For public observers

NICE National Institute for Health and Care Excellence

Darvadstrocel for treating complex perianal fistula in Crohn's disease

Chair's presentation

2nd appraisal committee meeting 18.09.18
Committee A
Lead team: Paul Robinson, Brian Shine and Pamela Mary Rees
ERG: School of Health and Related Research (ScHARR), Sheffield
NICE technical team: Boglarka Mikudina, Joanna Richardson
Company: Takeda

Key issues for consideration

- The committee noted that the benefit of darvadstrocel appeared 'modest' compared with placebo, and the long term effectiveness unknown. Is the committee more confident about the long term benefits of darvadstrocel in light of the new evidence from the literature search and Delphi-panel questionnaire?
- What is the likely position the darvadstrocel in the treatment pathway? Would it only be used in people who are getting maintenance anti-TNF therapy?
- Is the eligible population in the NHS in line with the trial population?
- Many of those who had a remission relapsed within 1 year (50.8% on darvadstrocel). No reliable trial data is available beyond 1 year, and the predicted rate of relapse is the major driver of the cost effectiveness model.
  What is the most plausible extrapolation method for modelling long term recurrence rates? Are the additional evidence by the company useful for updating the modelling and producing more reliable estimates?

[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. A complication of such tissue damage is the development of perianal fistulae
- Symptoms include skin irritation around the anus, pain, passing of blood or pus when having a bowel movement and leakage of faecal matter
- Fistulas are described as simple or complex depending on the location and whether there is a singular fistula tract or interlinking connections
- 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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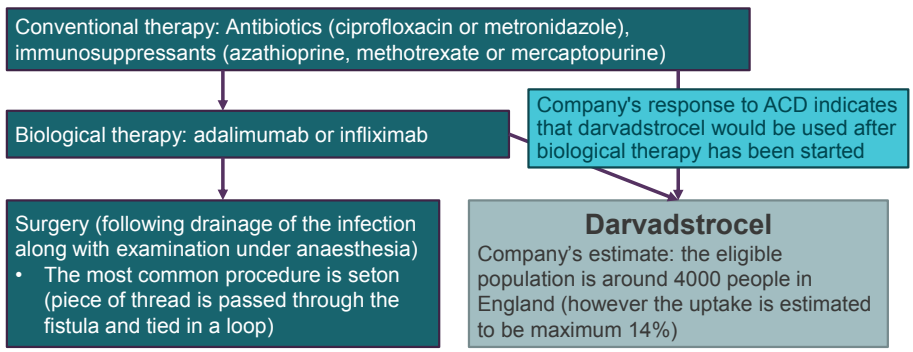
Treatment pathway

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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Darvadstrocel (Alofisel)

Mechanism of action	Suspension of allogenic expanded human adipose-derived stem cells. Has the potential to regulate the function of immune-cells Results in local immunosuppression.
Marketing authorisation **(March 2018)**	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.
Method of administration and dosage	2 vials (60 million cells) are injected into the fistula 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 Patient Access Scheme has been approved by the Department of Health and Social Care

ACD Preliminary recommendation:
Darvadstrocel is not recommended, within its marketing authorisation, for previously treated complex perianal fistulas in adults who have non-active/mildly active luminal Crohn's disease

[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)

Post hoc analyses of outcomes

- Based on feedback from clinicians, the patient assessed outcomes should be included
- Post hoc endpoint of 'clinical and patient-centric (CPC) remission defined.
  - clinical remission **plus** the patient does not experience any pain or discharge (no MRI assessment was included)
- Analysed as
  - Time to CPC remission
  - Time to CPC relapse (time to relapse from CPC remission)

ACD conclusion (section 3.7)

- Using CPC remission is appropriate.
- However concerns were raised that these outcomes were defined post hoc and that the trial was not powered to detect changes in these outcomes.

