redacted]	[redacted]	[redacted][b]	[redacted][b]
Proctalgia	5 (4.9%)	9 (8.8%)	5 (4.9%)	8 (7.8%)
Serious TEAEs	18 (17.5%)	14 (13.7%)c	25 (24.3%)	21 (20.6%)
Anal abscess	9 (8.7%)	7 (6.9%)	14 (13.6%)[a]	8 (7.8%)[a]
Anal fistula	[redacted]	[redacted]	4 (3.9%)[a]	1 (<1.0%)[a]
Treatment-related TESAEs in ≥2% of patients				
TESAEs	5 (5%)[d]	7 (7%)[d]	7 (6.8%)	7 (6.9%)
Anal abscess/fistula	5 (5%)[d]	5 (5%)[d]	7 (6.8%)[e]	5 (4.9%)[e]

AE, Adverse event; TEAE, Treatment-emergent adverse event

a - TiGenix Clinical Study Report[22] and EPAR[17]
b - Unpublished data TiGenix Clinical Study Report[22]
c -Erroneously reported in CS, Table 22 as n=6 (5.9%).
d -Panes *et al*.[7]
e - Unpublished data TiGenix Clinical Study Report[22] on anal abscess only [redacted]

The frequency of AEs in the ADMIRE-CD trial was generally similar to that reported for an earlier Phase I/II trial,[8] which also had 24-week follow-up (CS, Appendix F). However, the frequency was lower for 24-week data for the ADMIRE-CD trial for some events (see Table 11). For example, the frequency of patients with treatment-related TEAEs at 24 weeks in ADMIRE-CD was 4.9% (5/103) compared with 21% (5/24) in the Phase I/II trial; the frequency of patients with treatment-related anal abscess was 5.8% (6/103) in the ADMIRE-CD trial compared with 12.5% (3/24) in the Phase I/II trial; and the frequency of TESAEs was 5% (5/103) in ADMIRE-CD compared with 8% (2/24) in the Phase I/II trial (CS,[1] Appendix F). It is not clear why the reported frequency of patients with treatment-related TEAEs in particular was lower in the ADMIRE-CD trial compared with the earlier Phase I/II trial. However, this might be explained by the lower dose of darvadstrocel in the Phase I/II trial, i.e. up to a maximum of 60 million expanded adipose-derived allogeneic mesenchymal stem cells (eASCs)[8] compared with 120 million cells in the ADMIRE-CD trial[7] and the potential for these key AEs to be considered as efficacy rather than safety outcomes.

In summary, TEAEs were common and were reported by approximately two-thirds of patients receiving darvadstrocel. The most common TEAEs were proctalgia, anal abscess, nasopharyngitis and diarrhoea.

The frequency of the principal TEAEs was generally similar across the treatment and control arms, but the ERG noted that proctalgia, anal abscess and anal fistulae are symptomatic of the indication in this appraisal and are therefore indicative of treatment failure rather than being treatment-related AEs. The ERG also noted that the percentages of TEAEs, treatment-related TEAEs, TESAEs, and withdrawals due to treatment-related TEAEs among patients in the darvadstrocel arm were all higher at 52 weeks than at 24 weeks. It was also the case that the percentages of patients experiencing key TEAEs, previously similar between arms at 24 weeks, had become noticeably higher in the darvadstrocel arm than the control arm of the trial at 52 weeks. The ERG also noted that the frequency of treatment-related TEAEs at 24 weeks was higher in the earlier phase I/II trial[8] than the later ADMIRE-CD trial,[7, 9] which might be explained by the much lower dose of darvadstrocel in the earlier trial (≤60 million eASCs versus 120 million eASC) and the issue that some AEs might represent a lack of efficacy rather than AEs.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison was undertaken by the company to supplement the direct evidence as there is only one trial that has evaluated the use of darvadstrocel in the treatment of non-active/mildly active luminal Crohn's disease, with complex perianal fistulas which have shown an inadequate response to at least one conventional or biologic therapy (CS,[1] Section B.29, pages 53-54). The ERG agrees with this position, which is in line with the final scope issued by NICE.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

No indirect comparison was undertaken by the company (see Section 4.3).

4.5 Additional work on clinical effectiveness undertaken by the ERG

As the company undertook a reasonably comprehensive systematic review (no major limitations were noted) of darvadstrocel for treating complex perianal fistula in Crohn's disease, no additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence in the CS[1] is based on a systematic review of darvadstrocel for the treatment of complex perianal fistulae in patients with Crohn's disease. The ERG is confident that all relevant controlled trials (published and unpublished) were included in the CS,[1] including data from ongoing/planned studies.

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

A key limitation of the efficacy and safety data for darvadstrocel reported in the CS[1] relates to the *post hoc* analyses of CPC-remission (an outcome used in the economic model) and CPC relapse. These endpoints were not designed or powered to test formal hypotheses. As such, these results should be treated with caution. Another issue is the lack of a confirmatory study. As noted in the EPAR,[17] the effect size in the ADMIRE-CD trial was considered to be modest and less than the 25 percentage difference that it was designed to detect, yet this was considered clinically meaningful given that other treatment options for fistulas had failed. A post-authorisation efficacy and safety trial, ADMIRE-CD-II[18] is expected to help address this concern. This study is similar to the ADMIRE-CD study in that it is a Phase-III, randomised, double-blind, parallel-group, placebo-controlled, multicentre study evaluating the efficacy and safety of darvadstrocel compared to placebo for the treatment of complex perianal fistula(s) in patients with Crohn's disease at week 24 with a follow-up period up to 52 weeks. This study is being conducted to include patients from the USA and to satisfy FDA licensing requirements. However, the study is expected to complete in October 2021 and the final clinical study report to the EMA is expected in 2022.[17]

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The key uncertainties in the clinical evidence for darvadstrocel relate to repeated administration, optimal dosing and long-term efficacy and safety. Further details are provided below.

- *Repeated administration*

The EPAR[17] states that '*While treatment with Alofisel [darvadstrocel] is proposed for single dose administration, the need for repeated treatment in the clinical setting seems foreseeable in the targeted patient population*'. The company's clarification response to question A1[2] suggest that '*Although some clinicians believe that Alofisel [darvadstrocel] may be beneficial for retreatment in the following patient groups; (i) partial responders; (ii) responders who have relapsed, there is no current evidence to support this treatment approach… therefore elected to base the submission on single use only. Some patients who have responded to Alofisel treatment and achieved healing over a significant period of time may develop a new fistula tract (recurrence). We believe this should be considered as a new fistula and should therefore be treated as such*.' The ERG notes that although darvadstrocel offers a novel treatment option with curative intent, there are no robust supporting data beyond 52 weeks follow-up; there is no evidence on the repeated use of darvadstrocel (licensed dose) when new fistulas open and it is unclear whether patients who have not achieved complete closure with one injection would benefit from an additional injection.

- *Optimal dosing*

In the ADMIRE-CD study,[7, 9] patients with complex perianal fistulising (maximum of 2 internal openings and a maximum of 3 external openings) Crohn´s disease who were refractory to conventional (antibiotics, immunosuppressants) or biological treatment strategies received a single intralesional injection containing 120 million darvadstrocel cells. Although no formal dose finding studies have been conducted (see clarification response,[2] question A6), it remains unclear whether alternative dosage regimens may have been clinically effective with fewer AEs or whether stem cell therapy would be effective in patients with very complicated perianal fistulising disease who may have more than two internal and three external openings (see clarification response,[2] question A4).

- *Long-term efficacy and safety*

In the ADMIRE-CD,[7, 9] the follow-up was extended from 24 weeks to 104 weeks to allow for the assessment of long-term efficacy and clinical and immunological safety of darvadstrocel treatment. However, as noted in the CS[1] (page 64), the available efficacy data beyond 52 weeks were limited because the protocol change occurred when various patients had already finished the 52 week trial period. The CS states *'...This resulted in a low level of patient data, and so generalisation of results beyond 52 weeks is difficult and should be approached with care*'. As a result, there is uncertainty regarding the long-term efficacy and safety of darvadstrocel. The SmPC[6] and EPAR[17] for darvadstrocel also advise for monitoring and reporting of any suspected adverse reactions after authorisation for signs of infection after administration and immunogenicity/ all-immunoreactions.

5 COST EFFECTIVENESS

5.1 ERG's comment on company's review of cost-effectiveness evidence

5.1.1 Objective of cost effectiveness review

The company performed two broad searches. The first search was undertaken to identify economic evaluations, resource use and costing studies in Crohn's disease and people with perianal fistulas. Terms for Crohn's disease were combined with a cost-effectiveness filter (CS,[1] Appendix G). The following sources were searched: MEDLINE [via Embase.com], MEDLINE In-Process [via PubMed], Embase [via Embase.com] NHS EED [via Wiley Online Library] and EconLit [via AEAweb.org]. Supplementary searches in Research papers in Economics (RePEC) and the cost-effectiveness analysis (CEA) Registry were carried out by the company to identify further resource use and cost data studies in people with perianal fistulas and Crohn's disease (CS,[1] Appendix I). The search covered the period from 2000 up to 22 January 2018.

The second search was undertaken to identify HRQoL studies in Crohn's disease where terms for the disease were combined with a QoL filter. Full details of the searches carried out in MEDLINE [via Embase.com], MEDLINE In-Process [via PubMed], Embase [via Ovid] and NHS EED [via Wiley Online Library] are presented in the CS (Appendix H).[1] Supplementary searches included searching several online websites: Tufts CEA Registry database, NICE and School of Health and Related Research Health Utilities Database (ScHARR HUD). The search covered the period from 2000 up to 22 January 2018.

The ERG considers that the searches were fully reported in the CS (Appendices G, H and I) that they were sufficiently comprehensive.[1] There were no studies that the ERG or their clinical advisors were aware of that were missed.

5.1.2 The inclusion and exclusion criteria used in the study selection

The inclusion criteria for the systematic review of the cost-effectiveness evidence is briefly summarised

Table 12. It is unclear why the company applied intervention criterion in the inclusion criteria, as the objective of the review was to identify relevant cost-effectiveness studies in the same disease area. However, as the inclusion criteria cover most relevant interventions for people with Crohn's disease and complex perianal fistulae, it is unlikely that any relevant studies will have been missed.

Table 12: Inclusion criteria used in the company's review of cost-effectiveness evidence (reproduced from CS,[1] Appendix G, Table 18)

Studies to include	
Study Design	• Cost studies/surveys/analyses • Cost/economic burden of illness • Resource use studies • Cost-effectiveness analyses • Cost-utility analyses • Cost-benefit analyses • Cost-minimization analyses • All economic evaluation studies based on models • Budget impact models • Database analyses with cost
Population	• Patients with perianal fistula in Crohn's disease • No age, gender or race restriction
Intervention/ Comparator	• Cx601/darvadstrocel • Ciprofloxacin • Infliximab • Adalimumab • Certolizumab • Fibrin glue • Metronidazole • Azathioprine • 6-MP • Cyclosporine • Tacrolimus • Methotrexate • Thalidomide • Surgery (fibrin glue, advancement flap, LIFT, diverting stoma, proctectomy, colectomy, fistula plugs, fistulotomy, exam under anaesthesia, multiple seton placement, ileostomy, colostomy, stem cells, VAAFT and Filac)
Language	English only
Country	No restriction
Publication timeframe	2000-2018

LIFT - Ligation of the inter-sphincteric fistula tract; VAAFT - Video assisted anal fistula treatment

5.1.3 Findings of the cost-effectiveness review

Following de-duplication, the company's searches found 335 publications. Two hundred and fifty six publications were excluded at the abstract review and a further 72 publications were excluded at the full text stage. This left seven remaining publications. A further two publications were identified through searching of conference records and bibliographic searching. In total, nine publications (reporting on seven studies) were identified; two of these studies reported cost-utility analyses. Only one study, by Lindsay *et al*, related to a UK health care setting.[23] Lindsay *et al*. assessed the cost-effectiveness of infliximab versus standard care for luminal and fistulising Crohn's disease patients in England and

Wales. Whilst a useful source of information, this study was not directly relevant to the cost-effectiveness of darvadstrocel compared with standard care.

5.1.4 Conclusions of the cost-effectiveness review

The CS concludes that the existing evidence is insufficient to determine the cost-effectiveness of darvadstrocel as a specific treatment for complex perianal fistula in Crohn's disease patients, as the previous model examined a patient population treated for both luminal and fistulising Crohn's disease.[1] As such, it was necessary to develop a *de novo* model for this appraisal. The ERG agrees with this conclusion.

5.2 Summary of the company's submitted health economic analysis

5.2.1 Population

The population included in the company's health economic analysis reflects people with complex perianal fistulae and Crohn's disease who have two or less internal openings and three or less external openings of their complex perianal fistula; are naïve to darvadstrocel treatment, and; are refractory to conventional first-line therapy. Failure of conventional first-line therapy was defined to consist of at least one of: no therapeutic effect of an antibiotic (recommended treatments were ciprofloxacin and metronidazole) after one month; no response to an immunosuppressant (azathioprine [2-2.5 mg/kg] or 6-mercaptopurine [1-1.5 mg/kg]) after three months, or; no response to an anti-TNF either 12 weeks after initiation of induction treatment or loss of response after 12 weeks of maintenance treatment under a stable dose.

5.2.2 Interventions and comparators

In the ADMIRE-CD study, four vials of darvadstrocel (total dose = 120 million cells) were administered as an intralesional injection during an EUA after the fistula had been conditioned. Conditioning of the fistula consisted of: an EUA; curetting (scraping anything out of) the fistula tract; and if indicated, setons (surgical cords used to open the fistula so that it drains) were placed during the EUA. If setons were placed whilst conditioning the fistula, they were removed immediately prior to the administration of darvadstrocel. Darvadstrocel injections were given in addition to standard care therapies for people who were already refractory to first-line treatment.

In the UK, standard care for people who are refractory to conventional therapy consists of at least one of the following options: surgically managing the fistula; antibiotics; immunosuppressants and/or, biologics. Whilst surgical treatments are similar between first- and second-line treatments, different antibiotics, immunosuppressants and/or biologics than the treatment which failed at first-line will typically be used.

If a patient does not respond to their initial treatment (either darvadstrocel or standard care) within one year or if the patient relapses after achieving remission of their fistula, they subsequently receive salvage therapy. Salvage therapy is similar to standard care in that one of the following treatments will be used: surgically managing the fistula; antibiotics; immunosuppressants and/or biologics. Typically, different medical management of the fistula will be undertaken (antibiotics, immunosuppressants and biologics) and possibly different surgical procedures will be considered. After several failed lines of salvage therapy, last resort surgeries are considered. These consist of defunctioning surgery, in which the fistula is temporarily bypassed to allow healing, and proctectomy, in which a proportion of the bowel is permanently bypassed.

5.2.3 Perspective, time horizon and discounting

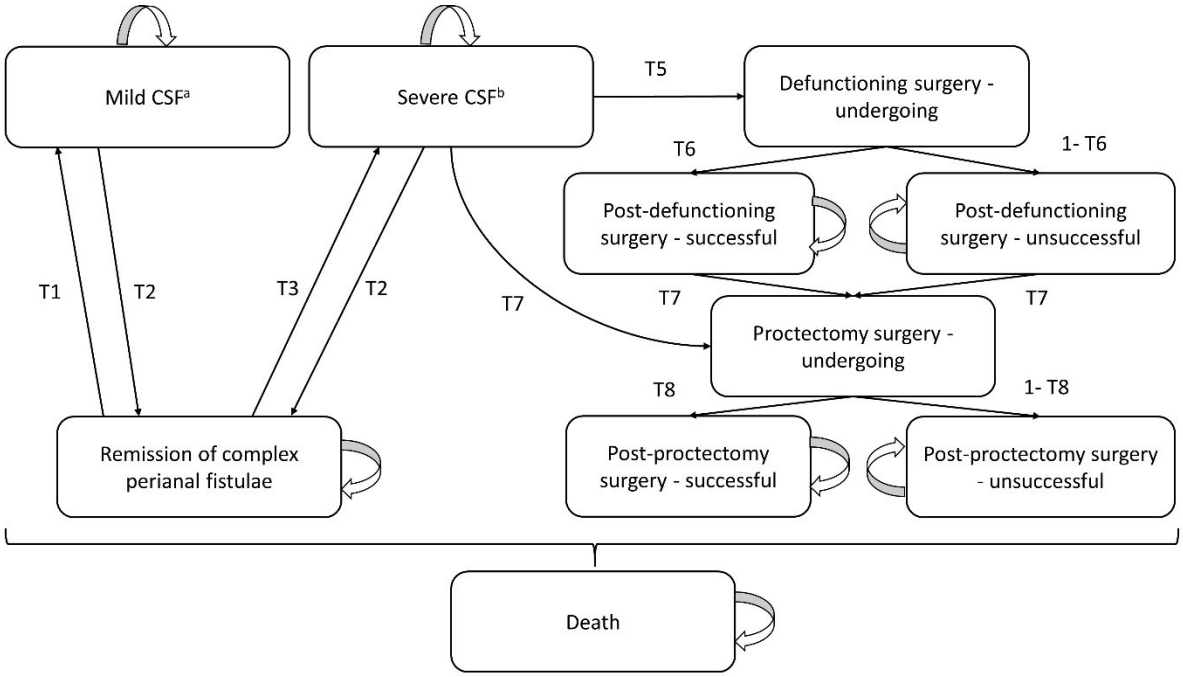
The base case model adopts an NHS and Personal Social Services (PSS) perspective. The time horizon of the base case model was 40 years from the model start. Costs and QALYs were discounted at 3.5% and at 1.5% respectively, as the company states that "*It was considered that a non-reference discount rate of 1.5% per annum for health outcomes was applicable, as darvadstrocel demonstrates long term healing potential in this population with a significant impact on QoL … as per the NICE methods guide.*"(CS,[1] page 74) The ERG notes that section 6.2.19 of the NICE methods guide states that "*In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs.*"(page 66 -67).[10] This means that the originally presented analyses in the CS are out of scope, as the NICE methods guide does not advocate differential discounting of costs and QALYs, even if these criteria are met.[1, 10] Two sets of in scope analyses, one using discount rates of 1.5% for both costs and QALYs and the other 3.5% for both costs and QALYs were provided in the company's clarification response (question B7).[2] The in scope analyses are the focus of the ERG's summary of the company's submitted analyses (see Sections 5.2.7 and 5.2.8).

5.2.4 Model structure

The company's model adopts a state transition approach and is constructed in Microsoft Excel® (see Figure 2). The model includes eight main health states: (1) mild chronic symptomatic complex perianal fistulae (CSF); (2) severe CSF; (3) remission; (4) defunctioning surgery (cycle 1); (5) defunctioning surgery (subsequent cycles); (6) proctectomy (cycle 1); (7) proctectomy (subsequent cycles) and (8) death. Patients with mild or severe CSF (model states 1 or 2) experience AEs (abscesses and proctalgia)

which are dependent on treatment and the severity of their CSF. The defunctioning surgery (subsequent cycles) and the proctectomy surgery (subsequent cycles) were both split into successful and unsuccessful surgeries. Transitions to the proctectomy and defunctioning surgery health states are assumed to not be possible from either the remission or the mild CSF health states. Patients who have had defunctioning surgery are not able to have this reversed in the model; as such, the only possible transitions from the defunctioning surgery states are to proctectomy or death.

Figure 2: Model diagram (adapted from CS,[1] Figure 17)



a – 40.1% of people start the model in this health state; b – 59.9% of people start the model in this health state; T1 – time to relapse * probability that a CSF is mild; T2– time to remission; T3 - time to relapse * (1- probability that a CSF is mild); T5 – time to defunctioning surgery; T6 – probability that a defunctioning surgery is successful; T7 – time to proctectomy; T8 – probability that a proctectomy is successful

Patients enter the model in either one of the two CSF health states (40.1% mild, 59.9% severe) at a mean age of 38.27 years. Health state transitions are estimated over 520 4-weekly cycles (approximately 40 years); at this time point, only 31.7% of patients in each treatment group have died. The treatment-specific transitions from the CSF mild (state 1) and CSF severe health states (state 2) to the remission health state (state 3) are based on the same parametric model (Gompertz distribution) fitted to the CPC remission outcome from the ADMIRE-CD.[1] The treatment-specific transitions to the CSF mild (state 1) and CSF severe health states (state 2) from the remission health state (state 3) are based on the same parametric model (Gompertz distribution) fitted to the CPC relapse outcome from the ADMIRE-CD trial and the probability that a CSF is mild.[1] The Gompertz distributions are different in the darvadstrocel and standard care groups, as a treatment effect covariate (HR) is estimated for both the

time to relapse and time to remission Gompertz distributions. After one completed line of either darvadstrocel or standard care (defined as achieving remission or remaining in the CSF health state for more than 13 model cycles), patients go on to receive salvage therapy in both arms. To estimate the time to remission and relapse for people who have received salvage therapy, these transitions are estimated by applying a HR based on an expert elicitation exercise to the respective time to event function for patients receiving standard care. The probability that a CSF is mild is estimated from the ADMIRE-CD trial data.[1] Transitions to the defunctioning surgery state were based on a parametric model (exponential distribution) fitted to digitised individual-level patient data (IPD) from a subgroup of people with a complex perianal fistulae in a prospective cohort study on surgical outcomes in people with perianal fistulae and Crohn's disease by Mueller *et al*.[24] The digitised IPD were reconstructed from the Kaplan-Meier time-to-event function using the Guyot *et al*[25] method. Transitions to the proctectomy state were based on an analysis of the St Mark's retrospective dataset.[1] The St Mark's retrospective data set is retrospective cohort study of 78 consecutive patients who presented at St Mark's hospital, London, with complex perianal fistulae in Crohn's disease between January 1st 2008 and July 1st 2017. Transitions to the death state from all states are based on general population life tables.[26]

5.2.4.1 Modelling HRQoL impacts

The model assumes that HRQoL is principally determined by time spent in each health state and therefore the patient's HRQoL is driven by time to remission, time to relapse and the timing of defunctioning surgery or proctectomy. Whilst patients were receiving darvadstrocel, standard care or salvage therapy, utility decrements for the incidence of TEAEs were applied, resulting in different HRQoL in the mild CSF (state 1) and severe CSF (state 2) health states across the three treatment groups. The HRQoL effects associated with each health state are not age-adjusted.

5.2.4.2 Modelled treatment pathway and associated costs

The company's model includes the following cost components: (1) drug acquisition; (2) drug administration; (3) TEAEs, and (4) health state resource use (hospital visits and tests). The only differences in the model pathways between the darvadstrocel and standard care arms are that in the initial CSF health states (either mild or severe). Patients in the darvadstrocel arm receive a single course of darvadstrocel in addition to the standard care treatments; therefore patients in the darvadstrocel arm receive different time to remission and time to relapse functions which influence the transitions to and from the remission health state (state 3). Consequently, this leads to a differences in the amount of time spent at risk of receiving defunctioning (state 5) or protectomy surgery (state 7) between the treatment groups. Patients experience different rates of TEAEs in the two treatment groups. Upon the first relapse (transition from remission (state 3) to a CSF health state (state 1 or state 2)), patients in both the standard care and darvadstrocel arms are assumed to receive salvage therapy.

Within the standard care group, the model assumes the following treatment pathway:

- The average patient receives surgical (EUA and/or seton placement) and medical management for their complex perianal fistula. The exact treatments used for surgical and medical management are based on data from the ADMIRE-CD study.

Within the darvadstrocel group, the model assumes the following treatment pathway:

- All patients receive a single course of four vials (120 million cells) of darvadstrocel within the first cycle (four weeks).
- Darvadstrocel is administered using one additional EUAs compared to standard care (two EUAs in total). The first EUA is used to condition the fistula and the second to administer darvadstrocel.
- Patients receiving darvadstrocel also receive the same medical management of their fistula as people in the standard care group
- Upon relapse, no further administrations of darvadstrocel are given.

Upon relapse, all patients in both groups receive salvage therapy. This consists of surgical and medical management. The exact treatments used for surgical and medical management are different from the standard care group and are based on expert clinical opinion.

5.2.5 Key structural assumptions employed within the company's model

The company's model employs the following structural assumptions:

- All patients enter the model in either the mild active complex perianal fistula health state or the severe complex perianal fistula health state.
- HRQoL is principally determined by time spent in remission (state 3) and CSF (state 1 and state 2), post-defunctioning surgery (state 5) and post-proctectomy (state 6) health states.
- All darvadstrocel administration is completed within the first model time cycle (4 weeks).
- The hazard rate for time to remission is assumed to follow a Gompertz distribution in the darvadstrocel, standard care and salvage therapy groups.
- The hazard rate for time to relapse is assumed to follow a Gompertz distribution in the darvadstrocel, standard care and salvage therapy groups.
- Patients are only eligible to receive one line of treatment (i.e. darvadstrocel or standard care); following relapse, patients are assumed to receive salvage therapy.
- Patients who do not achieve remission within one year of treatment with either darvadstrocel or standard care are assumed to receive salvage therapy.
- The probabilities of undergoing proctectomy and defunctioning surgery are assumed to be constant with respect to time.

- It is only possible to enter the defunctioning surgery health state from the severe CSF health state.
- It is only possible to enter the proctectomy surgery health state from either the severe CSF health state or either of the post-defunctioning surgery health states.
- It is not possible for a proctectomy or a defunctioning surgery to be reversed.
- It is not possible for a successful proctectomy to become unsuccessful or *vice versa.*
- It is not possible for a successful defunctioning surgery to become unsuccessful or *vice versa.*

The structural assumptions in the company's model are commented on by the ERG in the critical appraisal section (see Section 5.3.4.8)

5.2.6 Evidence used to inform the company's model parameters

The evidence sources used to inform the model parameters are summarised in

Table 13. These are discussed in further detail in the subsequent sections.

Table 13: Evidence sources used to inform the company's model parameters

Parameter type	Parameter	Source(s)
Time-to-event parameters	Remission – darvadstrocel	CPC definition of remission in the ADMIRE-CD trial[1]
	Remission – standard care	
	Relapse – darvadstrocel	CPC definition of relapse in the ADMIRE-CD trial[1]
	Relapse – standard care	
	Remission – HR of salvage therapy versus standard care	Company's expert elicitation exercise[1]
	Relapse – HR of salvage therapy versus standard care	
	Time to defunctioning surgery	Mueller *et a l*prospective cohort study[24]
	Receiving a proctectomy surgery	Bell *et al.*prospective study[27]
Time independent probabilities	Probability complex perianal is mild	ADMIRE-CD trial[1]
	Probability proctectomy is successful	St Mark's retrospective study[1]
	Probability defunctioning surgery is successful	St Mark's retrospective study[1]
Mortality	Age-dependent probability of death	ONS[26]
HRQoL	Health utility – all model health states	Vignette study[1]
	Disutility associated with abscesses	Vignette study[1]
	Disutility associated with proctalgia	Assumption[1]
Resource use and costs	Health state related inpatient, outpatient resource use and associated costs	Expert opinion,[1] NHS Reference Costs 2016-17,[28] PSSRU,[29] NICE TA 329,[30] NICE DG11[31]
	Darvadstrocel acquisition cost (including PAS)	Company[1]
	Frequency of use for different surgical and drug treatments for complex perianal fistulae	ADMIRE-CD trial,[1] expert opinion[1]
	Unit costs of surgical procedures used to treat complex perianal fistulae	NICE MIB 102,[32] NICE MIB 105,[33] NHS Reference Costs 2016-17[28]
	Unit costs and dosing related to drug treatments	BNF,[34] SmPC,[6] NICE TA187[35]

5.2.6.1 Time-to-event analyses

CPC definition of remission

The company fitted parametric survival functions to time-to- remission data from the ADMIRE-CD trial. In the company's base case analysis, remission was defined as the interval from the date of treatment completion for darvadstrocel (four weeks post-randomisation) to the time of remission of the fistula, which was defined as the fistulae not draining when gently compressed and the patient reporting a PDAI score of 0 in the pain and discharge dimensions (CPC remission). Relapse was defined as the interval from achieving CPC remission to either the fistulae re-opening (determined by gentle finger compression) or the patient reporting a PDAI score of ≥ 1 in the pain or discharge dimensions.

