NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Takeda (including new evidence)
   - British Society of Gastroenterology (BSG)*
   - Crohn's and Colitis UK
   - School of Health and Related Research, University of Sheffield (ScHARR)
   - **Royal College of Physicians endorse the response from BSG*
   - *DHSC submitted a no comment response*

   There were no comments received from patient or clinical experts.

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Evidence Review Group critique of company ACD response and new evidence**

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

Darvadstrocel for treating complex perianal fistula in Crohn's disease

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
4		[British Society of Gastroenterology]	I think that the NICE committee have made a fair assessment of the data and whilst we are excited about the prospect of a new treatment for this group of patients with a difficult condition, I would agree that the available data (from a single clinical trial) does suggest a modest treatment effect. The cost of the medicine is relative high and I acknowledge that the cost effective estimates are very variable. I have one or two comments to make:	Thank you for your comment. Please see responses to the individual comments below.
5		[British Society of Gastroenterology]	In section 3.10 – I would disagree that the standard of care in the UK is solely surgical intervention. The standard of care is a multidisciplinary approach including both medical and surgical treatments.	As the clinical experts explained and as the evidence suggested the main interventions that aim to treat fistulas if medical therapies do not work is seton placement with examination under anaesthesia. Please also see section 3.1 of the FAD. Section 3.10 aims to explain the part of the treatment pathway where darvadstrocel is likely to be used; in complex perianal fistula that has not responded to treatment with antibiotics, immune-modulators, TNF-alpha inhibitors, or a combination of these treatments.
6		[British Society of Gastroenterology]	Study population - I think that the study population is as similar to UK populations as in many other clinical trials and I do not accept that this is a major reason not to accept the data.	See section 3.10 of the FAD.
7		[British Society of Gastroenterology]	We would support the use of the medicine in further clinical trials and that these should be done in the UK to gain some relevant experience.	See section 4 of the FAD.
8		[British Society of Gastroenterology]	I acknowledge and support the fact that the medicine will be reviewed again when further data is available.	See section 5 of the FAD.
9		Crohn's and Colitis UK	We are very disappointed that the Committee has chosen not to recommend this innovative stem cell treatment. Perianal fistulas in people with Crohn's disease are associated with pain, discharge and considerable morbidity rates (including sphincter and perineal tissue destruction), negatively impacting on a person's quality of life and ultimately	See sections 3.1 and 3.2 of the FAD on the committee's consideration on patients and clinicians experience of the disease and the limited treatment options and section 3.23 on committee's considerations on the innovative nature of darvadstrocel.

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			their life outcomes. Our position remains that darvadstrocel should be made available on the NHS, given the limited availability of effective treatment options currently offered, the significant unmet need identified within this patient population, and the strength of evidence demonstrating the severely debilitating nature of perianal fistulas. If upheld, this decision is likely to leave groups of patients with no or limited effective medical treatment options and very low quality of life. *"My mother suffered with fistulas for many years; in the last few years of her life they became more chronic and numerous. She suffered constant pain, which was at times so excruciating she could barely stand. These waves of intense pain could come at any time, making her wary of going out. Eventually she had to have district nurses visit the house every day to change her dressings. About 2 years ago she developed cancer within one of the fistulas. Doctors concluded that it was untreatable: surgery was ruled out because they would have had to remove such a large area (one leg and buttock), radiotherapy was ruled out because the affected area was too large and chemotherapy wasn't possible because the surrounding tissue was too badly damaged. My mum sadly passed away about a month ago (in her late sixties) from the cancer after a lifetime of pain and discomfort".* Furthermore, the introduction of **this innovative therapy has the potential not just to introduce a specific healing option for patients, but to raise the standards and expertise** of healthcare professionals – across the multidisciplinary team - in treating this condition. We would strongly encourage the Committee to revisit their decision.	
10		Crohn's and Colitis UK	We wish to draw the Committee's attention to the fact that darvadstrocel significantly increases the chances of remission in one year in comparison to the placebo group. This is likely to have far-reaching effects for people affected both mentally and physically. *"I can't say it enough that having Crohn's in this way is greatly debilitating both physically and mentally. Having been very headstrong prior to my diagnoses, the result of how I've had to live since as left me a different person. This drug might not work in every case but offers patients some hope and a new alternative."*	See sections 3.2 and 3.8 of the FAD.
11		Crohn's and Colitis UK	We are very concerned that the current recommendation does not accurately reflect the physically and emotionally debilitating impact of existing surgical options felt by patients, particularly in comparison to the approach offered by	See sections 3.2 and 3.22 of the FAD.

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			darvadstrocel. Furthermore, we would ask the Committee to place more emphasis, when coming to a final decision, on evidence that indicates it is more often the case that patients will face **multiple interventions, of limited efficacy, over many years** with current treatment options. *"I've suffered with Crohn's…for nearly 10 years, and I just want my life back!* *I haven't had any partners since this due to the sheer embarrassing state of my body with setons left in place…. I don't see setons as fixing the problem other than patching it up.* *The current level of treatment can only be described as not good enough… with the prospect of reoccurring abscesses and more time spent in A&E using surgeons time... I've had too many visits for abscess surgery than I care to remember in the same spot that has been causing trouble for years. There is a great need for this treatment".* As demonstrated by evidence submitted by patients, seton surgery: • Can negatively impact on a person's quality of life; setons are reported by patients to be painful, intrusive and uncomfortable affecting self-esteem, sexual activity and everyday functions such as riding a bike or walking. • Impact on daily life/routine- for example changing (needing assistance to change) daily dressings and maintenance. • Risk continued symptoms and faecal incontinence. • May involve numerous surgeries to drain or reposition the seton. • The success of the intervention (efficacy and comfort) is dependent on the experience of the surgeon (which currently varies). • There are the associated risks of (multiple) surgery. Furthermore**, we do not consider that the decision document accurately describes** proctectomy and defunctioning surgery from the patient perspective: • Multiple surgical treatments are usually required to achieve healing, with a median of six procedures for complex fistulas and median of three for simple fistulas (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4188928/) • These are life-changing interventions which: • impact on a person's daily life of surgery, such as managing a stoma/wounds that do not heal, • can impact self-esteem, sexual relationships and **reduce fecundity,** • are stigmatising interventions, • carry the associated risks of surgery,	

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			• bring the associated costs of further surgery, lifetime costs of stoma nursing support and appliances. **In comparison to having to manage and/or live with setons and/or ostomy, this new treatment offers a much more manageable and attractive alternative to current treatment options. We feel strongly that the final recommendation does not reflect this.**	
		Crohn's and Colitis UK	We would also welcome further consideration by the Committee of the fact that immunosuppressants and antibiotics are ongoing treatments and have associated risks such as cancer, infection and antibiotic resistance (as well resources and costs associated with their prescribing and monitoring).	Darvadstrocel would likely to be used in people with Crohn's disease with complex perianal fistulas which did not respond to antibiotics, immune-modulators, TNF-alpha inhibitors, or a combination of these treatments. As it is stated in section 3.13 of the FAD, maintenance TNF-alpha-inhibitor therapy would be continued after a patient had had darvadstrocel, therefore the associated risks would not be eliminated by darvadstrocel treatment.
12		Crohn's and Colitis UK	See above. We are concerned that the current recommendation may not take account of the physically and emotionally debilitating impact of existing surgical options in comparison to the approach offered by darvadstrocel. We are disappointed that the final recommendation does not give more consideration to the evidence offered detailing the impact that this condition has on sexual relationships, pregnancy rates and the impact of current treatment options on fecundity.	See sections 3.2 and 3.22 of the FAD.
13		Crohn's and Colitis UK	A number of equalities issues were raised in evidence and discussed by the Committee such as: - sexual relationships - pregnancy - fecundity 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.	See section 3.22 on the equalities considerations of the committee.