[redacted]

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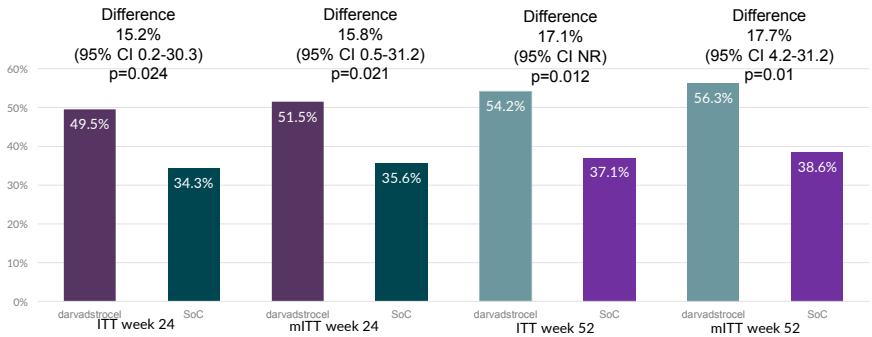
Results - Primary endpoint

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 – CPC remission (used in model)

	Darvadstrocel	Control	Difference
CPC remission			
Patients at risk	N=107	N=105	
CPC remission, n (%)	59 (55.1%)	43 (41.0%)	16 (14.1%)
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%)	2 (-9%)
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

ACD conclusion (section 3.8)

- ADMIRE-CD shows a benefit of darvadstrocel compared with placebo but this is not large, and there are uncertainties about how long the benefit will be maintained
- The additional CPC remission rate (14.1%) is disappointingly modest
- Data are also only reliable up to 52 weeks although lifetime benefit

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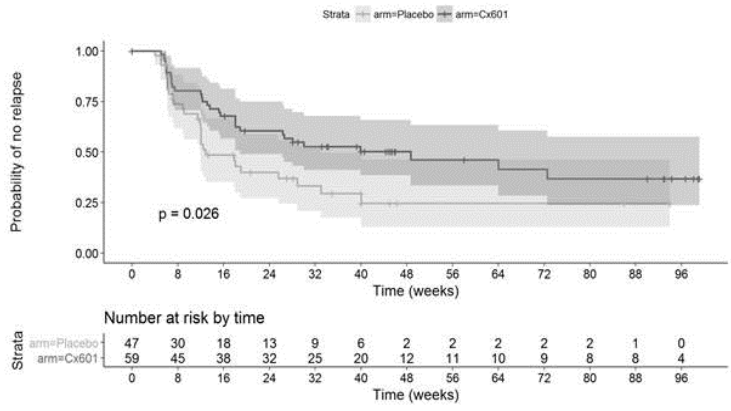
Time to relapse from CPC remission, ITT population



[redacted] Source: figure 12 of company submission B

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Committee's considerations - clinical issues

- The evidence on the natural history of the disease and outcome of current practice in the UK is only available from a retrospective cohort study from St Mark's Hospital, which did not report on the outcome of treatments (provides no evidence about the success rates of current NHS practice)
- Darvadstrocel would only be appropriate for the population in line with ADMIRE-CD
- Clinical-effectiveness data for darvadstrocel is from only 1 trial with a relatively short time-frame, but after a single use, is predicted to have lifelong benefit
- Using the preferred post hoc outcome, only 14% of patients who received the stem cells demonstrated a response rate above that of placebo
- The treatment effects/results observed in the placebo group of ADMIRE-CD resulted in a much higher rate of remission than would be expected in the NHS -reasons for this are unclear, it may be a placebo effect or reflect differences between the trial setting and real life clinical practice
- Careful conditioning of the fistula and thorough abscess drainage and curettage is key to successful treatment and perhaps more experienced surgeons were involved in the trial, which may have increased the remission rate with placebo.
- Careful planning and scheduling is necessary, because of darvadstrocel's short self life - should be restricted to specialist centres where a multidisciplinary team is available and training will be required before introduction

[redacted]

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Utility values

Health state		Mean utility value
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

- ERG's clinical advisers considered that the utility value following successful defunctioning (0.567) or proctectomy surgery (0.564) and the utility value for the 'mild chronic symptomatic fistulae' health state (0.578) may be underestimated
- ERG explored the impact of using the same utility value as for the remission health state (0.865), for all these health states (see above in bold)

ACD conclusion (section 3.17)
- the utilities in some heath states might be underestimated
- however based on what the committee heard from clinical and patient experts, the ERG's suggested scenario is extreme and not plausible
- but was informative in showing the impact that the utility values had on the cost-effectiveness results (see next slide)

