For public observers

NICE National Institute for Health and Care Excellence

Darvadstrocel for treating complex perianal fistula in Crohn's disease

Lead team's presentation

1st appraisal committee meeting
Committee A
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ERG: School of Health and Related Research (ScHARR), Sheffield
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Company: Takeda

19.07.2018

Clinical effectiveness

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Key issues: clinical effectiveness

- Some potential patient groups are absent from the trial:
  - people with more than two internal openings or more than three external openings
  - people with recurrent/new fistulae
- In the NHS, in whom would darvadstrocel be used?
  - How would they be defined?
  - Would it be used only after biologic therapy had failed?
- Generalisability to UK population- ADMIRE-CD trial did not include patients from the UK
- Does the ADMIRE-CD control group represent current UK clinical practice?
- 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. The cost effectiveness results are driven by the long term effectiveness/cure of fistulae, what is the committee's view of this?
- If recurrence has been avoided for 2 years will the remission be sustained?
- Does the committee accept that the clinical trial evidence shows darvadstrocel to be more effective than standard of care?
- The model uses a post hoc definition of remission, using a combined clinical and patient assessment of healing and symptoms (CPC) which was not the primary endpoint in the trial in which remission was defined as clinical and MRI scan evidence of healing. What is the committee's view of this?

[redacted]

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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 fistulae
- A perianal fistula is an abnormal connection between the bowel and the skin near the anus.
- Symptoms 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 common
- 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

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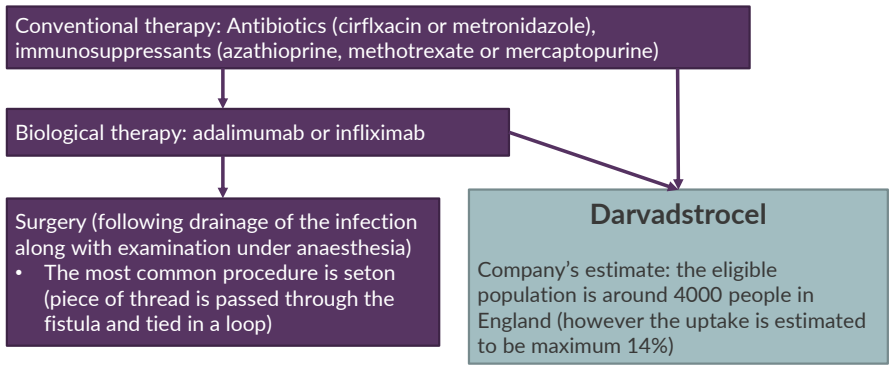
Treatment pathway

for non-active/mildly active luminal Crohn's disease with fistula

- Aim of treatment is to treat and drain the underlying infection and heal the fistula.



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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

[redacted]

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Typographical error corrected on the slide after committee meeting.

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)	• Combined remission (Primary pre-specified) • Clinical and Patient Centred (CPC) remission (Post hoc) • Clinical remission (Pre-specified) • AEs of treatment • HRQoL	Clinical outcomes presented as per ADMIRE-CD clinical trial. CPC endpoint considered more patient-relevant **ERG comments**: Continence was not reported. Clinical advisers stated that it is unlikely to differ between the two arms.

Technology darvadstrocel

UK approved name	Darvadstrocel (Brand name: Alofisel)
Mechanism of action	Suspension of allogenic expanded human adipose-derived stem cells. Have the potential to regulate the function of immune-cells (B & T lymphocytes, neutrophils, NK & monocyte-derived dendritic cells) Results in local immunosuppression.
Marketing authorisation	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.
Method of administration and dosage	2 vials (60 million cells) is injected into the fistula walls along the length of the fistula tract and another 2 vials around the internal opening during examination under anaesthesia (EUA). Darvadstrocel will be added to current standard care 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

Patient's perspective (I)

Crohn's and Colitis UK

- "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.... Just wiping your bottom can make you cry, catching a seton string can be agony..."
- Living with or caring for someone with perianal fistula can have a profound and detrimental impact on physical, emotional and social wellbeing including, but not limited to:
- Severe pain; restricted mobility and activities; loss of confidence; low self esteem; altered body image; anxieties relating to social and sexual relations, treatment, the future.
- Negative impact on sexual life for men and women with this condition and their partners.
- Managing a fistula is an involved and painful activity. "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 consider that physical and psychological support is variable.