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14		School of Health and Related Research, University of Sheffield	Typographical error In Section 3.15, it is stated that "The company presented a base-case cost-effectiveness estimate of £21,685 per quality-adjusted life year (QALY) gained (incremental costs £21,811; incremental QALYs 1.01), 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." These numbers are inconsistent with the company's base case cost-effectiveness estimate in which a 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. Please amend the numbers to be consistent with the company's response to clarification question B7. "The company presented a base-case cost-effectiveness estimate of £20,591 per quality-adjusted life year (QALY) gained (incremental costs £21,639; incremental QALYs 1.05)…" These numbers are using the deterministic ICER, they will be slightly different if you want to report the probabilistic ICER.	In the ACD the probabilistic results were reported, but these have been changed to the deterministic results to be in line with the scenario analyses results reported from the ERG. See sections 3.17–3.21 of the FAD.
15		School of Health and Related Research, University of Sheffield	Inaccuracy and unclear text In Section 3.15, it is stated that "adjusting the probabilities of moving to the proctectomy and defunctioning surgery health states in the model, based on the available evidence from St Mark's study". It should also be noted that the data used to inform the transition to the defunctioning surgery was from the Mueller *et al* prospective cohort study and the transition to the proctectomy state was from the Bell *et* al prospective cohort study. Neither of these studies related to the St Mark's study data presented as part of the company's submission. Also whilst the sentence is otherwise accurate, it is unclear what the ERG did. I recommend the following text to replace the existing text "the probabilities of moving to the proctectomy and defunctioning surgery health states in the model, were adjusted so that the model predictions matched the evidence from the Mueller *et al* and Bell *et al* studies"	Thank you for the comment, the text in section 3.17 of the FAD has now been corrected.
16		School of Health and Related Research, University of Sheffield	Potentially misleading text In section 3.17 it is stated that "In a conservative scenario analysis, 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." Conservative could imply that the ERG though that this scenario analysis was a lower bound on the effect of this factor on the ICER. This is not the case, as the ERG report (page 105) explicitly states "This scenario should be interpreted with caution, as it is intended only to inform the direction and maximum magnitude of any changes in the ICER due to the possible under prediction of utility in these three health states. For this reason, it is not incorporated in the ERG's preferred base." I recommend the following text	The text in section 3.20 of the FAD has been amended.

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			"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 magnitude of any changes in the ICER due to the possible under prediction of utility in these three health states"	
17		Takeda UK	1. Executive Summary Takeda understands that the reason the appraisal consultation document does not recommend darvadstrocel within its marketing authorisation is due to the Committee's uncertainties regarding the clinical data, particularly the long-term outcomes following treatment. The Committee recognised that additional data, relating primarily to long-term outcomes and the natural history of the disease, has the potential to reduce the uncertainty associated with the magnitude of the long-term clinical benefits with darvadstrocel. The ERG broadly agreed with Takeda's base case assumptions in the economic model. In this response, Takeda provides evidence from the literature and a Delphi panel conducted with UK clinicians to support our base case assumptions regarding long-term relapse used in the submission, and we provide what we consider to be a plausible range of ICERs based on this evidence. The data obtained from a targeted literature review on long-term relapse rates as presented in this response document has come from studies conducted in both the pre-biologic and post-biologic eras. Takeda would like to emphasise to the Committee the importance of contextualising the evidence associated with long-term relapse, where rates are particularly influenced by the definition of remission, and the maintenance treatment used. This is particularly important in respect of the use of maintenance biologic therapy, which has been shown to reduce the risk of relapse. These factors are continually evolving within clinical practice and as such, long-term evidence from older studies in the literature are likely biased towards reporting higher relapse rates due to less strict definitions of remission, and the inclusion of patients who were treated in the pre-biologic era. In line with current UK clinical practice, the economic model in the Company Submission assumes that over 80% of patients are treated with maintenance biologic therapy, even when in remission, and this is likely to further reduce the risk of relapse. Takeda believes that we have demonstrated that darvadstrocel is a much-needed intervention that addresses unmet needs in a patient population with complex perianal fistula in Crohn's Disease who are refractory to antibiotics, immunosuppressants, and/or biologic treatment options for this debilitating disease. The effectiveness of darvadstrocel in this population is considered by UK clinical experts to be clinically meaningful, and the relative treatment benefit observed with darvadstrocel compared with placebo is in line with that of biologic therapies that are considered to have revolutionised the treatment of Crohn's Disease. Takeda also notes the patient expert statements discussing the "huge benefits", "hugely welcome" and "life-changing potential" of darvadstrocel that were included in the committee meeting papers.	See response to individual comments relating to specific issues below.

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			Takeda believes that the additional analyses included in this response document support our base case ICER of £20,591/QALY; with a narrow range of plausible ICERs of between £17,068 and £36,235, rather than the higher range specified by the Committee within the ACD. Takeda is optimistic that the steps we have taken in this ACD response can now allow the committee to conclude on the most plausible cost-effectiveness range and recommend darvadstrocel for use within the NHS in England and Wales. With that objective in mind, Takeda remains committed and willing to working constructively with NICE, and if necessary other stakeholders, to secure a positive outcome from this appraisal, thus allowing access for patients to darvadstrocel in this important indication.	
18		Takeda UK	2.1 Appraisal committee's preliminary recommendations On the 16th of August 2018, the Appraisal Committee of the National Institute for Health and Care Excellence (NICE) prepared an Appraisal Consultation Document (ACD) summarising the evidence, views and draft recommendations of the committee regarding the use of darvadstrocel for use in the National Health Service (NHS) in England for treating complex perianal fistulas in Crohn's disease. The ACD sets out the draft recommendations made by the committee which currently state that: '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.'	Comment noted.
19		Takeda UK	2.2 Response to the appraisal committee's standard key questions In this document Takeda have addressed issues raised by the Appraisal Committee, and provided what we think is a fair and balanced response which addresses the uncertainties associated with the long-term outcomes and natural history of perianal fistula in Crohn's disease to estimate what we believe to be the most plausible range of incremental cost-effectiveness ratios (ICERs) for previously treated complex perianal fistulas in adults who have non-active/mildly active luminal Crohn's disease. As it has been recognised in the ACD, the standard care for complex perianal fistulas in patients with Crohn's disease is surgical intervention and seton placement (Section 3.10 of the ACD) represented by the placebo arm of the ADMIRE-CD trial. Takeda understands the committee's concern that the uncertainty associated with long-term outcomes and the natural history of the disease may result in a wide range of ICERs as discussed in the current ACD (Section 1.6 of the ACD). As a result, the Committee consider that a plausible ICER cannot be determined without better data on these outcomes. The Committee recognised that additional data collection, relating primarily to long-term outcomes of the current standard of care, and natural history of the disease, has the potential to reduce the uncertainty associated with the magnitude of the long-term clinical benefits with darvadstrocel (Section 3.16 of the ACD). To explore this uncertainty, Takeda have conducted a targeted review of the literature to identify outcomes ≥2-years in patients with perianal fistula in Crohn's disease and a Delphi panel to achieve a consensus across UK clinical experts in relation to	See responses to the individual comments below.