Key cost effectiveness estimates (I)

Treatment	Total QALYs	Total costs (with PAS)	ICER
Company's base case, using 3.5% discount rate for both effects and costs and 40-year time horizon and PAS for darvadstrocel			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental Deterministic results	1.05	£21,639	**£20,591**
Incremental Probabilistic results	1.01	£21,811	**£21,685**
ERG base case (deterministic) corrected for programming errors, adjusted the probabilities of moving to the proctectomy and defunctioning surgery health states, amended the long-term remission rates for subsequent therapies on the SoC arm, applied a 60-year time horizon			
Darvadstrocel	[redacted]	[redacted]	-
Standard care	[redacted]	[redacted]	-
Incremental	1.01	£23,978	**£23,176**
ERG base case + using the same utility value (0.865) as for remission, for mild chronic symptomatic fistula health state and successful defunctioning and proctectomy surgery			
Darvadstrocel	[redacted]	[redacted]	-
Standard Care	[redacted]	[redacted]	-
Incremental	0.37	£23,738	**£63,721**

[redacted]

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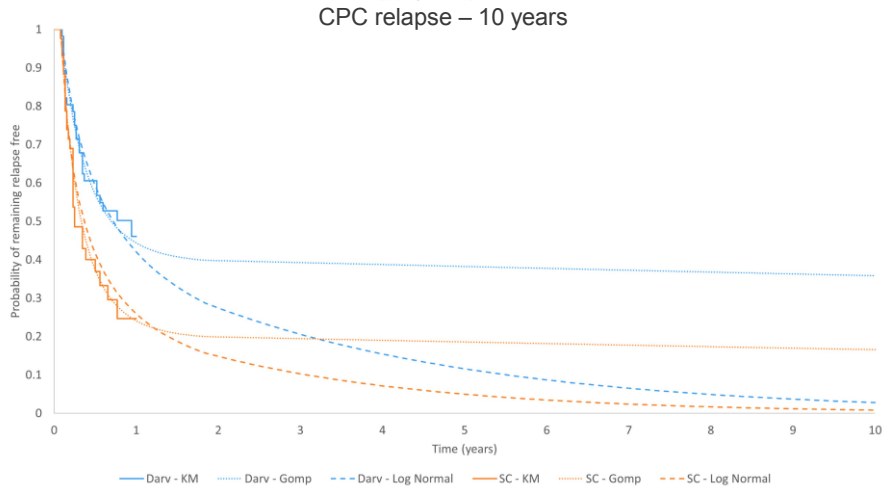
Reminder of parametric curves for time to relapse from CPC remission



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Key cost-effectiveness estimates (II)

Main driver of cost-effectiveness is the projection of time to relapse

ERG base case + Using different parametric distributions for time to remission and time to relapse								
Time to CPC remission	Time to relapse from CPC remission	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
Gompertz (base case)	Log-normal			£25,084			0.21	£119,514
Generalised gamma	Log-normal			£25,146			0.18	**£143,131**

ACD conclusion (section 3.16)

- The risk of relapse over time was a key driver of the model, the choice of curve has a large effect on the ICER (with a difference of more than £100,000/QALY between the best and second-best fitting curves)
- Clinical experts explained: without more evidence on the natural history of the disease, difficult to predict the relapse rate after the time horizon of the trial. If the fistula is healed and remission is maintained until 2 years, and no underlying risk for future recurrence, recurrence rates are likely to be very low after this time (around 10 to 20%), however not eliminated
- The company used a Gompertz curve to extrapolate both time to CPC remission and time to relapse after ERG scenario analysis: ERG's preferred base-case assumptions plus used generalised gamma curve for extrapolating time to CPC remission, and log-normal curve for time to relapse after CPC remission
- The committee was unable to select the most appropriate method for modelling the long-term effectiveness of darvadstrocel.

Goodness of fit of the different parametric models fitted to time to relapse from CPC remission

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.		

