

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal document

**Darvadstrocel for treating complex perianal
fistulas in Crohn's disease**

1 Recommendations

- 1.1 Darvadstrocel is not recommended, within its marketing authorisation, for previously treated complex perianal fistulas in adults with non-active or mildly active luminal Crohn's disease.

Why the committee made these recommendations

In a single clinical trial comparing remission rates for darvadstrocel and placebo, only an additional 14% of people showed a beneficial effect from darvadstrocel over and above placebo. Reliable follow-up results are only available for up to 1 year during which time more than 50% of patients relapsed in both the darvadstrocel and placebo arms, so it is unclear how long the treatment benefit will last. The additional evidence submitted after consultation did not clarify the uncertainties around long-term benefits of darvadstrocel. The committee considered that further research in this area would be beneficial (see section 4 for further details). The cost-effectiveness estimates are therefore highly uncertain and the committee was unable to decide on the most plausible cost-effectiveness estimate. Because of this, darvadstrocel cannot be recommended for routine commissioning for treating complex perianal fistulas in people with Crohn's disease.

2 Information about darvadstrocel

Marketing authorisation	Darvadstrocel (Alofisel, Takeda) 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 1 conventional or biologic therapy’.
Dosage in the marketing authorisation	A single dose of darvadstrocel consists of 120 million cells distributed in 4 vials. Each vial contains 30 million cells in 6 mL of suspension. The full content of the 4 vials must be administered for the treatment of up to 2 internal openings and up to 3 external openings. This means that with a dose of 120 million cells it is possible to treat up to 3 fistula tracts that open to the perianal area. There is currently limited experience with the efficacy or safety of repeat administration of darvadstrocel.
Price	The list price of darvadstrocel is £13,500 per vial. One course of treatment (4 vials) costs £54,000 (company submission). The company has a commercial arrangement (patient access scheme), which would apply if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Takeda and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Management of the disease

There are no targeted interventions for complex perianal fistulas in people who have Crohn’s disease

3.1 Perianal fistulas are abnormal passages between the lower parts of the gut and the skin near the anus. Complex perianal fistulas have several abnormal passages and openings, or passages that go deep inside the body, or have other complications such as abscesses. In adults with non-active or mildly active luminal Crohn’s disease, perianal fistulas are

managed with medical therapies including antibiotics, immunosuppressants and biological therapy. If the fistula and any associated abscesses do not heal, surgery is needed. Using general anaesthesia, the abscesses are drained and a seton (piece of thread) is passed through the fistula. This keeps the fistula open so that it can drain. The clinical experts explained that setons are not usually curative, but aim to reduce the risk of abscess formation. Long-term remission rates are relatively low (about 10%). The success rate of seton placement also depends on the surgeon's experience in treating complex perianal fistulas with multiple tracts. Because setons are not usually curative and remission rates are low, people may need to have defunctioning surgery (a temporary diversion of the bowel to allow healing of the perianal fistula) or a proctectomy (permanent removal of part of the bowel to bypass the perianal fistula).

New treatment option

Perianal fistulas are chronic and debilitating, and a new treatment option would be welcome

3.2 The patient experts explained that perianal fistulas are highly debilitating, have a big effect on the person's everyday life and greatly reduce their quality of life. People can experience excruciating pain and are limited in their everyday activities. The availability of systemic biological treatments has improved people's quality of life, but these treatments can have serious side effects and do not specifically treat the perianal fistula. Darvadstrocel is injected directly into the perianal fistula. It is the first stem-cell treatment that is specifically developed to promote healing of fistulas caused by Crohn's disease and, if curative, would be a life-changing intervention. At the second committee meeting, patient experts explained that any relief from the symptoms would be considered a huge benefit, even if it is only maintained for a short period of time (such as 24

to 52 weeks). This would allow people to reduce the amount of other concomitant therapies used in managing perianal fistulas (such as antibiotics and pain killers). In response to consultation, patients also expressed that seton placement can be very painful, uncomfortable and associated with faecal incontinence. It also negatively affects the patient's self-esteem, sexual activity and everyday functions. But, the subsequent therapies (proctectomy and defunctioning surgery) need multiple surgical treatments to achieve healing. They can be life-changing interventions that have an even bigger effect on a person's daily life, self-esteem, and sexual activity. They also reduce fertility and are potentially stigmatising interventions. Darvadstrocel has the potential to offer a more favourable outcome for patients and to raise the standards and expertise in treating perianal fistulas. The committee understood that patients and clinicians would welcome a new treatment option that is targeted to heal the perianal fistula rather than to reduce complications such as abscesses, even if the treatment benefits are only maintained for a few months before relapse.