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			long-term recurrence and relapse. These analyses are presented in Appendix 1. Please find below the responses of Takeda to the questions from the Appraisal Committee listed on page 1 of the ACD.	
20		Takeda UK	2.3 Has all of the relevant evidence been taken into account? Takeda have provided all relevant data currently available. The main clinical evidence to support the case for the clinical and cost-effectiveness of darvadstrocel versus standard of care is the ADMIRE-CD trial. Takeda consider that the Appraisal Committee has taken all relevant data from the original submission and the data from Takeda's response to the ERG questions into account. To address the uncertainty associated with long-term outcomes and the natural history of perianal fistulae in Crohn's disease, Takeda has conducted a targeted review of the literature and a Delphi panel consisting of views from UK clinical experts (Appendix 1). These analyses are included in response to the Committee's concern associated with the uncertainty encompassed within the ICER estimates. Takeda believe these data support the opinion of clinical experts stated at the appraisal committee meeting that relapse rates would be very low for patients who have achieved remission for two years.	See section 3.12 of the FAD.
21		Takeda UK	2.4 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Takeda consider that the summaries of clinical effectiveness presented in the ACD are reasonable interpretations of the evidence (Section 3.4 to 3.11). There are a number of issues raised in the ACD relating to the analysis of clinical and cost-effectiveness of darvadstrocel in patients with perianal fistulae in Crohn's disease which we have endeavoured to clarify and address within this document, including the following key issues: • Treatment benefit of darvadstrocel relative to placebo • Uncertainty associated with long-term outcomes and the natural history of disease • Plausibility of the utilities applied in the reference case Section 2.4.3 presents arguments on why the treatment benefit should not be considered modest in this patient population. Section 2.4.3.3 comments on the clinical uncertainty associated with long-term relapse rates and natural history of perianal fistula(e) in Crohn's disease and address this with evidence from the targeted review and the Delphi Panel. Section 2.4.4 translates these findings into a plausible range of ICERs; Takeda believe that the range of ICERs used for decision making should consider the impact of data available from the literature on long-term relapse rates and anti-TNF use. Section 2.4.4 details the validation supporting the utilities informing the company's reference case; Takeda believe that these utilities are in line with previous appraisals and the clinical literature.	Comment noted.
22		Takeda UK	2.4.1 Discussion on darvadstrocel as a new treatment option (response to	Comment noted

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			Sections 3.1 and 3.2 of the ACD) Takeda agrees with the committee's comments in Sections 3.1 – 3.2 inclusive of the ACD and would like to highlight the following statements; "There are no targeted interventions for complex perianal fistulas in people who have Crohn's disease." "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." "setons are not usually curative, but aim to reduce the risk of abscess formation. Long-term remission rates are relatively low (about 10%)." "Perianal fistulas are highly debilitating, have a big impact on the person's everyday life and greatly reduce the quality of life" "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"	
23		Takeda UK	2.4.2 Discussion on clinical management and expected use of darvadstrocel (response to Sections 3.3 and 3.4 of the ACD) 2.4.2.1 Clinical Management In relation to Section 3.3 of the ACD, Takeda agree with the following statements: "patients should be seen by a multidisciplinary team who are experienced in treating complex perianal fistulas" "[darvadstrocel] should be used in specialist centres where a multidisciplinary team are available, who could gain appropriate experience in the use of this technology" "noting the requirements and logistics of administration of darvadstrocel, it would only be used in specialist centres following additional training" Takeda fully support the Committee's recommendation that the administration of darvadstrocel should be limited to a small number of specialist physicians experienced in the diagnosis and treatment of perianal fistulae in Crohn's disease. Training will be provided by Takeda to all specialist centres who will be administering darvadstrocel. Many of the UK centres with specialist expertise in the treatment of perianal fistulae are currently working together under the auspices of collaborative groups such as ENIGMA which is a research group specialising in perianal disease. Such expert networks will be leveraged to ensure experience gained in the use of darvadstrocel is quickly shared between centres. The Alofisel global registry will also support identification and sharing of best practice helping to maximise the benefits that darvadstrocel can bring to patients. 2.4.2.2 Expected use of darvadstrocel Takeda would like to correct the statement (in Section 3.4 of the ACD) that the trial excluded patients "with one fistula with one single tract." The ADMIRE-CD trial only excluded patients with > 2 internal openings or > 3 external openings, no exclusion criteria specified a minimum number of tracts. This confusion may have resulted from the definition of a complex fistula which stated that patients had to have at least 1 of the following:	See sections 3.3 and 3.4 of the FAD.

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			• High inter-sphincteric, trans-sphincteric, extra-sphincteric or supra-sphincteric (tract) • Presence of ≥ 2 external openings (tracts) • Associated collections Takeda accept the specific restrictions to certain patient populations suggested by the NICE committee i.e. those patients with >3 fistula tracts or those patients with active proctitis. However, beyond that, we would urge caution and ideally further consultation with clinical experts because we are concerned that limiting the use of darvadstrocel to the identical population studied in the ADMIRE-CD trial could unfairly (and perhaps unintentionally) restrict access to certain patient groups as discussed below: 1. "CD patients with non-active or mildly active luminal CD defined by a CDAI ≤ 220., diagnosed at least 6 months earlier in accordance with accepted clinical, endoscopic, histological and/or radiological criteria" The license for darvadstrocel states that it can be used for patients with non-active or mildly active CD however it does not specifically state a CDAI cut-off. Firstly, the use of CDAI is not common in clinical practice for the monitoring of patients with fistulating disease. Secondly, the CDAI score, which was developed for the monitoring of Crohn's disease in general, not for the monitoring of fistulising disease in particular, will not differentiate between local (i.e. rectal) and distant (small bowel) active disease, and clinical feedback strongly suggests that the presence and degree of active inflammation in the rectum is a more important consideration in the treatment of a concomitant fistula than active CD in more distant GI sites. Luminal disease activity is classified in multiple ways in UK clinical practice including clinical assessment, endoscopic assessment and through the use of patient reported outcomes. Specifying one scoring system to be used could mean patients who clinicians would normally consider to be eligible for darvadstrocel could be excluded from receiving treatment. 2. "Patient who underwent surgery for the fistula other than drainage or seton placement" UK clinical opinion is that patients will have the best chance of fistula healing if they are provided access to the best medical and surgical treatment options available. If NICE restrict access to darvadstrocel in the manner proposed, then it will not be possible to combine treatment with darvadstrocel with any of the innovative surgical approaches being developed which may prove to be effective in this group of patients. Takeda do not see any rationale such an approach and do not believe it to be in the best interest of patients. 3. "Patient with a diverting stoma" Patients with a diverting stoma and ongoing perianal fistulae represent an extremely difficult to treat subgroup of patients with a high level of unmet medical need. Since the presence of a diverting stoma does not alter the fundamental pathology or anatomy of such fistulae, Takeda do not see any reason for denying these patients the opportunity to benefit from darvadstrocel. 4. "Renal or hepatic impairment" The regulatory authorities have concluded that despite no formal assessment of darvadstrocel having been undertaken in	

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			patients with renal or haptic impairment, it was not expected that the benefit-risk profile would differ from that observed in patients without renal or hepatic impairment. 5. "Contraindication to MRI scan (e.g., due to the presence of pacemakers, hip replacements or severe claustrophobia)". Although MRI imaging constitutes standard of care for the management of perianal fistulae in most UK centres, Takeda do not believe that patients where MRI scanning is contraindicated should be denied the opportunity to benefit from darvadstrocel. In such cases clinical evaluation of the patient's fistula, typically done under anaesthetic, should be sufficient to determine whether a patient is a suitable candidate for darvadstrocel. Takeda request that the NICE Committee should specify any specific exclusions which restrict the darvadstrocel patient population (e.g. patients with proctitis and those with >3 fistula tracts) rather than stating that it "should only be used in a population identical to the population in ADMIRE-CD" (as it currently does in Section 3.4 of the ACD). This would help to avoid any confusion which could result in unnecessary (and perhaps unintended) restrictions to patient access.	
24		Takeda UK	2.4.3 Discussion on clinical effectiveness (response to Sections 3.5, 3.6, 3.7, 3.8, 3.9 and 3.10 of the ACD) 2.4.3.1 Magnitude of treatment benefit Takeda would like to address the following comment: "While the committee understood the benefit to patients of achieving complete remission, it considered that this additional remission rate is disappointingly modest." (Pages 9-10 of the ACD). The Committee highlight that treatment with darvadstrocel results in 14.1% more patients achieving CPC remission compared with the placebo arm at 52-weeks. Takeda consider, based on feedback from clinical experts and in the context of complex perianal fistula in Crohn's disease, that this is a clinically relevant benefit that should not be termed 'modest'. The increased rate of achieving remission is of huge potential benefit to patients, giving an additional treatment option where limited choices are currently available. The magnitude of benefit from darvadstrocel relative to placebo is also felt by the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) members to be clinically relevant; a recent survey demonstrated that most of the IOIBD participants considered a 15% difference (delta) from placebo for clinical remission and/or endoscopic remission to be clinically relevant.1 Additionally, the relative benefit observed with darvadstrocel compared with placebo is in line with clinical trials investigating biologic therapies, which themselves have been considered to have revolutionise the treatment of patients with IBD (e.g. 18% delta with infliximab used in patients with Crohn's Disease2, 24% delta with adalimumab3, 7% delta with certolizumab4 and 12.8% delta with ustekinumab5). Therefore, whilst Takeda acknowledge the uncertainties associated with long-term benefits (which are discussed later in this section), we believe the benefit shown in the ADMIRE-CD trial should be considered clinically meaningful in relation to patients and clinicians. As stated by the British Society of Gastroenterology in their statement to NICE, the	See section 3.8 of the FAD.