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Patient's perspective(II)

Crohn's and Colitis UK

- Effective treatment options for perianal fistula are limited and suboptimal.
- "It has left me at times contemplating suicide to make it stop."
- Many individuals wish to avoid surgical options and subsequent complications, including potential reduction in fertility, incontinence, infection, damage to the anal sphincter muscles and reoccurrence of the fistula, especially when surgery does not offer a definitive cure.
- Darvadstrocel "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."
- 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.

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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.

[redacted]

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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. Assessments were performed by gastroenterologist and radiologist blinded to treatment allocation.	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.	Darvadstrocel 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)

[redacted]

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Outcomes in ADMIRE-CD trial

Primary endpoint

- Combined remission at week 24 (clinical remission and MRI assessment)

  Clinical remission = closure of all treated external openings that were draining
  MRI remission = absence of collections > 2 cm of the treated perianal fistula in at least two of three dimensions, confirmed by masked central MRI reporting .
  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 for patients should include a component of pain and discharge in addition to clinical remission
- Therefore post hoc endpoint of CPC remission defined.
  - clinical remission as judged by clinician **plus** the patient does not experience any pain or discharge, as determined by a zero score in both the pain and discharge dimensions of the PDAI
    (no MRI assessment was included)
- Analysed as
  - Time to CPC remission
  - Time to CPC relapse (time to relapse from CPC remission)

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Secondary outcomes in ADMIRE-CD

- Clinical remission (clinical assessment only by week 24)
- Response (closure of at least 50% of external openings that were draining at baseline by week 24)

- Various exploratory other secondary outcomes, including severity scores: PDAI, IBDQ, CDAI and Van Assche score at week 24, 52 and 104
- Safety analyses (throughout the study)
- Clinical remission (week 52 and 104)

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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
- However, both the company's and the ERG's clinical experts considered CPC remission the most relevant way to measure remission and relapse
- 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.

[redacted]

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St Mark's study

- Retrospective cohort study, used to externally validate the results from ADMIRE-CD and calculate transition to the proctectomy (major surgery) state.
- N=78 consecutive patients who presented at St Mark's hospital (UK), between January 2008 and July 2017.
- Enrolled people with complex perianal fistulae who would have been eligible for treatment with darvadstrocel.
- Patient characteristics are presented on the next slides.

[redacted]

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Patient characteristics (I)

		ADMIRE-CD		St Mark's study
Baseline characteristic ITT population		Darvadstrocel (N=107)	Control (N=105)	(N=78)
Gender, male, n (%)		56%	53%	[redacted]
Ethnic origin, n (%)	Caucasian	93%	91%	
CD treatment in past 6 months, any, n (%)	Antibiotics	77%	70%	
	Immunos.	83%	73%	
	Anti-TNF	78%	80%	
Background CD treatment (stratification factor), n (%)	Anti-TNF	35%	31%	
	Immunos.	15%	21%	
	Anti-TNF AND Immunos.	26%	30%	
	Neither	24%	18%	
Prior or current treatments (in St Mark's study prior or current treatments were presented together)	Anti-TNF Immunos. Anti-TNF and Immunos. None			[redacted]

Abbreviations: CD - Crohn's disease; SD - Standard deviation; TNF - Tumour necrosis factor, NR - Not reported; Immunos. – immunosuppressants
Source: Table 9 of Company Submission

[redacted]

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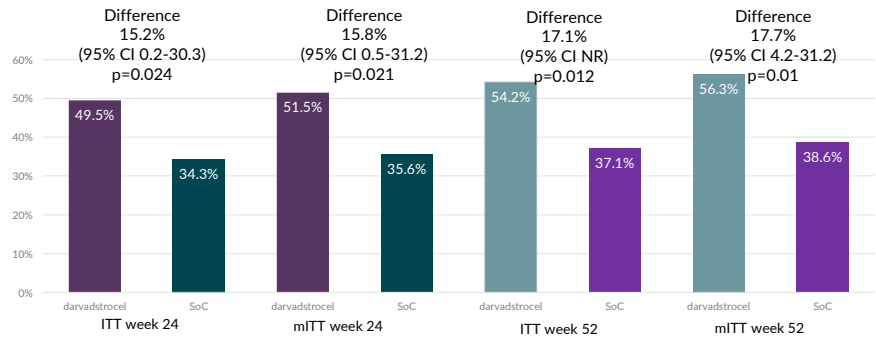
Results - Primary endpoint

Combined remission (clinical and MRI)

More patients in the darvadstrocel group achieved statistically significant combined remission at week 24 in the ITT (n=212) **49.4% vs 34.3%**
Also in modified ITT (all patients who received study treatment and had at least one efficacy assessment, n=204).
Improvement maintained at week 52.