The company fitted a range of standard parametric time to event distributions (exponential, Weibull, log normal, log logistic, generalised gamma, and Gompertz) to the data. The goodness-of-fit of each model was assessed using the methods detailed in NICE Decision Support Unit Technical Support

Document 14 (comparing Akaike information criterion [AIC] and Bayesian information criterion [BIC], and by visual assessment).[36] An assessment of the proportional hazards assumption was carried out only for the time to relapse functions, because the remission time-to-event functions for the darvadstrocel and standard care groups were not extrapolated beyond the 1-year follow-up data (CS,[1] page 79).It should be noted that when patients received salvage therapy, the time to remission function was extrapolated. An assessment of other plausible assumptions (e.g. accelerated failure time) were not conducted. In all analyses a treatment effect covariate (either a constant HR or constant acceleration factor, depending on the model type) was included in the statistical models to estimate the treatment effect parameter (the difference between the time-to-event for patients receiving darvadstrocel versus those receiving standard care). Piecewise exponential models were also fitted to the data, however the ERG notes that, it is unclear how these functions were fitted and which goodness-of-fit tests, if any, were conducted in these cases. The Gompertz distributions for time to remission and time to relapse were presented to the company's clinical experts to assess the clinical plausibility of the extrapolation (CS,[1] page 79).

Table 14 presents the AIC and BIC statistics for each of the fitted parametric time-to-event functions. These indicate that when the CPC definition of remission is used, the generalised gamma distribution provides the best fit to the observed time to remission data and the Gompertz distribution provides the best fit to the observed time to relapse data (although there is very little to distinguish between the Gompertz and the log normal models).

Table 14: AIC and BIC statistics for time-to-event functions fitted to data on time to remission and relapse using the CPC definition of remission, excluding the piecewise exponential model (adapted from CS,[1] Tables 32 and 38)

	Remission		**Relapse**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	980.8393	987.4459	539.436	544.606
Weibull	965.6205	975.5305	528.702	536.457
Gompertz	946.2664	956.1763	***517.572***	***525.327***
Log normal	954.7821	964.6920	518.216	525.971
Log logistic	954.7821	964.6920	521.644	529.399
Generalised gamma	***931.1734***	***944.3866***	522.156[a]	532.496[a]

AIC – Akaike information criterion; BIC – Bayesian information criterion; a - the stacy parametrisation used for the generalised gamma rather than the default prentice parameterisation
Text in ***bold and italics*** indicates the lowest value out of the converged time-to-event functions in each column

The appropriateness of the proportional hazards assumption was assessed by examining the log cumulative hazard plot. The log cumulative hazard plot for CPC remission is presented in

Figure 3; this plot shows that the lines are approximately parallel and do not cross, thereby indicating that the proportional hazards assumption is not violated. The plot of the empirical hazard function and fitted hazard function is given in

Figure 4. In Figure 4 the solid black lines represent the empirical hazard, the solid coloured line represents the central estimate of the fitted hazard for each treatment group, and the dotted coloured lines represent the 95% CI around the fitted hazard. This plot shows that the empirical hazards stay within the confidence interval of the predicted hazard for the Gompertz curve, but not for the other parametric time to event functions.

Figure 3: The log cumulative hazard plot for CPC remission data (reproduced from clarification response,[2] question B3)

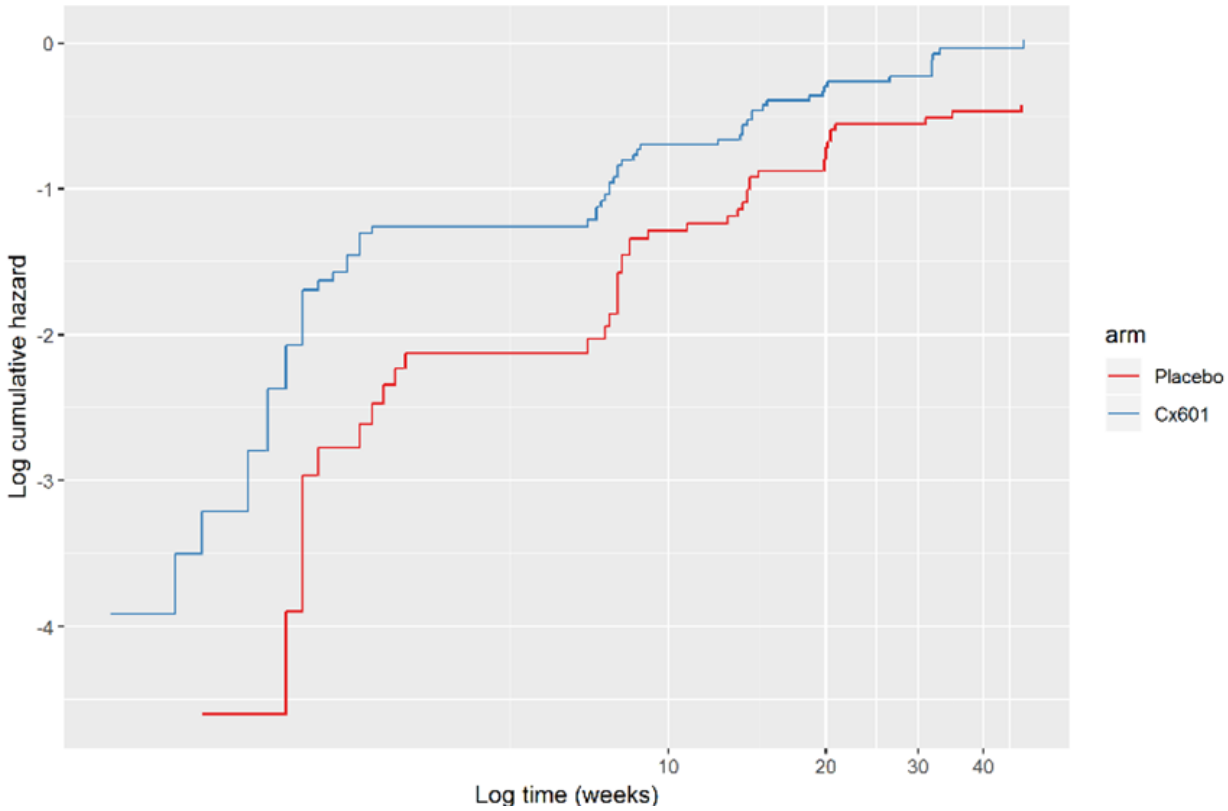


Figure 4: Empirical versus predicted hazards for CPC remission (reproduced from clarification response,[2] question B3)

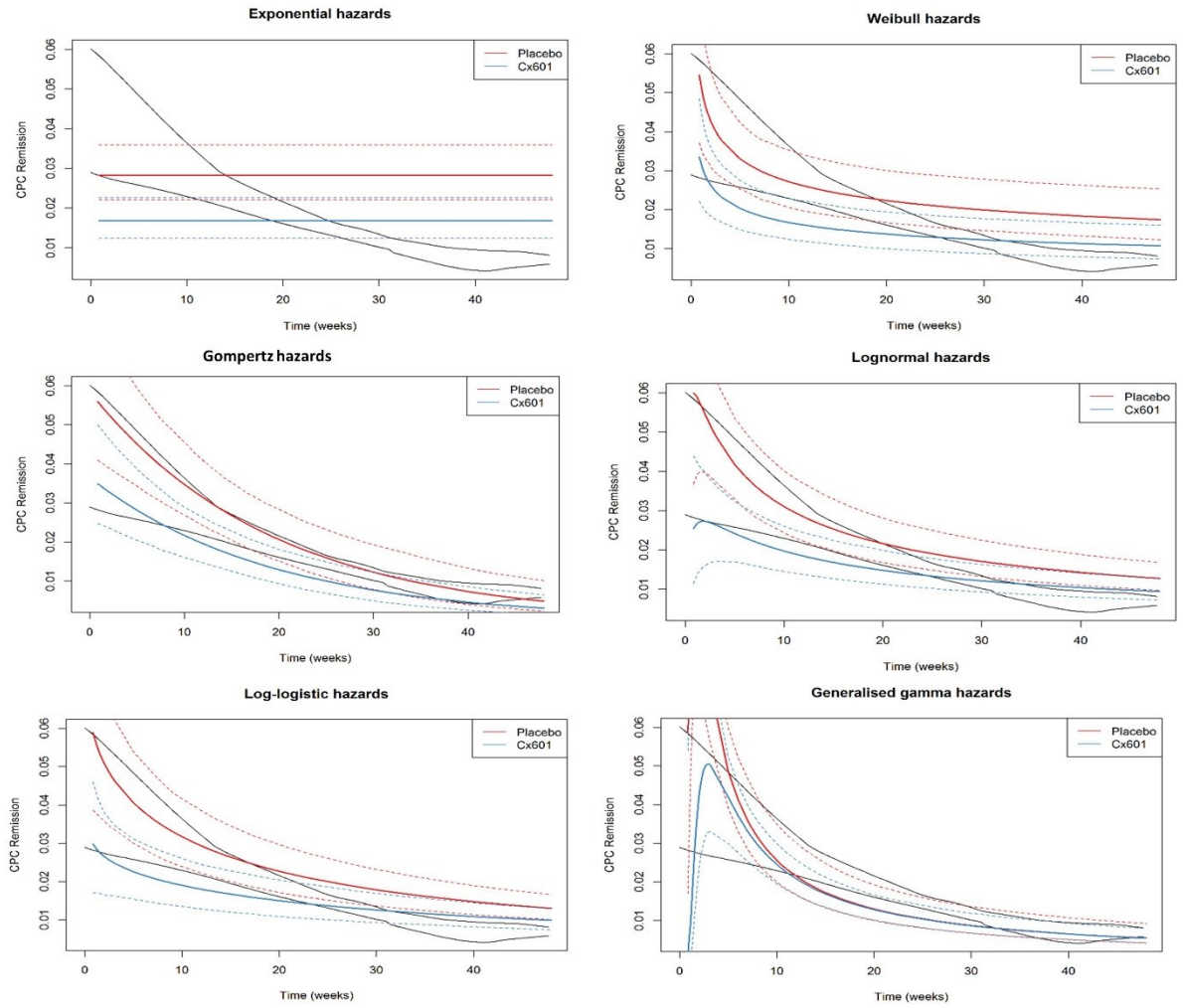


Figure 5 shows that for CPC relapse, the curves cross early and then separate at a later time point. The company states that the curves are approximately parallel in the medium to long-term. This indicates that the proportional hazards assumption for CPC relapse is likely to be inappropriate. A plot of the empirical and predicted hazard functions is given in

Figure 6; this shows that the shape of the empirical hazard function is not consistent with any of the fitted parametric curves across the full time period plotted, and that the Gompertz curve provides a reasonable fit up to around 40 weeks. The other curves fitted tend to over-predict the hazard in the darvadstrocel arm prior to 40 weeks.

Figure 5: Log cumulative hazard plot for CPC remission relapse data (reproduced from clarification response,[2] question B3)

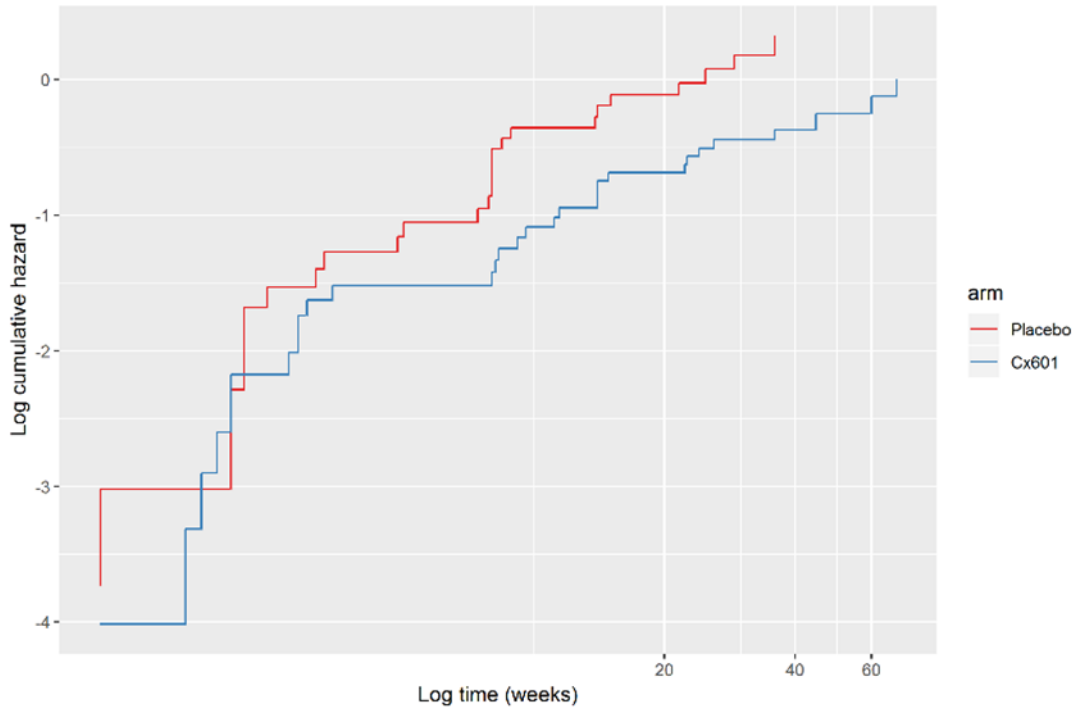
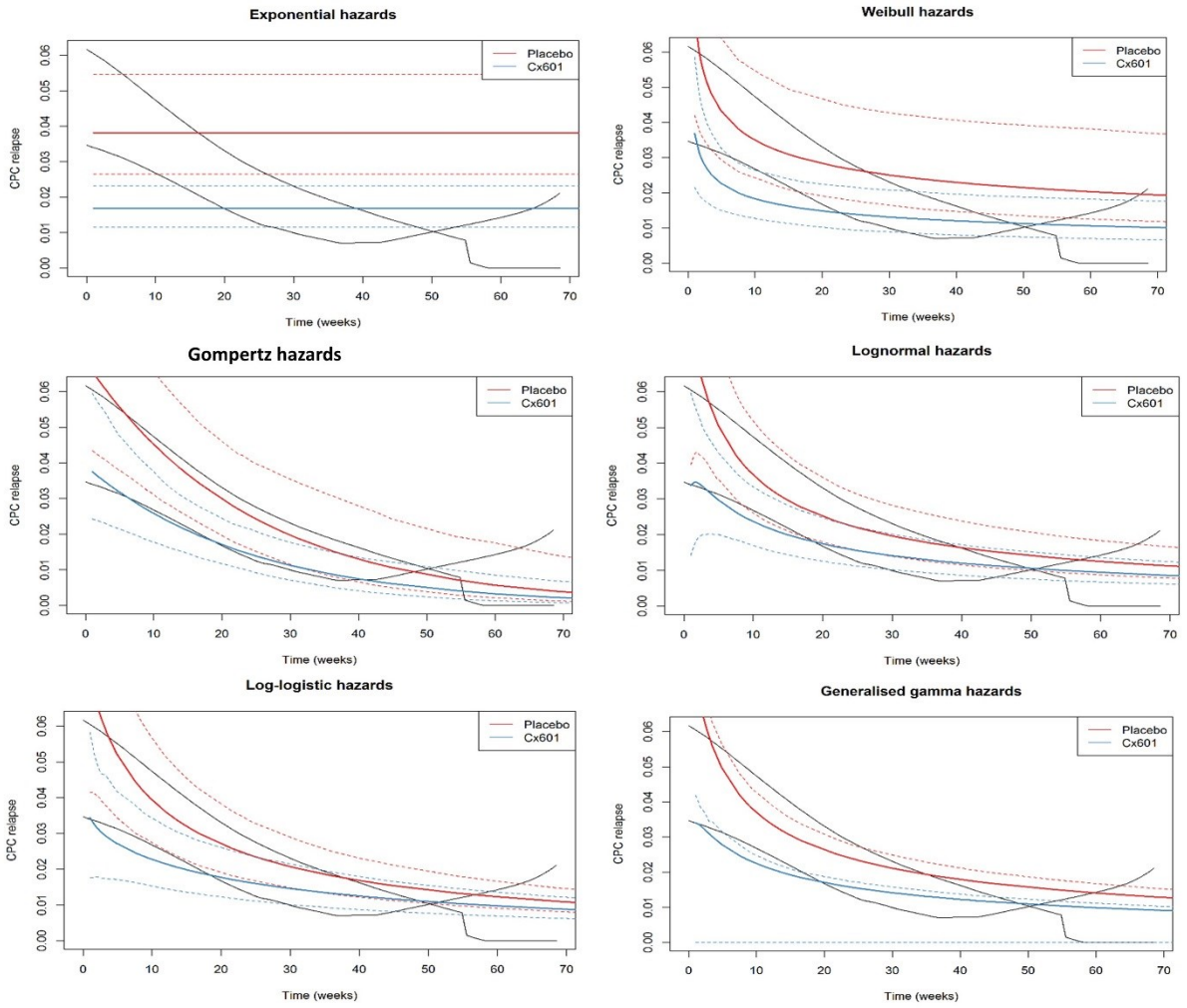


Figure 6: Empirical hazard versus predicted hazard plots for CPC remission (reproduced from clarification response,[2] question B3)



The company obtained expert opinion in two phases on the plausibility of the long-term extrapolations of the time-to-event functions. In the first phase, general opinions around the expected time-to-event function were sought from 10 experts (see clarification response,[2] question B4). This opinion indicated that "*... the risk of relapse for patients who have been in remission a long time would decrease…"*. This rationale was used to support the company's selection of the Gompertz time-to-event function in the base case. Visual comparison of the different parametric time-to-event models against the Kaplan-Meier time-to-event function are presented for CPC remission and CPC relapse in Figure 7 and

Figure 8, respectively. In both cases, the Gompertz time-to-event function was selected for use in the company's health economic model and was presented to a panel of seven clinical experts to assess the plausibility of that curve alone (clarification response,[2] question B4). Based on the information on the model diagnostics, clinical opinion around the long-term event hazards, and the fact that the company's elicitation exercise produced a HR, the company selected a Gompertz distribution for both the CPC remission and CPC relapse time-to-event functions.

Figure 7: Parametric time-to-event functions compared to the Kaplan-Meier time-to-event function for CPC remission (reproduced from clarification response,[2] question B13)

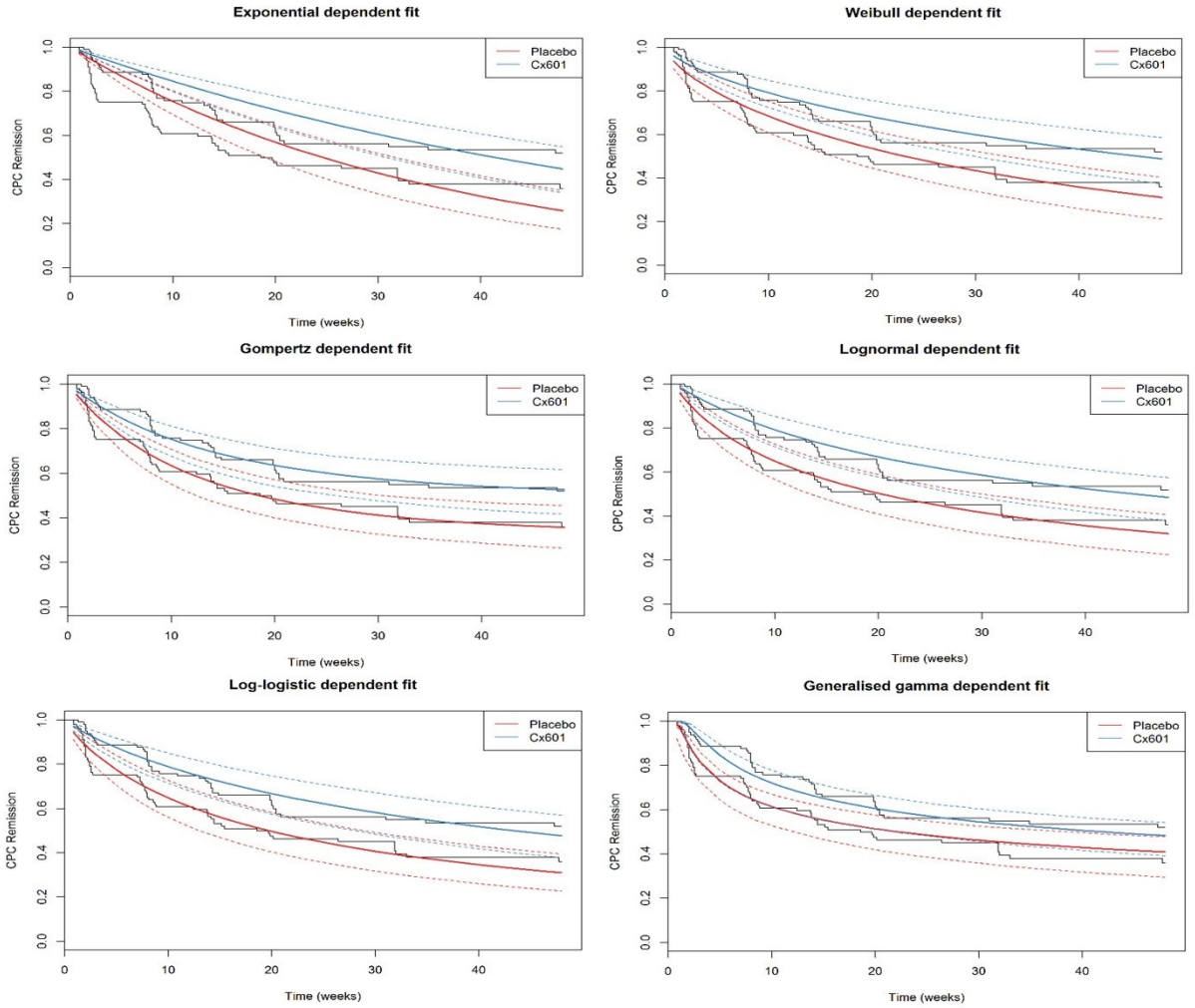
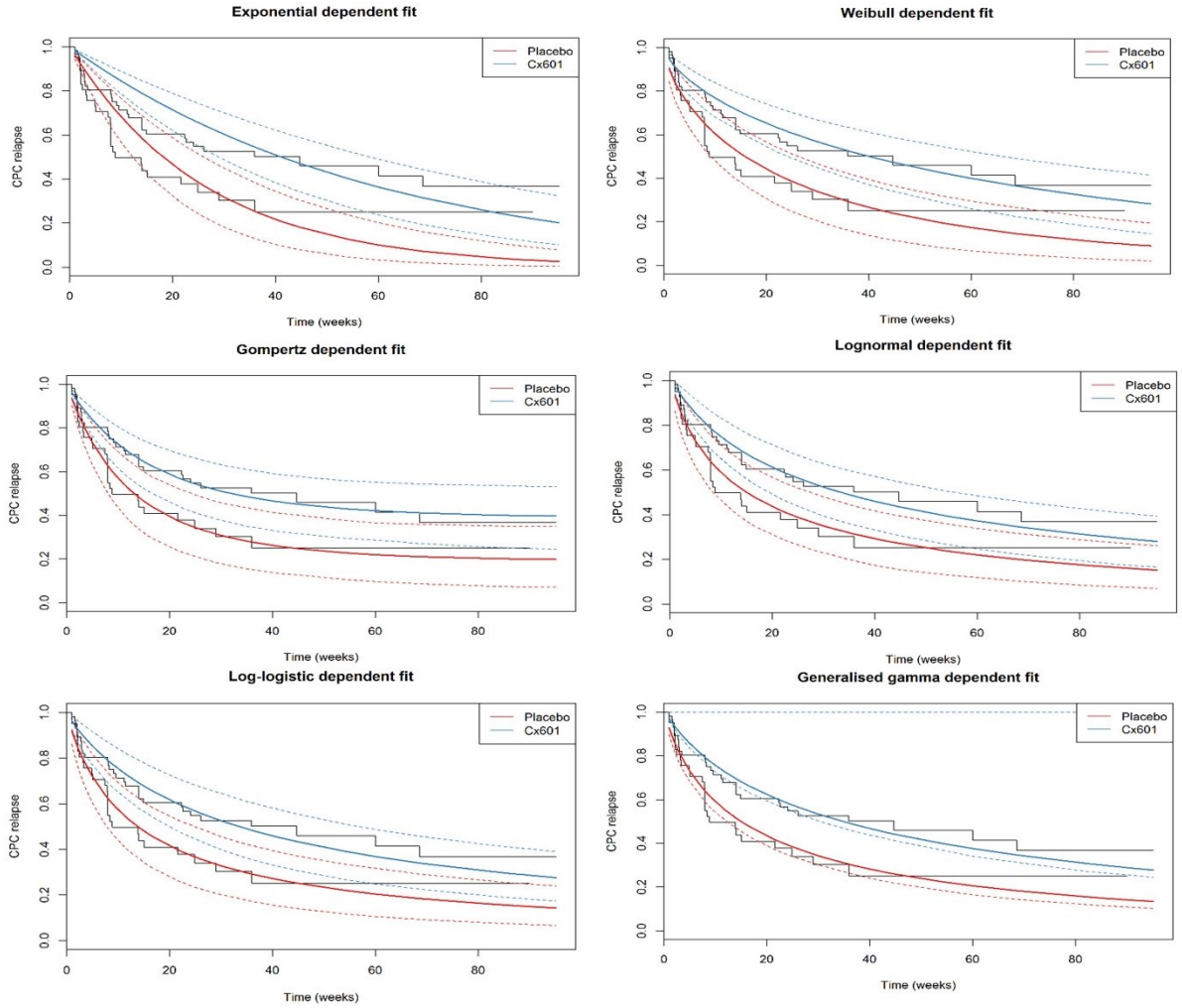


Figure 8: Parametric time-to-event functions compared to the Kaplan-Meier time-to-event function for CPC relapse (reproduced from clarification response,[2] question B13)



With respect to the long-term extrapolation, the company used the statistical time-to-event functions to estimate the probability of relapse (for darvadstrocel, standard care, and salvage therapy) or remission (for salvage therapy only) functions up to the 24th model cycle (approximately two years). After this point the company, estimated a time-to-event function specific constant probability of relapse or remission. This probability was assumed to be constant and calculated using two points of each fitted time-to-event function: (1) the cumulative probability of relapse or remission at 100 weeks post-randomisation, and (2) the cumulative probability of relapse or remission at 160 weeks post-randomisation. The company considered this approach to be appropriate, as their clinical advisors stated that they would expect there to be a higher risk of relapse in the long-term than was predicted by the Gompertz time-to-event functions. The company presented the resulting curve to seven clinical experts, which they deemed to be clinically plausible. (see clarification response[2], question B4) The ERG's critique of this approach is provided in Section 5.3.4.5. It should be noted that the time to remission functions were not extrapolated beyond 1 year for the darvadstrocel or standard care groups.

Time to remission and relapse for salvage therapy

In the modelled population, the time to remission and time to relapse need to be estimated for patients receiving salvage therapy. The company estimated the time to remission and time to relapse for people receiving salvage therapy by estimating treatments of salvage therapy compared to standard care in an expert elicitation exercise. The company estimated these treatment effects as HRs of 0.6 for time to remission and 1.0 for time to relapse.[1]

In response to a request for clarification from the ERG (question B16), the company provided the following additional details regarding the expert elicitation exercise.[2] The expert elicitation exercise followed no formal protocol. Six experts from the EU (three of whom were from the UK), were asked to identify the scenario regarding the effectiveness of salvage therapy compared with control that they believed best represented the effectiveness of future lines of therapy compared with standard care. The expert elicitation exercise was only designed to elicit a HR and other plausible treatment effect assumptions were not elicited from the six experts. The company's justification for this was that this assumption was "… *validated by clinical experts in Europe and the UK*…" and that "… *both control and salvage therapy broadly consisted of the same interventions, those being EUA +/- seton placement with background therapy consisting of antibiotics, immunosuppressants and biologic therapy* …" (clarification response,[2] question B16). Other details on the company's elicitation process and information presented to the experts during this process are unclear. The ERG's concerns regarding the expert elicitation exercise and the implementation of the estimated HRs are presented in Section 5.3.4.6.