The method of administration of darvadstrocel

Using darvadstrocel needs training of the multidisciplinary team and careful planning and scheduling of treatment

- 3.3 Darvadstrocel is a suspension of allogeneic expanded human adipose-derived stem cells. Administration involves re-suspension of the cells, which need to be used within 48 hours. Because of its short shelf life, careful planning and scheduling is necessary to avoid procedures being cancelled and darvadstrocel being wasted. The clinical experts explained that the pharmacist and surgeon would need training in its preparation and administration. They also emphasised that patients should be seen by a multidisciplinary team who are experienced in treating complex perianal fistulas. Not all fistulas would be considered suitable for this treatment

(see section 3.4). The committee noted that darvadstrocel needs an additional procedure compared with current management. Standard examination under anaesthesia, with conditioning of the fistula is done first, then another procedure is done 2 weeks later to administer darvadstrocel. The clinical experts explained that the outcome of the intervention is highly dependent on the appropriate conditioning of the fistula and optimal placement of the darvadstrocel injection. They suggested that it should only be used in specialist centres where a multidisciplinary team is available, who could gain appropriate experience in the use of this technology. However, the clinical experts did not consider this to be a barrier to implement darvadstrocel in the NHS. The company also explained in its response to consultation that training would be funded and provided by Takeda in collaboration with research groups in this area. The committee concluded that because darvadstrocel is the first stem-cell treatment in this disease area, and keeping in mind the logistics of administration of darvadstrocel, it would only be used in specialist centres, after further training.

Clinical evidence

Darvadstrocel would only be appropriate for a specific group of people with complex perianal fistulas, in line with the population enrolled into ADMIRE-CD trial

3.4 Clinical evidence comes from ADMIRE-CD, a randomised controlled trial. This included adults with Crohn's disease who had a complex perianal fistula with up to 2 internal openings and up to 3 external openings, which had not responded to treatment with antibiotics, immune-modulators, TNF-alpha inhibitors, or a combination of these treatments. The clinical experts explained that the trial excluded people with the most severe and the least severe fistulas (that is, people with multiple complex fistulas, and those with simple fistulas). The clinical experts noted that the benefit for

people with multiple fistulas would be limited because of the restrictions around the volume of darvadstrocel that can be used for a single administration. Therefore in NHS practice it would only be used in the fistula types specified in ADMIRE-CD and that patients would be carefully selected to achieve the best outcomes. The committee noted that people with proctitis were excluded from the clinical trial, because this condition makes perianal fistula healing unlikely. The clinical experts agreed that these patients are unlikely to benefit from darvadstrocel. The committee concluded that if darvadstrocel were recommended, it should only be used in a population similar to people who were enrolled in ADMIRE-CD.

The evidence on the natural history of the disease and outcome of current practice in the UK is limited

3.5 ADMIRE-CD was a multicentre trial but it did not include patients from the UK. To show that the data are generalisable to people in the UK, the company presented the results of a study from St Mark's Hospital in London. This was a retrospective cohort study that collected data from January 2008 until July 2017. It included people with complex perianal fistulas that would have met the eligibility criteria of ADMIRE-CD. It was used to externally validate the results from ADMIRE-CD and calculate the transition to the proctectomy state. The ERG also used the data for adjusting the probabilities in the model and updating it with missing transitions (see section 3.17). The committee noted that people in the St Mark's study were more likely to be male and had a different medication history than the people in ADMIRE-CD. In particular, a higher percentage had had biological treatments. Clinical experts explained that, because the St Mark's study reported previous and current treatment together, the data is of limited usefulness and would not help the committee to decide who would be eligible for darvadstrocel in the NHS. It also noted that the St Mark's study did not report on the outcome of treatments, so it provided

no evidence about the success rates of current NHS practice. The clinical experts also explained that evidence on the natural history of Crohn's disease with perianal fistulas is limited. The committee considered the St Mark's study useful for understanding the patient population in the NHS, but concluded that it does not contribute substantially to predicting the natural history of the disease and outcome of current UK clinical practice.