Abbreviations: CI, Confidence interval; (m)ITT, (Modified) intention-to-treat; SoC, standard of care; w, week; NR, not reported

[redacted] Source: figure 8 and tables 12 and 13 of company submission B

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Results - Primary and key secondary outcome, ITT population, week 24 follow-up (shortened)

	Darvadstrocel (N=107)	Control (N=105)
Combined remission (clinical remission and MRI)		
Combined remission, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI)	0.74* (0.48, 1.14)	
Response		
Response, n (%)	[redacted]	[redacted]
Hazard ratio (95% CI)	0.59* (0.43, 0.81)	

Abbreviations: CI, Confidence interval; ITT, Intention-to-treat
*Hazard ratio below 1 indicates more patients with remission (i.e. better results) on the darvadstrocel arm
Source: Table 15 company submission B and table 6 of ERG report

[redacted]

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Results - post hoc analyses (used in model)

	Darvadstrocel	Control
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%)
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%)
P-value	p=0.0262	

CI, Confidence interval; CPC, Clinical and patient-centric
Source: Table 8 of ERG report and section B.2.6.4.1 of Company Submission

As a reminder, results for Combined remission: 49.5% darvadstrocel vs 34.3% SoC

[redacted]

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Results - Disease severity

mITT population of ADMIRE-CD

Outcome	Darvadstrocel (n=103)	Change from baseline	Control (n=101)	Change from baseline	Treatment difference (95% CI)	p-value
Perianal Disease Activity Index (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
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

CI, Confidence interval; mITT, Modified intention-to-treat; SD, Standard deviation; NR, not reported
Source: Table 17 of Company Submission and Table 7 of ERG report

[redacted]

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Safety and adverse events

Number patients (%)	Week 24		Week 52	
	Darvadstrocel N=103	Control N=102	Darvadstrocel N=103	Control N=102
TEAEs	66.0%	64.7%	76.7%	72.5%
Proctalgia	12.6%	10.8%	**14.6%**	**11.8%**
Anal abscess	11.7%	12.7%	**19.4%**	**13.7%**
Anal fistula	3%	6%	10.7%	7.8%
Nasopharyngitis	9.7%	4.9%	10.7%	4.9%
Treatment-related TEAEs	17.5%	29.4%	20.4%	26.5%
Withdrawn due to AEs	4.9%	5.9%	8.7%	8.8%
Treatment-related TESAEs in ≥2% of patients				
TESAEs	5%	7%	6.8%	6.9%
Anal abscess/fistula	5%	5%	6.8%	4.9%

AE, Adverse event; TEAE, Treatment-emergent adverse event
Source: table 22 of Company submission B; Table 11 of ERG report

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

[redacted]

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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

[redacted]

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Key issues: clinical effectiveness

- Some potential patient groups are absent from the trial:
  - people with more than two internal openings or more than three external openings
  - people with recurrent/new fistulae
- In the NHS, in whom would darvadstrocel be used?
  - How would they be defined?
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- Generalisability to UK population- ADMIRE-CD trial did not include patients from the UK
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[redacted]

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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 remission and time to relapse post 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

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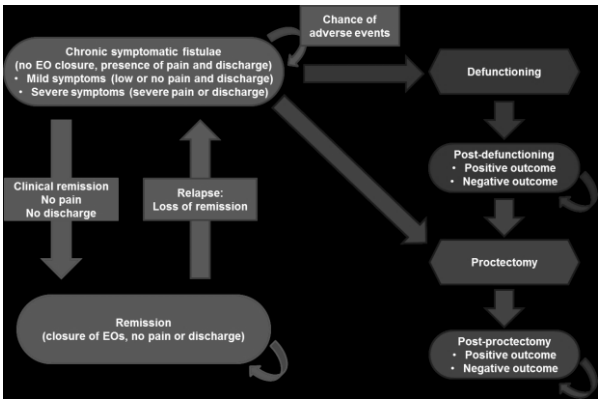
Model structure by company