The logic used to implement the time to remission and time to relapse functions for patients on salvage therapy is that: before 24 model cycles (approximately 2 years), the time-to-event functions for the salvage therapy group (standard care Gompertz distribution with a HR applied) is used; after 24 model cycles the constant probability of remission or relapse from the standard care arm is used (i.e. no HR is applied). This issue is further discussed in Section 5.3.3.

Probability of receiving defunctioning surgery

Mueller *et al.* was a prospective cohort study of 102 consecutive patients with Crohn's disease who presented with their first manifestation of perianal fistula or perianal abscess in a German outpatient ward between 1992 and 1995.[24] Out of the 102 patients recruited, 46 subjects had a complex perianal fistula. A Kaplan-Meier time-to-event function for the time to permanent faecal diversion from the year since each patient first presented with Crohn's disease was produced for the subgroup of study participants with a complex perianal fistula. The company calculated the time to defunctioning surgery, by digitising the Kaplan-Meier time-to-event function from Mueller *et al*, using the Guyot *et al.* method for reconstructing time-to-event data.[24, 25] The company fitted only an exponential distribution time-to-

event to the data as "… *an assumption required for simplification of the model structure*…" (clarification response,[2] question B6, page 63), i.e. they chose a distribution with a constant hazard rate to avoid the need for time dependent probabilities for transitions out of this health state which simplified the implementation of the model.

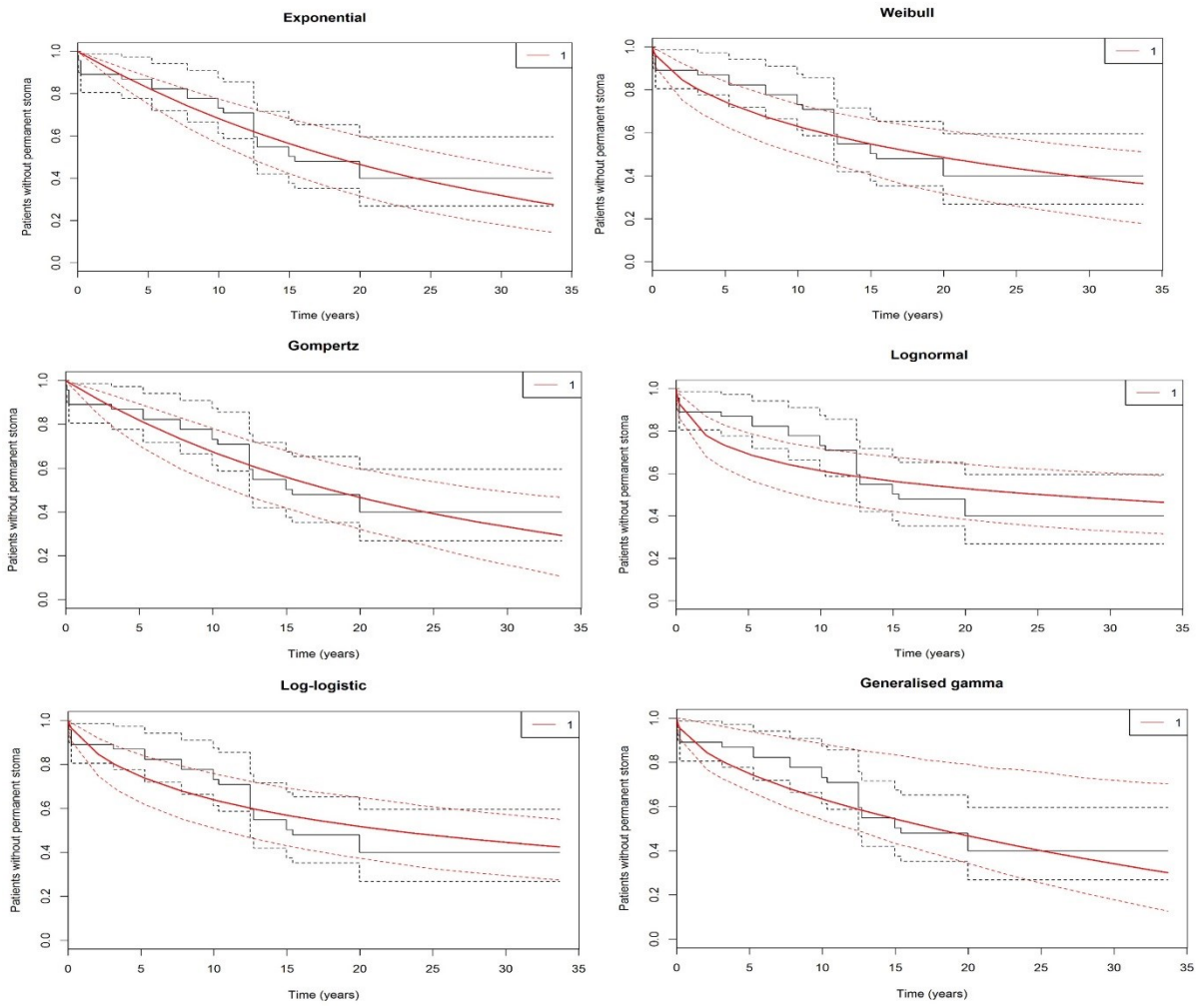
In response to a request for clarification from the ERG (question B6), the company provided AIC and BIC statistics and visual comparisons of the parametric time-to-event functions to the Kaplan-Meier curve. The AIC and BIC statistics are presented in Table 15; these show that the generalised gamma function provides the best fit to the underlying data based on the AIC criterion and that the Weibull function provides the best fit based on the BIC criterion. The visual plot of the parametric time-to-event models and the Kaplan-Meier curves are given in Figure 9. In this plot, the black line indicates the Kaplan-Meier curve, the red line indicates the fitted parametric time-to-event function, and the dotted lines indicate the 95% confidence intervals around these estimates. It is clear in Figure 9 that none of the curves provide a particularly good fit to the observed data, but the central estimates of the exponential and Gompertz functions provide the best approximation of the shape of the Kaplan-Meier curve.

Table 15: AIC and BIC statistics for the fitted parametric curves to the time to permanent stoma (adapted from clarification response,[2] question B6)

	AIC	**BIC**
Exponential	215.1842	217.0129
Weibull	210.6724	**214.3297**
Gompertz	217.1266	220.7839
Log normal	222.7323	226.3896
Log logistic	214.5136	218.1709
Generalised Gamma	**209.5852**	215.071

AIC –Akaike information criterion; BIC – Bayesian information criterion
Text in ***bold and italics*** indicates the lowest value in each column (best fitting to the data)

Figure 9: Observed and predicted time-to-event curves for permanent stoma (from clarification response,[2] question B6)



Probability of receiving proctectomy

The probability of receiving a proctectomy surgery was estimated by the company from Bell *et al*.[27] This prospective study collected data on the clinical course of 87 patients with Crohn's disease related fistulae between January 1993 and December 1994. Approximately 21%(18/87) of people with an active fistula and Crohn's disease subsequently received a proctectomy at a median time of 6 years (range 0.23 to 28.2 years) after their first presentation of a fistula. The company calculated the annual probability of undergoing a proctectomy to be 0.0385.

5.2.6.2 Time-independent probabilities

Probability that a CSF is mild

Data on the probability that a CSF is mild was obtained from the ADMIRE-CD trial.[1] The company defined mild CSF to be any person with a complex perianal fistulae and non-active / mildly active luminal Crohn's disease who had a score of 1 on either the pain or discharge dimensions of the PDAI and a score of ≤1 on the other dimension. Severe CSF was defined as any complex perianal fistulae

for people who had non-active / mildly active luminal Crohn's disease that were not either mild or in remission. The company estimated the proportion of cases that were mild and severe by taking an average of the PDAI score of people with CSF. Patients with missing data or in remission were excluded from these calculations. It was assumed that these probabilities were constant with respect to time.

Probabilities that a proctectomy or defunctioning surgery are successful

The probability that a proctectomy was successful and the probability that a defunctioning surgery was successful were obtained from the St Mark's retrospective cohort study (CS,[1] Appendix Q). In this prospective study, data was collected from 78 consecutive patients who presented with a complex perianal fistula and Crohn's disease at St Marks hospital between from 1st January 2008 to July 1st 2017. Data were collected at baseline, routine visits and study termination (lost to follow up, transferred to another hospital, or patient death). In this data source, the probability that a proctectomy was successful was 0.62 and the probability that a defunctioning surgery was successful was 0.80.

Mortality

The age-dependent probability of death was taken from general population life tables for England and Wales in 2013-15.[26]

HRQoL

The ADMIRE-CD trial[1] did not include a preference-based measure of HRQoL. The CS states that there are no disease-specific measures of HRQoL available for patients with perianal fistula.[1] The only patient reported outcome measure included in ADMIRE-CD was the IBDQ. The company considered whether it was possible to map from the PDAI, CDAI or IBDQ scores obtained in the trial to the EQ-5D. The CS states that there is insufficient conceptual overlap between the content of the PDAI and CDAI, which are considered to be measures of disease activity, and the relevant components of HRQoL.[1] The company cites a mapping study by Buxton *et al.*(2007)[37] which they claim supports the poor performance of CDAI as a predictor of utility. The ERG notes that the mapping algorithms reported by Buxton *et al*[37] were derived and validated in studies that included patients with moderately to severely active Crohn's disease. The company does not consider mapping from IBDQ to be appropriate because IBDQ is focused on luminal disease and not complex perianal fistulae. The ERGs clinical advisors agreed that IBDQ was a Crohn's disease specific measure of health. The company conducted a systematic review of HRQoL studies, but concluded that none of the studies identified were suitable for informing utility values in the model.

The health state utility values (HSUVs) used in the company's model were taken from a vignette study reported by Fountain *et al*.[38] which was funded by Takeda (the full study report is provided in

CS,[1] Appendix R). Vignettes were developed describing eight health states that were relevant to the model structure: (1) remission, (2) CSF with mild symptoms, (3) CSF with moderate symptoms, (4) abscess, (5) defunctioning surgery with positive outcome, (6) defunctioning surgery with negative outcome, (7) proctectomy with positive outcome and (8) proctectomy with negative outcome. The health state descriptions were derived with the input of both patients and clinicians. These were valued used a time-trade off (TTO) methodology by both a representative sample of the general public (n=835) and by a sample of patients with Crohn's disease, but not specifically CSF (n=162). The values generated by the general public sample were used in the company's base case analysis; the values from Crohn's disease patients were explored in a sensitivity analysis. The CS also reported in detail the validation of the utility values by EU and UK clinical experts (CS,[1] Appendix P).

The utility values applied in the company's base case analysis are summarised in Table 16. Whilst the vignette study measured the utility of CSF with abscess as a separate health state, the company incorporated a utility decrement associated with abscess into the model by calculating the difference between the utility values for CSF with abscess and CSF with severe symptoms. This resulted in a mean disutility of 0.16 (SE 0.026, 95% CI 0.11 to 0.21). The company's model assumes that there is no additional decrement associated with proctalgia as this event may be experienced by patients having CSF and was therefore already accounted for within the HSUVs for CSF.

Table 16: Vignette study results, general population sample (adapted from CS,[1] Table 46)

Health state		Observations	Mean utility	Standard deviation	Standard error	95% confidence interval
Remission		835	0.865	0.24	0.008	[0.85; 0.88]
Chronic symptomatic fistulae	**Mild symptoms**	835	0.578	0.44	0.015	[0.55; 0.61]
	Severe symptoms	835	0.383	0.50	0.017	[0.35; 0.42]
Abscess		835	0.223	0.55	0.019[a]	[0.19;0.26]
Defunctioning	**Undergoing**	Assumed equal to CSF with severe symptoms				
	Successful	835	0.567	0.46	0.016	[0.54; 0.60]
	Unsuccessful	835	0.193	0.56	0.019	[0.15; 0.23]
Proctectomy	**Undergoing**	Assumed equal to CSF with severe symptoms				
	Successful	835	0.564	0.50	0.017	[0.53; 0.60]
	Unsuccessful	835	0.202	0.57	0.020	[0.16; 0.24]

Abbreviations: CSF, chronic symptomatic fistulae. Notes: **, assumed equal to chronic symptomatic fistulae with severe symptoms.
Source: Takeda, data on file.
a calculated by ERG

Resource use and costs

Health state related inpatient and outpatient resource use

The health state resource use per 4-weekly model cycle, the unit cost of each resource use type and the total cost associated with each type of resource use for each health state are summarised in Table 17.

The unit costs of each resource use item were obtained from a variety of sources (NHS Reference Costs 2016-17[28], the Personal Social Services Research Unit (PSSRU),[29] NICE TA329[30] and NICE DG11[31]). For each health care resource use item, the number of items used in each 4-weekly cycle were obtained from the ADMIRE-CD trial and/or clinical expert opinion.

Table 17: Health state resource use and associated costs used in the company's model (adapted from CS,[1] Tables 52 and 53)

	Unit cost		Resource use (number of visits / tests) per 4 weekly cycle								
Resource item	**Cost per item of resource use (£)**	**Source**	**Remission**	**CSF**		**Defunctioning**			**Proctectomy**		
				Mild	**Severe**	**Undergoing**	**S**	**U**	**Undergoing**	**S**	**U**
Healthcare professional resource use											
GP visits	37.00	PSSRU[29]	0.06	0.12	0.14	1.38	0.10	0.21	1.38	0.10	0.25
Gastroenterologist visits	149.76	NHS Reference costs[28]	0.13	0.17	0.31	2.00	0.10	0.31	2.00	0.12	0.31
Surgeon visits	127.09	NHS Reference costs[28]	0.04	0.10	0.22	2.25	0.10	0.29	3.25	0.12	0.48
Nurse appointments	51.15	NHS Reference costs[28]	0.06	0.16	0.27	1.75	0.12	0.35	2.75	0.15	0.56
Nutritionist visits	81.33	NHS Reference costs[28]	0.02	0.02	0.08	0.25	0.04	0.12	0.25	0.06	0.12
Total cost of health care professional visits per four weekly cycle			***£31.70***	***£52.04***	***£99.35***	***£746.38***	***£39.21***	***£117.66***	***£924.62***	***£48.06***	***£154.34***
Monitoring resource use											
Rectal MRI	162.23	NHS Reference costs[28]	0.01	0.06	0.13	1.00	0.02	0.10	1.25	0.04	0.13
Endoscopy	182.10	NHS Reference costs[28]	0.06	0.06	0.13	1.00	0.06	0.13	1.25	0.00	0.06
Stoma care*	1,961.00	NICE TA 329[30]	0.00	0.00	0.00	0.08	0.08	0.08	0.08	0.08	0.08
Computerised tomography	85.56	NHS Reference costs[28]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Colonoscopy	334.76	NHS Reference costs[28]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total cost of monitoring patients per four weekly cycle			***£12.07***	***£19.87***	***£44.60***	***£495.18***	***£164.47***	***£190.83***	***£581.26***	***£157.09***	***£183.19***
Laboratory resource use											
Blood count	1.69	NHS Reference costs[28]	0.15	0.12	0.23	2.25	0.15	0.28	2.50	0.15	0.35
C-reactive protein	1.13	NHS Reference costs[28]	0.17	0.13	0.27	2.25	0.15	0.31	2.50	0.15	0.37
Haemoglobin	3.06	NHS Reference costs[28]	0.17	0.12	0.23	2.25	0.15	0.28	2.50	0.15	0.35
Faecal calprotectin	22.79	NICE DG11[31]	0.13	0.13	0.27	1.50	0.10	0.15	1.75	0.12	0.15
Total cost of laboratory tests per four weekly cycle			***£3.77***	***£7.54***	***£4.05***	***£47.42***	***£3.10***	***£5.19***	***£54.58***	***£3.53***	***£5.56***

	Unit cost	Resource use (number of visits / tests) per 4 weekly cycle								
Total health state resource use costs per four weekly cycle		**£47.82**	**£75.67**	**£151.49**	**£1288.97**	**£206.78**	**£313.68**	**£1560.46**	**£208.68**	**£343.09**

CSF – chronic symptomatic fistula; S – successful; U – unsuccessful; GP – general practitioner; PSSRU - Personal Social Services Research Unit; NHS – National Health Service; MRI – magnetic resonance imaging; NICE – National Institute for Health and Care Excellence; TA – technology appraisal; DG – diagnostics guidance; * - the unit cost applied is an annual cost

Darvadstrocel acquisition cost (including PAS)

Drug acquisition costs for darvadstrocel were provided by the company. The company has a Patient Access Scheme in place for darvadstrocel which takes the form of a simple price discount. Including the PAS, the price per vial of darvadstrocel is [redacted], giving a total cost of [redacted] per course of treatment. The model assumes that four vials are used in the EUA procedure in the darvadstrocel arm, which occurs in cycle 1 of the model. This is in line with the marketing authorisation for darvadstrocel.[6]

Frequency of different surgical and drug treatments for complex perianal fistulae

The proportion of patients who receive the different types of surgical and medical treatments are given by health state and treatment line in Table 18. These proportions were estimated from the ADMIRE-CD trial data for the darvadstrocel and standard groups when they were in the CSF mild or CSF severe health state. For the other health states and the people receiving salvage therapy group in the CSF mild or CSF severe health states, the proportions were estimated using UK expert clinical opinion. The exact number of experts used is unclear.

Costs of use for different surgical and medical treatments for complex perianal fistulae

The costs of the different surgical and medical treatments depends upon the health state in which the they are used. When patients received their initial treatment in the CSF health states (either darvadstrocel or standard care), the procedures and associated costs were split into those that would be delivered in the first cycle only and those that were delivered in all cycles. These costs were then applied at appropriate times within the state transition structure of the health economic model. For all other model health states, the mean cost of treatment over 13 model cycles was used to calculate the costs of treatment regardless of how many cycles patients spent in that particular health state. The cost of surgical and medical treatments are given by health state for cycle 1, subsequent cycles and the average over all cycles is given in

Table 19. In addition to the treatment costs, additional costs were applied relating to the administration of these treatments, these administration costs are provided in Table 20.

Table 18: Percentage of patients receiving each treatment by health state and treatment group (adapted from CS,[1] Table 54)

Treatment mix	Mild CSF			Severe CSF			Rem	Defunctioning		Proctectomy		Sources and assumptions
	DARV	Control	Salvage	DARV	Control	Salvage		S	U	S	U	
Darvadstrocel												
Darvadstrocel	100	0	0	100	0	0	0	0	0	0	0	
Antibiotics												
Ciprofloxacin	29.76	29.76	11.25	29.78	29.78	57.50	0	0	0	0	0	ADMIRE CD trial data
Metronidazole	38.05	38.05	55.28	38.05	38.05	58.75	11.20	18.56	57.81	1.09	32.66	
Immunosuppressants												
Azathioprine	46.23	46.23	46.37	46.23	46.23	47.50	51.32	58.99	46.88	45.01	52.50	ADMIRE CD trial data, clinical expert opinion
Methotrexate	0	0	9.05	0	0	0.5	7.29	0.00	5.84	11.66	0	
6-MP	0	0	7.50	0	0	26.75	10.00	11.88	11.88	0	0	
Biologics												
Adalimumab	33.59	33.59	30.65	33.59	33.59	19.17	31.76	21.32	27.03	12.86	25.47	ADMIRE CD trial data, clinical expert opinion
Infliximab	27.26	27.26	30.65	27.26	27.26	35.83	32.39	21.32	27.03	12.86	25.47	
Adalimumab dose escalation	0	0	5.94	0	0	7.5	4.92	3.38	10.21	0.75	8.75	
Infliximab dose escalation	0	0	5.94	0	0	7.5	4.92	3.38	10.21	0.75	8.75	
Vedolizumab	0	0	8.67	0	0	0	8.24	5.08	7.69	3.36	7.36	
Surgery												
Seton	95	95	20.56	95	95	48.5	5.21	11.54	11.96	0	2.50	ADMIRE CD trial data, clinical expert opinion
Fistulotomy	0	0	1.51	0	0	16.5	0	0	5.84	0	0	
Anal plug	0	0	12.50	0	0	11.25	0	0	0	0	0	
Fibrin glue	0	0	0	0	0	6.25	0	0	0	0	0	
Rectal flap	0	0	0	0	0	12.5	0	0	0	0	0	
EUA alone	0	0	43.09	0	0	0	11.12	6.59	37.38	0	26.43	
VAAFT	0	0	4.52	0	0	0	0	6.73	0	0	0	

CSF – chronic symptomatic fistulae; Rem – remission; DARV – darvadstrocel; Control – standard care; S – successful; U - unsuccessful; EUA, examination under anaesthesia; 6-MP, 6-mercaptopurine.

Table 19: Cost of pharmacological and surgical treatments given to each patient (adapted from CS,[1] Table 54)

Treatment	Unit cost	Doses per item	Source	Doses given in cycle 1	Doses given in subsequent cycles	Cost in cycle 1	Cost in subsequent cycles	Average Cycle cost across 13 model cycles
Darvadstrocel								
Darvadstrocel	[redacted]	1 unit	Takeda	4 units	0 units	[redacted]	£0	Not applicable
Antibiotics								
Ciprofloxacin	£0.089	500mg	BNF	56	56	£4.94	£4.94	£4.94
Metronidazole	£0.195	400mg	BNF	76.20	76.20	£14.88	£14.88	£14.88
Immunosuppressants								
Azathioprine	£0.039	50mg	BNF	91.44	91.44	£3.56	£3.56	£3.56
Methotrexate	£0.054	2.5mg	BNF	28	28	£1.51	£1.51	£1.51
6-MP	£1.966	50mg	BNF	50.80	50.80	£99.88	£99.88	£99.88
Biologics								
Adalimumab	£352.14	40mg	BNF	2	2	£704.28	£704.28	£704.28
Infliximab	£377.00	100mg	BNF	1.81	1.81	£684.01	£684.01	£684.01
Adalimumab dose escalation	£352.14	40mg	BNF	4	4	£1368.02	£1368.02	£1368.02
Infliximab dose escalation	£377.00	100mg	BNF	3.63	3.63	£1408.56	£1408.56	£1408.56
Vedolizumab	£2050	300mg	BNF	1.00	0	£2050	0	£78.85
Surgical procedures								
Seton	£0	1 set	Assumption	1	0	£0	£0	£0
Fistulotomy	£1,170.21	1 operation	NICE MIB 102	1	0	£1,170.21	£0	£78.85
Anal plug	£1,170.21	1 operation	Assumed equal to fisulotomy	1	0	£1,170.21	£0	£78.85
Fibrin glue	£724.19	1 set	NICE MIB 105	1	0	£724.19	£0	£55.71
Rectal flap	£1,170.21	1 operation	Assumed equal to fisulotomy	1	0	£1,170.21	£0	£78.85
EUA	£1,170.21	1 operation	NHS reference costs[28]	1	0	£1,170.21	0	£90.02
VAAFT	£1,195.40	1 operation	NICE MIB 102	1	0	£1,195.40	0	£91.95

BNF – British National Formulary; 6–MP - 6-mercaptopurine; NICE – national institute for health and care excellence; MIB – Medtech Innovation Briefing; EUA – examination under anaesthesia; VAAFT - video-assisted anal fistula treatment

Table 20: Cost of treatment administration methods (adapted from CS,[1] Table 55)

Administration method	Unit Cost	Source	Treatments delivered[a]
EUA	See Table 19	NHS reference costs[28]	Darvadstrocel, seton, fibrin glue
IV infusion	£284.49	NHS reference costs[28]	Infliximab, dose escalated infliximab, vedolizumab
SC injection	£0	Assumed to be self-administered	Adalimumab, dose-escalated adalimumab
Oral	£0	Assumption to be self-administered	Ciprofloxacin, Metronidazole, Azathioprine, Methotrexate, 6-MP

a - any treatment not included in this table did not have an administration cost
EUA – examination under anaesthesia; IV – intravenous; SC - subcutaneous

5.2.7 Cost effectiveness results

In the CS, the company discounts costs at a rate of 3.5% and QALYs at a rate of 1.5%.[1] The ERG considers this to be inappropriate, as differential discounting of costs and QALYs is not supported in the NICE Methods guide.[10] A further consideration is that the company states that they believe that: darvadstrocel restores people with complex perianal fistulae and non-active / mildly active luminal Crohn's disease to full health over a long period of time; people receiving standard care have a severely impaired quality of life, and; and that darvadstrocel would not commit the NHS to irrecoverable costs.[1] Consequently, section 6.2.19 of the methods guide may apply.[10] The company believes that "*…darvadstrocel demonstrates long term healing potential in this population with a significant impact on QoL…*" (CS,[1] page 74). The ERG has concerns about whether darvadstrocel meets the criteria in Section 6.2.19 of the Method Guide (see Section 5.3.4).

The ERG considers that the analyses presented in the original CS are out of scope, as differential discounting of costs and QALYs are used.[1] In the company's clarification response to question B7, two sets of in scope analyses were provided, in the first both costs and QALYs are discounted at a rate of 3.5% and in the second both costs and QALYs are discounted at a rate of 1.5%.[1] For completeness, the ERG presents the company's base case analysis both when using the company's preferred differential discounting and when using 3.5% discounting for both costs and QALYs as per the NICE Reference Case. The company's results using discount rates of 1.5% for both costs and QALYs are presented in Appendix 2.

Table 21 shows the results of the company's base case analysis in both the deterministic analysis and the PSA analysis when discount rates of 1.5% and 3.5% are used for QALYs and costs respectively.

Based on the probabilistic version of the company's model, darvadstrocel is expected to generate an additional 1.35 QALYs at an additional cost of £21,774, compared with standard care. The corresponding incremental cost-effectiveness ratio is £16,121 per QALY gained. The deterministic version of the company's model produces a similar ICER of £15,471 per QALY gained. These results are based on differential discounting of costs and QALYs, so the ERG urges caution in using these values.

Table 21: Company's base case results, including the patient access scheme for darvadstrocel, assuming 1.5% discount rate for QALYs and a 3.5% discount rate for costs (adapted from CS,[1] Table 66 and Table 67)

Treatment	Total QALYs	Total costs	ICER (£ per QALY gained)	Probability that the intervention is the most cost-effective at a maximum acceptable ICER of:	
				£20,000 per QALY gained	£30,000 per QALY gained
Probabilistic Sensitivity Analysis – based on rerun by the ERG					
Darvadstrocel	[redacted]	[redacted]	-	0.650	0.870
Standard care	[redacted]	[redacted]	-	0.350	0.130
Incremental	1.35	£21,773	£16,102	-	-
Deterministic					
Darvadstrocel	[redacted]	[redacted]	-	-	-
Standard care	[redacted]	[redacted]	-	-	-
Incremental	1.40	£21,639	£15,471	-	-

QALYs – quality adjusted life years; PAS – Patient Access Scheme; ICER – incremental cost-effectiveness ratio
As there was no differential mortality between the darvadstrocel and standard care group, both arms accrued 36.65 undiscounted life years gained over the 40-year time horizon.

Table 22 shows the results of the company's revised analysis using a discount rate of 3.5% for both costs and QALYs in both the deterministic analysis and a rerun of the PSA analysis by the ERG. Based on the probabilistic version of the company's model, darvadstrocel is expected to generate an additional 1.02 QALYs at an additional cost of £21,773, compared with standard care. The corresponding incremental cost-effectiveness ratio is £21,417 per QALY gained. The deterministic version of the company's model produces a similar ICER of £20,591 per QALY gained. As shown in

Table 22, increasing the discount rate to 3.5% for both costs and QALYs increases the ICER, compared to the company's original base case presented in the CS.[1]

Table 22: Company's revised base case results, including the patient access scheme for darvadstrocel, assuming 3.5% discount rate for both costs and QALYs (adapted from clarification response,[2] question B7, Table 23 and Table 24)

Treatment	Total QALYs	Total costs	ICER (£ per QALY gained)	Probability that the intervention is the most cost-effective at a maximum acceptable ICER of:	
				£20,000 per QALY gained	£30,000 per QALY gained
Probabilistic Sensitivity Analysis – based on rerun by the ERG					
Darvadstrocel	[redacted]	[redacted]	-	0.421	0.736
Standard care	[redacted]	[redacted]	-	0.579	0.264
Incremental	1.02	£21,773	£21,417	-	-
Deterministic					
Darvadstrocel	[redacted]	[redacted]	-	-	-
Standard care	[redacted]	[redacted]	-	-	-
Incremental	1.05	£21,639	£20,591	-	-

QALYs – quality adjusted life years; PAS – Patient Access Scheme; ICER – incremental cost-effectiveness ratio

Figure 10 and Figure 11 present the results of the company's PSA in the form of a cost-effectiveness plane and CEACs, based on a re-run of the company's original submitted model (based on discount rates of 3.5% for costs and 1.5% for QALYs). Assuming a maximum acceptable ICER (MAICER) of £20,000 per QALY gained, the company's model suggests that the probability that darvadstrocel produces more net benefit than standard care is 0.650. Assuming a MAICER of £30,000 per QALY gained, the company's model suggests that the probability that darvadstrocel produces more net benefit than standard care is 0.870.