Clinical-effectiveness data for darvadstrocel is from only 1 trial with a relatively short time-frame

3.6 ADMIRE-CD compared darvadstrocel with placebo (saline solution injection). The primary outcome of the trial was remission after 24 weeks, with clinical and MRI confirmation of fistula healing. Results from longer-term follow-up are also available (at 52 weeks and 104 weeks). The company and the ERG stated that the results are only reliable up to 52 weeks, because of a protocol change at that time, and the longer-term results are highly uncertain. The committee would have liked to have seen longer follow-up, given that darvadstrocel after a single use is expected to have lifelong benefit.

Using clinical and patient-centric assessment of remission is appropriate

3.7 Although the primary outcome of ADMIRE-CD was combined remission (assessed both clinically and by MRI), the company also did a post-hoc analysis of an alternative outcome. This had been suggested by clinicians who advised that, as well as clinically assessed remission, the outcome should include a component of patient-assessed pain and discharge (that is, clinical and patient-centric [CPC] remission). The time to CPC remission, and time to relapse after CPC remission, were considered to be indicators of the clinical effectiveness of darvadstrocel compared with placebo. The committee noted that the trial was not powered to detect changes in CPC remission and relapse. However, the ERG and the

clinical experts explained that this outcome would be the most relevant to clinicians and patients. The committee concluded that using CPC remission and relapse was appropriate, but remained concerned that these outcomes were defined post hoc and that the trial was not powered to detect changes in these outcomes.

ADMIRE-CD shows a statistically significant benefit of darvadstrocel compared with placebo but by 1 year more than 50% of patients with remission had relapsed

3.8 ADMIRE-CD showed a statistically significant difference in combined remission for darvadstrocel compared with placebo at week 24 (49.5% and 34.3%, respectively; difference 15.2%, $p=0.024$). This statistically significant difference was maintained at week 52 (54.2% compared with 37.1%, respectively; difference 17.1%, $p=0.012$). The committee also considered the results of the post-hoc analysis which showed that a statistically significantly higher number of people responded to darvadstrocel and achieved CPC remission compared with placebo (55.1% and 41.0%, respectively, $p=0.014$). It noted that only around 14.1% ($n=16$) more patients experienced CPC remission with darvadstrocel, compared with placebo. The committee understood the benefit to patients of achieving complete remission. However, it considered that this additional remission rate is disappointing for a highly complex, one-off treatment, which is associated with high upfront costs. Darvadstrocel retained a higher remission rate than placebo during the 1 year of the trial, but during that time there were also high relapse rates seen in both arms (50.8% for darvadstrocel and 59.6% for placebo; $p=0.0262$). In both arms, patients who were in remission were relapsing and the patient numbers who were still in remission at 1 year were low (29 [27.1%] for darvadstrocel and 19 [18.1%] for placebo). It also noted that the data are only reliable up to 52 weeks (see section 3.6) and the

number of patients who were followed up between 52 and 104 weeks was extremely low. The committee concluded that 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.

There is an ongoing clinical trial, which will provide further results on the clinical effectiveness of darvadstrocel

3.9 The committee noted that an ongoing clinical trial (ADMIRE-CD II) is expected to provide more evidence on the clinical effectiveness of darvadstrocel for a complex perianal fistula in people who have Crohn's disease. The study is planning to recruit more people (n=326) than were included in ADMIRE-CD (n=212). However, the committee noted that it will not collect data on health-related quality of life and there is no plan to collect longer-term data beyond 52 weeks. The company also explained in its response to consultation that a global registry (INSPIRE) has been set up by Takeda to collect data about patients having darvadstrocel therapy across the world. But long-term outcomes are not likely to be available in the near future. The committee considered that the results of the 2 studies together and from the registry will form a more robust evidence base. It also noted that the European Medicines Agency considers that further information on efficacy is necessary, and that the marketing authorisation is subject to the submission of the results of ADMIRE-CD II.