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			most important outcome for patients is sustained remission at 12 months; of patients with combined remission at week 24, a greater proportion of those treated with darvadstrocel versus control had no relapse at week 52 (75.0% vs. 55.9%). 50% and 34% of patients achieved combined remission at week 24 in the darvadstrocel and placebo arms, respectively; this results in twice as many patients achieving sustained remission at week 52 in the darvadstrocel arm (i.e. 75% x 50% = 38%) relative to placebo (i.e. 55.9% x 34% = 19%), indicating that darvadstrocel both increases the chance of achieving remission and increases the chances of a patient sustaining remission.	
25		Takeda UK	2.4.3.2 Clinical-effectiveness data for darvadstrocel is from only 1 trial with a relatively short time-frame The outcomes from the ADMIRE-CD trial demonstrate that combined remission for both the ITT and mITT populations at week 24 and week 52 show similar benefit with highly significant p values, demonstrating the reliability of these data. There are now several phase I, II and III trials which have demonstrated good outcomes with both autologous and allogenic mesenchymal stem cell therapy in the treatment of perianal fistulae in Crohn's disease.6 Of those trials that used allogenic stem cells, similar rates of fistula healing have been seen in the intervention arms of a phase IIa trial performed in the Netherlands, with 47%, (n=7/15) patients with healed fistulae at Week 127, than that seen in ADMIRE-CD, further supporting these results. Section 2.4.4 details how Takeda have validated the long-term natural history outcomes within the model.	See section 3.6 of the FAD
26		Takeda UK	2.4.3.3 The evidence on the natural history of the disease and outcome of current practice in the UK is limited (Section 3.5 of the ACD) Takeda understand that the Committee require more robust information on the natural history of the disease to assess the most plausible ICER (page 15 of the ACD). To support this decision-making process, Takeda has conducted a targeted review of the literature and a Delphi Panel to elicit clinical expert consensus. A clinical systematic literature review was conducted as part of the original NICE submission for darvadstrocel. However, this review was intended to identify clinical trials relevant to the NICE decision problem and, as such, was restricted to patients with complex perianal fistula(e) and evidence from clinical trials. The targeted review now detailed within this Section expands on this evidence base by: (1) including studies reporting complex perianal fistula and those reporting on both complex and simple perianal fistulae in patients with Crohn's disease and (2) imposing no restriction on study type. Additionally, the review is focused on providing evidence on the long-term (defined as ≥2-years) perianal fistula relapse rates. The scope of the review was expanded to consider cohorts with both complex and simple perianal fistula due to the differences in classification of fistula between countries and across time. It was hypothesised that the inclusion of simple fistula may cause improved outcomes to be reported. However, Bouguen et al. (2013)8 and Haennig et al. (2015)9 find a non-significant difference in closure rates between complex and simple fistula in multivariate analyses. Therefore, we	See section 3.5 and 3.12-3.13 of the FAD.

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			do not expect to see a big impact on reported outcomes, particularly in the longer term where fistulae are expected to have 'healed'. The Delphi Panel elicited expert opinion (n=20) from the first questionnaire and (n=10) from the second questionnaire; clinical experts included gastroenterologists, surgeons and nurses within the UK. Responses from the Delphi Panel in relation to the proportion of patients expected to maintain remission are presented in Appendix 1. These responses indicated a higher rate of relapse than observed in the literature. However, comments collected as part of the Delphi exercise indicated that there were biases arising from differences in remission definition, limited experience and selection biases (for example: surgeons would likely report a high rate of relapse as these healthcare professionals only see patients whose fistula has recurred) when estimating such long-term outcomes. Therefore, the responses to the Delphi Panel are used as supportive information only. Appendix 1 presents the methodology followed and results associated with both methods. Key findings and interpretation in relation to the decision problem are presented here. Takeda understand the limitations associated with these forms of data generation compared with the "gold-standard" randomised clinical trial. However, in the absence of long-term clinical trial data, Takeda believe that, taken together, these data suggest a plausible upper bound for long-term relapse rates for consideration by the Committee. Figure 1 presents all identified data on long-term relapse from 2-years from the targeted review; six studies were identified in the review of which five provide Kaplan-Meier data. Hellers et al. (1980)10 report a point estimate; 35% of patients who achieved healing experienced relapse within 2.5-years. *Figure 1 has been presented, but not replicated here.* Figure 1 highlights that there are differences between the short-term outcomes (<2-years) between the ADMIRE-CD trial and the observed data. There are key differences across the ADMIRE-CD trial and between the studies identified in the literature review, including: different definitions of remission, maintenance biologic usage, time points (impacting the clinical management of disease), different populations, countries, and methodologies (retrospective vs. prospective) The key factor driving the short-term divergence is likely due to the timing of remission assessment and classification. Within the ADMIRE-CD trial, patients could be assessed as in remission and relapse after one visit. Feedback from clinical experts indicates that in clinical practice, patients are classified as in remission across at least two separate visits. The timings related to assessment of remission are less clear within the six identified studies. Only one study reported remission as defined from time of the first fistula closure (Bouguen et al. (2013)8 Kim et al. (2011)11 and Haennig et al. (2015)9 both specified that remission was assessed across a prolonged period: at least 3 months and 4 months, respectively. Gottgens et al. (2015)12 and Legue et al. (2018)13 appear to assess	

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			outcomes from the point of treatment discontinuation and Hellers et al. (1980)10 did not provide sufficient detail on remission assessment. Therefore, the relapse rates presented in the literature in the short-term are likely to reflect a subgroup of patients with a more sustained remission than in the ADMIRE-CD trial data. This could account for the rapid relapse rates observed within the first 2-3 months of the ADMIRE-CD trial. Figure 2 compares the rates of clinical remission between the ADMIRE-CD trial and the ACCENT II trial; this demonstrates that the rates of relapse are aligned with other prospective randomised controlled trials using the same definition of remission and highlight that the differences observed in Figure 2 are likely due to the different definitions. *Figure 2 has been presented, but not replicated here* As outcomes are available from the ADMIRE-CD trial up to 2-years, Figure 3 presents all identified data on long-term relapse from 2-years from the targeted review with the objective of exploring the long-term natural history of perianal fistula in Crohn's disease. Table 1 presents the minimum and maximum relapse rates reported in the identified literature for patients who are in remission at 2-years. These results are compared with the linear rate applied within the model from 2-years for darvadstrocel and placebo in the base case (ICER = £20,591). *Figure 3 has been presented, but not replicated here* *Table 1 has been presented, but not replicated here* Key factors driving differences in long-term relapse rates are likely due to the definitions of remission and the evolution of clinical management. The definitions of remission warrant consideration as this directly influences the rate of relapse. The ADMIRE-CD trial uses a much stricter definition of remission than other studies reported in the literature, as does CPC remission. Therefore, patients with true healing will be identified rapidly and we will likely see a lower relapse rate in these patients. We would expect those who did not achieve true healing to relapse quickly. Simply using a clinical definition of healing, as considered by the majority of identified studies (n=5, Appendix 1), would be expected to result in a steadier decline over time. It is more difficult to achieve radiological healing. However, once patients achieve radiological remission more patients would sustain this. Gottgens et al. (2017)12 is the only identified study that considers both clinical and radiological healing for defining remission; these data present with a clear "plateau" and most closely reflect the long-term relapse rates applied within the base case model (Figure 1). This "plateau" effect is likely to be more apparent the stricter the definition of remission that is used; this is supported by feedback from the clinical experts at the first Committee meeting and responses to the Delphi Panel (Appendix 1). Feedback from the clinical experts at the Committee meeting highlighted that: "if	