[redacted]

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Committee's considerations – cost effectiveness

- The long-term benefits of darvadstrocel are highly uncertain.
  - The committee expressed concern that no reliable data on the number of people in remission at 2 years is available, and concluded that only better data on long-term outcomes from the ongoing trial, or more robust information on the natural history of the disease, would make it possible to decide which is the most plausible ICER.
- There is limited evidence available on health-related quality (HRQoL) of life for Crohn's disease with complex perianal fistula
  - No relevant HRQoL measurement was included in ADMIRE-CD trial. The company did a vignette study to derive utility values for each health state (not in line with the NICE reference case). Alternative values have an upward effect on the cost effectiveness estimates
- A reference case discount rate of 3.5% should be used for both benefits and costs
- Time horizon was not a driver of cost-effectiveness, however using a 60-year time horizon in the model, as suggested by the ERG, is in line with the NICE reference case

[redacted]

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ACD consultation comments from:

- Consultee comments:
  - British Society of Gastroenterology (endorsed by the Royal College of Physicians)
  - Crohn's and Colitis UK
  - Takeda
- Commentator comments:
  - Evidence Review Group: ScHARR (suggesting amendments to the wording of the ACD only)
- Web comments:
  - (from 9 NHS professionals and 1 patient)

[redacted]

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British Society of Gastroenterology (endorsed by RCP)

- Agree that the available data suggest a modest treatment effect and that the cost of the medicine is relatively high and that the cost effective estimates are very variable
- Standard of care in the UK is not solely surgical intervention, but is a multidisciplinary approach including both medical and surgical treatments (relating to section 3.10 of ACD)
- The ADMIRE-CD trial population is as similar to the UK population as in many other clinical trials and this should not be a reason not to accept the data
- Supports the use of the medicine in further clinical trials and that these should be done in the UK to gain some relevant experience
- Supports the fact that the medicine will be reviewed again when further data is available

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Crohn's and Colitis UK

- Disappointed in the negative decision
- Perianal fistulas are associated with huge disease burden (pain, discharge and other complications) and negatively impact the quality of life and mental health of the patients
- High unmet medical need, current treatment options are limited. Surgery is both physically and emotionally a debilitating
- Setons are painful, uncomfortable, associated with faecal incontinence, negatively affect self-esteem, sexual activity and everyday functions (e.g. changing, walking, riding a bike) Successful intervention (efficacy and comfort) depends on the experience of the surgeon
- Proctectomy and defunctioning surgery are not described accurately from the patients point of view. They require multiple surgical treatments to achieve healing (median 6). They are life changing interventions and have impact on a person's daily life, self-esteem, sexual relationship, reduce fecundity, stigmatising interventions and highly costly (including the management post surgery)
- Darvadstrocel is a highly innovative treatment, offers a more favourable outcome from the patients point of view. Has the potential to raise the standards and expertise in treating this condition
- The results of the clinical trial show significant increase in remission

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Company's comments (I)

- Training will be provided by TAKEDA to all specialist centres on administering darvadstrocel and will also encourage research collaborations such as the ENIGMA network (section 3.3)
- Restricting the use of darvadstrocel to the population in line with ADMIRE-CD (section 3.4) would disadvantage people:
  - with CDAI score more than 220
  - who underwent surgery for the fistula other than drainage or seton placement
  - with diverting stoma
  - with renal or hepatic impairment
  - with contraindication to MRI scan
- No exclusion criteria specified the minimum number of tracts, therefore the statement that the trial excluded patients with one fistula with one single tract is invalid.
- The treatment benefit of darvadstrocel (14.1% more CPC remission compared with placebo) is a clinically relevant benefit that should not be considered 'modest'. Darvadstrocel also increases the chance of getting remission and sustaining remission.

[redacted]

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Company's comments (II)

- The ongoing clinical trial ADMIRE-CD II will only provide results in 2022 and will be limited to 1-year follow up also (section 3.9).
- In the meantime a global registry (INSPIRE) has been set up by Takeda to collect data on patients receiving darvadstrocel globally, however long term outcomes are not likely to become available in the near future.
- Probabilities for receiving proctectomy or defunctioning surgery in the population relevant for this appraisal is likely to be less than in the general population, therefore the ERG's transition probabilities are an over estimation (section 3.15).
- The vignette study was a methodologically robust study with a significant number of participants (n=835), therefore it provides reliable estimates of utilities. The values are in line with previous NICE appraisals and utility values in the literature (sections 3.11 and 3.17).