Generalisability of ADMIRE-CD data to UK clinical practice

The treatment effect seen in the placebo group of ADMIRE-CD is better than achieved in UK clinical practice

3.10 The clinical and patient experts explained that standard care for complex perianal fistulas in people with Crohn's disease is surgical intervention and seton placement, which allows free drainage to prevent deep abscess formation. As the ADMIRE-CD trial did not include patients from the UK, it

is unclear to what extent the outcomes seen in the placebo group of the trial reflect the outcome of clinical practice in the UK. In ADMIRE-CD, the interventions given in the placebo arm resulted in a much higher rate of remission than would be expected with standard care in the UK. The reasons for this are unclear. It may be a placebo effect or it may reflect differences between the trial setting and real-life clinical practice. The clinical experts indicated that careful conditioning of the fistula and thorough abscess drainage and curettage is key to successful treatment and that perhaps more experienced surgeons were involved in the trial, which may have increased the remission rate with placebo. They explained that there is variability in the level of service across the NHS. The clinical expert at the second committee meeting also explained that in clinical trials for Crohn's disease a high placebo effect is usually seen because of the more careful management of the disease in a clinical trial setting. The committee considered that this might have underestimated the benefits of darvadstrocel compared with placebo seen at 1 time point (24 or 52 weeks), but this does not indicate if the response to darvadstrocel therapy is maintained in the longer term. The committee reiterated its previous conclusion that darvadstrocel would only be suitable for use in specialist centres (see section 3.3). It concluded that there was uncertainty in the generalisability of the placebo arm of the ADMIRE-CD trial to UK clinical practice, and therefore it is uncertain whether the benefit shown for darvadstrocel in the trial would translate to the same benefit compared with standard care in the NHS.

ADMIRE-CD did not collect patient-reported health-related quality of life data

3.11 ADMIRE-CD collected disease severity scores as secondary outcomes (Perianal Disease Activity Index and Van Assche Score). The clinical experts explained that although the Perianal Disease Activity Index is a patient-reported outcome measure, it does not capture health-related

quality of life. The committee noted that the reference case in section 5.3.1 of NICE's [guide to the methods of technology appraisal](#) (2013) specifies that health-related quality of life data should be obtained from patients using the EQ-5D questionnaire. The committee concluded that it would have welcomed the collection of health-related quality of life outcomes in the trial, particularly using EQ-5D.

The new evidence does not clarify the uncertainties around long-term benefits of darvadstrocel compared with placebo

3.12 In response to consultation, the company did a literature search to determine long-term relapse rates in patients with Crohn's disease with perianal fistulas (both complex and simple). It identified 6 potentially relevant studies. However, there were some key differences between the ADMIRE-CD trial and these studies:

- definition of remission amongst studies
- maintenance use of biological treatments
- time points for outcome assessments
- populations and countries where the studies were conducted
- methodology of the study (prospective or retrospective).

Comparing the Kaplan-Meier curves showed more rapid relapse rates in the ADMIRE-CD trial than in the other studies, regardless of treatment arm. According to the company, this suggests that the population of the studies reflect a subgroup with a more sustained remission than the population in ADMIRE-CD. The company considered that the results showed a 'plateau' effect once remission is reached at 2-years and that therefore remission is likely to be maintained in the long term. The committee noted that relapse may be less frequent the longer remission is maintained, but did not consider a 'plateau' effect had been proven.

Moreover, there was a high relapse rate during year 1 and no reliable trial

data for year 2 after which a plateau effect was suggested. Therefore, the number of relapses that would have happened before the rate plateaued was unknown. Using the results from 2 of the studies that according to the company best reflected UK clinical practice and were most comparable with ADMIRE-CD (Bouguen et al. 2013 and Gottens et al. 2017), the company presented scenario analyses. In these analyses, the 4-weekly constant relapse rate was adjusted (also see section 3.19). The ERG explained that as well as the differences listed above, there were differences in types of fistulas (simple or complex) that were included in the studies and it was unclear what proportion of the different type of fistulas responded to treatment. The ERG considered these differences to be important and did not think that the studies were comparable with the ADMIRE-CD trial and would be suitable to inform the analyses on long-term extrapolation methods. The committee considered the new evidence from the company and also understood the ERG's concerns. It concluded that the new evidence does not clarify the uncertainties around the long-term benefits of darvadstrocel compared with placebo.