- The model assumes one single administration of darvadstrocel and no retreatment at recurrence
- Subsequent treatment: Salvage therapy (Seton and EUA) or last resort surgery
- Background therapy: immunosuppressants, biologics, antibiotics



Perspective: NHS/PSS
Time horizon: 40 years
Cycle length: 4 weeks
Discount rate
- 3.5% for costs
- 1.5% for QALYs

Mean age: 38.27 years

ERG critique:
- Time horizon: By 40 years only 31.7% of patients were dead. ERG explored the impact of using a 60-years time horizon in exploratory analysis 4
- Using 1.5% discount rate for QALYs is not appropriate.

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Discount rate

- Company suggests to use 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 criteria:
  - when treatment restores people who would otherwise die or have a very severely impaired life 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
- The NICE Guide to the methods of technology appraisals does not support differential discounting of costs and QALYs
- The ERG conducted an exploratory analyses examining the extent to which darvadstrocel restores people with complex perianal fistulae to near full health
- The results show that 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 that darvadstrocel does not restore the average patient with complex perianal fistulae and Crohn's disease to full or near full health (also see Table 33 of ERG report). Therefore the ERG considers that a 3.5% discount rate should be used for costs and benefits.

[redacted]

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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
Source: table 67 of company submission and company response to clarification question B7, table 24.

[redacted] 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.

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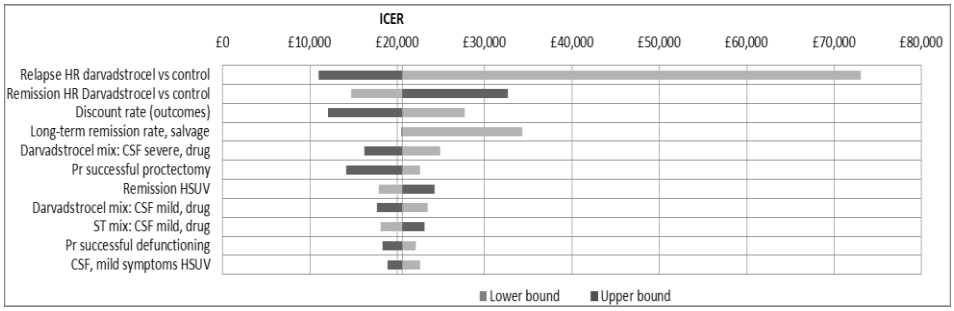
Tornado diagram one way sensitivity analyses, using 3.5% discount rate



Source: Company clarification response B7, figure 20

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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 proctectomy surgery	Bell et al. prospective study

[redacted]

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Main issues identified by the ERG

- Selection of time-to-event functions (Gompertz used in base case by the company):
- 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
- Wastage of darvadstrocel

[redacted]

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Impact of alternative curves for modelling time to remission and time to relapse post CPC remission

ERG critique:

- Not adjusting for interval censoring might lead to bias, however it is unknown in which direction
- The ICER is 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
- ERG explored the impact of using Generalised gamma curve instead of Gompertz for time to CPC remission
- And using Log-normal curve instead of Gompertz for time to relapse post CPC remission
- Changing the time to CPC remission curves had only minor effect, but using log-normal for time to relapse had major effect on the ICER (Figures to follow in ERG exploratory analysis 8) suggesting that the curve chosen is a major driver of the cost effectiveness

[redacted]