Figure 10: Cost-effectiveness plane, including the patient access scheme for darvadstrocel, comparing darvadstrocel to standard care, using a discount rate of 3.5% for costs and 1.5% for QALYs

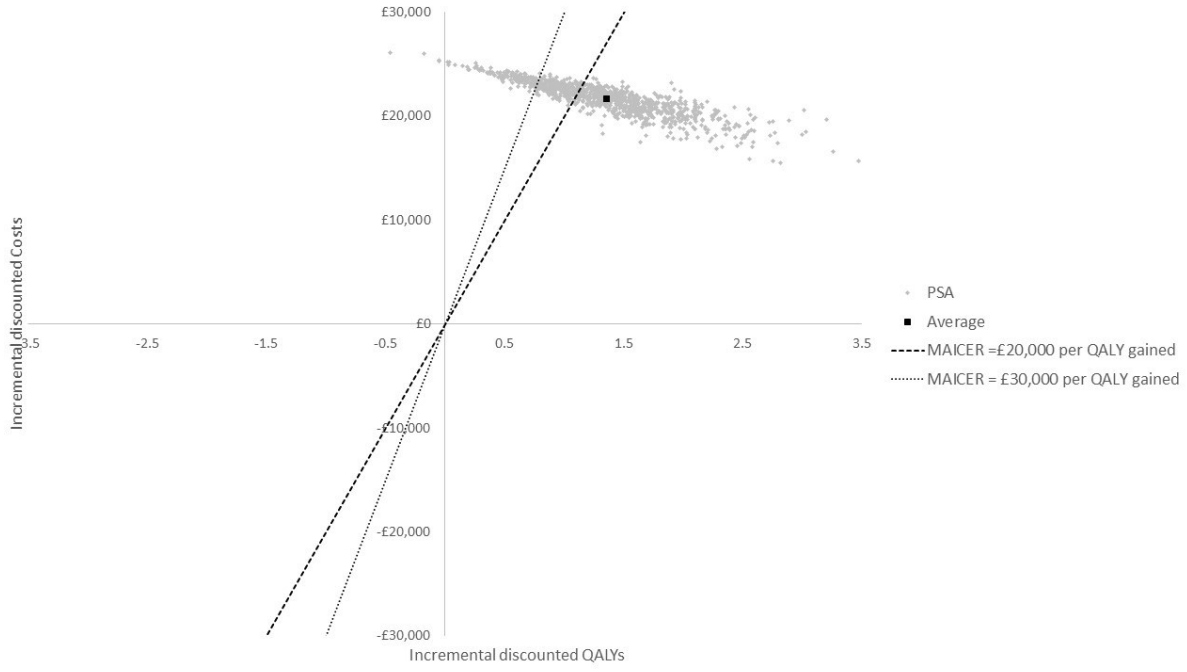


Figure 11: Cost effectiveness acceptability curve, including the patient access scheme for darvadstrocel, using a discount rate of 3.5% for costs and 1.5% for QALYs

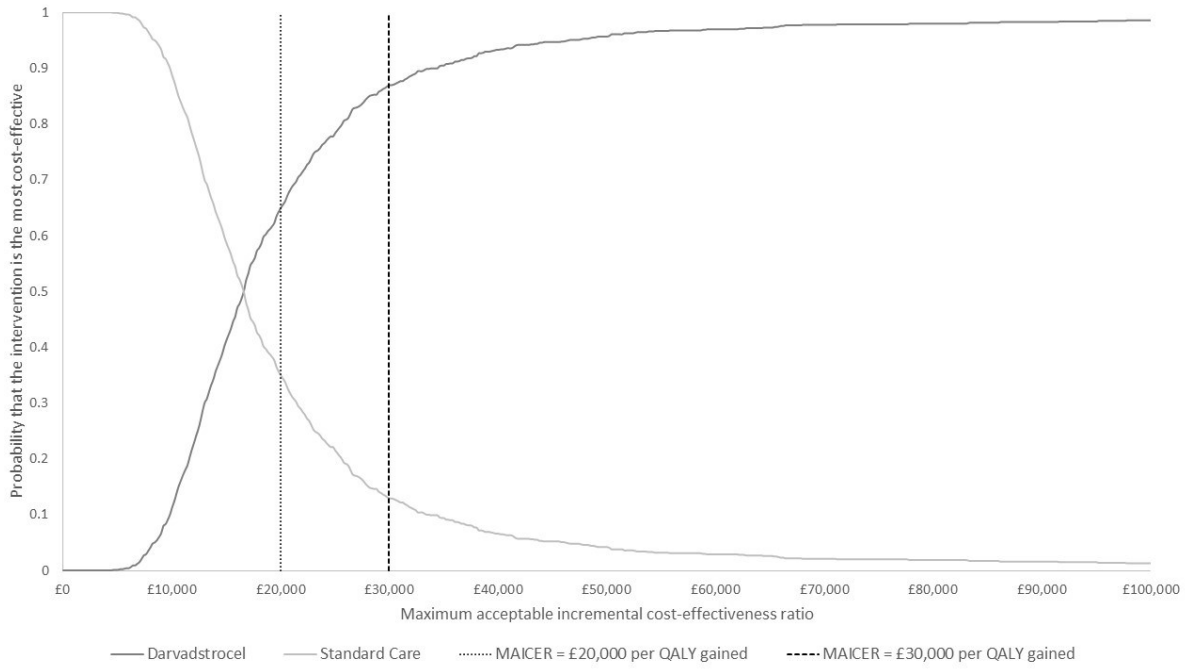


Figure 12 and
Figure 13 present the results of the company's was used in the form of a cost-effectiveness plane and a CEAC, based on a re-run of the company's model (using a discount rate of 3.5% for both costs and QALYs). Assuming a MAICER of £20,000 per QALY gained, the company's model suggests that the probability that darvadstrocel produces more net benefit than standard care is 0.421. Assuming a MAICER of £30,000 per QALY gained, the company's model suggests that the probability that darvadstrocel produces more net benefit than standard care is 0.736.

Figure 12: Cost-effectiveness plane, comparing darvadstrocel to standard care, including the patient access scheme for darvadstrocel, using a discount rate of 3.5% for both costs and QALYs

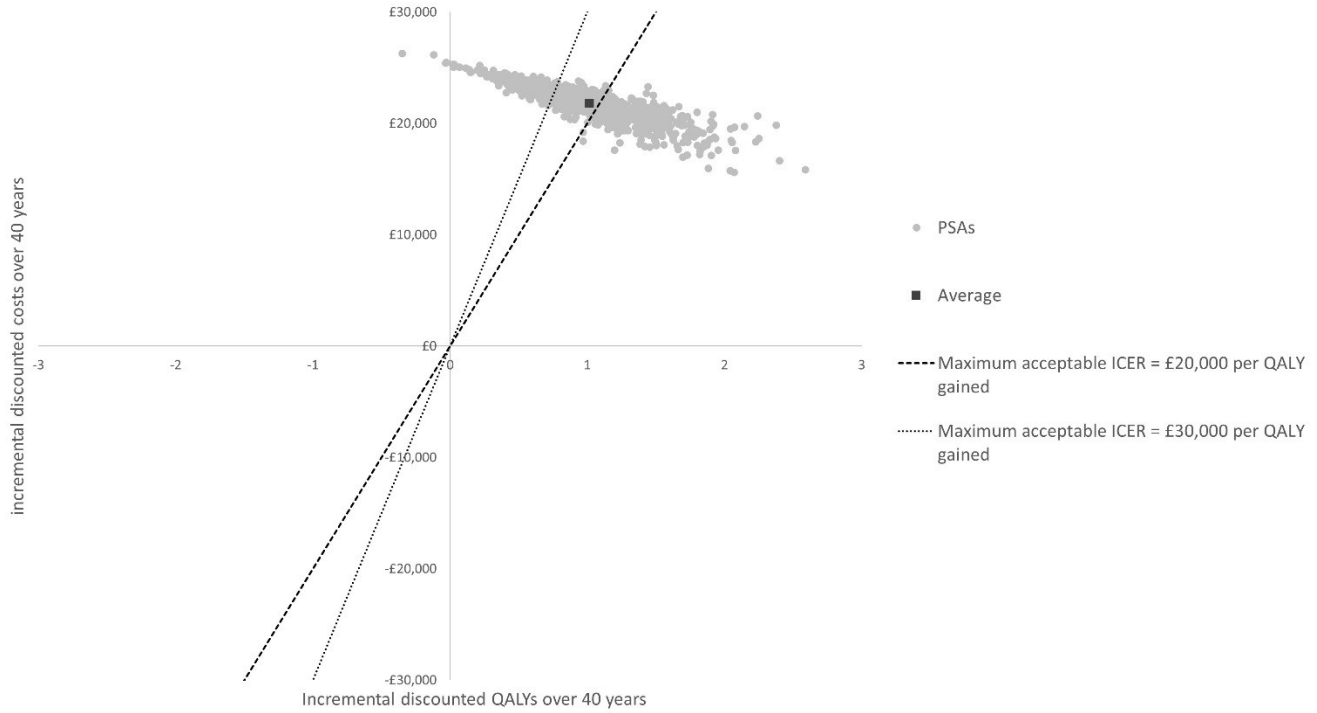
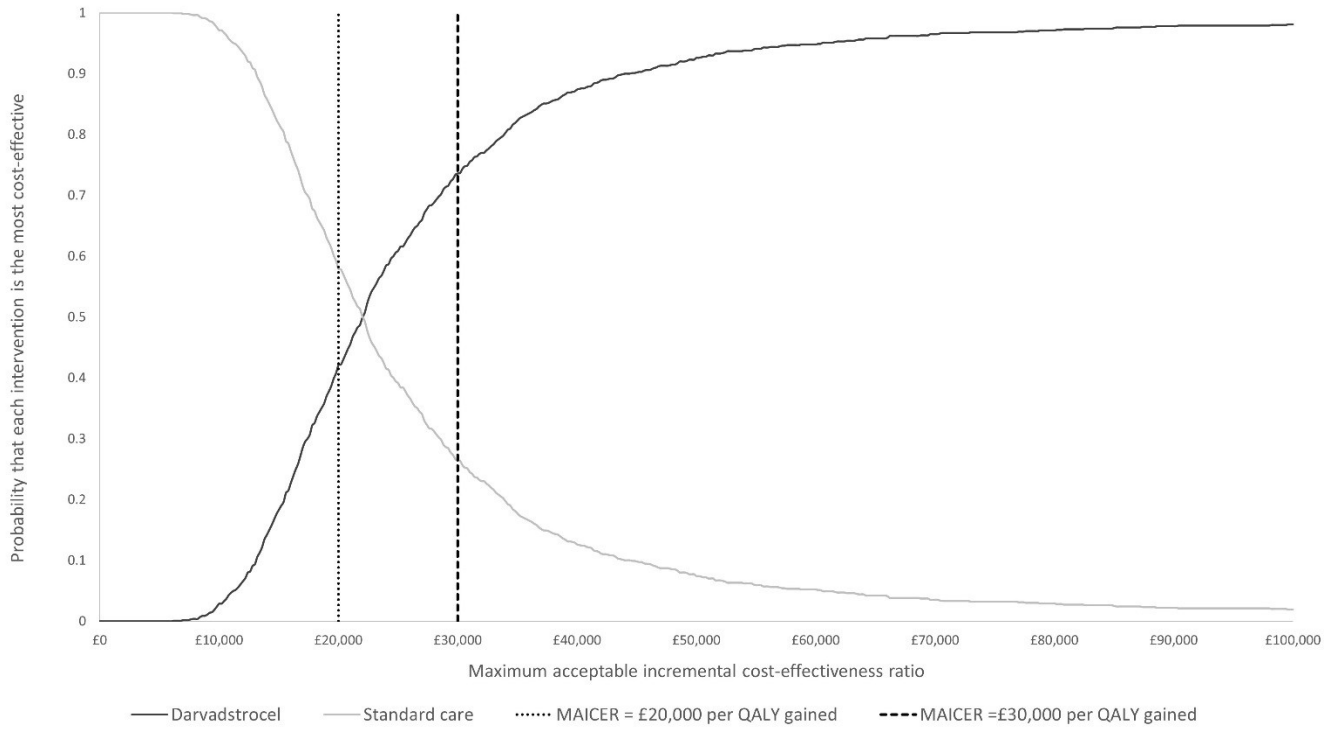


Figure 13: Cost-effectiveness acceptability curve including the patient access scheme for darvadstrocel, using a discount rate of 3.5% for both costs and QALYs



5.2.8 Sensitivity analyses

For the sensitivity analyses, the results corresponding to the company's original sensitivity analyses are presented when a using a discount rate of 3.5% for cost and QALYs. Sensitivity analyses using a discount rate of 1.5% for both costs and QALYs are presented in Appendix 2. The company's original sensitivity analyses using a discount rate of 1.5% for QALYs and 3.5% for costs are presented in the CS[1]; as the ERG considers these to be inappropriate, for brevity, these results are not reproduced here.

The company conducted a wide range of sensitivity analyses, which included: (i) a tornado diagram to show the influence of uncertainty in individual model parameters on the ICER; (ii) assessing the impact of using alternative data and/or assumptions on the ICER; (iii) assessing the impact of using alternative parametric time-to-event functions on the ICER; (iv) assessing the impact of using different definitions of remission and relapse on the ICER, and; (v) assessing the impact of directly using data collected in the St Mark's retrospective cohort study.

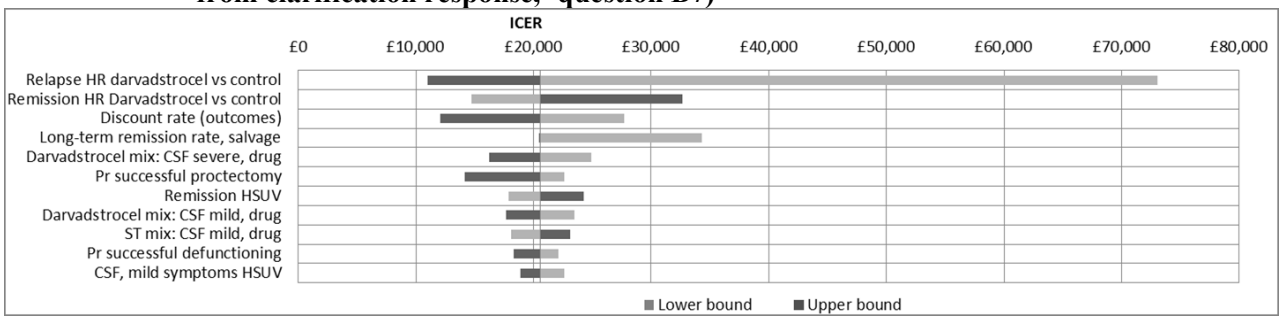
5.2.8.1 Tornado diagram

The tornado diagram presented in

Figure 14 shows the ten most influential parameters in the company's base case model, assuming a discount rate for costs and QALYs of 3.5% per annum. Within this sensitivity analysis, parameters which were included in the PSA were assessed at the upper and lower limits of their 95% CIs; parameters which were not included in the PSA were assessed at 70% of their mean value for the lower bound and 130% of their mean value for the upper bound. This analysis indicates that the company's model is particularly sensitive to:

- The HR of darvadstrocel compared to standard care for remission
- The HR of darvadstrocel compared to standard care for relapse
- The estimated remission rate for salvage therapies in year two onwards
- The probability that a proctectomy is successful
- The HSUV for remission
- The overall cost of treatments for people receiving darvadstrocel (including the fixed cost per vial of darvadstrocel) in the mild CSF health state
- The overall cost of treatments for people receiving standard care in the mild symptomatic CSF health state
- The probability that a defunctioning surgery is successful
- The HSUV for mild symptomatic complex perianal fistulae.

Figure 14: Company's tornado diagram showing the one way sensitivity analyses conducted by the company using 3.5% discounting for both costs and QALYs (reproduced from clarification response,[2] question B7)



5.2.8.2 Impact of alternative data sources and assumptions

The company undertook several additional sensitivity analyses (see Table 23). In these analyses, the ICER ranges from £11,380 per QALY gained to £28,438 per QALY gained. Across the range of analyses presented, the lowest ICER was generated from the sensitivity analysis in which costs and QALYs were undiscounted, the highest ICER was generated from the scenario in which the discount rates for costs and health outcomes were set equal to 6%.

Table 23: Sensitivity analyses conducted by the company (reproduced from clarification response, question B7,[2] Table 25)

Scenario description	Total costs			Total QALYs			ICER (£ per QALY gained)
	Darv	Standard care	Difference	Darv	Standard care	Difference	
Base case, 3.5% discount for costs and QALYs	[redacted]	[redacted]	£21,639	[redacted]	[redacted]	1.05	£20,591
0% discount rate for costs and QALYs	[redacted]	[redacted]	£20,400	[redacted]	[redacted]	1.79	£11,380
6% discount rate for costs and QALYs	[redacted]	[redacted]	£22,233	[redacted]	[redacted]	0.78	£28,438
10% annual proctectomy probability post defunctioning	[redacted]	[redacted]	£22,024	[redacted]	[redacted]	1.04	£21,124
50% annual stoma reversal probability from successful defunctioning state	[redacted]	[redacted]	£21,186	[redacted]	[redacted]	1.04	£20,312
Upper bound of annual stoma care costs (£2,682 per year)	[redacted]	[redacted]	£20,944	[redacted]	[redacted]	1.05	£19,930
Infusion costs halved (£142.25)	[redacted]	[redacted]	£21,514	[redacted]	[redacted]	1.05	£20,472
HSUVs based on CD patients vignette study set	[redacted]	[redacted]	£21,639	[redacted]	[redacted]	0.98	£22,095
Relapse HR for salvage therapy vs. control equal to 1.20	[redacted]	[redacted]	£21,566	[redacted]	[redacted]	1.07	£20,131
Time horizon: 20 years	[redacted]	[redacted]	£21,846	[redacted]	[redacted]	0.78	£28,181
Time horizon: 60 years	[redacted]	[redacted]	£21,706	[redacted]	[redacted]	1.10	£19,719

No inclusion of Biologic usage within salvage therapy (all other assumptions as per base case)	[redacted]	[redacted]	£17,557	[redacted]	[redacted]	1.05	£16,707
Wastage assumed to result in 5% additional cost for darvadstrocel	[redacted]	[redacted]	£22,889	[redacted]	[redacted]	1.05	£21,781

QALYs - quality-adjusted life years; ICER - incremental cost-effectiveness ratio; Darv – darvadstrocel; HSUV - health state utility value; CD - Crohn's disease; HR - hazard ratio

5.2.8.3 The use of alternative parametric time-to-event functions

Table 22 shows the sensitivity of the company's model to the choice of the two best fitting models (in terms of AIC and BIC) for both the time to remission and time to relapse outcomes. This shows that the model is highly sensitive to the choice of the parametric function used to model these data. The lowest ICER of £20,591 per QALY gained is produced when a Gompertz distribution is used to model both the remission and relapse time-to-event functions. The highest ICER of £133,311 per QALY gained is produced when the generalised gamma distribution is used to model the time to remission and the log normal distribution is used to model the time to relapse. These limited results also appear to indicate that the model is more sensitive to the time to relapse function than it is the time to remission function.

Table 24: Impact of different parametric time-to-event functions on the company's base case using a discount rate of 3.5% for both costs and QALYs (reproduced from clarification response,[2] question B7, Table 26)

Time to remission function	Time to relapse function	Total costs			Total QALYs			ICER
		Darv	SC	Incr	Darv	SC	Incr	
Gompertz (base case)	Gompertz (base case)	[redacted]	[redacted]	£21,639	[redacted]	[redacted]	1.05	£20,591
Generalised gamma	Gompertz (base case)	[redacted]	[redacted]	£22,653	[redacted]	[redacted]	0.75	£30,064
Gompertz (base case)	Log-normal	[redacted]	[redacted]	£24,740	[redacted]	[redacted]	0.24	£104,398
Generalised gamma	Log-normal	[redacted]	[redacted]	£24,754	[redacted]	[redacted]	0.19	£133,311

Darv – darvadstrocel; SC – standard care; Incr – incremental difference between darvadstrocel and standard care; ICER - incremental cost-effectiveness ratio; QALYs – quality adjusted life years

5.2.8.4 Using different definitions of remission and relapse

Three other definitions of remission were evaluated within the CS. These were: (1) clinical remission alone, (2) CPC + MRI remission, and (3) combined remission (clinical +MRI remission). Clinical remission was defined as "…*closure of all treated external openings that were draining at baseline despite gentle finger compression*…" (CS,[1] page 30). Combined remission (ADMIRE-CD primary outcome measure) was defined as the closure of all treated external openings that were draining at baseline despite gentle finger compression, and the absence of collections larger than 2 cm of the treated perianal fistula in at least two of three dimensions, confirmed by masked central MRI (CS,[1] page 30). CPC + MRI remission was defined as CPC remission and the absence of collections larger than 2 cm of the treated perianal fistula in at least two of three dimensions, confirmed by masked central MRI.

For clinical remission, Kaplan-Meier curves were produced and parametric time-to-event functions were fitted to the underlying data. Details of the goodness-of-fit of these parametric time-to-event functions to the clinical remission data are provided in Appendix 1. In summary, AIC and BIC statistics both indicate that the log normal distribution provides the best fit to the time to remission and time to relapse, when the clinical definition of relapse is used (see Appendix 1,

Table 37). It is unclear from the CS whether an assessment of the clinical plausibility of the curves fitted to the clinical remission definition was conducted. The company again adopted the Gompertz distribution as the preferred model for the clinical definition of relapse and remission (CS,[1] page 81, page 86)

For combined remission and CPC +MRI remission, Kaplan-Meier time-to-event functions were not produced by the company, *"... due to the limited time points that combined remission was reported in the ADMIRE-CD trial.*"(clarification response,[2] question B3). Instead, HRs were estimated for the effect of MRI on the time to relapse and time to remission for both definitions of remission (CPC or clinical). This was done by comparing the number of events including an MRI definition of remission (at 24 and 52 weeks post-darvadstrocel administration) with the number of events without including the MRI criterion. The number of events at 24 and 52 weeks post-darvadstrocel administration were pooled to estimate a HR between using MRI in the definition of remission and not using MRI in the definition of remission. This process was conducted separately for the two definitions of remission (clinical remission and CPC). The HRs estimated from this process are presented in Table 25. The exact statistical process used by the company to estimate these HRs is unclear.

Table 25: Hazard ratios applied for the calibration of the remission time-to-event functions to incorporate MRI criterion in the definition of achievement of remission (reproduced from CS,[1] page 83, Table 37)

Definition comparison	HR	SE [ln(HR)]	95% CI
CPC vs. CPC + MRI	0.922	0.135	[0.708, 1.200]
Clinical vs. Combined (Clinical + MRI)	0.896	0.111	[0.721; 1.113]

HR - hazard ratio; SE - standard error; ln – natural logarithm; CI - confidence interval; CPC – clinical and patient centric; MRI – magnetic resonance imaging

Table 26 shows the sensitivity of the model results to the different definitions of remission in the ADMIRE-CD study. It should be noted that the choice of parametric model did not differ in the different scenarios on the underlying remission survivor function. In response to clarification question B3, the company clarified that they believed that the Gompertz parametric model provided the best fit to the clinical and CPC definition of relapse and remission.[2]

Table 26: Results of the scenario analyses surrounding the definition of relapse in the company's submitted economic model (adapted from company's clarification response,[2] question B7, Table 27)

Scenario	Definition of remission, parametric function	Total Costs			Total QALYs			ICER
		Darv	SC	Incr	Darv	SC	Incr	
Base case	CPC, Gompertz	[redacted]	[redacted]	£21,639	[redacted]	[redacted]	1.05	£20,591
1	Clinical, Gompertz	[redacted]	[redacted]	£23,343	[redacted]	[redacted]	0.68	£34,177
2	CPC+ MRI, Gompertz	[redacted]	[redacted]	£21,755	[redacted]	[redacted]	1.01	£21,446
3	Clinical + MRI, Gompertz	[redacted]	[redacted]	£23,367	[redacted]	[redacted]	0.68	£34,295

QALYs- quality-adjusted life years; ICER – incremental cost-effectiveness ratio Darv – darvadstrocel; SC –standard care; CPC – clinical and patient centric; MRI – magnetic resonance imaging

5.2.8.5 Using the St Mark's retrospective study data directly in the company's model

Table 27 shows the impact of using data from the St Mark's retrospective study instead of the model base case parameters to inform: (i) the transition probabilities related to salvage therapy, proctectomy and defunctioning surgery health states; (ii) the salvage therapy treatment mix; (iii) maintenance and post-surgery treatment mixes and (iv) health care resource utilisation.

Table 27: Effect of using data from the St Mark's retrospective cohort study (reproduced from clarification response,[2] question B7, Table 28)

Scenario	Total costs			Total QALYs			*ICER*
	Darv	Control	Incremental	Darv	Control	Incremental	
Base case	[redacted]	[redacted]	£21,639	[redacted]	[redacted]	1.05	£20,591
St Mark's retrospective data set	[redacted]	[redacted]	£26,201	[redacted]	[redacted]	1.11	£23,524

Darv – darvadstrocel; ICER - incremental cost-effectiveness ratio.

5.3 Critical appraisal of the company's submitted evidence

This section presents a critical appraisal of the health economic analysis presented in the CS.

5.3.1 Methods for reviewing the company's economic evaluation and health economic model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which this was based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists[39] to critically appraise the company's model and analysis.
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.
- Examination of the correspondence between the description of the model reported within the CS and the company's executable model.
- Where possible, checking of parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation.

5.3.2 Adherence of the company's model to the NICE reference case

The company's economic model is generally in line with the NICE Reference Case.[10] The ERG notes that the model excludes relevant patient subgroups, which are included in the scope and may be covered by the marketing authorisation. In addition, there is a lack of evidence on repeated administration of darvadstrocel, but the licence does not indicate that darvadstrocel should be a single use treatment. The ERG also notes that analyses presented in the original CS, were out of scope as they discounted at a rate of 1.5% for QALYs and 3.5% for costs.[1] The NICE Methods Guide does not

support differential discounting.[10] In scope analyses using discount rates of 3.5% for both costs and QALYs and 1.5% for both costs and QALYs were provided by the company at clarification.[2]

Table 28: Adherence of the company's model to the NICE Reference case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The model reflects people with non-active / mildly active luminal Crohn's disease and complex perianal fistulae. However, a subgroup of the patient population whose complex perianal fistulae have more than two internal openings or more than three external openings are not considered within the company's analysis of the available evidence or the company's submitted model. It is unclear whether this missing population is included within the licence population for darvadstrocel (see Section 3.1)
Comparator(s)	As listed in the scope developed by NICE	The company's model compares darvadstrocel against standard care surgical interventions combined with associated medical management.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are modelled in terms of QALYs gained.
Perspective on costs	NHS and PSS	The model takes an NHS and PSS perspective
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's economic evaluation takes the form of a cost-utility analysis. The results of the analysis are presented in terms of the incremental cost per QALY gained for darvadstrocel versus standard care
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 40-year time horizon. By this time point, only 38.1% of people have died in each group.
Synthesis of evidence on health effects	Based on systematic review	Based on the ADMIRE-CD study, which is the only study of the effectiveness of darvadstrocel in this population at the dose stated in the marketing authorisation.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health effects are expressed in QALYs. A vignette study, using time-trade off (TTO) valuations by members of the general public was used to inform HRQoL parameters in the model. EQ-5D data were not available from the ADMIRE-CD trial and mapping from the trial outcomes to the EQ-5D was not considered appropriate by the company.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No. The utility values used in the model were based on vignettes, not a description of HRQoL provided directly by patients. Patients did have input into the health state descriptions.
Source of preference data for	Representative sample of the UK population	Yes. The vignette study used a representative sample of the UK population to value the health states using the time

valuation of changes in HRQoL		trade off method. Patient valuations of the vignettes using TTO methodology were considered in a scenario analysis
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity rating is applied to estimate QALY gains
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource components include those relevant to the NHS and PSS. Whilst not explicitly stated in the CS, unit costs are valued in 2016/17 prices
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	The base case in the CS used 3.5% discounting for costs and 1.5% discounting for benefits, as the company claims that Section 6.2.19 of the NICE Methods Guide applies (see Section 5.2.3).[10] In response to clarification question B7, the company provided analyses where both health effects and costs are discounted at 3.5% and analyses where both the health effects and costs are discounted at 1.5%.