[redacted]

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Web comments (key themes)

- Huge disease burden, symptoms are very severe and have a huge impact on mental health, relationships and social life of patients and quality of life
- High unmet medical need in this patient population, currently available options are life altering surgeries with very poor outcomes and success rates
- Innovative technology, first targeted therapy for fistulas. For patients it would give hope for better outcomes that are possible to maintain
- Clinicians in general agree with the committee's considerations about the evidence
- Understand that long term results and benefit is key driver of decision making, however they reiterate that recurrence tends to occur in the first few years (1-2 years) and remission is possible to be maintained after this period. On the other hand it is unrealistic to expect evidence from really long follow-up studies
- Robust evidence base, with strict outcome definitions, clinically and statistically significant results compared with placebo. The high success rate on the placebo arm suggests that the benefit would be even higher in general UK clinical practice
- Agrees with restricting the use to specialist centres only
- Urges financial agreements with the NHS to reduce the very high price of the technology
- Some comments suggests a review when more evidence becomes available or formulating a research recommendation to collect more evidence.

[redacted]

23

Equality issue

- Comment from Crohn's and Colitis UK:
  - There are significant equality/diversity issues in terms of effectively compelling patients in this group to having surgery:
    - particularly for young people who have not begun a family and whose fertility may be affected,
    - and for religious groups such as Muslims, for whom this may impact on religious practices and cause distress.
  - We would ask the Committee to outline to what degree these issues have been taken into consideration when making their final decision.

[redacted]

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New evidence submitted by the company

[redacted]

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Literature search on long-term relapse rates for patients in remission at 2-years

- Company conducted a literature search to determine long-term relapse rates in patients with Crohn's disease with perianal fistulas (both complex and simple). Six studies were identified.
- Key differences between ADMIRE-CD and the studies: definition of remission, maintenance biologic use, time points for outcome assessments, populations, countries and methodology of the study (prospective or retrospective)
- Results show that once remission is reached at 2-years, a "plateau" effect is observed and remission is more likely to be maintained.

Long-term relapse rates if remission is maintained at 2 years

	Identified from targeted literature review		Applied in the economic model	
	Minimum	Maximum	Darvadstrocel	Placebo
3-years	4.51%	13.77%	1.19%	2.08%
5-years	14.32%	33.60%	3.82%	6.60%
7-years	14.32%	33.60%	6.20%	10.59%
10-years	16.92%	39.25%	9.87%	16.64%

Source: Table 1 of company's ACD response

[redacted]

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Long-term relapse rates identified from a targeted literature review and compared with time to CPC relapse from the ADMIRE-CD clinical trial (figure AIC)

[redacted]

The relapse rates presented in the literature in the short term are likely to reflect a subgroup with a more sustained remission than in the ADMIRE-CD, therefore the relapse rates observed in ADMIRE-CD are more rapid.

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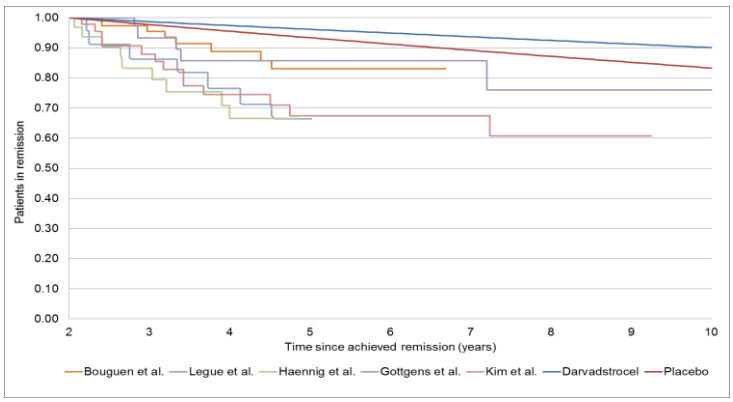
Long-term relapse rates for patients in remission at 2-years identified from a targeted literature review and compared with rates applied in the economic model



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Results of the Delphi-panel survey