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			the fistula is healed and remission is maintained until 2-years, and there is no underlying risk for future relapse, rates are likely to be very low after this time (around 10 to 20%)" (page 15 of the ACD). Specific comments from the Delphi Panel related to outcomes associated with complete closure indicate that if complete closure is achieved, then the likelihood of relapse is less. The unmet need is related to achieving genuine fistula closure which translates to long-term freedom from fistula and from symptoms. The strict criteria for remission within the ADMIRE-CD trial and the economic model mean that a greater proportion of patients in remission will have genuine fistula closure. Another difference expected to impact long-term relapse rates is the evolution of clinical management for patients with complex perianal fistula in Crohn's disease. Data identified from the targeted review ranged from 1955 to 2016; it is only from the early 2000s that anti-TNF maintenance therapy has been used in these patients14, 15 Note that the use of anti-TNF maintenance therapy was high in both arms of ADMIRE-CD. Table 2 presents the anti-TNF therapy use described within the identified literature. Note: studies presented anti-TNF therapy use in differing levels of detail. Therefore, it cannot always be ascertained which therapy was associated with maintenance use. *Table 2 has been presented but not replicated here*. The multivariate and univariate analyses conducted within the literature emphasise the positive impact of continued maintenance therapy on sustaining fistula closures. Two papers (Bouguen et al. (2013)8 and Kim et al. (2011)11) provide Kaplan-Meier data for patients receiving treatment with anti-TNF maintenance therapy compared with those patients that are not receiving this treatment (Appendix 1); these analyses show much improved outcomes for anti-TNF treated patients. Additionally, a letter to the editor published in the Journal of Crohn's and Colitis from St. Marks Hospital within the UK supports these findings; no patients (n=11) with radiologically defined healing were found to relapse who were maintained on biologic therapy as compared to 2/3 (n=6 of 9) of patients who relapsed once biologic therapy was discontinued.16 These papers emphasise the improved outcomes experienced with biologic maintenance therapy given whilst a patient with perianal Crohn's Disease is in remission; the ECCO guidelines now recommend continuing biologic therapy in patients with perianal fistula due to these improved outcomes.17 Clinical practice within the UK reflects this; the Delphi Panel indicates the majority of clinicians would treat patients with biologic maintenance therapy following darvadstrocel and would expect to see improved outcomes associated with this clinical management approach. The UK advisory board informing the treatment mix for the remission health state estimated that >80% of patients would be receiving biologic therapy; this is costed within the economic model. Bouguen et al. (2013)8 and Gottgens et al. (2016)12 consider up to 57% and 41% of patients receiving anti-TNF therapy, respectively. Whilst this use is still considerably less than we would expect to see	

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			in current UK practice, this represents the highest anti-TNF therapy use across the identified literature and so provides the best comparison of long-term relapse rates for the economic model. With the stricter definition of remission and the evolved clinical management, Takeda consider that better long-term outcomes following darvadstrocel will be observed in UK clinical practice compared with those identified within the literature. The outcomes presented in Gottgens et al. (2016)12 provide the best approximation of long-term relapse rates in current clinical practice; the definition of remission and the biologic therapy use best approximate those inputs used within the economic model. Outcomes presented in Bouguen et al. (2013)8 provide a supportive comparison as the anti-TNF therapy use approximates the inputs used within the economic model. However, this paper considers a looser definition of remission (clinical remission). Therefore, Takeda believe that the long-term relapse rates applied in the base case of the economic model, and as presented in Figure 1, provide the best approximation of the "true" underlying relapse rate. Takeda consider that the maximum relapse rates at 5- and 10-years are 16.92% and 24.02%, as defined by Bouguen et al. (2013)8 and Gottgens et al. (2016).12 The impact of these relapse rates on the model results are presented in Section 2.4.4.2.	
27		Takeda UK	2.4.3.4 There is an ongoing clinical trial, which will provide further results on the clinical effectiveness of darvadstrocel Takeda agree that the ongoing ADMIRE-CD II trial may provide further evidence on the clinical effectiveness of darvadstrocel for the treatment of complex perianal fistula in patients with Crohn's disease. However, these data are only expected to be available in 2022, and will be limited to a one-year follow up. A global registry of patients (the INSPIRE registry) is being funded by Takeda as our commitment to provide additional data. The INSPIRE registry is anticipated to collect data on all patients treated with darvadstrocel globally. It will however take several years to generate a meaningful amount of data on long term outcomes following darvadstrocel treatment.	See section 3.9 of the FAD.
28		Takeda UK	2.4.4 Discussion on modelling the long-term benefits of darvadstrocel (response to Section 3.16 of the ACD) Section 2.4.4.1 presents the long-term relapse rates and anti-TNF use from the literature identified within the targeted review. In this Section, scenarios within the economic model explore the impact of these inputs on the ICER. In doing so, Takeda present the clinically plausible range of ICERs: from £17,068 to £36,235. Additionally, given the data presented, we hope to demonstrate to the Committee the clinical implausibility of the log-normal parametric curve for time to CPC relapse data within the economic model. Please note that all scenarios are presented for validation purposes only, no changes have been made to the base case economic model from the model that was originally submitted (with a 3.5% discount rate for both costs and QALYs). 2.4.4.1 Long-term relapse rates	See sections 3.18-3.19 of the FAD.

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			Results of the targeted literature review and interpretation relative to similarities with the application of the ADMIRE-CD data within the model indicate that maximum long-term relapse rates for the subgroup of patients who are in remission at 2-years are: 16.92% at 5-years and 24.02% at 10-years (based on Bouguen et al. (2013)8 and Gottgens et al. (2016)12). To align the long-term relapse rates between the model and the literature, the 4-weekly constant relapse rate (applied from 2-years and presented on the "Clinical inputs" sheet) was varied. Note: for simplicity equal long-term relapse rates were assumed across the placebo, salvage therapy and darvadstrocel arms. Therefore, no additional long-term benefit of darvadstrocel vs control was applied after 2-years. This is a pessimistic scenario as the data indicate a trend for improved remission maintenance with darvadstrocel relative to placebo. Assuming equal relapse rates increases the base case ICER from £20,591 to £22,273. When setting the constant cyclical rate to reflect 16.92% relapse at 5-years, the resultant ICER was £36,235. When setting the rate to reflect 24.02% relapse at 10-years, the resultant ICER was £28,370. When accounting for the relapse rates and reduced anti-TNF use as maintenance therapy across the literature, the ICERs were £29,038 and £17,068, respectively (accounting for 57% and 41% use in the Bouguen et al. (2013)8 and Gottgens et al. (2016)12 studies, respectively). Results of the scenarios are presented in Table 3. *Table 3 has been presented but not replicated here* The long-term relapse rates applied within the model in each of these two scenarios is presented in Figure 5. It should be noted that, due to the model structure, a constant linear relapse rate is applied from 2-years for the duration of the model time horizon. This simplifying feature means that the "plateau" effect is not accounted for when exploring these scenarios. Consequentially, the modelled relapse rates beyond 10-years are higher than would likely be observed. Feedback from clinical experts, responses to the Delphi Panel and the shape of the Kaplan-Meier curves identified from the literature indicate that for patients who have achieved true fistula closure (clinical and radiological healing) and maintained remission for 10-years, a very small rate of relapse would be expected. This should be considered when interpreting the ICER estimates of £28,370 and £36,235; inclusion of the "plateau" effect would reduce these estimates. The long-term relapse rates applied in the model base case (ICER = £20,591) is shown for the placebo arm in Figure 2. As discussed in Section 2.4.3.3, the "true" relapse rates are likely lower than observed in the literature due to stricter definitions of remission and increased anti-TNF use. Additionally, a "plateau" effect would be observed in the long-term which is not reflected in the current application. Therefore, Takeda believe that the base case economic model accurately reflects a plausible reference point. *Figure 4 has been presented but not replicated here.*	