5.3.3 Model validation and face validity check

The ERG rebuilt the deterministic version of the company's base case model in order to verify its implementation.

Table 29 shows that the ERG's rebuilt model produces very similar estimates of undiscounted life years gained, health gains, costs and cost-effectiveness. This double-programming exercise led to the identification of three minor implementation errors:

i. When estimating the average risk of relapse and the average risk of remission across weeks 104 to 164, to inform the long-term relapse and remission rates, the company divides by 16 instead of 15 cycles.
ii. The per-cycle probability of all-cause mortality was subject to a minor error which led to a small over-prediction of the number of deaths throughout the model time horizon.
iii. The long-term remission rates in the salvage therapy arm were specific to the standard care arm time-to-event function, not the salvage therapy time-to-even function.

Table 29: Comparison of the company's base case model and the ERG's rebuilt model including PAS and using 3.5% discounting for both cost and QALYs

Treatment	Total Life years gained (undiscounted)	Total QALYs	Total costs (with PAS)	ICER (£ per QALY gained)
The company's deterministic base case model				
Darvadstrocel	36.65	[redacted]	[redacted]	-
Standard care	36.65	[redacted]	[redacted]	-
Incremental	0	1.05	£21,639	£20,591
The ERG's rebuild of the company's deterministic base case model				
Darvadstrocel	36.85	[redacted]	[redacted]	-
Standard care	36.85	[redacted]	[redacted]	-
Incremental	0	1.05	£21,657	£20,639

QALYs – quality-adjusted life years; PAS – patient access scheme; ICER – incremental cost-effectiveness ratio

Given the results of the rebuild of the company's base case economic model, the ERG is satisfied that the company's model has been implemented without any significant errors.

5.3.4 Main issues identified within the critical appraisal

The main issues identified by the ERG within the ERG's critical appraisal of the company's economic analysis are given in Box 1.

Box 1: Summary of the issues raised by the ERG in the critical appraisal of the company's cost-effectiveness evidence

1. Exclusion of relevant patient groups from the economic analysis
2. Possibility of **Error! Reference source not found.**
3. **Error! Reference source not found.**, is justified
4. Wastage of darvadstrocel
5. **Error! Reference source not found.**
6. Concerns regarding the company's expert elicitation exercise to
7. **Error! Reference source not found.**
8. Missing transitions within the model structure
9. The company's approach to identifying HRQoL data from the literature
10. The estimates of utilities from the vignette study
11. Adoption of a 40-year time horizon

5.3.4.1 Exclusion of relevant patient groups from the economic analysis

The EPAR and the final NICE scope relate to the use of darvadstrocel for "… *the treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy. Alofisel [darvadstrocel] should be used after conditioning of fistula*" (EPAR, page 82).[17] The clinical effectiveness evidence used to populate the comparative effectiveness of darvadstrocel compared with standard care in the CS is based solely on the ADMIRE-CD trial (CS,[1] page 77). In this trial, only people whose fistula had two or less internal openings and three or less external openings were eligible for inclusion in the study (CS,[1] page 28). In response to a request for clarification from the ERG (question A4), the company stated "… *SPC [SmPC] for darvadstrocel specifies that 4 vials must be administered for the treatment of up to two internal openings and up to three external openings*" and "*Without further data we cannot be certain that 120 million cells is sufficient to adequately treat disease that is characterised by a greater number of internal and external openings*" (Company's clarification response,[2] question A4, pages 10-11). Whilst the use of darvadstrocel within the clinical trial was consistent with the posology and method of administration described within the SmPC, the ERG is unclear as to whether people with more than two internal openings or more than three external openings would be ineligible for any treatment with darvadstrocel. It is possible that these patients may have some but not all of their fistula treated with a single course of darvadstrocel or they may have multiple courses of treatment over multiple procedures. Neither of these scenarios have been modelled by the company. As such, no evidence is provided on the effectiveness or cost-effectiveness of darvadstrocel in this population.

On the basis of the evidence submitted in the CS[1], the ERG believes that it is not possible to produce a reliable estimate of the cost-effectiveness of darvadstrocel in this excluded population group.

5.3.4.2 Possibility of repeat administrations of darvadstrocel

The ADMIRE-CD trial only tested a single use of darvadstrocel. The company's model is consistent with the single use of darvadstrocel observed in the ADMIRE-CD trial In response to a request for clarification from the ERG (question A1), the company stated *"Although some clinicians believe that Alofisel [darvadstrocel] may be beneficial for retreatment in the following patient groups; (i) partial responders; (ii) responders who have relapsed, there is no current evidence to support this treatment approach.*"(Company's clarification response,[2] question A1). The company's clarification response also states "*Some patients who have responded to Alofisel [darvadstrocel] treatment and achieved healing over a significant period of time may develop a new fistula tract (recurrence). We believe this should be considered as a new fistula and should therefore be treated as such."*(Clarification response[2], question A1)

The ERG notes that there are two key uncertainties with this statement. Firstly, the clinical effectiveness, and consequently the cost-effectiveness, of darvadstrocel upon a repeat administration is unknown. Secondly, it is unclear what is meant by a "significant period of time". Two of the clinical advisors to the ERG believed that darvadstrocel may be reused if the time to relapse was more than two years. The ERG believes that it is not possible to make a reliable estimate of the cost-effectiveness of darvadstrocel for use in treating a fistula which has relapsed following prior darvadstrocel administration, regardless of time since relapse, as it is unknown how effective darvadstrocel will be upon repeat administration. In addition, the ERG notes that the cost-effectiveness of using darvadstrocel for the first time is likely to be affected by the costs of downstream therapies used to treat patients who have relapsed. Therefore, any future use of darvadstrocel may increase the ICER compared to the company's analyses which assume no repeated use.

5.3.4.3 Whether the discounting of costs and QALY at 1.5%, in accordance with Section 6.2.19 of the NICE Methods Guide, is justified

The company claims that darvadstrocel meets the criteria in Section 6.2.19 of the NICE Methods Guide (see Section 5.2.3).[10] These criteria require that: (1) standard care would result in death or a severely impaired quality of life for the population being considered; (2) darvadstrocel would restore this population to near full health over a very long period (usually 30 years), and (3) that the Appraisal Committee is satisfied that the introduction of darvadstrocel does not commit the NHS to significant irrecoverable costs. No quantitative analyses were provided by the company to demonstrate that these criteria had been met. The ERG considers that exploratory analyses should have been conducted by the company in which undiscounted QALYs were presented and compared to undiscounted life years gained so that it can be assessed whether darvadstrocel meets the first and second of these criteria (see Section 5.4).

5.3.4.4 Wastage of darvadstrocel

The EPAR states that darvadstrocel has a shelf life of 48 hours (EPAR,[17] page 75). The ERG has concerns that in clinical practice, some doses of darvadstrocel could be wasted and that this was not accounted for in the company's model. In their clarification response[2] (question B18), the company stated that "… *no wastage was observed for the 107 patients assigned to darvadstrocel*…". As part of their clarification response on this issue, the company presented an additional sensitivity analysis in which 5% wastage for darvadstrocel was assumed; this resulted in an ICER of £15,911 per QALY gained when a 1.5% discount rate was used for both costs and QALYs are used. This compares to a deterministic base case ICER of £15,017 per QALY gained when a 1.5% discount rate for both costs and QALYs are used in the company's model. This is a modest increase in the ICER. One of the clinical advisors to the ERG believed that this represented a high estimate of wastage and that they would expect

that 5% would likely be an overestimate of wastage in clinical practice. Consequently, 5% wastage is likely to represent an upper limit of the impact of wastage in clinical practice on the company's ICER.

5.3.4.5 The company's selection of time to relapse and time to remission time-to-event functions

a) Ignoring the interval censored nature of the data

In the ADMIRE-CD trial, remission and relapse were effectively assessed at 6 week intervals at which the PDAI survey was administered to patients. This raises a concern about interval censoring, as people who report a remission/relapse on the PDAI score may have experienced the remission/relapse at any time between the six-weekly data collection points. As the PDAI score is a key component of CPC remission, this means that interval censoring is potentially a consideration. Interval censoring is a minor issue when the interval between assessments is short compared to the average time to relapse.[40] The ERG is concerned that the CPC time to relapse analysis may not meet this criterion, as the median time to relapse was 12.9 weeks in the standard care arm (see Table 8). Not accounting for the interval censoring is likely to bias the fitted parametric time to event functions. However, it is unclear whether this bias is favourable to darvadstrocel when it is compared to standard care. Consequently, the direction and magnitude of any changes in the ICER due to not adjusting the time to event analyses for interval censoring is unknown. It should be noted that the company's analyses demonstrated that the ICER is highly sensitive to the curve selection for time to relapse for people on darvadstrocel (see Table 24). The ERG considers the parametric time to event functions should have been fitted using interval censoring techniques, as detailed in Chapter 9 of Collett.[40]

b) Method used to extrapolate the time-to-event functions

In the company's model, the fitted statistical models are not used to extrapolate the time-to-event functions beyond two years (see Section 5.2.6). Instead, a time-invariant probability was calculated based on the follow up data at 104 weeks post-baseline to 164 weeks post-baseline (note this includes the 4 week period in which the time-to-event functions were not estimated due to the structural absence of events). The rationale for this is unclear and does not appear to be supported by data or clinical opinion that the hazard rate would change at 104 weeks. Furthermore, it is unclear why the time invariant event hazard used in the extrapolated period should be based on the points of the time-to-event function at 104 and 164 weeks. As such, the ERG does not consider the company's approach to be a reliable estimate of the time-to-event function over the long-term. The ERG notes that mixture cure models may have provided a more plausible long-term fit, given the company's clinical expert advice. However, the company's submitted model would require significant adaptation to use parametric functions over the full model time horizon due to the current model structure having only a limited number of tunnel states (24 tunnel states per health state).

5.3.4.6 Concerns regarding the company's expert elicitation exercise to The company's expert elicitation exercise to estimate the time to relapse and remission for people on third or later line therapies

The ERG notes that there are three key issues when considering the robustness of the evidence generated by the company to estimate the effectiveness of salvage therapy compared to standard care which are: (i) the methodological rigour of the exercise; (ii) the design of the expert elicitation exercise, and (iii) the estimation of uncertainty in the exercise.

The expert elicitation exercise conducted by the company did not follow a formal elicitation protocol (clarification response,[2] question B16). Despite additional information provided during the clarification process, it was unclear what information was presented to the experts at the elicitation exercise. This is a source of uncertainty which is not captured in the economic model. This means that the ERG cannot adequately asses if the estimate of the treatment effect of salvage therapy compared with standard care (both time to relapse and the time to remission) generated from the elicitation process is likely to be robust or unbiased.

The ERG notes that the effectiveness of salvage therapy compared to standard care was only elicited as a HR. The rationale for only eliciting a HR was that the proportional hazards assumption was "…*validated by clinical experts in Europe and the UK. This assumption was originally based on the fact that both control and salvage therapy broadly consisted of the same interventions, those being EUA +/- seton placement with background therapy consisting of antibiotics, immunosuppressants and biologic therapy*."(Company's clarification response,[2] question B16). Given this justification, it is unclear how the assumption of proportional hazards was validated with clinicians and the relevance of the justification provided by company does not appear to support eliciting only a HR. The ERG considers it possible that the most appropriate treatment effect was not elicited within the company's exercise. Consequently, the ICER may not be a robust estimate of the cost-effectiveness of darvadstrocel compared to standard care.

Finally, the ERG notes that uncertainty was not elicited from the company's clinical experts and instead it was assumed that the variance of the HR was equal to 15% of the mean. Several formal elicitation procedures include methods for formally eliciting uncertainty from experts, which capture the magnitude and distribution of the experts' uncertainty.[41] Consequently, the uncertainty in the ICER may have been overestimated or underestimated within the CS. The company provided several exploratory analyses exploring the uncertainty in the HR in response to a request for clarification by the ERG (question B16).[2] The assumed variance in the HR was changed to 30% and 60% of the mean HR and the PSA was rerun, a 1.5% discount rate was assumed for both costs and QALYs. A summary of these results is provided in Table 30. The ICER increased slightly when the variance in the HR was increased,

with the ICER being £15,017 per QALY gained when the variance was 15% of the mean HR increasing to £15,666 per QALY gained when the variance was 60% of the mean HR. Even though the analyses indicate that the ICER is relatively robust to increases in the assumed coefficient of variance in the HRs for salvage therapy versus control, it may be the case that the experts were more uncertain than the scenarios presented by company and their distributions could be different to the one's assumed by the company. It is unclear what direction directly eliciting the uncertainty and the associated probability distribution would move the ICER. However, these sensitivity analyses indicate that any changes in the uncertainty due to following an elicitation process which can capture uncertainty is likely to have only a modest effect on the ICER.

Table 30: Sensitivity analysis on the assumed hazard ratio for the effectiveness of salvage therapy compared to standard care using a discount rate of 1.5% for both costs and QALYs and including the PAS for darvadstrocel (adapted from clarification response,[2] questions B7, Table 30 and Table 35)

Scenario	Incremental costs[a]	Incremental QALYs[a]	ICER (£ per QALY gained)	Probability that darvadstrocel provides the most net benefit at:	
				£20,000 per QALY gained	£30,000 per QALY gained
Base case – variance is equal to 15% of the mean	£21,161	1.35	£15,017	0.66	0.87
Variance is equal to 30% of the mean	£21,011	1.35	£15,311	0.67	0.88
Variance is equal to 60% of the mean[a]	£21,140	1.35[b]	£15,666	0.67	0.87

a – incremental differences were calculated as the mean value for darvadstrocel – the mean value for standard care; b – recalculated by the ERG, as the reported incremental QALYs were inconsistent with; the difference between the mean QALYs for darvadstrocel and standard care, and; the reported ICER

5.3.4.7 The data used to populate the transitions to the defunctioning and proctectomy health states

The ERG noted that the model outputs for defunctioning surgery and proctectomy do not match the data used to populate the model. These two issues are dealt with separately in the subsequent sections.

Defunctioning surgery

The CS, suggests that there is an annual probability of 3.75% for people with complex fistulising Crohn's disease receiving a defunctioning surgery over a median time of 16 years after the person's fistulae first presented.[1] This estimated is based on the exponential curve fitted to the Mueller *et al*. data (see Section 5.2.6). Between year 0 and year 1, the company's model predicts that 1.48% of people in the darvadstrocel arm receive a defunctioning surgery and 1.75% of people in the standard care arm

receive a defunctioning surgery. The reason for the discrepancy is that the data used to populate the model relate to all people with complex fistulising Crohn's disease, whereas this transition probability is only applied to a subset of the population (those patients in the model who are in the severe CSF health state). Consequently, the ERG considers that the company's model underestimates the risk of receiving a defunctioning surgery for those people in the severe CSF health state. This will have an impact on the ICER, as increasing this probability will reduce the time spent in the severe CSF health state and increase the time spent in the post defunctioning health state. This is associated with the potential for patients to have lower or higher utility than severe CSF (see Table 16) and higher health state resource use (see Table 17). The impact of this factor on the ICER is addressed in the ERG's exploratory analyses (see Section 5.5).

Proctectomy

The data used in the CS suggests that approximately 20.7% (18/87) people with complex perianal fistulae and Crohn's disease would have a proctectomy after a median time of 6 years since the first presentation of fistulising disease.[27] This data was obtained from the Bell *et al.* prospective study (see Section 5.2.6). The company's model suggests that by year 6 of the company's base case model: 8.5% of people in the darvadstrocel group have received a proctectomy, and; 10.2% of people in the standard care group have received a proctectomy. Similar to the lack of fit to the defunctioning surgery data, the reason for this discrepancy is that the company's model structure only allows patients in the severe CSF and defunctioning surgery health states to transition to proctectomy. The reason for the discrepancy, is that the data used to populate the model relate to all people with complex fistulising Crohn's disease, whereas this transition probability is only applied to a subset of the population (those patients in the model who are in the severe CSF or post-defunctioning health states).

The ERG also notes that some of the assumptions regarding the equal probability of transitioning to the proctectomy health state from the severe CSF and post-defunctioning health states may not be clinically plausible. The company's clinical advisors noted that "… *at least 9 out of 10 defunctioned patients would eventually go on to receive proctectomy; therefore, the rate of proctectomy events derived from Bell et al. (2003) is likely to underestimate the transition probability from the post-defunctioning surgery health state*…". The clinical advisors to the ERG agree that proctectomy is more likely for a patient who has had a defunctioning surgery than a patient who has not. However, the company's model assumes that the probability of transitioning to the proctectomy state is the same for people in the severe CSF and post-defunctioning health states. Consequently, the ERG considers that the model's assumptions do not reflect clinical reality. The impact of all three points on the ICER are explored in the ERG exploratory analysis (see Section 5.5).

5.3.4.8 Missing transitions within the model structure

The ERG noted that the company conducted an analysis of data of 78 patients who presented at St Mark's hospital from 1st January 2008 to July 1st 2017 (CS,[1] Appendix Q). Data were collected at baseline, routine visits and study termination (lost to follow up, transferred to another hospital, or patient death). Transition probabilities to each of the company's health economic model health states were estimated from the data using a statistical Markov multi state model for panel data.[42] The observed data in the CS (Appendix Q, Table 29) suggest that it was possible for people with: a successful defunctioning surgery to transition to an unsuccessful defunctioning surgery state; a successful proctectomy to transition to a unsuccessful proctectomy state; and an unsuccessful proctectomy to a successful proctectomy state.[1] All other transitions in this fitted model are possible either directly (from one health state to another) or indirectly (the patient has to move from one health state, to a second health state, to a third health state) within the company's submitted health economic model. Despite the small sample size of the St Mark's retrospective cohort study (n=78), the ERG considers it inappropriate to assume that these transitions cannot occur (directly or indirectly) in the company's submitted model. The impact on the ICER of using these specific transitions from the St Mark's data set is explored in the ERG's exploratory analyses (see Section 5.5).

5.3.4.9 The company's approach to identifying HRQoL data from the literature

In general, the ERG was satisfied with the company's rationale for not mapping from the ADMIRE-CD outcomes (PDAI, CDAI or IBDQ) to EQ-5D. It was therefore reasonable for the company to look for alternative estimates of HSUVs from published or *de novo* studies. The ERG agrees that none of the studies identified in the company's review of HRQoL studies provide relevant and methodologically robust utility values for inclusion within the company's model. However, the CS does not provide sufficient information to determine whether any relevant studies were discarded from the company's HRQoL review. Specifically, 35 of the 37 included studies appear to have been discarded based on their relevance to the model; without more information, it was not possible for the ERG to determine whether these decisions were reasonable.

5.3.4.10 The estimates of utilities from the vignette study

The ERG notes that the use of utility values obtained from direct valuation of health states vignettes is not consistent with the NICE Reference Case.[10] The ERG considers that the valuations of the vignettes by the general population were closer to the Reference Case requirements than those obtained from the sample of patients with Crohn's disease.

The ERG has some concerns regarding the face validity of some of the estimates obtained from the vignette study. The ERG notes that the clinical experts at the EU Advisory Board felt that the utility values for CSF with severe symptoms were slightly higher than expected (CS,[1]Appendix P) and that

three of seven experts at the UK Advisory Board felt that the utility values for the CSF with mild symptoms state were underestimated (CS,[1] Appendix P); this issue was also noted by one of the ERG's clinical advisors. In addition, one of the clinical advisors to the ERG believed that the utility values for a successful outcome following surgery were underestimated; this would underestimate the benefits to patients of a successful surgical procedure.

The report by Fountain *et al*. (2017)[38] (which is provided in the CS,[1] Appendix R) assessed the external validity of the estimates derived from the vignettes by comparing them to values reported in the literature from 21 studies. Seventeen of these studies focussed on Crohn's disease and four studies focussed on IBD or UC but reported surgical states which are similar to the surgical states described in this study.[38] Seven of these studies reported values obtained from the EQ-5D (Richards 2001[43], Kuruvilla 2012[44], Casellas 2005[45], Stark 2010,[46] Benedini 2012[47], Casellas 2000[48], Casellas 2007[49]). Fountain *et al*. (2017)[38] conclude that *"all health states valued in [the vignette] study had lower utility estimates than other studies reporting utilities in Crohn's disease; however it is not possible to make direct comparisons due to the lack of data for many of the specific states and conditions included in [the vignette] study"*. The ERG noted in particular, that many of the studies estimating the utility values in patients following surgical intervention gave higher utility estimates than the utilities for those patients with positive surgical outcomes estimated in the Fountain *et al*. vignette study. In particular, in the study by Casellas *et al.*(2000)[48], the EQ-5D estimates for patients in remission following surgery were much closer to those for patients in medically induced remission (median values of 0.87 vs 0.86, respectively in Casellas 2000). This suggests that the benefits to patients of defunctioning or proctectomy surgery may be underestimated in the company's model. However, the ERG accepts that any differences between the utility values obtained in the vignette study and those identified from the literature may be due to differences in the population studied, as few of the studies were specific to patients with mildly or inactive Crohn's disease and complex perianal fistulea. Fountain *et al*.[38] also state, "*Lower utility estimates could have been generated because of use of condition specific vignettes (as opposed to generic measure) that may cause a focussing effect, whereby attention is drawn to health problems that may not be considered as so severe when placed in the context of a broader description of health (Brazier and Tsuchiya, 2010).*[50]" This supports the ERG's concern regarding the use of a non-Reference Case method of measuring utility. The potential impact of this on the ICER is explored in the ERG's exploratory analyses (see Section 5.5)

5.3.4.11 Adoption of a 40-year time horizon

The ERG noted that in the company's submitted model only 38.1% of people in the model are in the death health state at the end of the model's 40-year time horizon. The ERG considers that it is possible that the company's base case model may not capture all important differences in costs and QALYs between darvadstrocel and standard care. The company did submit a scenario analysis in

which, the time horizon was set to 60 years (CS[1] and clarification response[2]). Changing the time horizon to 60 years decreases the ICER from £20,591 per QALY gained in their base case to £19,719 per QALY gained. The ERG considers this to be a more appropriate time horizon, as at this time point 97.0% of people have died in both treatment groups.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

Exploratory analysis 1: Correction of errors.

Within this analysis, the three programming errors identified during the ERG's rebuild of the company's deterministic base case model (see Section 5.3.3) were rectified

Exploratory analysis 2: Probability of proctectomy and defunctioning surgery.

The ERG had concerns about how well the model fitted the data used to populate the transitions to the defunctioning surgery and proctectomy health states (see Section 5.3.4). Two general approaches were taken in this exploratory analysis. In the first approach, the company's model was calibrated using the Solver Excel add-in so that the company's model matched the data sources for the probability of proctectomy (18/87 people received a proctectomy after 6 years) and the probability of defunctioning surgery (average 0.0375 annual probability of receiving a defunctioning surgery after 16 years). This was done for defunctioning surgery (analysis 2a) and proctectomy (analysis 2b) separately and then again for both surgical treatments together (analysis 2c). When both surgical treatments were calibrated, the ERG selected the combination of the two annual probabilities of defunctioning surgery and proctectomy that minimised the company's ICER.

In the second approach (analysis 2d) data presented in the CS (Appendix Q, Table 28) on the yearly probability of transitioning between the model health states observed in the St Mark's retrospective cohort study was used. The data were from 78 consecutive patients with Crohn's disease and complex perianal fistulae from St Mark's Hospital. These transition probabilities were derived by fitting a statistical model called a Markov multi-state model (for panel data) to the data. Further details on this statistical model are given in the CS.[1] The results of this exploratory analysis should be interpreted with caution as: the goodness of fit of the company's statistical model and the follow up duration are unclear. However, the values produced from this analysis of the St Mark's data has a higher risk of receiving proctectomy for someone who has received a defunctioning surgery compared to someone who is the CSF severe health state. This is consistent with advice from the ERG's clinical advisors, who consider that people who have previously had a defunctioning surgery are more likely to have a proctectomy than someone who has not previously has a defunctioning surgery.

A comparison of the company's annual probabilities of proctectomy and defunctioning surgery, to the ones used by the ERG in this exploratory analysis are given in Table 31.

Table 31: Comparison of three different annual transition probabilities used in the company's base case analysis and those used this exploratory analysis

Transition		Annual probabilities		
From health state	**To health state**	**Values used in the company's base case model**	**ERG calibrated values[a]**	**St Mark's retrospective data**
CSF severe	Defunctioning surgery	0.0375	0.2929	0.1975
CSF severe	Proctectomy	0.0385	0.0797	0.1555
Defunctioning surgery	Proctectomy	0.0385	0.0797	0.1706

ERG –evidence review group; CSF – chronic symptomatic fistulae
a – these values are from the calibration of the company's model to both the proctectomy and defunctioning surgery data

Exploratory analysis 3: Long-term remission rate for salvage therapy

The ERG had concerns that the long term rate used to extrapolate the company's curves had a treatment effect applied between the darvadstrocel and standard care groups but did not have a treatment effect applied between the standard care and salvage therapy groups (see Section 5.3.4). This resulted in the long term extrapolation rates being the same for the standard care and salvage therapy groups, whilst the rates differed for the darvadstrocel group. In this sensitivity analysis the ERG amended the long term rates so that the long term rates were based on the salvage therapy time to event functions and not on the standard care time to event functions.

Exploratory analysis 4: Setting the model time-horizon to 60 years

As the ERG believes that a longer-term (60 year) time-horizon is more appropriate than the shorter term time horizon applied in the company's base case (40 years). This analysis by the ERG replicates the company's analysis of the model time horizon presented in Table 23.

The ERG's preferred base case model

The ERG's preferred base case model combines ERG analyses 1, 2c, 3 and 4. Unless otherwise stated, all subsequent analyses start from the ERG preferred base case analysis and include discounting of 3.5% for both costs and QALYs.

Exploratory analysis 5: Exploration of the extent to which darvadstrocel restores people with complex perianal fistulae and Crohn's disease to near full health

The ERG has concerns about whether darvadstrocel meets two of the criteria set out in the NICE Methods Guide for the Committee to consider using discount rates of 1.5%. These are that over a long period of time (usually 30 years): (1) currently people will die or have a very severely impaired quality of life; and (2) the treatment restores these people to full or near full health.

The ERG explored the extent to which darvadstrocel meets these two criteria. In order to do this, the discount rate was set to equal to 0% and the time horizon of the model was set to 30 years. The mean utility value accrued in each treatment group per year was then calculated by dividing the undiscounted QALYs by the undiscounted life years gained. These average utility values accrued per year, were then compared to the highest utility value used in the model (0.865 for the remission health state). As the model utilities were not adjusted for age, a simple division of the mean utility accrued each year by the highest utility value used in the model was conducted to calculate the proportion of the maximum available health gain in each treatment group. This exploratory analysis was conducted with both the ERG's preferred base case and the company's base case model.

Exploratory analysis 6: Inclusion of missing transitions

The ERG had concerns that the St Mark's retrospective study indicated that some transitions were possible, yet these were not permitted to occur within the company's submitted model structure (see Section 5.3.4.8). In this sensitivity analysis, three additional transitions were added to the company's model structure based on the four weekly transitions probabilities estimated from the St Mark's retrospective study (CS,[1] Appendix Q, Table 29). These were: successful defunctioning surgery to unsuccessful defunctioning surgery (4-weekly probability 0.03); successful proctectomy to unsuccessful proctectomy (4-weekly probability 0.02), and; unsuccessful proctectomy to successful proctectomy (4-weekly probability 0.05).