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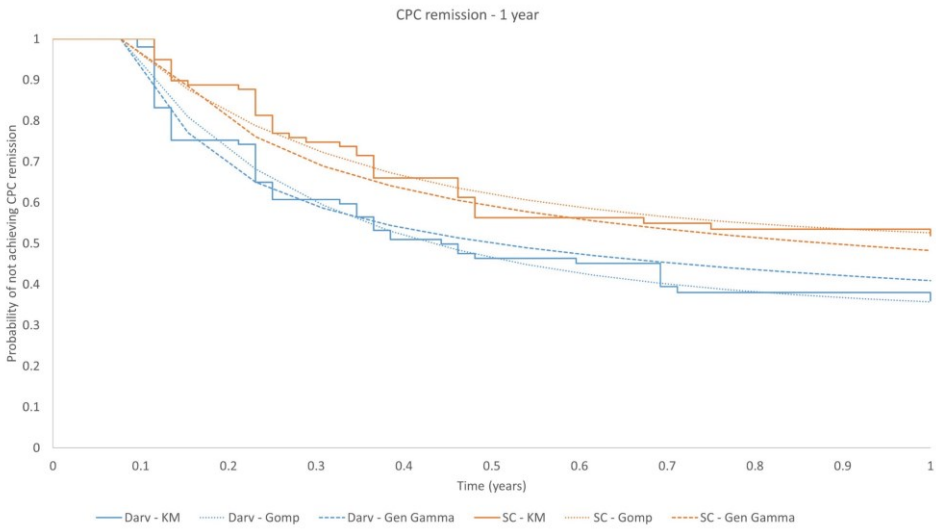
Parametric curves for CPC remission



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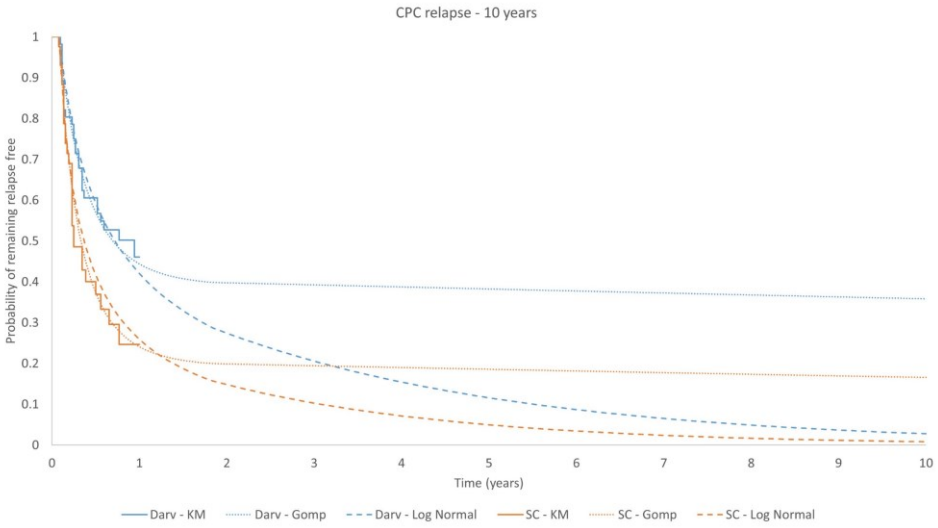
Parametric curves for CPC relapse



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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.

[redacted]

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ERG critique on assumptions for subsequent therapies

- Elicitation of time to relapse and remission for people on salvage therapy (methodological rigour and design of the expert elicitation)
- Transitions to the defunctioning and proctectomy health states: the model outputs do not match the data used to populate the model
- Data from the St Mark's study suggest that it was possible for people with:
  - 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
- Adding these transitions to the model was explored in ERG exploratory analysis 2.

[redacted]

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Modelling health-related quality of life

- No relevant health-related quality of life (HRQoL) measurement was included in ADMIRE-CD trial
- HRQoL is principally determined by the time spent in the different model health states, driven by time to remission, time to relapse and timing of defunctioning surgery or proctectomy and is split between mild and severe CSF
- Utility values were derived from a vignette study (Fountain et al.)
- Health state descriptions were derived with the input of patients and clinicians, valued using a time-trade off (TTO) methodology by a sample of the general public (n=835) and a sample of patients with Crohn's disease (not specifically CSF n=162) Values generated by the general public sample used in the company's base case; values from Crohn's disease patients explored in a sensitivity analysis.
- Utility decrements for treatment emergent adverse events were applied (for proctalgia and anal abscess), resulting in different HRQoL in the mild CSF and severe CSF health states.