- 3.13 The company also did a Delphi-panel survey, which sought expert opinion from 20 clinicians across the UK, including gastroenterologists, surgeons and nurses. Experts were asked to give a view on long-term outcomes with darvadstrocel and the natural history of fistulising Crohn's disease. Their initial response noted a higher rate of relapse in the ADMIRE-CD trial than has previously been reported in the literature. There was a consensus that relapse rates would reduce the longer the remission was maintained, particularly because maintenance TNF-alpha-inhibitor therapy would be continued after a patient had had darvadstrocel. However, it was only possible to get qualitative evidence from the results of the survey and no consensus was reached when the company tried to quantify the results. The responses also indicated differences in the definition of true

healing of fistula and remission. The committee found the results from the literature review and the survey informative but concluded that they did not consider it robust evidence that would alter their decision.

The company's economic model

The company's model structure is appropriate and suitable for decision making

3.14 The company presented a semi-Markov state transition cohort model, which assumed a single administration of darvadstrocel (the committee noted no evidence had been presented by the company for repeated treatments with darvadstrocel), and a lifetime benefit for patients. It used a 40-year time horizon and a 4-week cycle length. The committee agreed with the structure of the model and considered it suitable for decision making.

Discounting future costs and benefits

A reference case discount rate of 3.5% should be used for both benefits and costs

3.15 The company deviated from the reference case in its base-case analysis, using a 1.5% discount rate for future benefits and a 3.5% discount rate for costs, because it considered that section 6.2.19 of NICE's [guide to the methods of technology appraisal](#) applies. This 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, a non-reference-case discount rate of 1.5% for costs and benefits may be considered. The ERG commented that evidence does not support the suggestion that darvadstrocel restores quality of life to full or near-full health for a prolonged period (at least 30 years, as defined by section 6.2.19 of NICE's guide to the methods of

technology appraisal). The committee agreed that it has not been shown that darvadstrocel restores a patient's quality of life to full or nearly-full health (partly because it does not treat the underlying condition, Crohn's disease). It also noted the lack of evidence on the long-term benefits of darvadstrocel. Also, the committee noted that NICE's guide to the methods of technology appraisal does not support using different discount rates for costs and benefits. The committee concluded that a reference case discount rate of 3.5% should be used for both costs and benefits in the economic model.

Time horizon of the model

Using a 60-year time horizon in the economic model is in line with the NICE reference case

3.16 The company's model used a 40-year time horizon. The ERG explained that at 40 years, only 31.7% of patients will have died, so the time horizon might be too short to capture differences in costs and benefits for darvadstrocel compared with standard care. The ERG explored the impact of using a 60-year time horizon. The committee noted this had a minimal impact on the incremental cost-effectiveness ratio (ICER) and concluded that time horizon was not a driver of cost effectiveness.

Base-case cost-effectiveness estimates

3.17 The company presented a deterministic base-case cost-effectiveness estimate of £20,591 per quality-adjusted life year (QALY) gained (incremental costs £21,639; incremental QALYs 1.05), using the following assumptions: the reference case discount rate of 3.5% for both costs and QALYs; a 40-year time horizon; and applying the patient access scheme for the treatment costs of darvadstrocel. The committee noted that the ERG's preferred inputs into the company's base-case analysis produced

an ICER of £23,176 (incremental costs £23,978; incremental QALYs 1.01), using the following corrections and assumptions:

- correcting for programming errors in the model
- updating the model structure with adding the missing transitions of successful defunctioning surgery to unsuccessful defunctioning surgery, successful proctectomy to unsuccessful proctectomy, and unsuccessful proctectomy to successful proctectomy to reflect the evidence from St Mark's study
- adjusting the probabilities of moving to the proctectomy and defunctioning surgery health states in the model, so that the data matched the evidence from the Mueller et al and Bell et al studies
- amending the long-term remission rates for subsequent therapies in the standard-care group, based on the time-to-event functions of subsequent therapies and the methods used in the darvadstrocel group
- using a 60-year time horizon.

The committee considered the ERG's corrections and assumptions to be appropriate.