ERG exploratory analysis 7: CSF mild, successful defunctioning surgery and successful proctectomy health states have the same utility value as the remission health state

The ERG is concerned that the vignette study may have underestimated the utility of people in the CSF mild, successful defunctioning surgery and successful proctectomy health states as the differences between these health states and the remission health states are larger than those observed in other literature (see Section 5.3.4). To provide an upper limit on the effect of under predicting the utility in these health states, the ERG set the utility for these health states equal to those of remission (0.865). This scenario should be interpreted with caution, as it is intended only to inform the direction and maximum magnitude of any changes in the ICER due to the possible under prediction of utility in these three health states. For this reason, it is not incorporated in the ERG's preferred base.

ERG exploratory analysis 8: Use of different parametric distributions for the time to relapse and time to relapse.

The ERG has concerns that the company may not have fitted the most appropriate parametric model. In order to explore the impact of alternative functions on the ICER, this analysis replicates the company's sensitivity analysis on the parametric time-to-event functions in the ERG's preferred base case model.

5.5 Impact on the ICER of Additional Clinical and Economic Analyses Undertaken by the ERG

The results of each set of exploratory analyses are addressed below. In these analyses, costs and QALYs are discounted at 3.5%, unless otherwise specified. The results of the ERG exploratory analyses using a 1.5% discount rate for costs and QALYs are given in Appendix 4.

Exploratory analyses 1 to 4

Table 32 shows the results of the ERG exploratory analyses 1 to 4. Each analysis was conducted individually on the company's base case model. When combined these four exploratory analyses form the ERG's preferred base case, also provided in

Table 32.

Table 32 shows that in the ERG preferred base darvadstrocel is expected to generate an additional 1.01 QALYs at an additional cost of £23,978. The corresponding ICER is £23,176 per QALY gained. This compares to an ICER of £20,591 per QALY gained in the company's base case. The results of each individual change suggest that the key driver of the differences between the ERG's preferred base case and the company's base case is the calibration of the probabilities of proctectomy and defunctioning surgery (i.e. analysis 2c). The other three factors have a modest impact on the ICER.

Table 32: The results of the ERG exploratory analyses for analysis sets 1 to 4, including the PAS for darvadstrocel

Treatment	Total QALYs	Total costs (with PAS)	ICER (£ per QALY gained)
Company's base case			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.05	£21,639	£20,591
1) ERG exploratory analysis – correction of implementation errors			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.05	£21,666	£20,700
2a) ERG exploratory analysis – only proctectomy calibrated			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.01	£23,127	£22,887
2b) ERG exploratory analysis – only defunctioning surgery calibrated			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.01	£22,024	£21,824
2c) ERG exploratory analysis – proctectomy and defunctioning surgery calibrated			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	0.96	£23,241	£24,115
2d) ERG exploratory analysis – proctectomy and defunctioning surgery probabilities were obtained from the St Mark's retrospective cohort study			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	0.95	£24,530	£25,530
3) ERG exploratory analysis – long term remission and relapse rates for salvage therapy are obtained from the salvage therapy arm			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.05	£21,628	£20,540
4) Time horizon is set to 60 years (replication of the company's scenario analysis)			
Darvadstrocel	[redacted]	[redacted]	-
Standard Care	[redacted]	[redacted]	-
Incremental	1.10	£21,706	£19,719
ERG base case: 1 + 2c + 3 + 4			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.01	£23,978	£23,176

QALYs – quality-adjusted life years; PAS – patient access scheme; ICER – incremental cost-effectiveness ratio; ERG – Evidence Review Group

Exploratory analysis 5: Analysis of the extent that darvadstrocel restores people with complex perianal fistulae and Crohn's disease to near full health

Table 33 shows that in the ERG's preferred model over a 30-year time horizon; patients in both treatment groups accrue 28.82 life years; patients in the standard care group accrue [redacted] undiscounted QALYs, and; patients in the darvadstrocel group accrue [redacted] undiscounted QALYs. This results in darvadstrocel accruing an average utility of [redacted] per year and standard care accruing an average utility of [redacted] per year. These two values correspond to [redacted] and [redacted] of the utility value for the remission health state, respectively.

The equivalent values using the company's base case model show that over a 30-year time horizon; patients in both treatment groups accrue 28.78 life years; patients in the standard care group accrue [redacted] undiscounted QALYs, and; patients in the darvadstrocel group accrue [redacted] undiscounted QALYs. This results in darvadstrocel accruing an average utility of [redacted] per year and standard care accruing an average utility of [redacted] per year. These two values correspond to [redacted] and [redacted] of the utility value for the remission health state, respectively.

Table 33: Assessment of the proportion of health achieved in each model arm using the company's and the ERG's base case model over a 30-year time horizon and a 0% discount rate

Treatment	Undiscounted life years	Undiscounted QALYs	Mean utility accrued per year	Highest health state utility value	Percentage of maximum health achieved
Company's base case model					
Standard Care	28.78	[redacted]	[redacted]	0.865	[redacted]
Darvadstrocel	28.78	[redacted]	[redacted]	0.865	[redacted]
ERG's base case model					
Standard Care	28.82	[redacted]	[redacted]	0.865	[redacted]
Darvadstrocel	28.82	[redacted]	[redacted]	0.865	[redacted]

QALYs – quality-adjusted life years

On the basis of these results the ERG believes that: (1) the average patient with complex perianal fistulae and Crohn's disease does not have a very severely impaired quality of life when treated with standard care and (2) that darvadstrocel does not restore the average patient with complex perianal fistulae and Crohn's disease to full or near full health. As such, the ERG considers that darvadstrocel does not meet the criteria described in Section 6.2.19 of the guide to the NICE Methods Guide.[10] Consequently, the ERG believes that costs and QALYs should be discounted at a rate of 3.5% for both costs and QALYs.

Exploratory analysis 6: Inclusion of missing transitions

Table 34 shows the impact of adding transitions between: (1) the successful and unsuccessful defunctioning surgery health states; (2) the successful and unsuccessful proctectomy health states, and; (3) the unsuccessful and successful proctectomy health states. This suggests that adding these transitions will decrease the ICER to £19,452 per QALY gained from the ERG's base case ICER of £23,176 per QALY gained.

Table 34: Impact of three additional transitions on the ICER the ERG's base case model, including the PAS for darvadstrocel

Treatment	Total QALYs	Total costs (with PAS)	ICER
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.11	£21,655	£19,452

QALYs – quality-adjusted life years; PAS – patient access scheme; ICER – incremental cost-effectiveness ratio

Exploratory analysis 7: CSF mild, successful defunctioning surgery and successful proctectomy health states have the same utility value as the remission health state

The results in Table 35 indicate that the ICER for the ERG's preferred base case scenario would increase from £23,176 per QALY gained to £63,721 per QALY gained, if the utilities in the CSF mild, successful defunctioning surgery and successful proctectomy health states were the same as the utilities in the remission health sate. This indicates that applying lower utility values to these three health states produces a more favourable ICER for darvadstrocel, and also that, the ICER is sensitive to changes in the utility values for these health states. Consequently, if the utility values for these health states have been significantly under-predicted, then the ICER may have also been significantly underestimated.

Table 35: The effect of setting the utility for patients in the CSF mild, successful defunctioning surgery and successful proctectomy health states to the same value as patients in the remission health state, including the PAS for darvadstrocel

Treatment	Total QALYs	Total costs (with PAS)	ICER (£ per QALY gained)
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	0.37	£23,738	£63,721

QALYs – quality-adjusted life years; PAS – patient access scheme; ICER – incremental cost-effectiveness ratio

Exploratory analysis 8: *The use of different parametric distributions for the time to relapse and time to relapse*

The results of the ERG's exploratory analysis on the base case curve selection is presented in Table 36. These analyses show that the ICER is particularly sensitive to the time to relapse function (Gompertz

distribution). As the ERG is concerned that the time-relapse-function may have been biased due to informative censoring (see Section 5.3.4.5), this analysis indicates that the ICER may be significantly higher or lower than those presented by the ERG and company. The direction of bias will depend on whether the impact of informative censoring is favourable or unfavourable to darvadstrocel.

Table 36: The effect of changing the time-to-event functions on the ICER in the ERG's base case model, including the PAS for darvadstrocel

Time to remission function	Time to relapse function	Total costs			Total QALYs			ICER
		Darv	SC	Incr	Darv	SC	Incr	
Gompertz (base case)	Gompertz (base case)	[redacted]	[redacted]	£23,378	[redacted]	[redacted]	1.01	£23,176
Generalised gamma	Gompertz (base case)	[redacted]	[redacted]	£24,033	[redacted]	[redacted]	0.82	£29,200
Gompertz (base case)	Log-normal	[redacted]	[redacted]	£25,,084	[redacted]	[redacted]	0.21	£119,514
Generalised gamma	Log-normal	[redacted]	[redacted]	£25,146	[redacted]	[redacted]	0.18	£143,131

Darv – darvadstrocel; SC – standard care; Incr – incremental difference between darvadstrocel and standard care; ICER - incremental cost-effectiveness ratio; QALYs – quality adjusted life years

5.6 Conclusions of the cost effectiveness section

The ERG were satisfied that the company's review of published economic evaluations did not exclude any cost-effectiveness studies which were relevant to the scope of this appraisal.

The CS argues darvadstrocel should be assessed using a discount rate of 1.5% for QALYs and 3.5% for costs.[1] The ERG notes that the NICE methods guide specifies that in the Reference Case a discounting rate of 3.5% should be used for both costs and QALYs and that a rate of 1.5% for both costs and benefits may be considered by the Appraisal Committee under specific circumstances.[10] The ERG therefore notes that the use of differential discounting is not supported within the NICE methods guide.

Based on the probabilistic version of the model in the CS (using a discount rate of 1.5% for QALYs and 3.5% for costs) darvadstrocel is expected to generate an additional 1.35 QALYs at an additional cost of £21,773, compared with standard care: the corresponding incremental cost-effectiveness ratio is £16,102 per QALY gained.[1] The deterministic version of the company's model produces a similar ICER of £15,471. At clarification the company's presented additional analyses using: (1) a discount rate of 3.5% for both costs and QALYs and (2) a discount rate of 1.5% for both costs and QALYs.[2] When a discount rate of 3.5% was used for both costs and QALYs, the updated model suggested that darvadstrocel is expected to generate an additional 1.02 QALYs at an additional cost of £21,773, compared with standard care, giving an ICER of £21,417 per QALY gained. The results of the analysis using 1.5% discount rates are presented in Appendix 2.

The ERG critically appraised the company's economic analysis and double programmed the deterministic version of their model. The ERG's critical appraisal identified eleven issues relating to the company's economic analysis and the evidence used to inform it, each of these are addressed in turn.

The ERG believes that a longer-term (60 year) time-horizon is more appropriate than the shorter term time horizon applied in the company's base case (40 years). The ERG considered that the model submitted by the company did not adequately predict the data used in the model for the receipt of defunctioning surgery or proctectomy. The ERG considered that the long term event rates for the salvage therapy arm should have been estimated using the time to event functions for salvage therapy. The ERG's preferred base case analysis addressed these issues, and corrected several minor errors in the company's model. This resulted in a moderate increase in the deterministic ICER from £20,591 per QALY gained in the company's deterministic base case to £23,176 per QALY gained in the ERG's preferred base case

The CS did not include any data on the cost-effectiveness of darvadstrocel for people with complex perianal fistulae and Crohn's disease whose fistulae has more than two internal openings or more than three external openings, however the marketing authorisation does not specifically exclude this population. The ERG considers that an ICER for darvadstrocel cannot be reliably estimated for this population. The marketing authorisation for darvadstrocel does not preclude people who have previously been treated with darvadstrocel receiving another treatment course, however the submitted evidence only relates to a single use of darvadstrocel. The ERG considers that the ICER for darvadstrocel may increase if repeated use were to be included compared to the company's analyses which assume no repeated use.

The ERG considers that a discounting rate of 3.5% should be applied to both costs and QALYs, as per the NICE Reference Case, because the company has not demonstrated that: (1) standard care would result in death or a severely impaired quality of life for the population being considered; and (2) darvadstrocel would restore this population to near full health over a very long period (usually 30 years). The ERG considers that the exploratory analysis on whether darvadstrocel meets the criteria in Section 6.2.19 of the NICE methods guide indicates that these criteria are not met.[10]

The ERG were concerned that in clinical practice doses of darvadstrocel would be wasted, as it has a shelf life of 48 hours. An analysis by conducted by the company in response to a clarification question suggested that wastage would have a minor impact on the ICER. The ERG's advisors indicated that the assumed wastage in the company's analysis was likely to be an upper estimate of what would be observed in clinical practice.

The ERG had concerns that the company's estimated time to event functions did not control for interval censoring, which may bias these functions, and the long term extrapolations were not reliable. The direction and magnitude of any changes in the ICER is unknown, however the company's sensitivity analyses and the ERG's exploratory analyses indicate that the ICER is highly sensitive to the assumed time to event function.

The ERG had two concerns that the expert elicitation exercise: firstly, the exercise was not adequately reported, so the ERG could not assess whether the estimated produced from the exercise were robust or unbiased; and secondly, the exercise did not capture the uncertainty that the experts had in their elicitation. Analyses conducted by the company in response to clarification suggested that different assumed uncertainty in the elicited values had a modest impact on the ICER, but the effect on the ICER of any bias in the elicited values is unknown.

The ERG noted that the company's analysis of the St Mark's dataset suggests that some transition probabilities which were not possible within their model structure, were possible in clinical practice. The ERG explored the effect of adding these transition probabilities to the company's model in an exploratory analysis. This exploratory analysis suggested that adding these transitions would moderately decrease the ICER

The ERG notes that the method used to estimate the utility values incorporated in the economic analysis was not consistent with the NICE reference case and that in general the method used to estimate utilities may influence the values obtained. The ERG were concerned that the utility values applied to some model states may have been underestimated, based both on comparisons made with published estimates and the opinion of clinical experts. The ERG's exploratory analyses suggest that applying higher utility values for those model states that may have been underestimated would tend to increase the ICER, but the ERG was unable to identify a more plausible estimate of utilities than those used by the company.

The ERG considers the following to represent the key uncertainties within the company's health economic analysis:

- The absence of comparative clinical evidence for darvadstrocel versus standard care within people with complex perianal fistulae and Crohn's disease whose fistula has more than two internal openings or more than three external openings.
- The absence of clinical evidence regarding the repeat administration of darvadstrocel.
- The potential introduction of bias in the estimation of the time to event functions, as interval censoring techniques were not applied.

6 END OF LIFE

NICE end of life supplementary advice should be applied in the following circumstances and when both the criteria referred to below are satisfied:

1) The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
2) There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company does not claim that darvadstrocel meets NICE's end of life criteria. The ERG concurs with this view.

7 OVERALL CONCLUSIONS

Clinical effectiveness

The efficacy (in terms of combined remission and CPC remission) and safety of a single intralesional injection of darvadstrocel added on to standard of care (compared with placebo sham and standard of care) was positively demonstrated in the ADMIRE-CD study. However, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. Whilst the study was generally well reported and conducted, a key limitation of the efficacy and safety data for darvadstrocel reported in the CS relates to the post hoc analyses of CPC-remission (an outcome used in the economic model) and CPC relapse.[1] These endpoints were not designed or powered to test formal hypotheses. Another issue is the lack of a confirmatory study. As noted in the EPAR, the effect size in the ADMIRE-CD trial was considered to be modest and less than the 25 percentage difference that it was designed to detect, yet this was considered clinically meaningful given that other treatment options for fistulas had failed.[17] A post-authorisation efficacy and safety trial, ADMIRE-CD-II is expected to help address this concern. However, this study is not expected to be complete until October 2021. The key uncertainties in the clinical evidence for darvadstrocel relate to repeated administration, optimal dosing and long-term efficacy and safety

Cost-effectiveness

Notwithstanding uncertainties regarding the statistical analysis of the time to event data and the utilities for the CSF mild, successful defunctioning and successful proctectomy health states, the ERG's preferred base case increases the ICER for darvadstrocel versus standard care from £20,591 per QALY gained to £23,176 per QALY gained. On the basis of an exploratory analysis conducted by the ERG, the ERG does not consider that darvadstrocel meets the criteria in Section 6.2.19 of the NICE Methods Guide.[10] Consequently, the ERG believes that costs and QALYs should both be discounted at a rate of 3.5%. Additional exploratory analyses indicate that including additional transitions in the company's model structure only has a minor impact on the ICER for darvadstrocel versus standard care. Conversely, the selected time to event distributions for time to relapse and time to remission and the utility values for the CSF mild, successful defunctioning surgery and successful proctectomy health states have a significant impact on the ICER for darvadstrocel versus standard care. The ERG notes that no comparative clinical or economic evidence is available for the comparison of darvadstrocel versus standard care in patients with complex perianal fistula and Crohn's disease whose fistula has more than two internal openings and/or more than three external openings. Furthermore, no comparative clinical or economic evidence is available in which repeated administration of darvadstrocel is compared to either the single use of darvadstrocel or standard care.

7.1 Implications for research

The ERG considers that future research should be undertaken in the four key areas. Firstly, a confirmatory study that is statistically powered to detect a difference in remission and relapse using the CPC definition should be conducted. Secondly, a study is required to evaluate the optimal dose and treatment duration of darvadstrocel. Thirdly, a study to investigate efficacy and safety of repeat administration of darvadstrocel and administration of darvadstrocel to people with more than two internal openings and/or more than three external openings of their complex perianal fistula is required. Finally, longer term epidemiological studies and clinical experience are required to estimate the long term remission and relapse rates and fully assess the risk of AEs associated with darvadstrocel.

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APPENDICES

Appendix 1: The goodness of fit of the company's parametric models to relapse and remission data when remission is defined using the clinical remission criterion

Table 37: The AIC and BIC statistics for the different fitted parametric time-to-event functions to the time to remission and relapse using the clincal definition of remission, excluding the piecewise exponential model (adapted from CS Table 35 and Table 41)

	Remission		**Relapse**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	1156.866	1163.463	791.794	797.774
Weibull	1127.301	1137.196	763.665	772.636
Gompertz	1089.373	1099.268	757.079	766.050
Log normal	***1017.138***	***1030.331***	***749.776***	***758.747***
Log logistic	1091.477	1101.372	756.516	765.487
Generalised Gamma	Not converged	Not converged	754.526	766.488

AIC –Akaike information criterion; BIC – Bayesian information criterion;
Text in ***bold and italics*** indicates the lowest value out of the converged time-to-event functions in each column

Figure 15: Log cumulative hazard plot for clinical remission data (from clarification response,[2] question B3, Figure 8)

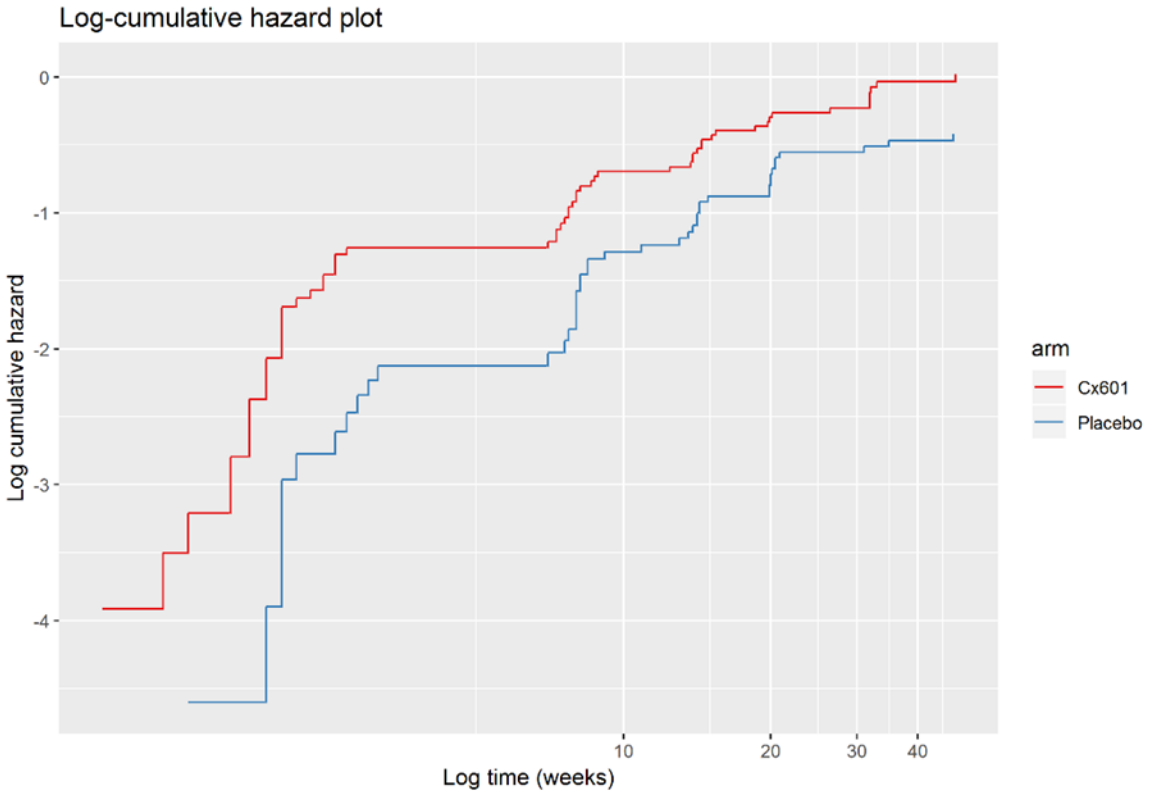


Figure 16: Empirical hazard plot vs. predicted Gompertz hazards for clinical remission outcome (from clarification response,[2] question B3, Figure 10)

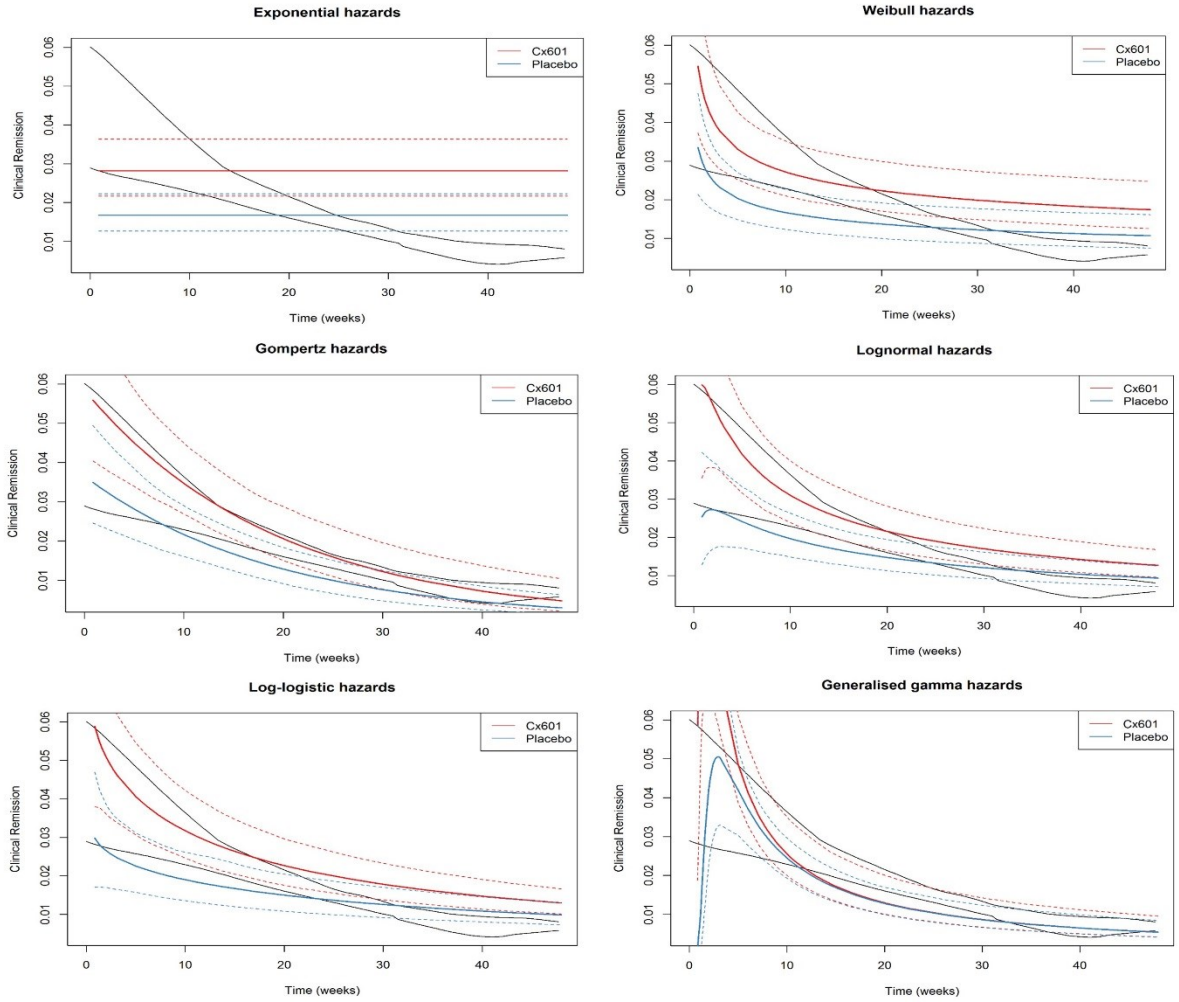


Figure 17: Log cumulative hazard plot for clinical relapse data (from Clarification response[2], question B3, Figure 15)