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			For reference, Table 4 displays the proportion of relapses predicted by each parametric curve within the model for the subgroup of patients who have sustained remission for 2-years – using the model reference case (ICER = £20,591). This table emphasises that all other parametric curves within the model over-predict relapse rates beyond 2-years – this is mainly due to the constant rate that is derived from the curve choice and applied within the model from 2-years. When the log-normal curve is selected for time to relapse outcomes within the base case model the ICER increases from £20,591 to £104,398. However, if the constant relapse rates beyond 2-years are set equal to those applied under the Gompertz selection, the ICER is £29,929. This emphasises that the ICER is driven by the long-term relapse rates (rather than curve choices) which has been addressed above. *Table 4 has been presented but not replicated here.*	
29		Takeda UK	2.4.4.2 Long-term remission rates In the ACD, the Committee consider the generalised gamma parametric curve for extrapolating time to CPC remission within their scenarios exploring the range of ICERs (page 14 of the ACD). This increases the ICER from £20,591 to £30,064. In this Section, we discuss why we believe the Gompertz parametric function has both external and internal validity in both its application and in terms of the derived results. Takeda acknowledge that the AIC and BIC statistics indicate that the generalised gamma, the Gompertz and the log-normal provide reasonable fits to the data. However, these statistics only inform us on the fit to the observed data. The underlying hazard associated with the generalised gamma is clinically implausible in this setting; extrapolation of this curve assumes all patients would achieve remission over time. Feedback from clinical experts and observed data indicate that a proportion of patients do not achieve remission. Additionally, statistical validation shows that the shape of the empirical hazards does not approximate the generalised gamma and follows (closely) to the Gompertz distribution (as shown in the response to the clarification questions). As highlighted within the ERG report, the empirical hazards remain within the confidence intervals of the Gompertz at all time points; the only parametric curve where this is the case. Additionally, clinical experts believe that the rate of remission will decline to zero over time without a further intervention. Therefore, the Gompertz presents the only statistically and clinically plausible curve choice. As a result of providing a better statistical fit to the data, the Gompertz model is more accurate in predicting the probability of remission at week-52. The Gompertz predicts 64% and 47% of patients to achieve CPC remission in the darvadstrocel and control arms, respectively (delta of 17%). This is in line with the data from the ADMIRE-CD trial which shows 64% and 48%, respectively (delta of 16%). Conversely, the generalised gamma predicts 59% and 52%, respectively (delta of	See section 3.18 of the FAD.

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			7%), further indication that this is not a good fit to the data.	
30		Takeda UK	2.4.5 Discussion on the health-related quality of life evidence (response to Section 3.11 and 3.17 of the ACD) We understand NICE's concerns relating to the lack of EQ-5D data in the ADMIRE-CD trial. However, the vignette study commissioned to estimate utility values for this submission was a robust, methodologically robust study with a significant number of participants (n=835 general public and n=162 patients with Crohn's disease). Therefore, we consider that this vignette study provides reliable estimates of utilities. Additionally, the derived utility estimates are in line with values used in previous NICE appraisals and with average utility values reported in the literature. The Committee notes that the ERG's clinical experts considered that the utility values following successful defunctioning (0.567), successful proctectomy (0.564) and in the "mild chronic symptomatic fistulae" health state (0.578) may be underestimated. Whilst there is no evidence available within the relevant population, there is evidence available within similar populations for proctectomy. Previous NICE appraisals for biologics in Ulcerative Colitis (UC) have also considered post proctectomy as a health state and this has been associated with utility values between 0.6 and 0.61.21 The same procedure would be conducted for patients with UC and patients with perianal fistula in Crohn's disease. However, outcomes are often worse for patients with perianal fistula in Crohn's disease; patients with UC would often have a pouch formed and, as UC is limited to the large bowel, proctectomy should fully resolve their symptoms. Comparatively, patients with perianal fistula in Crohn's disease would require a stoma and - as Crohn's disease can occur at any site within the digestive tract (from the mouth to the anus) - proctectomy may not alleviate all symptoms of Crohn's disease. Therefore, we consider that the utility value used in this appraisal in the successful proctectomy health state accurately reflects the quality of life associated with these patients. Additionally, the average utility predicted by the model for patients with active disease (0.48-0.54) aligns with the literature (0.47) and the responses of patients with perianal fistula in Crohn's disease participating in the vignette study (0.47). The average utility predicted by the model is calculated by dividing the number of undiscounted QALYs gained within each of the active health states (all of CSF Mild, CSF Severe, Unsuccessful Proctectomy and Unsuccessful Defunctioning, or the non-surgical health states of CSF Mild and CSF severe) by the average time spent in each health state. This gives an average utility predicted by the model for patients with active disease as between 0.48 and 0.54. As discussed in the original submission dossier, the Mahadev study22 showed that patients with perianal Crohn's disease were willing to trade an average of 5.3-years of life for a cure, this equates to an average utility of 0.47. Some of the patients with Crohn's disease participating in the vignette had a perianal fistula, these patients were	See section 3.20 of the FAD.

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			asked to rate their current health state and this gave an average utility value of 0.468. Therefore, the model's prediction of utility for patients with active disease is slightly higher than in the literature and from that reported by patients with Crohn's disease and an active fistula in the vignette study. Where validation has been possible, the results from the vignette study are shown to be comparable with the literature and patients' feedback. Therefore, we consider that the utility values elicited from the vignette study are an accurate representation of the significant impact that perianal fistula in Crohn's disease has on patients' quality of life. Additionally, within the one-way sensitivity analysis, utility values derived from the vignette study were varied across their reported confidence intervals and showed only a minor impact on the ICER.	
		Takeda UK	2.4.6 Discussion on the most plausible cost-effectiveness range: "The most plausible cost-effectiveness estimate is uncertain, and darvadstrocel is unlikely to be a cost-effective use of NHS resources" (response to Section 3.18 of the ACD) The Committee considers that the clinical uncertainty associated with the long-term benefit of darvadstrocel and the underlying natural history of the disease could translate into ICERs for darvadstrocel compared with placebo up to £143,131 (with the Department of Health approved patient access scheme, PAS). Based on this, the Committee states that darvadstrocel is not recommended for patients with complex perianal fistula in Crohn's disease. The company's response to the ACD within this document aims to address the uncertainty associated with long-term relapse rates and the natural history of perianal fistula in Crohn's disease. Exploratory analyses modelling the identified long-term evidence results in an ICER range of £17,068 and £36,235 (including PAS). Takeda consider that the analyses presented to the Committee provide additional validation of the company's base case (ICER of £20,591) and bookend the potential for the residual uncertainty to drive results above an ICER of £36,235. Takeda believe the exploratory analyses and validation support a case for darvadstrocel to be considered as plausibly cost-effective at willingness to pay threshold of £30,000.	See section 3.21 of the FAD.
31		Takeda UK	2.5 Are the provisional recommendations sound and a suitable basis for guidance to the NHS? In conclusion, Takeda disagree that the committee's provisional negative recommendation for darvadstrocel is sound and a suitable basis for guidance to the NHS (see Section 1.1 and Section 3.18 of the ACD). Takeda acknowledge the uncertainty associated with long-term outcomes. However, exploratory analyses and validation, as presented within this document, indicate that the uncertainty associated with results could drive the ICER down to £17,068 as well as up to £36,235. Only one scenario results in an ICER above the £30,000 willingness to pay threshold.	See section 3.24 of the FAD.