- Expert opinion elicited from 20 clinical experts including gastroenterologists, surgeons and nurses from the UK on the log-term outcomes and natural history of the disease.
- Initial responses (questionnaire 1) indicated a higher rate of relapse than observed in the literature.
  - On average, clinical experts expected 44% of patients who had maintained remission for 2-years to continue in remission for 5-years (range: 11%-80%).
  - On average, clinical experts expected 29% of patients who had maintained remission for 10-years to continue in remission for a lifetime (range: 0%-90%).
  - On average, respondents expected half of their patients to have relapsed with recurrent fistula(e) after 7-years (range: 1-50).
- There was consensus on the "plateau" effect and that maintenance anti-TNF therapy would be continued after a patient had received darvadstrocel. It was only possible to obtain qualitative evidence from the results of the survey. No consensus was reached when company tried to quantify the results.
- The responses also indicated differences in the definition of true healing of fistula and remission.

[redacted]

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Comparison of relapse rates across different parametric curves

	Relapse rates at 5-years		Relapse rates at 10-years	
	Darvadstrocel	Placebo	Darvadstrocel	Placebo
Gompertz	3.82%	6.60%	9.87%	16.64%
Weibull	70.66%	90.06%	96.20%	99.79%
Log-normal	57.37%	66.03%	89.71%	94.38%
Log-logistic	56.48%	61.52%	89.12%	92.16%
Exponential	90.80%	99.45%	99.83%	100.00%
Literature estimates	14.32%-33.60%		16.92%-39.25%	

Company considers the Gompertz curve to be the most plausible for long-term extrapolation.
For the scenario analyses only 2 studies (out of 6) were used to inform the relapse rates (Buoguen et al. 2013 and Gottens et al. 2016).

[redacted]

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Company's final base case cost-effectiveness results

- Company maintains it's position that it's original base case cost-effectiveness estimates are the most plausible
- Presented a scenario analyses where it assumed equal long-term relapse rates for both darvadstrocel and placebo, which increased the ICER to £22,273.
- In additional scenarios it altered the 4-weekly constant relapse rate (applied from 2-years onwards in the model) using the results of the literature search.
  - Scenario 1 assumes that 16.92% of people who had not relapsed at two years would relapse at 5 years, and the corresponding rate at 10 years was 39.01%
  - Scenario 2 assumes that 24.02% of people who had not relapsed at two years would relapse at 10 years, and the corresponding rate at 5 years was 9.79%
- In these scenarios the "plateau" effect is not accounted for, therefore the relapse rates beyond 10-years are higher than what would be observed.

	5-year relapse rate given in remission at 2-years	10-year relapse rate given in remission at 2-years	Anti-TNF use in remission health state	ICER
Base case	Darvadstrocel = 3.82% Placebo = 6.60%	Darvadstrocel = 9.87% Placebo = 16.64%	82.22%	£20,591
Scenario 1a	16.92% both arms	39.01% both arms	82.22%	£36,235
Scenario 1b	16.92% both arms	39.01% both arms	57%	£29,038
Scenario 2a	9.79% both arms	24.02% both arms	82.22%	£28,370
Scenario 2b	9.79% both arms	24.02% both arms	41%	£17,068

ERG's critique of new evidence (I)

- The two studies that were used in the company's scenario analyses predated the ADMIRE-CD trial
- When compared the study populations with the population of the ADMIRE trial, the ERG identified 4 key differences:
  - Difference in types of fistulas (the studies included non complex fistulas as well and it's unclear what proportion of the fistulas did not respond to first line treatment)
  - The age ranges are not comparable between the 3 studies
  - The studies were conducted in different time periods, which makes it unclear if the long term relapse rates are comparable
  - The definition of remission differs across studies
    - ADMIRE-CD: CPC remission
    - Buoguen et al.: clinical assessment
    - Gottens et al.: new visible fistula at the same sight or return of symptoms
- These lead to significant differences amongst the trials and it's unclear if the studies are relevant to inform the analyses on long term extrapolation methods

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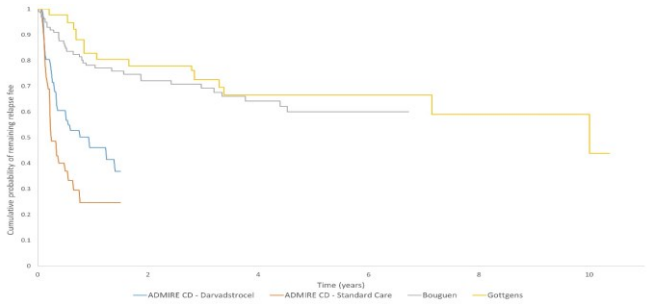
Comparison of the Kaplan-Meier curves: ADMIRE-CD, Buoguen et al., Gottens et al.