[redacted]

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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 (CSF)	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	[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]
Source: table 16 of ERG report, adapted from table 46 of company submission					

[redacted]

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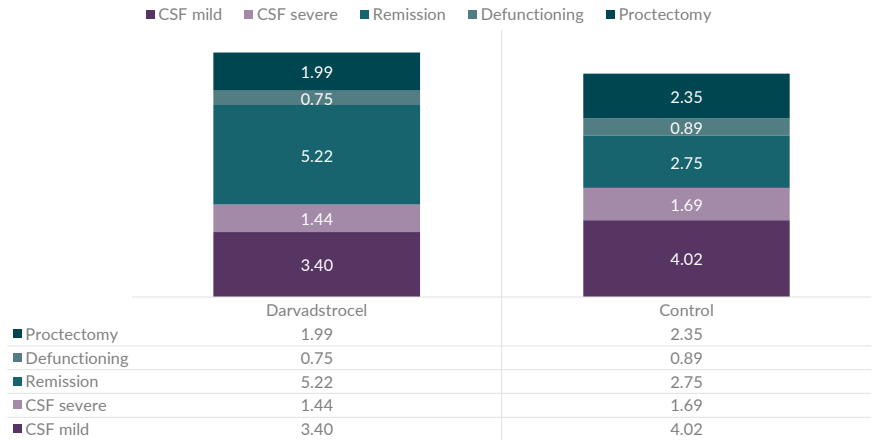
Total QALYs accrued by health state company's model, using 3.5% discount rate



	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

[redacted]

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ERG critique on utility values

- ERG agrees with not mapping IBDQ to EQ-5D from the ADMIRE-CD trial because not a relevant measure (relates to luminal disease)
- Using utility values obtained from 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).

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Costs and health care resource use

- Unit costs were based on NHS Reference Costs 2016-17, the Personal Social Services Research Unit (PSSRU), NICE TA329 and NICE DG11
- Health care resource use in each 4-weekly cycle was based on the ADMIRE-CD trial and/or clinical expert opinion
- The only difference in the model pathways between the costs 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).

ERG critique:

- 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.

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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

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**

Reminder of utility values

Health state		Mean utility
Remission		**0.865**
Chronic symptomatic fistulae (CSF)	Mild symptoms	**0.578**
	Severe symptoms	0.383
Abscess		0.223
Defunctioning	Undergoing	Assumed equal to CSF with severe symptoms
	Successful	**0.567**
	Unsuccessful	0.193
Proctectomy	Undergoing	Assumed equal to CSF with severe symptoms
	Successful	**0.564**
	Unsuccessful	0.202

[redacted]

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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]		£23,378	[redacted]		1.01	£23,176
Generalised gamma	Gompertz (base case)	[redacted]		£24,033	[redacted]		0.82	£29,200
Gompertz (base case)	Log-normal	[redacted]		£25,084	[redacted]		0.21	£119,514
Generalised gamma	Log-normal	[redacted]		£25,146	[redacted]		0.18	£143,131

[redacted]

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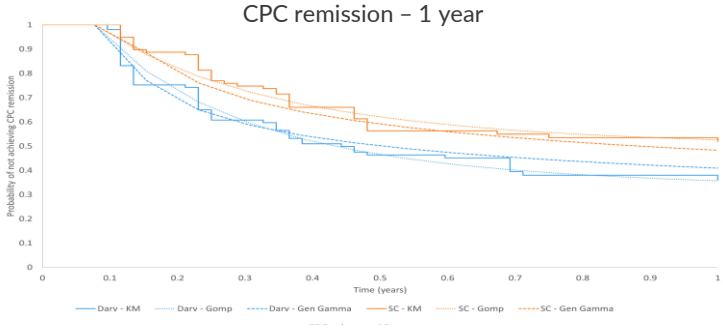
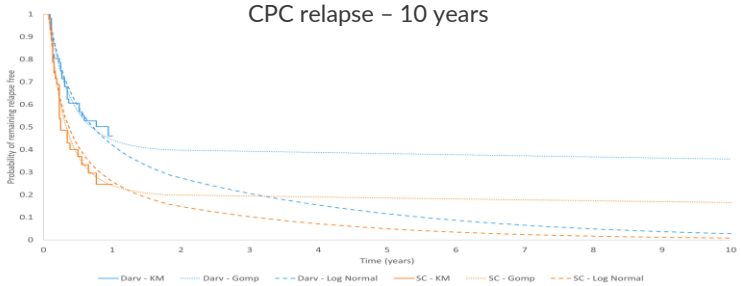
Reminder of parametric curves for CPC remission and relapse

CPC remission – 1 year



CPC relapse – 10 years



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Innovation & equality

- 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 & represents a new and novel treatment paradigm, and will be the first licensed allogenic stem cell treatment in the UK
- 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

[redacted]

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