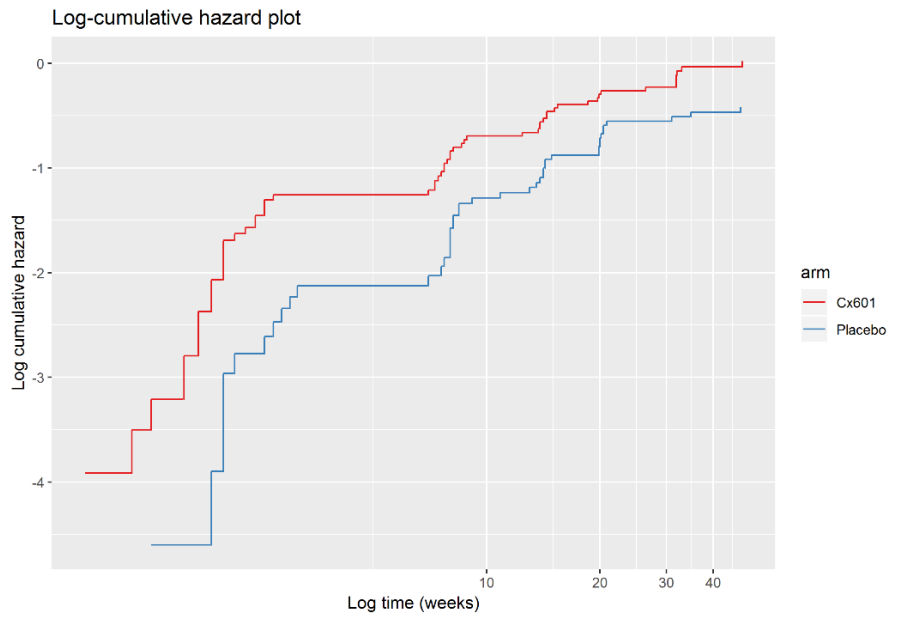
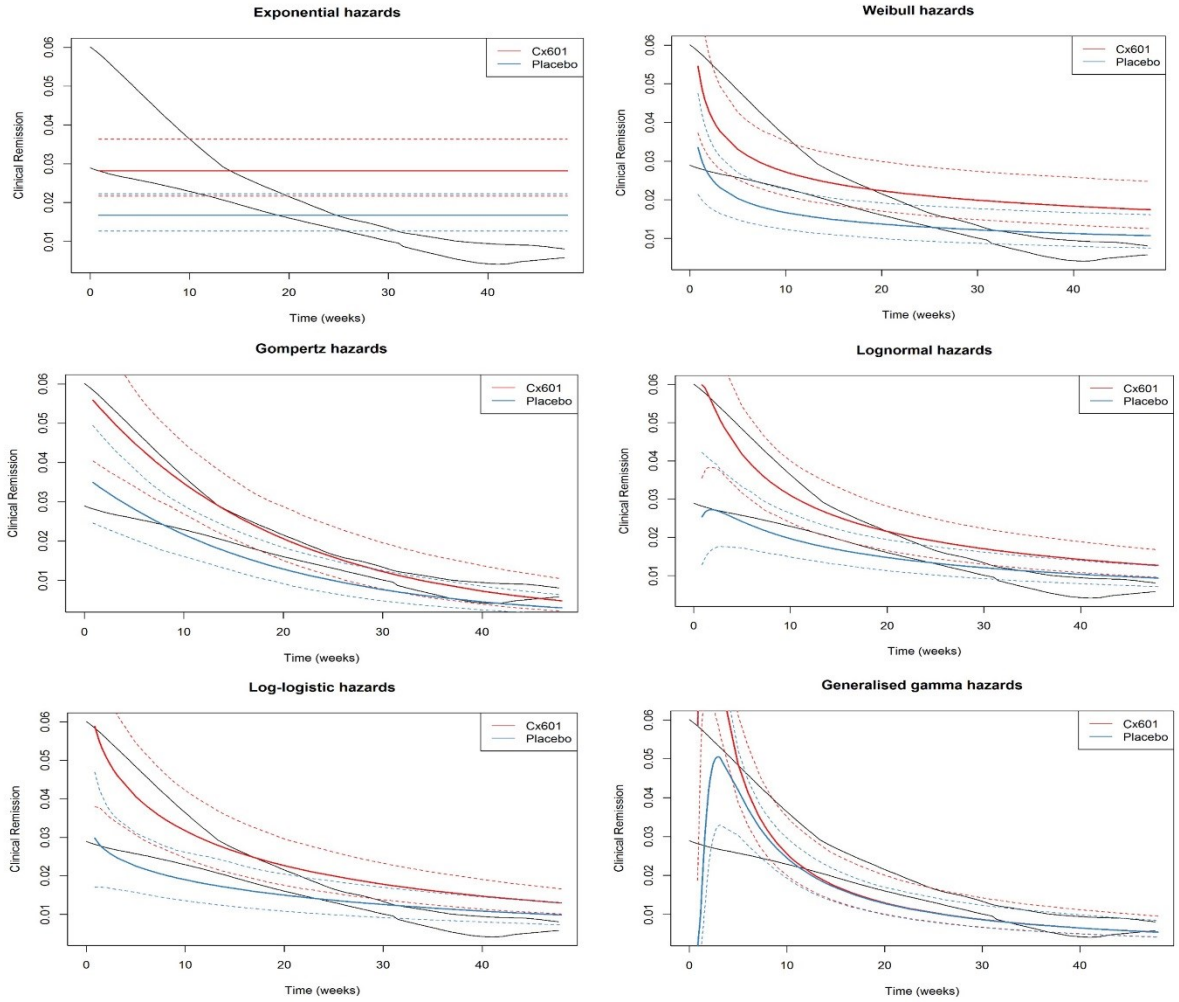


Figure 18: Empirical hazard plot vs. predicted Gompertz hazards for clinical remission outcome (from clarification response,[2] question B3, Figure 17)



Appendix 2: Technical Appendix - The company's results, when a discount rate of 1.5% for both costs and QALYs are used

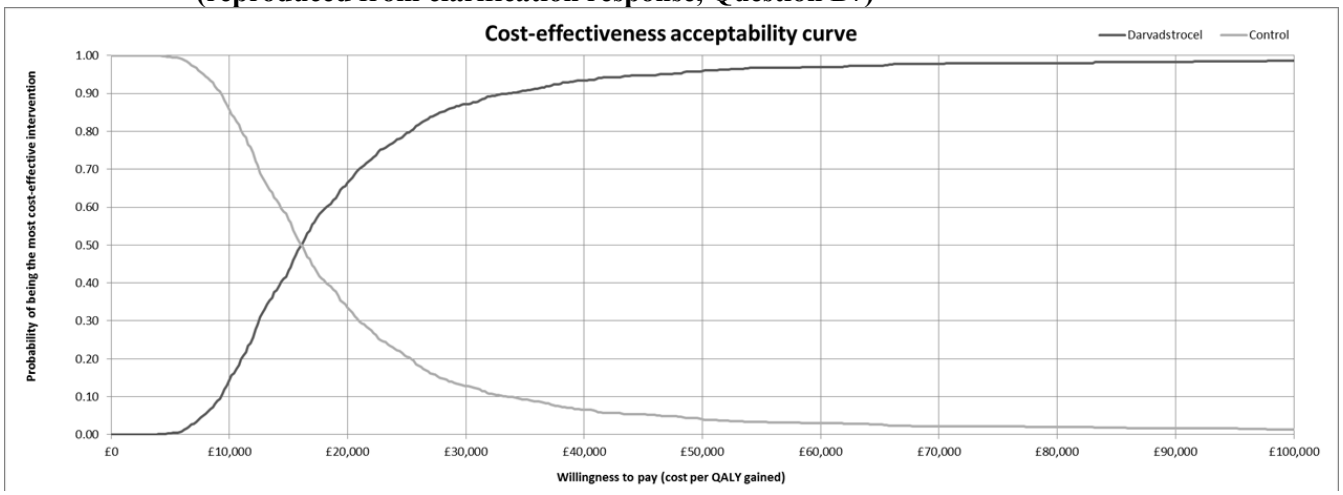
Table 38 shows the results of the company's base case analysis in both the deterministic analysis and the PSA analysis. Based on the PSA version of the company's model, darvadstrocel is expected to generate an additional 1.40 QALYs at an additional cost of £21,004, compared with standard care. The corresponding incremental cost-effectiveness ratio is £15,017 per QALY gained. The deterministic version of the company's model produces a similar ICER of £15,649 per QALY gained.

Table 38: Company's base case results, including the patient access scheme for darvadstrocel, assuming 1.5% discount rate for both costs and QALYs (adapted from clarification response, question B7)

Treatment	Total QALYs	Total costs	ICER (£ per QALY gained)	Probability that the intervention is the most cost-effective at a maximum acceptable ICER of:	
				£20,000 per QALY gained	£30,000 per QALY gained
Probabilistic Sensitivity Analysis					
Darvadstrocel	[redacted]	[redacted]	-	0.66	0.87
Standard care	[redacted]	[redacted]	-	0.34	0.13
Incremental	1.35	£21,161	£15,649	-	-
Deterministic					
Darvadstrocel	[redacted]	[redacted]	-	-	-
Standard care	[redacted]	[redacted]	-	-	-
Incremental	1.40	£21,004	£15,071	-	-

QALYs – quality adjusted life years; PAS – Patient Access Scheme; ICER – incremental cost-effectiveness ratio

Figure 19: Cost effectiveness acceptability curve, including the patient access scheme for darvadstrocel, using a discount rate of 1.5% for both costs and QALYs (reproduced from clarification response, Question B7)



QALY – quality-adjusted life year

Figure 20: Company's tornado diagram showing the one way sensitivity analyses conducted by the company using a discount rate of 1.5% for both costs and QALYs (reproduced from clarification response, question B7)

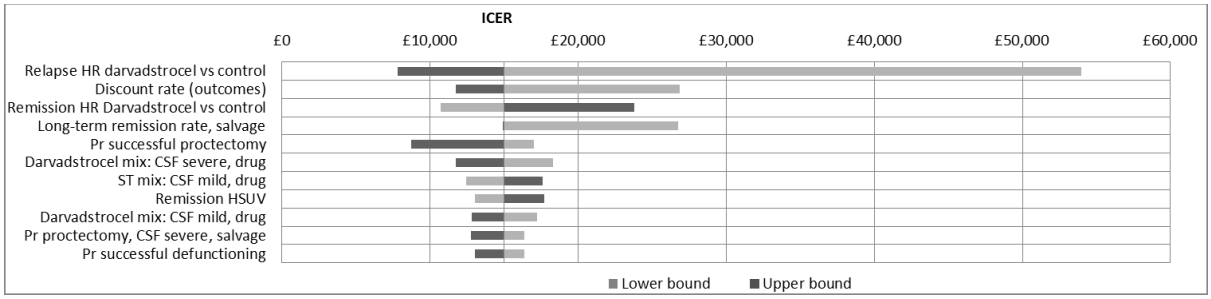


Table 39: Sensitivity analyses conducted by the company using a discount rate of 1.5% for both costs and QALYs (reproduced from clarification response, question B7, Table 31)

Scenario description	Total costs			Total QALYs			ICER (£ per QALY gained)
	Darv	Standard care	Difference	Darv	Standard care	Difference	
Base case, 3.5% discount for costs and QALYs	[redacted]	[redacted]	21,004	[redacted]	[redacted]	1.40	15,017
0% discount rate for costs and QALYs	[redacted]	[redacted]	21,625	[redacted]	[redacted]	1.39	15,603
6% discount rate for costs and QALYs	[redacted]	[redacted]	20,313	[redacted]	[redacted]	1.39	14,651
10% annual proctectomy probability post defunctioning	[redacted]	[redacted]	19,972	[redacted]	[redacted]	1.40	14,280
50% annual stoma reversal probability from successful defunctioning state	[redacted]	[redacted]	20,809	[redacted]	[redacted]	1.40	14,878
Upper bound of annual stoma care costs (£2,682 per year)	[redacted]	[redacted]	21,004	[redacted]	[redacted]	1.31	16,057
Infusion costs halved (£142.25)	[redacted]	[redacted]	20,922	[redacted]	[redacted]	1.43	14,676

HSUVs based on CD patients vignette study set	[redacted]	[redacted]	21,323	[redacted]	[redacted]	0.92	23,191
Relapse HR for salvage therapy vs. control equal to 1.20	[redacted]	[redacted]	21,172	[redacted]	[redacted]	1.52	13,926
Time horizon: 20 years	[redacted]	[redacted]	15,297	[redacted]	[redacted]	1.40	10,937
Time horizon: 60 years	[redacted]	[redacted]	22,254	[redacted]	[redacted]	1.40	15,911
No inclusion of Biologic usage within salvage therapy (all other assumptions as per base case)	[redacted]	[redacted]	21,004	[redacted]	[redacted]	1.40	15,017
Wastage assumed to result in 5% additional cost for darvadstrocel	[redacted]	[redacted]	21,625	[redacted]	[redacted]	1.39	15,603

QALYs - quality-adjusted life years; ICER - incremental cost-effectiveness ratio; Darv – darvadstrocel; HSUV - health state utility value; CD - Crohn's disease; HR - hazard ratio

Table 40: Impact of different parametric time-to-event functions on the company's base case ICER using a discount rate of 1.5% for both costs and QALYs (reproduced from clarification response, question B7, Table 33)

Time to remission function	Time to relapse function	Total costs			Total QALYs			ICER
		Darv	SC	Incr	Darv	SC	Incr	
Gompertz (base case)	Gompertz (base case)	[redacted]	[redacted]	21,004	[redacted]	[redacted]	1.40	15,017
Generalised gamma	Gompertz (base case)	[redacted]	[redacted]	22,316	[redacted]	[redacted]	0.99	22,432
Gompertz (base case)	Log-normal	[redacted]	[redacted]	24,952	[redacted]	[redacted]	0.25	99,339
Generalised gamma	Log-normal	[redacted]	[redacted]	24,924	[redacted]	[redacted]	0.20	123,732

Darv – darvadstrocel; SC – standard care; Incr – incremental difference between darvadstrocel and standard care; ICER - incremental cost-effectiveness ratio; QALYs – quality adjusted life years

Table 41: Results of the scenario analyses surrounding the definition of relapse in the company's submitted economic model (reproduced from clarification response, question B7, Table 34)

Scenario	Total costs			Total QALYs			
	Darv	Control	Incremental	Darv	Control	Incremental	
Base case	[redacted]	[redacted]	21,004	[redacted]	[redacted]	1.40	15,017
St Mark's retrospective data set	[redacted]	[redacted]	27,893	[redacted]	[redacted]	1.51	18,529

Darv – darvadstrocel; ICER - incremental cost-effectiveness ratio.

Appendix 3: Technical appendix detailing methods for applying the ERG's exploratory analyses within the company's model

Note when using the company's model, the discount rates for costs and QALYs should be changed to either 3.5% for both or 1.5% for both. To do this change the discount rates in Sheet "Settings", cells E29 and E30.

Exploratory analysis 1

1) Start with the Company's model
2) Go to the sheet "TimeToRemission", cell AC65
3) Change the formula to "=-(LN(1-(AC48-AC63)/AC48)/(COUNT(AC48:AC63)-1))"
4) Paste the formula to cells AF6, AI65, AL65, AO65, AR65
5) Go to the Sheet "TimeToRelapse", cell AA65
6) Change the formula to "=-(LN(1-(AA48-AA63)/AA48)/(COUNT(AA48:AA63)-1))"
7) Drag the formula across to cell AR65
8) Go to the sheet "Patient flow – Darvadstrocel", cells E7:GE7
9) Change the array formula to "=MMULT(E6:GE6,'Transition matrices'!$D$6:$GD$188)*(1-VLOOKUP(ROUNDDOWN(D6,0),Mortality!$R$13:$Y$116,8,FALSE))"
10) Go to cell GF7
11) Change the formula to: "=GF6+(SUM(E6:GE6)*VLOOKUP(ROUNDDOWN(D6,0),Mortality!$R$13:$Y$78,8,FALSE))"
12) Select cells E7:GF7
13) Copy the formulae down to the row 786
14) Go to the sheet "Patient flow-Control", cells E7:GE7
15) Change the array formula to:"=MMULT(E6:GE6,'Transition matrices'!$D$193:$GD$375)*(1-VLOOKUP(ROUNDDOWN(D6,0),Mortality!$R$13:$Y$78,8,FALSE))"
16) Select cell GF7, ant type the formula "=GF6+SUM(E6:GE6)*(VLOOKUP(ROUNDDOWN(D6,0),Mortality!$R$16:$Y$78,8,FALSE))"
17) Select cells E7:GF7
18) Copy the formulae down.

Exploratory analysis 2

1) For all parts of exploratory analysis 2, enable the solver add in to Excel, if you have not already done so.

2a) Proctectomy

1) Start with the Company's model
2) Go to Sheet "Clinical inputs" cell E128, change the formula to "='Patient flow-Control'!$E$2"
3) Go to Sheet "Clinical inputs" cell E127, change the formula to "='Patient flow-Control'!$E$2"
4) Go to Sheet "Clinical inputs" cell E125, change the formula to "='Patient flow-Control'!$E$2"
5) Go to the sheet Patient flow-Control'
6) Open solver and use the following settings:
    a. Set objective HL$84
    b. To: value of 0.2068965517 (18/87 to 10 dp)
    c. By changing variable cells: $E$2
    d. No constraints
    e. Solving method: GRG Nonlinear

2b) Defunctioning

1) Start with the Company's model
2) Go to Sheet "Clinical inputs" cell E111, change the formula to ='Patient flow-Control'!$F$2
3) Go to Sheet "Clinical inputs" cell E113, change the formula to ='Patient flow-Control'!$F$2
4) Go to Sheet "Patient flow-Control"
5) Go to cell G2 and input the following formula "=HK214"
6) Go to cell H2 and input the following formula: "=-(LN(1-G2))/16"
7) Go to cell I2 and input the following formula "=1-EXP(-H2*1)"
8) Set up solver with the following settings
    a. Set objective I2
    b. To: value of 0.03752771 (value given elsewhere in the model for the annual probability of undergoing a defunctioning surgery)
    c. By changing variable cells: $F$2
    d. Constraints: $F$2 ≤ 1
    e. Solving method: GRG Nonlinear

2c)

1) Start with the Company's model
2) Do 2a, steps 1 to 3
3) Do 2b, steps 1 to 6

4)

5) Run solver with the following settings
    a. Set objective I2
    b. To: value of 0.03752771 (value given elsewhere in the model for the annual probability of undergoing a defunctioning surgery)
    c. By changing variable cells: $E$2:$F$2
    d. Constraints: HL$84 = 0.2068965517; $F$2 ≤ 1; $F$2 ≥ 0; $E$2 ≤ 1; $E$2 ≥ 0
    e. Solving method: GRG Nonlinear
6) Put the following formula in cell J2 "=dICER"
7) Run a new solver with the following settings
    a. Set objective J2
    b. To: Min
    c. By changing variable cells: $E$2:$F$2
    d. Constraints: I2 = 0.03752771; HL$84 = 0.2068965517; $F$2 ≤ 1; $F$2 ≥ 0; $E$2 ≤ 1; $E$2 ≥ 0
    e. Solving method: Evolutionary

2d)

1) Start with the Company's model
2) Go to Sheet "Clinical Inputs", cell E111 & cell E113, set the formula to "=0.111609+0.085896"
3) Go to Sheet "Clinical Inputs", cell E125 & cell E127, set the formula to "=0.118666+0.036848""
4) Go to Sheet "Clinical Inputs", cell E128. Set the formula to "=E116*(0.041258+0.022391)+E117*(0.228007+0.117161)"

ERG exploratory analysis 3

1) Start with the Company's model
2) Go to Sheet "TimeToRemission", insert new columns AD, AH, AL, AP, AT, AX
3) In cell AD23 type the formula "=AC23^'Clinical inputs'!$E$68"
4) Copy the formula down to row 63
5) Copy the formula in AD23 and paste into the cells AH23, AL23, AP23, AT23, AX23
6) Copy these new formulae down to row 63
7) In cell AC65 change the formula to "=-(LN(1-(AD48-AD63)/AD48)/(COUNT(AD48:AD63)))"
8) Copy the formula in cell AC65 and paste into cells AG65, AK65, AO65, AS65, AW65
9) Go to Sheet "TimeToRelapse", insert new columns AD, AH, AL, AP, AT, AX

10) In cell AD23 type the formula "=AB23^'Clinical inputs'!$E$95"
11) Drag the formula down to row 63
12) Copy the formula in cell AD23 and paste it to cells AH23, AL23, AP23, AT23, AX23
13) Copy the formulae down to row 63
14) Go to cell AC65 and change the formula to "=-(LN(1-(AD48-AD63)/AD48)/(COUNT(AD48:AD63)))"
15) Copy the formula in cell AC65 and paste to cells AG65, AK65, AO65, AS65, AW65

ERG exploratory analysis 4

1) Start with the Company's model
2) Go to Sheet "Settings", cell E18 and change the value to 60

ERG preferred base case

1) Follow the steps in ERG exploratory analysis 1
2) Follow the steps in ERG exploratory analysis 2c
3) Follow steps 1 to 5 in ERG exploratory analysis 3
4) In Sheet "TimeToRemission", cell AC65 change the formula to "=-(LN(1-(AD48-AD63)/AD48)/(COUNT(AD48:AD63)-1))"
5) Follow steps 7 to 12 in ERG exploratory analysis 3
6) In Sheet "TimeToRelapse" change the formula to "=-(LN(1-(AD48-AD63)/AD48)/(COUNT(AD48:AD63)-1))"
7) Follow step 14 in ERG exploratory analysis 3
8) Follow the steps in ERG exploratory analysis 4

ERG exploratory analysis 5

1) Start with the ERG preferred base case or the Company's base case model (as appropriate)
2) Go to Sheet "Settings", go to cells E29 and E30 and set the value to 0
3) Go to cell E18 and set the value to 30
4) Go to Sheet "Results", go to cell E49 and input the formula "=E42/E48"
5) Go to cell E50 and input the formula "=E49/'Clinical inputs'!$E$185"
6) Copy cells E49:E50, paste the formulae into cells G49:G50

ERG exploratory analysis 6

1) Start with the ERG preferred base case
2) Go to Sheet "transition matrices", cell GB 185, input the value 0.031640929
3) Go to cell GD187, input the value 0.016770373
4) Go to cell GC188, input the value 0.048945715

5) Go to cell GB372, input the value 0.031640929
6) Go to cell GD374, input the value 0.016770373
7) Go to cell GC375, input the value 0.048945715

ERG exploratory analysis 7

1) Start with the ERG preferred base case
2) Go to Sheet “Clinical inputs”, go to cell E186 and input the formula “=$E$185”
3) Copy cell E186
4) Paste the formula into cells E190 and E192

Appendix 4: Technical appendix detailing the results of the ERG exploratory analyses when a discount rate of 1.5% for both costs and QALYs are used

Table 42: The results of the ERG exploratory analyses for analysis sets 1 to 4, including the PAS for darvadstrocel when a discount rate of 1.5% for both costs and QALYs is used

Treatment	Total QALYs	Total costs (with PAS)	ICER (£ per QALY gained)
Company's base case			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.40	£21,004	£15,017
1) ERG exploratory analysis – correction of implementation errors			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.39	£21,046	£15,117
2a) ERG exploratory analysis – only proctectomy calibrated			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.34	£23,155	£17,231
2b) ERG exploratory analysis – only defunctioning surgery calibrated			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.35	£21,548	£16,015
2c) ERG exploratory analysis – proctectomy and defunctioning surgery calibrated			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.28	£23,315	£18,152
2d) ERG exploratory analysis – proctectomy and defunctioning surgery probabilities were obtained from the St Mark's retrospective cohort study			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.27	£24,665	£19,465
3) ERG exploratory analysis – long term remission and relapse rates for salvage therapy are obtained from the salvage therapy arm			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.40	£20,988	£14,973
4) Time horizon is set to 60 years (replication of the company's scenario analysis)			
Darvadstrocel	[redacted]	[redacted]	-
Standard Care	[redacted]	[redacted]	-
Incremental	1.52	£21,172	£13,926
ERG base case: 1 + 2c + 3 + 4			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.40	£23,639	£16,198

QALYs – quality-adjusted life years; PAS – patient access scheme; ICER – incremental cost-effectiveness ratio; ERG – evidence review group

ERG exploratory analysis 5

No change, as this exploratory analysis is based on undiscounted costs and QALYs

ERG exploratory analysis 6

Table 43: Impact of three additional transitions on the ICER the ERG's base case model, including the PAS for darvadstrocel

Treatment	Total QALYs	Total costs (with PAS)	ICER
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.53	£31,352	£13,922

ERG exploratory analysis 7

Table 44: The effect of setting the utility for patients in the CSF mild, successful defunctioning surgery and successful proctectomy health states to the same value as patients in the remission health state, including the PAS for darvadstrocel

Treatment	Total QALYs	Total costs (with PAS)	ICER (£ per QALY gained)
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	0.48	£23,639	£49,610

ERG exploratory analysis 8

Table 45: The effect of changing the time-to-event functions on the ICER in the ERG's base case model, including the PAS for darvadstrocel

Time to remission function	**Time to relapse function**	**Total costs**			**Total QALYs**			**ICER**
		Darv	**SC**	**Incr**	**Darv**	**SC**	**Incr**	
Gompertz (base case)	Gompertz (base case)	[redacted]	[redacted]	£23,639	[redacted]	[redacted]	1.40	£16,918
Generalised gamma	Gompertz (base case)	[redacted]	[redacted]	£34,627	[redacted]	[redacted]	1.15	£21,487
Gompertz (base case)	Log-normal	[redacted]	[redacted]	£25,342	[redacted]	[redacted]	0.22	£113,960
Generalised gamma	Log-normal	[redacted]	[redacted]	£25,470	[redacted]	[redacted]	0.19	£134,063

Darv – darvadstrocel; SC – standard care; Incr – incremental difference between darvadstrocel and standard care; ICER - incremental cost-effectiveness ratio; QALYs – quality adjusted life years

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Darvadstrocel for treating perianal fistula in Crohn's disease [ID960]

You are asked to check the ERG report from ScHARR to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Tuesday 3 July 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 : AIC and BIC values for CPC remission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In table 14 page 60, AIC and BIC values for the lognormal parametric function are incorrectly stated as 954.7821 and 954.6920, respectively. These values are incorrect.	AIC and BIC values for log normal parametric function should be corrected. The correct values are 946.6324 and 956.5423 respectively.	These values are used to inform the choice of curve used which can have a large impact on the ICER.	The AIC and BIC values in Table 14 have been amended

Issue 2 : Typographical error – probability of last resort surgery

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 70 the ERG state “In this data source, the probability that a proctectomy was successful was 0.62 and the probability that a defunctioning surgery was successful was 0.80“. This is the wrong way around.	The sentence should read “In this data source, the probability that a proctectomy was successful was 0.80 and the probability that a defunctioning surgery was successful was 0.62.	Use of these incorrect values would impact the ICER.	The typographical errors on page 70 have been amended

Issue 3 : Linkage to CS for health state resource use and costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 17, page 73 refers to Tables 52 and 53 in the CS; this actually refers to tables 50 and 58 in the main dossier and Table 29 in the appendix.	Update table references if deemed appropriate	Factual inaccuracy but no impact	The table references for Table 17 have been amended

Issue 4 : Linkage to CS for percentage of patients receiving each treatment by health state and treatment group

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 18, page 76 refers to Table 54 CS, this actually refers to Tables 52 and 53 in the CS	Update Table references if deemed appropriate	Factual inaccuracy but no impact	The table references for Table 18 have been amended.

Issue 5 : Incorrect values in Table 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 19, page 77 has a number of incorrect values	The correct values for Table 19 are included in the table below with the amended values highlighted in grey.	Factual inaccuracy – correct values used in model so no impact.	The incorrect values in Table 19 have been amended

Table 1: Cost of pharmacological and surgical treatments given to each patient (adapted from CS,[1] Table 54)

Treatment	Unit cost	Doses per item	Source	Doses given in cycle 1	Doses given in subsequent cycles	Cost in cycle 1	Cost in subsequent cycles	Average Cycle cost across 13 model cycles
Darvadstrocel								
Darvadstrocel	[redacted]	1 unit	Takeda	4 units	0 units	[redacted]	£0	Not applicable
Antibiotics								
Ciprofloxacin	£0.089	500mg	BNF	56	56	£4.98	£4.98	£4.98
Metronidazole	£0.195	400mg	BNF	76.20	76.20	£14.88	£14.88	£14.88
Immunosuppressants								
Azathioprine	£0.039	50mg	BNF	91.44	91.44	£3.56	£3.56	£3.56
Methotrexate	£0.054	2.5mg	BNF	28	28	£1.51	£1.51	£1.51
6-MP	£1.966	50mg	BNF	50.80	50.80	£99.88	£99.88	£99.88
Biologics								
Adalimumab	£352.14	40mg	BNF	2	2	£704.28	£704.28	£704.28
Infliximab	£377.00	100mg	BNF	1.81	1.81	£684.01	£684.01	£684.01
Adalimumab dose escalation	£352.14	40mg	BNF	4	4	£1408.56	£1408.56	£1408.56
Infliximab dose escalation	£377.00	100mg	BNF	3.63	3.63	£1368.02	£1368.02	£1368.02
Vedolizumab	£2050	300mg	BNF	1.00	0	£1025	£1025	£78.85
Surgical procedures								
Seton	£0	1 set	Assumption	1	0	£0	£0	£0
Fistulotomy	£1,170.21	1 operation	NICE MIB 102	1	0	£1,170.21	£0	£90.02
Anal plug	£1,170.21	1 operation	Assumed equal to fisulotomy	1	0	£1,170.21	£0	£90.02
Fibrin glue	£724.19	1 set	NICE MIB 105	1	0	£724.19	£0	£55.71
Rectal flap	£1,170.21	1	Assumed equal	1	0	£1,170.21	£0	£90.02

		operation	to fisulotomy					
EUA	£1,170.21	1 operation	NHS reference costs[28]	1	0	£1,170.21	0	£90.02
VAAFT	£1,195.40	1 operation	NICE MIB 102	1	0	£1,195.40	0	£91.95

Issue 6 : Typographical error in Table 29

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 29, page 92 and text on page 102 state that 38.1% of patients in the model have died at the end of the 40 year time horizon, the correct figure is 31.7%	Amend incorrect text if deemed appropriate	Factual inaccuracy but no impact	The incorrect value in Table 28 (referred to as Table 29, page 92) and on page 102 have been amended

Issue 7 : Inconsistency between the text and Table 31 for probabilities of transitioning to last resort surgery

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 31, page 104 and associated text on page 103 are not consistent. The ERG state that patients have a higher probability of transitioning from defunctioning to proctectomy compared with CSF severe to proctectomy. However, Table 31 states an	Please check if these figures are correct. Setting the transition probability from CSF severe to proctectomy to 7.97% and the transition probability from defunctioning to proctectomy to 29.29% changes the ICER for scenario 2C to £23,853 and changes the ICER for the ERG base case to £22,902	This has a small impact on the ICER as discussed.	Neither of these issues are factual errors. In the scenario analysis been discussed when the ERG state that patients have a higher probability of transitioning from defunctioning to proctectomy compared with CSF severe to proctectomy (exploratory

equal probability between defunctioning and protectomy and between CSF severe and proctectomy.			analysis 2d), the annual probability of transitioning from defunctioning surgery to proctectomy is 0.1706 and the annual probability of transitioning from CSF severe to proctectomy is 0.1555. For clarity, additional information has been added to Table 31 regarding which scenario each set of values relate to. The values in Table 31 are correct to 4 decimal places. The full values given by the calibration are: 0.079711872024472 for the annual probability of transitioning from the CSF severe or defunctioning surgery to proctectomy, and 0.292857665170441 for the annual probability of transitioning from CSF severe to defunctioning surgery For clarity, it is now mentioned in the title that the values are given to 4 decimal places. Through checking appendix 3, an amendment has been made to the ERG's description of how to implement exploratory

			analysis 2c on page 129. Step 2 now reads “Do steps 2 to 4 of exploratory analysis 2a” and step 3 now reads “Do steps 2 to 7 of exploratory analysis 2b”. All other steps for implementing exploratory analysis 2 remain the same.