Modelling the long-term benefits of darvadstrocel

The long-term benefit of darvadstrocel is highly uncertain, and the model is highly sensitive to the choice of parametric curve for long-term extrapolation of relapse rate

3.18 To model the long-term clinical effectiveness of darvadstrocel, the company used a Gompertz curve to extrapolate both time to CPC remission and time to relapse after CPC remission. The ERG explained that the choice of curve is a key driver of the model and that the cost-effectiveness results are very sensitive to the extrapolation method used, particularly the time to relapse. The ERG presented a scenario analysis,

similar to that presented by the company, but including the ERG's preferred base-case assumptions and using the second-best options according to AIC and BIC statistics which were the generalised gamma curve for extrapolating time to CPC remission, and the log-normal curve for time to relapse following CPC remission. This results in a substantially higher ICER (£143,131 per QALY gained) compared with the company's base case (see section 3.17). The committee discussed the clinical plausibility of the different curves with the clinical experts, particularly the choice of curve for time to relapse after CPC remission. The clinical experts explained that without more evidence on the natural history of the disease, it is difficult to predict the relapse rate after the time horizon of the trial. However, the experts highlighted that if the fistula is healed and remission is maintained until 2 years, and there is no underlying risk for future recurrence, recurrence rates are likely to be very low after this time (around 10 to 20%), but it is not eliminated. They also explained that relapse tends to happen soon after treatment, rather than later. The committee noted that it had no reliable figures for the number of patients in remission at 2 years from the ADMIRE-CD trial. The company stated that its model assumes 40% of people remain relapse free, with a low ongoing risk of relapse, after remission has been maintained with darvadstrocel for 2 years. The committee concluded that the risk of relapse over time (hence the method of extrapolation from the trial to the long term) is a key driver of the model. It was unable to select the most appropriate method for modelling the long-term effectiveness of darvadstrocel. The committee expressed concern that no reliable data on the number of people in remission at 2 years is available, and that the choice of curves has a large effect on the ICER (with a difference of more than £100,000 per QALY gained between the best and second-best fitting curves). It 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.

The new scenarios were not based on robust evidence and the committee did not consider these any more plausible than the original assumptions

3.19 In response to consultation, the company also presented the results of scenario analyses, where it altered the rate of 4-weekly constant relapse rate that was applied from 2-years onwards in the model. In scenario 1, it assumed that 16.92% of people who had not relapsed at 2 years would relapse at 5 years. The corresponding rate at 10 years was 39.01%. This resulted in an ICER of £36,235 per QALY gained. In scenario 2 it assumed that 24.02% of people who had not relapsed at 2 years would relapse at 10 years, and the corresponding rate at 5 years was 9.72%. This resulted in an ICER of £28,370 per QALY gained. The committee also noted the ERG's alternative cost-effectiveness results using their base-case assumptions, which resulted in £40,900 for scenario 1 and £31,925 for scenario 2. The committee considered the scenario analyses results by the company and the ERG, but did not consider that they were based on more robust evidence or more plausible assumptions than the original base-case cost-effectiveness results.

There is limited evidence available on health-related quality of life for Crohn's disease with complex perianal fistula

3.20 ADMIRE-CD did not include a direct health-related quality of life measurement, and there are no published utility values for this disease area. To calculate the health-related quality of life benefits of darvadstrocel, the company did a vignette study to derive utility values for each health state in the model. The committee noted that this is not in line with the NICE reference case. The ERG's clinical experts considered that the utility value after successful defunctioning (0.567) or proctectomy surgery (0.564) may be underestimated in the company's base case, as

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well as the utility value for the 'mild chronic symptomatic fistulae' health state (0.578). The ERG explored the impact of using the same utility value (0.865) for remission (for a mild chronic symptomatic fistula and for successful defunctioning and successful proctectomy surgery), to establish the direction and maximum size of any changes in the ICER because of the possible under prediction of utility in these 3 health states. The resulting ICER was £63,721 per QALY gained. The committee discussed this scenario with the patient and clinical experts at the meeting. They explained that a patient's quality of life after defunctioning surgery is expected to be substantially lower than the quality of life of a patient in remission. At the second meeting and in response to consultation, patient experts also explained the devastating symptoms of Crohn's disease with perianal fistulas, especially if they have severe symptoms. They explained that having mild symptoms, even if the fistula is not completely healed, is a relief and allows them to maintain a relatively normal life. But is conditional on the seton being placed carefully and not causing pain, and that they do not experience major adverse events from the underlying medical treatments. The committee considered that the utilities in some health states might be too low, and that correctly derived utility values for these 3 health states could result in higher ICERs. However, it concluded that the ERG's suggested scenario is extreme and not plausible, but found that it was informative because it showed the impact that the utility values had on the cost-effectiveness results.