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			Takeda are collecting outcomes through the INSPIRE registry. The INSPIRE registry is a global registry that aims to collect data on all patients treated with darvadstrocel with the intention of ensuring best value is achieved. This is a significant investment by Takeda and highlights the commitment that we, as a company, have for maximising the benefits that darvadstrocel can bring to patients. A steering group has been set up which includes both clinician and pharmacy representation from the UK. With the collaboration that is apparent with the UK community through groups such as ENIGMA (a research group specialising in perianal disease) and the availability of global data on darvadstrocel treated patients, we are confident that clinicians will be able to quickly identify best practice to ensure that the best possible outcomes are achieved with darvadstrocel. Takeda fully support the Committee's recommendation that the administration of darvadstrocel should be done by a limited number of specialist physicians experienced in the diagnosis and treatment of conditions for which darvadstrocel is indicated. Training will be provided to all specialist centres, initially this will utilise the expertise gained by European clinical experts through the ADMIRE-CD trial but over time will utilise the expertise gained by UK surgeons and clinicians from early experience centres. Many of the UK specialist centres are currently working together through groups, such as ENIGMA. These networks will be leveraged to ensure experience can be quickly shared across these centres. Taking all factors into account, Takeda is optimistic that the steps we have taken in this ACD response can reduce the clinical uncertainty felt by the Committee and allow the committee to conclude on the most plausible cost-effectiveness range and recommend darvadstrocel for use within the NHS in England and Wales. Such an outcome would allow patients and the NHS to benefit from timely access to darvadstrocel as a treatment option for complex perianal fistula in Crohn's disease. With that objective in mind, Takeda remains committed and willing to working constructively with NICE, and if necessary other stakeholders, to secure a positive outcome from this appraisal. *List of references had been presented but not replicated here.*	

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
ID960 darvadstrocel ACD stakeholder comments form BSG.doc	[British Society of Gastroenterology]	[Insert disclosure here]	5	
ID960 darvadstrocel ACD stakeholder comments form Crohns and Colitis.doc	Crohn's and Colitis UK	None	5	
ID960 darvadstrocel ACD stakeholder comments form-ScHARR.doc	School of Health and Related Research, University of Sheffield	None	3	
ID960 darvadstrocel ACD response v0.1 05.09.18	Takeda UK			

Comments received from members of the public through the NICE Website

Role	Section	Comment [sic]	Response
NHS Professional		I am concerned about the negative review as this is a viable treatment option for patients with refractory perianal Crohn's disease. Several of these patients end up with a permanent end stoma	Thank you for your comment. See section 3.2 of the FAD
Patient		Hello, having read the recent reports that this drug is not to be authorised is great disappointment to me. I've suffered in this area of Crohns for 10 years since I was 20. As a gay male this is absolutely torturing me. There is a great need for developments to specifically treat perianal fistulas and to read that this isn't going to be authorised has killed any hope I had. Surgery has failed as an option for me. Immunosuppressants haven't worked. The success stories of this drug speak for them selves. I'm desperate for this to be become legalised. The easiest way of putting is by putting your self in the shoes of someone that has this specific condition. It's had impact on my confidence. I'm too embarrassed of my body to meet anyone. When I first heard of this drug I thought amazing, and now hearing that for economic concerns has really made me feel let down. Can't this even be given privately at cost? All I can say is whoever has made the decision not to authorise probably hasn't met anyone with this area of Crohns. I strongly urge you to reconsider your opinion on this. This has been the only thing keeping me sane and positive. I can't face more years with no treatment developments. Please reconsider and think how this impacts people with perianal fistulas. There is no other way of getting rid of mine due to how it passes the anal muscles. If I have surgery I could run a risk of incontinence. Therefore this been less evasive sounded like the perfect treatment. My consultants in Leeds even said the same. Before I heard of the trials for this I even considered taking my own life I was that depressed about my health. This drug would give me the chance to get my life back! Even consider as a private treatment. Please reconsider and think the benefits outweigh the reoccurring hospital visits and surgery. The cost would surely level out. I have puss the drains by my back end and a seton stitch. There is a need for this I can't stress this enough. I moved to Kuwait for work and was hoping by January 2019 this would be available. Please take into account my situation or please call me to discuss. Kind Regards [redacted] I can't stress enough how much this new innovative treatment is needed. I can't have surgery on my fistula due to the complexity of where it lies across the schincter muscles and infusion treatments have failed me. This	Thank you for your comment. See sections 3.2 of the FAD on the committee's consideration on how people are affected by the condition; Section 3.7 on what the most appropriate outcome measure for both patients and clinicians in this disease area; Section 3.8 on the committee's consideration of the clinical trial results; Section 3.22 on the equality considerations and section 3.23 on the innovative nature of darvadstrocel.

		to me is the only thing keeping me positive that an actual tailored non evasive treatment to help cure the fistula. I have had this ongoing for ten years almost and cannot stress enough how much my anxiety levels have raised as a result. I can't meet anyone sexually, my confidence is at an all time low. I've had re-occurring absesses several times and this treatment would potentially put an end to years of suffering. I used to be a very head strong person. This complication of crohns has ruined my personal relationships and is almost on the edge of ruining my career. I've considered suicide many times and cannot face more years without no cure for the fistula. I'm desperate. The medicine might be expensive but the results I've heard are extremely positive. The time I've spent in hospital, failed infusion treatments which aren't specifically designed to treat fistulas have failed me. Please consider the people who can't tolerate infusions or where surgery isn't an option. I'm desperate need this	
NHS Professional		The committee have rightly questioned the relevance of an approximately 15% difference from the sham-surgery arm. I think it is worth pointing out that this population of patients really do currently lack good alternative treatment options beyond surgical interventions that lack a solid evidence base and that have poor published success rates that have tended to further decline in subsequent case series. The long term outcome of fistula tracts that have healed will be critical to determine the benefit of this intervention. The committee have rightly commented that there is much uncertainty in this area, but I would agree with the expert advice that the committee has been given suggesting that relapse is generally an early phenomenon noted in the first 1-2 years and that, whilst relapse can occur after this time, it is less common. There is some support for this in the published literature - see for example the survival curve in figure 4 from the relatively large case series presented by Bouguen et al Clin Gastroenterol Hepatol. 2013. The effectiveness of the present therapy in achieving fistula healing to by a robust assessment method at 1 year has been proven, with some data available beyond the first year. It would seem to me that we have a therapy that has the potential to achieve fistula closure by one of the more stringent definitions used in clinical trials of late, to at least the timepoint when most fistula recurrence would have been expected, and that we have effective therapies (anti-TNF) for preventing relapse/new fistula formation (see eg ACCENT-II trial). This is not to say that there is much room in the literature for more information and longer term studies. But it is unrealistic to expect some of the sorts of really long term followup studies to be available - and indeed	Thank you for your comments. See sections 3.5, 3.6, 3.8, 3.12, 3.13 and 3.18 on the committee's considerations on the disease burden of Crohn's disease, the evidence on the natural history of the disease, the evidence on clinical effectiveness of darvadstrocel and the uncertainties around long-term benefits of darvadstrocel.