- People in ADMIRE-CD relapse at a much greater rate than in Buoguen and Gottens studies, which indicates that the studies are not suitable for estimating long term rate of remission after 2 years for the population of the ADMIRE-CD trial.
- Patient numbers are also very low towards the ends of the curves
  - in Gottens only 4 patients (8.5%) remained in remission at 10 years
  - in Buoguen et al. only 11 (10.2%) patients remained in remission at 300 weeks (approx. 5 years)

[redacted]

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ERG critique of new evidence (II)

- ERG disagrees with the method the company applied for estimating long term relapse rates
  - It would have preferred fitting an exponential curve to the digitised data instead of making the 5 year of 10 year relapse rate conditional on being in remission at 2 years. The company's method leads to bias as it only used the last part of the Kaplan-Meier curves, where the patient numbers are very low
- Assuming lower anti-TNF use in the analyses, as presented in the company's scenario analysis is not in line with UK clinical practice, even if it was lower in the studies used for the scenario analyses

[redacted]

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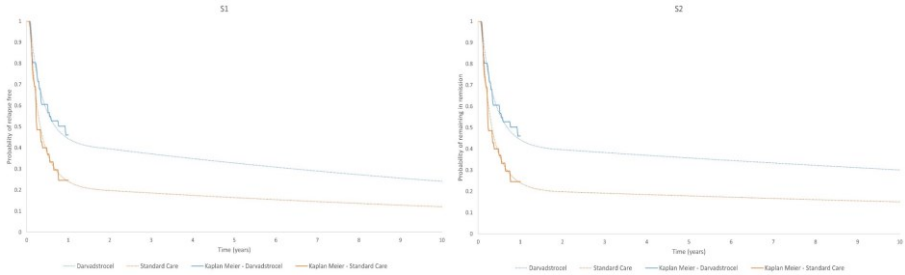
Long term extrapolation methods

- The risk of relapse is lower for the whole population as compared with the company's estimation which was based on people who are in remission at 2 years
- The ERG scenario analyses show that the relative effect of darvadstrocel is slightly diminishing over time, however it is likely to be maintained over a 10 years time horizon



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ERG's revised cost-effectiveness results after ACD response

	The probability of relapsing between year 2 and year 5, conditional on being in remission at 2 years	The probability of relapsing between year 2 and year 10, conditional on being in remission at 2 years	Anti-TNF use in the remission health state	ICER (£/QALY gained)
ERG verification of the company's additional scenarios (in the company's base case model)				
Base case	Darvadstrocel = 3.82% Placebo = 6.60%	Darvadstrocel = 9.87% Placebo = 16.64%	82.22%	£20,591
Scenario 1a	Darvadstrocel = 16.92% Placebo = 16.92%	Darvadstrocel = 39.00% Placebo = 39.00%	82.22%	£36,232
Scenario 1b	Darvadstrocel = 16.92% Placebo = 16.92%	Darvadstrocel = 39.00% Placebo = 39.00%	57%	Not verified
Scenario 2a	Darvadstrocel = 9.79% Placebo = 9.79%	Darvadstrocel = 24.02% Placebo = 24.02%	82.22%	£28,369
Scenario 2b	Darvadstrocel = 9.79% Placebo = 9.79%	Darvadstrocel = 24.02% Placebo = 24.02%	41%	Not verified
ERG's preferred base case model				
Base case	Darvadstrocel = 4.07% Placebo = 7.02%	Darvadstrocel = 10.49% Placebo = 17.64%	82.22%	**£23,176**
Scenario 1a	Darvadstrocel = 16.92% Placebo = 16.92%	Darvadstrocel = 39.00% Placebo = 39.00%	82.22%	**£40,900**
Scenario 2a	Darvadstrocel = 9.79% Placebo = 9.79%	Darvadstrocel = 24.02% Placebo = 24.02%	82.22%	**£31,925**

[redacted]