Most plausible cost-effectiveness estimate

The most plausible cost-effectiveness estimate is uncertain, and darvadstrocel is unlikely to be a cost-effective use of NHS resources

3.21 The key factors affecting the ICER are the parametric curve chosen for extrapolating the time to CPC remission and particularly time to relapse

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after CPC remission. To a smaller extent, the utility values for a mild chronic symptomatic fistula and for successful defunctioning and successful proctectomy surgery also affect the ICER. Using a generalised gamma curve to extrapolate time to CPC remission, and log-normal curve to extrapolate time to CPC relapse, resulted in an ICER of £143,131 per QALY gained. The committee noted that this ICER is considerably higher than the company's base case and, given the reasonable fit of the curves, it could be correct. The very large difference in the ICERs, depending on the curves chosen, emphasises how sensitive the cost-effectiveness estimate is to the duration of remission. The lack of long-term evidence from the trial and limited evidence on the natural history of the disease, particularly on long-term relapse rates after successful treatment, make it very difficult to decide the most plausible estimate of cost effectiveness. Therefore the committee was unable to conclude on the most plausible cost-effectiveness estimate.

Other factors

3.22 In response to consultation, a patient group stated that some equality issues needed to be considered by the committee in terms of leaving patients with no option but to have defunctioning surgery or a proctectomy. It was noted that having pelvic surgery may be an issue for people who have not completed their family and whose fertility may be affected, and that the condition and potentially having defunctioning surgery or a proctectomy may raise particular issues for certain religious groups. The committee acknowledged that having Crohn's disease presents certain difficulties for some groups, but considered that due to the lack of clear evidence on long term clinical effectiveness of darvadstrocel and not recommending darvadstrocel does not exclude or impact differently on any populations. It also discussed that it is not proven by the clinical evidence that subsequent surgery will be avoided in

any of the patient groups as an outcome of treatment with darvadstrocel. Therefore the committee concluded that this did not represent an equalities issue and that there was no need to alter its recommendations.

- 3.23 The company stated that darvadstrocel is innovative and the first licensed allogenic stem-cell treatment in the UK for this disease. The clinical experts explained that this is the first targeted treatment option for complex perianal fistulas in Crohn's disease, and that it represents a step-change in the management of the disease. The committee considered these factors to be important and concluded that darvadstrocel is potentially innovative in the short term, but its long-term benefit is uncertain.

Conclusion

- 3.24 The committee understood the huge disease burden that patients experience and how severely impaired quality of life is for patients with this condition. Data on clinical effectiveness of darvadstrocel shown only modest benefit over and above placebo and data is only available for up to 1 year, so the duration of this benefit is also uncertain. The committee concluded that the clinical benefit to patients in the NHS is not known. The cost-effectiveness estimates are therefore highly uncertain. This reflects the uncertainty about how long treatment benefit will last and the most appropriate extrapolation method for time to CPC remission and particularly time to relapse after CPC remission. Taking all the uncertainties into account, the committee concluded that darvadstrocel was not a clinically or cost-effective use of NHS resources and could not be recommended for routine commissioning.

4 Recommendations for research

- 4.1 The results of ADMIRE-CD showed that most patients tend to relapse within the first year after achieving remission and healing of the fistula in both arms of the trial. Unfortunately, there are limited data between year 1 and 2 for data on relapse and no data on relapse is available for year 2 and beyond. The committee considered that the outcomes of the ADMIRE-CD and the ongoing ADMIRE-CD II trial did not capture fully the relapsing remitting nature of Crohn's disease with perianal fistulas. The new evidence submitted after consultation did not clarify the uncertainties around the long-term benefits of darvadstrocel compared with placebo either, because the results from the literature were very different from the results of ADMIRE-CD.
- 4.2 Further research is recommended to resolve the uncertainties about the long-term clinical effectiveness of darvadstrocel compared with standard care. In particular, estimates of long-term remission rates (minimum of 2 years follow-up) in Crohn's disease with perianal fistulas are needed.
- 4.3 The health-related quality of life evidence of patients with perianal fistulas is also lacking, therefore further research is recommended. Any research should measure the effect of treatment using preference-based measures (such as use of the EQ-5D questionnaire).

5 Review of guidance

- 5.1 The guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Jane Adam
Chair, appraisal committee
September 2018

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee A](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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Final appraisal document

Darvadstrocel for treating complex perianal fistulas in Crohn's disease

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