Issue 8 : Inconsistency between Table 31 and the ERG model for probabilities of transitioning to last resort surgery

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 31, page 104 suggests a value of 29.29% as the transition probability from CSF severe to proctectomy. The ERG base case model uses a value of 29.35%.	No change required as this has a minimal impact on the ICER	Factual accuracy but no significant impact.	This is not a factual error, the values in Table 31 are the values used in scenario 2c, not the ERG’s base case. For clarity, the title of Table 31 has been amended so that it is clear that the values in the table only apply to exploratory analysis 2. Also for clarity, a footnote has been added to Table 31 to make it clear that the calibrated values depend on the occupancy of the CSF severe and defunctioning surgery health states. As such, the calibration used to calculate these values may produce

			different results when other exploratory analyses are also implemented.

Issue 9 : Typographical error in text and Table 33 for life years and QALYs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 33, page 108 and associated text suggest 28.78 life years are gained and 16.82 QALYs are gained. These values are incorrect.	The correct values are 28.76 life years gained and 16.85 QALYs are gained. These should be amended in the text and in Table 33.	Factual accuracy but no significant impact.	The values in Table 33 and the associated text on page 108 have been amended.

Darvadstrocel for treating complex perianal fistula in Crohn's disease: A Single Technology Appraisal

Erratum in response to the Factual Accuracy Check

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	Date completed 21/06/2018

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Document 14 (comparing Akaike information criterion [AIC] and Bayesian information criterion [BIC], and by visual assessment).[36] An assessment of the proportional hazards assumption was carried out only for the time to relapse functions, because the remission time-to-event functions for the darvadstrocel and standard care groups were not extrapolated beyond the 1-year follow-up data (CS,[1] page 79).It should be noted that when patients received salvage therapy, the time to remission function was extrapolated. An assessment of other plausible assumptions (e.g. accelerated failure time) were not conducted. In all analyses a treatment effect covariate (either a constant HR or constant acceleration factor, depending on the model type) was included in the statistical models to estimate the treatment effect parameter (the difference between the time-to-event for patients receiving darvadstrocel versus those receiving standard care). Piecewise exponential models were also fitted to the data, however the ERG notes that, it is unclear how these functions were fitted and which goodness-of-fit tests, if any, were conducted in these cases. The Gompertz distributions for time to remission and time to relapse were presented to the company's clinical experts to assess the clinical plausibility of the extrapolation (CS,[1] page 79).

Table 1 presents the AIC and BIC statistics for each of the fitted parametric time-to-event functions. These indicate that when the CPC definition of remission is used, the generalised gamma distribution provides the best fit to the observed time to remission data and the Gompertz distribution provides the best fit to the observed time to relapse data (although there is very little to distinguish between the Gompertz and the log normal models).

Table 1: AIC and BIC statistics for time-to-event functions fitted to data on time to remission and relapse using the CPC definition of remission, excluding the piecewise exponential model (adapted from CS,[1] Tables 32 and 38)

	Remission		**Relapse**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	980.8393	987.4459	539.436	544.606
Weibull	965.6205	975.5305	528.702	536.457
Gompertz	946.2664	956.1763	***517.572***	***525.327***
Log normal	946.6324	956.5423	518.216	525.971
Log logistic	954.7821	964.6920	521.644	529.399
Generalised gamma	***931.1734***	***944.3866***	522.156[a]	532.496[a]

AIC – Akaike information criterion; BIC – Bayesian information criterion; a - the stacy parametrisation used for the generalised gamma rather than the default prentice parameterisation
Text in ***bold and italics*** indicates the lowest value out of the converged time-to-event functions in each column

The appropriateness of the proportional hazards assumption was assessed by examining the log cumulative hazard plot. The log cumulative hazard plot for CPC remission is presented in

for people who had non-active / mildly active luminal Crohn's disease that were not either mild or in remission. The company estimated the proportion of cases that were mild and severe by taking an average of the PDAI score of people with CSF. Patients with missing data or in remission were excluded from these calculations. It was assumed that these probabilities were constant with respect to time.

Probabilities that a proctectomy or defunctioning surgery are successful

The probability that a proctectomy was successful and the probability that a defunctioning surgery was successful were obtained from the St Mark's retrospective cohort study (CS,[1] Appendix Q). In this prospective study, data was collected from 78 consecutive patients who presented with a complex perianal fistula and Crohn's disease at St Marks hospital between from 1st January 2008 to July 1st 2017. Data were collected at baseline, routine visits and study termination (lost to follow up, transferred to another hospital, or patient death). In this data source, the probability that a proctectomy was successful was 0.80 and the probability that a defunctioning surgery was successful was 0.62.

Mortality

The age-dependent probability of death was taken from general population life tables for England and Wales in 2013-15.[26]

HRQoL

The ADMIRE-CD trial[1] did not include a preference-based measure of HRQoL. The CS states that there are no disease-specific measures of HRQoL available for patients with perianal fistula.[1] The only patient reported outcome measure included in ADMIRE-CD was the IBDQ. The company considered whether it was possible to map from the PDAI, CDAI or IBDQ scores obtained in the trial to the EQ-5D. The CS states that there is insufficient conceptual overlap between the content of the PDAI and CDAI, which are considered to be measures of disease activity, and the relevant components of HRQoL.[1] The company cites a mapping study by Buxton *et al.*(2007)[37] which they claim supports the poor performance of CDAI as a predictor of utility. The ERG notes that the mapping algorithms reported by Buxton *et al*[37] were derived and validated in studies that included patients with moderately to severely active Crohn's disease. The company does not consider mapping from IBDQ to be appropriate because IBDQ is focused on luminal disease and not complex perianal fistulae. The ERGs clinical advisors agreed that IBDQ was a Crohn's disease specific measure of health. The company conducted a systematic review of HRQoL studies, but concluded that none of the studies identified were suitable for informing utility values in the model.

The health state utility values (HSUVs) used in the company's model were taken from a vignette study reported by Fountain *et al*.[38] which was funded by Takeda (the full study report is provided in

Table 2: Health state resource use and associated costs used in the company's model (adapted from CS,[1] Tables 50, 58, and appendix Table 31)

	Unit cost		Resource use (number of visits / tests) per 4 weekly cycle								
Resource item	**Cost per item of resource use (£)**	**Source**	**Remission**	**CSF**		**Defunctioning**			**Proctectomy**		
				Mild	**Severe**	**Undergoing**	**S**	**U**	**Undergoing**	**S**	**U**
Healthcare professional resource use											
GP visits	37.00	PSSRU[29]	0.06	0.12	0.14	1.38	0.10	0.21	1.38	0.10	0.25
Gastroenterologist visits	149.76	NHS Reference costs[28]	0.13	0.17	0.31	2.00	0.10	0.31	2.00	0.12	0.31
Surgeon visits	127.09	NHS Reference costs[28]	0.04	0.10	0.22	2.25	0.10	0.29	3.25	0.12	0.48
Nurse appointments	51.15	NHS Reference costs[28]	0.06	0.16	0.27	1.75	0.12	0.35	2.75	0.15	0.56
Nutritionist visits	81.33	NHS Reference costs[28]	0.02	0.02	0.08	0.25	0.04	0.12	0.25	0.06	0.12
Total cost of health care professional visits per four weekly cycle			***£31.70***	***£52.04***	***£99.35***	***£746.38***	***£39.21***	***£117.66***	***£924.62***	***£48.06***	***£154.34***
Monitoring resource use											
Rectal MRI	162.23	NHS Reference costs[28]	0.01	0.06	0.13	1.00	0.02	0.10	1.25	0.04	0.13
Endoscopy	182.10	NHS Reference costs[28]	0.06	0.06	0.13	1.00	0.06	0.13	1.25	0.00	0.06
Stoma care*	1,961.00	NICE TA 329[30]	0.00	0.00	0.00	0.08	0.08	0.08	0.08	0.08	0.08
Computerised tomography	85.56	NHS Reference costs[28]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Colonoscopy	334.76	NHS Reference costs[28]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total cost of monitoring patients per four weekly cycle			***£12.07***	***£19.87***	***£44.60***	***£495.18***	***£164.47***	***£190.83***	***£581.26***	***£157.09***	***£183.19***
Laboratory resource use											
Blood count	1.69	NHS Reference costs[28]	0.15	0.12	0.23	2.25	0.15	0.28	2.50	0.15	0.35
C-reactive protein	1.13	NHS Reference costs[28]	0.17	0.13	0.27	2.25	0.15	0.31	2.50	0.15	0.37

Haemoglobin	3.06	NHS Reference costs[28]	0.17	0.12	0.23	2.25	0.15	0.28	2.50	0.15	0.35
Faecal calprotectin	22.79	NICE DG11[31]	0.13	0.13	0.27	1.50	0.10	0.15	1.75	0.12	0.15
Total cost of laboratory tests per four weekly cycle			***£3.77***	***£7.54***	***£4.05***	***£47.42***	***£3.10***	***£5.19***	***£54.58***	***£3.53***	***£5.56***
Total health state resource use costs per four weekly cycle			**£47.82**	**£75.67**	**£151.49**	**£1288.97**	**£206.78**	**£313.68**	**£1560.46**	**£208.68**	**£343.09**

CSF – chronic symptomatic fistula; S – successful; U – unsuccessful; GP – general practitioner; PSSRU - Personal Social Services Research Unit; NHS – National Health Service; MRI – magnetic resonance imaging; NICE – National Institute for Health and Care Excellence; TA – technology appraisal; DG – diagnostics guidance; * - the unit cost applied is an annual cost

Table 3: Percentage of patients receiving each treatment by health state and treatment group (adapted from CS,[1] Tables 52 and 53)

Treatment mix	Mild CSF			Severe CSF			Rem	Defunctioning		Proctectomy		Sources and assumptions
	DARV	Control	Salvage	DARV	Control	Salvage		S	U	S	U	
Darvadstrocel												
Darvadstrocel	100	0	0	100	0	0	0	0	0	0	0	
Antibiotics												
Ciprofloxacin	29.76	29.76	11.25	29.78	29.78	57.50	0	0	0	0	0	ADMIRE CD trial data
Metronidazole	38.05	38.05	55.28	38.05	38.05	58.75	11.20	18.56	57.81	1.09	32.66	
Immunosuppressants												
Azathioprine	46.23	46.23	46.37	46.23	46.23	47.50	51.32	58.99	46.88	45.01	52.50	ADMIRE CD trial data, clinical expert opinion
Methotrexate	0	0	9.05	0	0	0.5	7.29	0.00	5.84	11.66	0	
6-MP	0	0	7.50	0	0	26.75	10.00	11.88	11.88	0	0	
Biologics												
Adalimumab	33.59	33.59	30.65	33.59	33.59	19.17	31.76	21.32	27.03	12.86	25.47	ADMIRE CD trial data, clinical expert opinion
Infliximab	27.26	27.26	30.65	27.26	27.26	35.83	32.39	21.32	27.03	12.86	25.47	
Adalimumab dose escalation	0	0	5.94	0	0	7.5	4.92	3.38	10.21	0.75	8.75	
Infliximab dose escalation	0	0	5.94	0	0	7.5	4.92	3.38	10.21	0.75	8.75	
Vedolizumab	0	0	8.67	0	0	0	8.24	5.08	7.69	3.36	7.36	
Surgery												
Seton	95	95	20.56	95	95	48.5	5.21	11.54	11.96	0	2.50	ADMIRE CD trial data, clinical expert opinion
Fistulotomy	0	0	1.51	0	0	16.5	0	0	5.84	0	0	
Anal plug	0	0	12.50	0	0	11.25	0	0	0	0	0	
Fibrin glue	0	0	0	0	0	6.25	0	0	0	0	0	
Rectal flap	0	0	0	0	0	12.5	0	0	0	0	0	
EUA alone	0	0	43.09	0	0	0	11.12	6.59	37.38	0	26.43	
VAAFT	0	0	4.52	0	0	0	0	6.73	0	0	0	

CSF – chronic symptomatic fistulae; Rem – remission; DARV – darvadstrocel; Control – standard care; S – successful; U - unsuccessful; EUA, examination under anaesthesia; 6-MP, 6-mercaptopurine.

Table 4: Cost of pharmacological and surgical treatments given to each patient (adapted from CS,[1] Table 54)

Treatment	Unit cost	Doses per item	Source	Doses given in cycle 1	Doses given in subsequent cycles	Cost in cycle 1	Cost in subsequent cycles	Average Cycle cost across 13 model cycles
Darvadstrocel								
Darvadstrocel	[redacted]	1 unit	Takeda	4 units	0 units	[redacted]	£0	Not applicable
Antibiotics								
Ciprofloxacin	£0.089	500mg	BNF	56	56	£4.98	£4.98	£4.98
Metronidazole	£0.195	400mg	BNF	76.20	76.20	£14.88	£14.88	£14.88
Immunosuppressants								
Azathioprine	£0.039	50mg	BNF	91.44	91.44	£3.56	£3.56	£3.56
Methotrexate	£0.054	2.5mg	BNF	28	28	£1.51	£1.51	£1.51
6-MP	£1.966	50mg	BNF	50.80	50.80	£99.88	£99.88	£99.88
Biologics								
Adalimumab	£352.14	40mg	BNF	2	2	£704.28	£704.28	£704.28
Infliximab	£377.00	100mg	BNF	1.81	1.81	£684.01	£684.01	£684.01
Adalimumab dose escalation	£352.14	40mg	BNF	4	4	£1408.56	£1408.56	£1408.56
Infliximab dose escalation	£377.00	100mg	BNF	3.63	3.63	£1368.02	£1368.02	£1368.02
Vedolizumab	£2050	300mg	BNF	1.00	0	£1025	£1025	£78.85
Surgical procedures								
Seton	£0	1 set	Assumption	1	0	£0	£0	£0
Fistulotomy	£1,170.21	1 operation	NICE MIB 102	1	0	£1,170.21	£0	£90.02
Anal plug	£1,170.21	1 operation	Assumed equal to fisulotomy	1	0	£1,170.21	£0	£90.02
Fibrin glue	£724.19	1 set	NICE MIB 105	1	0	£724.19	£0	£55.71
Rectal flap	£1,170.21	1 operation	Assumed equal to fisulotomy	1	0	£1,170.21	£0	£90.02
EUA	£1,170.21	1 operation	NHS reference costs[28]	1	0	£1,170.21	0	£90.02
VAAFT	£1,195.40	1 operation	NICE MIB 102	1	0	£1,195.40	0	£91.95

BNF – British National Formulary; 6–MP - 6-mercaptopurine; NICE – national institute for health and care excellence; MIB – Medtech Innovation Briefing; EUA – examination under anaesthesia; VAAFT - video-assisted anal fistula treatment

support differential discounting.[10] In scope analyses using discount rates of 3.5% for both costs and QALYs and 1.5% for both costs and QALYs were provided by the company at clarification.[2]

Table 5: Adherence of the company's model to the NICE Reference case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The model reflects people with non-active / mildly active luminal Crohn's disease and complex perianal fistulae. However, a subgroup of the patient population whose complex perianal fistulae have more than two internal openings or more than three external openings are not considered within the company's analysis of the available evidence or the company's submitted model. It is unclear whether this missing population is included within the licence population for darvadstrocel (see Section **Error! Reference source not found.**)
Comparator(s)	As listed in the scope developed by NICE	The company's model compares darvadstrocel against standard care surgical interventions combined with associated medical management.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are modelled in terms of QALYs gained.
Perspective on costs	NHS and PSS	The model takes an NHS and PSS perspective
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's economic evaluation takes the form of a cost-utility analysis. The results of the analysis are presented in terms of the incremental cost per QALY gained for darvadstrocel versus standard care
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 40-year time horizon. By this time point, only 31.7% of people have died in each group.
Synthesis of evidence on health effects	Based on systematic review	Based on the ADMIRE-CD study, which is the only study of the effectiveness of darvadstrocel in this population at the dose stated in the marketing authorisation.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health effects are expressed in QALYs. A vignette study, using time-trade off (TTO) valuations by members of the general public was used to inform HRQoL parameters in the model. EQ-5D data were not available from the ADMIRE-CD trial and mapping from the trial outcomes to the EQ-5D was not considered appropriate by the company.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No. The utility values used in the model were based on vignettes, not a description of HRQoL provided directly by patients. Patients did have input into the health state descriptions.

Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes. The vignette study used a representative sample of the UK population to value the health states using the time trade off method. Patient valuations of the vignettes using TTO methodology were considered in a scenario analysis
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity rating is applied to estimate QALY gains
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource components include those relevant to the NHS and PSS. Whilst not explicitly stated in the CS, unit costs are valued in 2016/17 prices
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	The base case in the CS used 3.5% discounting for costs and 1.5% discounting for benefits, as the company claims that Section 6.2.19 of the NICE Methods Guide applies (see Section **Error! Reference source not found.**).[10] In response to clarification question B7, the company provided analyses where both health effects and costs are discounted at 3.5% and analyses where both the health effects and costs are discounted at 1.5%.

5.3.3 Model validation and face validity check

The ERG rebuilt the deterministic version of the company's base case model in order to verify its implementation. **Error! Reference source not found.** shows that the ERG's rebuilt model produces very similar estimates of undiscounted life years gained, health gains, costs and cost-effectiveness. This double-programming exercise led to the identification of three minor implementation errors:

i. When estimating the average risk of relapse and the average risk of remission across weeks 104 to 164, to inform the long-term relapse and remission rates, the company divides by 16 instead of 15 cycles.

ii. The per-cycle probability of all-cause mortality was subject to a minor error which led to a small over-prediction of the number of deaths throughout the model time horizon.

iii. The long-term remission rates in the salvage therapy arm were specific to the standard care arm time-to-event function, not the salvage therapy time-to-even function.

three of seven experts at the UK Advisory Board felt that the utility values for the CSF with mild symptoms state were underestimated (CS,[1] Appendix P); this issue was also noted by one of the ERG's clinical advisors. In addition, one of the clinical advisors to the ERG believed that the utility values for a successful outcome following surgery were underestimated; this would underestimate the benefits to patients of a successful surgical procedure.

The report by Fountain *et al*. (2017)[38] (which is provided in the CS,[1] Appendix R) assessed the external validity of the estimates derived from the vignettes by comparing them to values reported in the literature from 21 studies. Seventeen of these studies focussed on Crohn's disease and four studies focussed on IBD or UC but reported surgical states which are similar to the surgical states described in this study.[38] Seven of these studies reported values obtained from the EQ-5D (Richards 2001[43], Kuruvilla 2012[44], Casellas 2005[45], Stark 2010,[46] Benedini 2012[47], Casellas 2000[48], Casellas 2007[49]). Fountain *et al*. (2017)[38] conclude that *"all health states valued in [the vignette] study had lower utility estimates than other studies reporting utilities in Crohn's disease; however it is not possible to make direct comparisons due to the lack of data for many of the specific states and conditions included in [the vignette] study".* The ERG noted in particular, that many of the studies estimating the utility values in patients following surgical intervention gave higher utility estimates than the utilities for those patients with positive surgical outcomes estimated in the Fountain *et al*. vignette study. In particular, in the study by Casellas *et al*.(2000)[48], the EQ-5D estimates for patients in remission following surgery were much closer to those for patients in medically induced remission (median values of 0.87 vs 0.86, respectively in Casellas 2000). This suggests that the benefits to patients of defunctioning or proctectomy surgery may be underestimated in the company's model. However, the ERG accepts that any differences between the utility values obtained in the vignette study and those identified from the literature may be due to differences in the population studied, as few of the studies were specific to patients with mildly or inactive Crohn's disease and complex perianal fistulea. Fountain *et al*.[38] also state, "*Lower utility estimates could have been generated because of use of condition specific vignettes (as opposed to generic measure) that may cause a focussing effect, whereby attention is drawn to health problems that may not be considered as so severe when placed in the context of a broader description of health (Brazier and Tsuchiya, 2010).*[50]" This supports the ERG's concern regarding the use of a non-Reference Case method of measuring utility. The potential impact of this on the ICER is explored in the ERG's exploratory analyses (see Section **Error! Reference source not found.**)

5.3.4.11 Adoption of a 40-year time horizon

The ERG noted that in the company's submitted model only 31.7% of people in the model are in the death health state at the end of the model's 40-year time horizon. The ERG considers that it is possible that the company's base case model may not capture all important differences in costs and QALYs between darvadstrocel and standard care. The company did submit a scenario analysis in

Table 6: Comparison of three different annual transition probabilities, to four decimal places, used in the company's base case analysis and those used in exploratory analysis 2

Transition		Annual probabilities		
From health state	**To health state**	**Values used in the company's base case model**	**ERG calibrated values[a] (Exploratory analysis 2c)**	**St Mark's retrospective data (Exploratory analysis 2d)**
CSF severe	Defunctioning surgery	0.0375	0.2929	0.1975
CSF severe	Proctectomy	0.0385	0.0797	0.1555
Defunctioning surgery	Proctectomy	0.0385	0.0797	0.1706

ERG –evidence review group; CSF – chronic symptomatic fistulae
a – these values are from the calibration of the company's model to both the proctectomy and defunctioning surgery data. These values depend upon the health state occupancy of the CSF severe and defunctioning surgery health states, so the calibration used to calculate these values may produce slightly different results when other exploratory analyses are also implemented.

Exploratory analysis 3: Long-term remission rate for salvage therapy

The ERG had concerns that the long term rate used to extrapolate the company's curves had a treatment effect applied between the darvadstrocel and standard care groups but did not have a treatment effect applied between the standard care and salvage therapy groups (see Section **Error! Reference source not found.**). This resulted in the long term extrapolation rates being the same for the standard care and salvage therapy groups, whilst the rates differed for the darvadstrocel group. In this sensitivity analysis the ERG amended the long term rates so that the long term rates were based on the salvage therapy time to event functions and not on the standard care time to event functions.

Exploratory analysis 4: Setting the model time-horizon to 60 years

As the ERG believes that a longer-term (60 year) time-horizon is more appropriate than the shorter term time horizon applied in the company's base case (40 years). This analysis by the ERG replicates the company's analysis of the model time horizon presented in **Error! Reference source not found.**.

The ERG's preferred base case model

The ERG's preferred base case model combines ERG analyses 1, 2c, 3 and 4. Unless otherwise stated, all subsequent analyses start from the ERG preferred base case analysis and include discounting of 3.5% for both costs and QALYs.

Exploratory analysis 5: Exploration of the extent to which darvadstrocel restores people with complex perianal fistulae and Crohn's disease to near full health

The ERG has concerns about whether darvadstrocel meets two of the criteria set out in the NICE Methods Guide for the Committee to consider using discount rates of 1.5%. These are that over a long period of time (usually 30 years): (1) currently people will die or have a very severely impaired quality of life; and (2) the treatment restores these people to full or near full health.

Exploratory analysis 5: Analysis of the extent that darvadstrocel restores people with complex perianal fistulae and Crohn's disease to near full health

Table 7 shows that in the ERG's preferred model over a 30-year time horizon; patients in both treatment groups accrue 28.82 life years; patients in the standard care group accrue [redacted] undiscounted QALYs, and; patients in the darvadstrocel group accrue [redacted] undiscounted QALYs. This results in darvadstrocel accruing an average utility of [redacted] per year and standard care accruing an average utility of [redacted] per year. These two values correspond to [redacted] and [redacted] of the utility value for the remission health state, respectively.

The equivalent values using the company's base case model show that over a 30-year time horizon; patients in both treatment groups accrue 28.76 life years; patients in the standard care group accrue [redacted] undiscounted QALYs, and; patients in the darvadstrocel group accrue [redacted] undiscounted QALYs. This results in darvadstrocel accruing an average utility of [redacted] per year and standard care accruing an average utility of [redacted] per year. These two values correspond to [redacted] and [redacted] of the utility value for the remission health state, respectively.

Table 7: Assessment of the proportion of health achieved in each model arm using the company's and the ERG's base case model over a 30-year time horizon and a 0% discount rate

Treatment	Undiscounted life years	Undiscounted QALYs	Mean utility accrued per year	Highest health state utility value	Percentage of maximum health achieved
Company's base case model					
Standard Care	28.76	[redacted]	[redacted]	0.865	[redacted]
Darvadstrocel	28.76	[redacted]	[redacted]	0.865	[redacted]
ERG's base case model					
Standard Care	28.82	[redacted]	[redacted]	0.865	[redacted]
Darvadstrocel	28.82	[redacted]	[redacted]	0.865	[redacted]

QALYs – quality-adjusted life years

On the basis of these results the ERG believes that: (1) the average patient with complex perianal fistulae and Crohn's disease does not have a very severely impaired quality of life when treated with standard care and (2) that darvadstrocel does not restore the average patient with complex perianal fistulae and Crohn's disease to full or near full health. As such, the ERG considers that darvadstrocel does not meet the criteria described in Section 6.2.19 of the guide to the NICE Methods Guide.[10] Consequently, the ERG believes that costs and QALYs should be discounted at a rate of 3.5% for both costs and QALYs.

Exploratory analysis 2

1) For all parts of exploratory analysis 2, enable the solver add in to Excel, if you have not already done so.

2a) Proctectomy

1) Start with the Company's model
2) Go to Sheet "Clinical inputs" cell E128, change the formula to "='Patient flow-Control'!$E$2"
3) Go to Sheet "Clinical inputs" cell E127, change the formula to "='Patient flow-Control'!$E$2"
4) Go to Sheet "Clinical inputs" cell E125, change the formula to "='Patient flow-Control'!$E$2"
5) Go to the sheet Patient flow-Control'
6) Open solver and use the following settings:
    a. Set objective HL$84
    b. To: value of 0.2068965517 (18/87 to 10 dp)
    c. By changing variable cells: $E$2
    d. No constraints
    e. Solving method: GRG Nonlinear

2b) Defunctioning

1) Start with the Company's model
2) Go to Sheet "Clinical inputs" cell E111, change the formula to ='Patient flow-Control'!$F$2
3) Go to Sheet "Clinical inputs" cell E113, change the formula to ='Patient flow-Control'!$F$2
4) Go to Sheet "Patient flow-Control"
5) Go to cell G2 and input the following formula "=HK214"
6) Go to cell H2 and input the following formula: "=-(LN(1-G2))/16"
7) Go to cell I2 and input the following formula "=1-EXP(-H2*1)"
8) Set up solver with the following settings
    a. Set objective I2
    b. To: value of 0.03752771 (value given elsewhere in the model for the annual probability of undergoing a defunctioning surgery)
    c. By changing variable cells: $F$2
    d. Constraints: $F$2 ≤ 1
    e. Solving method: GRG Nonlinear

2c)

1) Start with the Company's model
2) Do steps 2 to 4 of exploratory analysis 2a
3) Do steps 2 to 7 of exploratory analysis 2b