		such studies are often flawed by the time they do get published since standards of care and available medications move on. I feel we should be cautious about denying a patient group with a condition that currently lacks effective treatments access to a treatment of proven benefit in this context.	
NHS Professional		I have been through the useful slides and appraisal document in its entirety. They both make a great deal of sense to me and I am in agreement with the vast majority. I was also slightly surprised by the costs of a single course of Darvadstrocel, although I am led to believe that the NHS would pay an undisclosed but reduced price, to be agreed with Takeda. This also seems entirely appropriate.	Thank you for your comment. See section 2 for information about the price of darvadstrocel. And section 3.21 on the committee's consideration on the most plausible cost-effectiveness results.
NHS Professional		This is a massively important issue for patients with Crohn's disease. Patient involvement exercises undertaken to underpin research activity has indicated that the debility caused is significant, underreported and symptoms that are reported are under-appreciated by clinicians. Existing treatments have a high rate of primary and secondary failure. The difference between Darvadstrocel and standard care in the trial by Panes was statistically significant and clinically important - particularly given Comment 1 above, and limited options for therapy. This was a group who had already failed available treatments and where the intervention proved superior to optimised standard care where great attention to preparing the fistula track had been taken. Given the debility experienced, and failed alternative therapies, options for patients here include a defunctioning stoma (which is usually not reversed) or proctectomy - both life altering surgeries. The data suggests that fistula closure is likely to be sustained - obviously important in reducing debility. Clearly longer term results beyond the currently available studies are not available to determine subsequent relapse rates. It is certainly possible that having achieved fistula closure for intervals of 12-24 months, that this might be sustained. It shoudl be remembered that loss of response occurs regularly with antiTNF agents, and as a result patients may require repeated examinations under anaesthetic, drainage of sepsis and seton insertion, followed by further antiTNF or switch of agents if antidrug antibodies develop.	Thank you for your comment. See section 3.1 on the committee's consideration on currently available treatment options; section 3.8 on the committee's consideration on the clinical trial evidence and section 3.6 and 3.18 on evidence on the long-term benefits of darvadstrocel.
NHS Professional		This is a careful and well conducted appraisal. The only comments I would make are 1) this is a very difficult clinical problem representing possibly the greatest unmet need in the management of complex Crohn's disease. Current	Thank you for your comment. See section 3.1 and 3.2 of the FAD on the committee's consideration on the disease burden of Crohn's disease with perianal fistulas and the

		treatments are unsatisfactory 2) The reasoning in section 3.10 does not make sense: if placebo response in the ADMIRE CD in a nonUK trial population is higher than expected in a UK population, then this makes it more likely that the IMP would have a greater effect in a UK population, not less. 3) The economics are difficult to refute - but it would be very useful to have this agent available for selected patients.	currently available treatment options. See section 3.10 of the FAD on the treatment effect observed in the placebo group of the trial. See section 4 on recommendations for research.
NHS Professional		I agree with the committee findings. This is an exciting new treatment for patients whose illness is often difficult to treat and debilitating. However given the concerns re long term outcomes, apllicability to uk population together with cost and logistical issues , I agree that we should wait for data from the next study before approving use	Thank you for your comments. See section 4 on recommendations for research
NHS Professional		The RCN Inflammatory Bowel Disease Network Group have concerns that a new treatment for perianal Crohn's disease, a disease area of significant unmet need, has been given an unfavourable review. Perianal disease has a massive impact upon the mental health, quality of life, psychosocial well-being, as well as having a significant symptom burden including perianal pain, abscesses, faecal incontinence and drainage of blood and pus via the external wounds. The impact upon patients lifestyle and relationships is immeasurable. Perianal Crohn's disease patients have very much been the â€˜poor relations in terms of positive medical care improvements. Alofisel very much offers a shift change to redress this balance in a cohort of predominantly young people whose luminal disease is well managed, but they continue to endure the complications of a devastating disease. Current treatment results in repeated perianal surgeries which are painful, intrusive and potentially destructive to continence mechanisms. Repeated abscesses also risk faecal continence, the impact of which cannot and should not be underestimated. As the EMA license is for patients with complex perianal fistulae who have mildly or inactive luminal disease, and the complexity of the surgical administration will dictate the treatment will be reserved for highly specialised centres and candidates will be carefully selected, treatment outcomes are likely to be very good. Ongoing research into producing acellular matrix to provide scaffolding for stem cells to stay and proliferate is likely to maximise benefits to a wider patient group going forward. We feel it is unfair to deny patients potential relief from a dreadful disease because the long-term efficacy data is not yet available. It offers an alternative treatment option for people with significant, debilitating disease. [redacted], on behalf of the RCN IBD Network	Thank you for your comment. See section 3.1 and 3.2 of the FAD on the committee's consideration on the disease burden of Crohn's disease with perianal fistulas and the currently available treatment options.

		Group	
NHS Professional		Thank you for consulting on this issue. Perianal Crohn's disease is an area of huge unmet need internationally, identified in several publications and by the James Lind Alliance priority setting exercise as a priority for research and clinical advance. The scale of morbidity, symptoms and impact on quality of life of this condition can be enormous and I've no doubt that patients and charities such as CCUK will have made contact with you to make that point. I can certainly echo it, as I operate on these patients regularly to try to keep their symptoms under control as best I can and in some cases, ultimately, to defunction or even remove the rectum entirely. The principle medical treatments have limited efficacy. They certainly help a good number of patients and induce improvement and even sometimes 'remission', although the definition of this in the medical treatment trials tend to be fairly loose, being based entirely on symptoms and the appearance of the external opening which tends to fluctuate over time in some patients anyway. We desperately need a treatment which actually closes fistulae, with deep tissue healing of the tracts, and does so in a greater proportion of patients. The potential for stem cells is that they may do just that, providing robust healing of fistulae in a group of patients. The ADMIRE-CD study certainly raises the possibility of sustained remission in a group of patients much larger than in the comparator group. The delta of 15% is significant given the morbidity that patients face and also because the comparator group has what is probably an elevated success rate initially thanks to the closure of the IO which probably gives an early benefit before the rates of remission fall away to those we would expect from medical treatment alone as time goes on (at 1 and 2 years, for example), when they represent the true current clinical picture, and the delta at this point is larger as a result. We very much want to be able to offer this to patients who have not benefitted from the advanced medical treatments (e.g. anti-TNF agents) currently available and who will head, in some cases, towards a permanent stoma. The evidence for long term healing is scant but it is my view that in those patients in whom we do see genuine deep tissue remission, it is likely that that remission will persist. The disappointing rates we often see are, in my view, related to a much looser definition of remission which is therefore more likely to ebb away, and to a selection bias that most clinicians with an interest in this area see, since the patients who do well tend to vanish from our clinics into those of the IBD nurses etc. If stem cells can produce robust fistula closure, it may well be the case that this persists in the longer term in which case it would be a very powerful resource in refractory disease. Many thanks for considering this agent.	Thank you for your comments See sections 3.1 and 3.2 of the FAD on the committee's consideration on the disease burden of Crohn's disease with perianal fistulas and the currently available treatment options. See section 3.8 on the committee's consideration on the clinical trial evidence and section 3.6 and 3.18 on evidence on the long-term benefits of darvadstrocel.

NHS Professional		Thank you for the opportunity to respond to this consultation document.I comment on this as a surgical registrar with an IBD interest, and as I have just completed my thesis on this subject. THE EVIDENCE BASE One of the key considerations of this new treatment is where it sits in the evidence base. As you will be aware, the treatment of Crohn's anal fistula is a multi-modal approach combining medicine and surgery [1]. Thanks to the many medical trials in the field, we can identify drugs to use in the induction and maintenance of clinical response or remission[2]. Unfortunately the surgical literature is underdeveloped; it is based on retrospective studies of poorly defined cohorts, with poorly defined outcomes [3]. In comparison, we are presented with a randomised trial, with a well defined cohort, intervention and outcomes for darvadstrocel [4]. This means that we have a high level evidence for this treatment, if not a large volume as for other treatments. Despite this, the reported benefits from the RCT report outcomes which compare favourably to those reported elsewhere in the literature. The inclusion criteria used in this trial are not overly restrictive when compared to others reported in the literature [5, 6]. The limited evidence in the field is recognised by the panel and by clinicians [7]. A recommendation from NICE to encourage research into quality of life, stratification and robust outcomes measurement would be helpful when proposing research to funders. THE CLINICAL NEED This treatment is the potentially the most significant innovation in the field since the ACCENT II trial [8], and is much needed a field with significant clinical need. We have cared for patients who would fit the criteria for darvadstrocel, but are facing the near to mid-term prospect of stoma formation/protectomy. This group of patients is typically young and economically active. They are keen to avoid the either of these interventions for their own quality of life and mental wellbeing, as well as to minimise their economic well being and risk of losing their jobs. LOCATION OF CARE SERVICES Given both the cost, and the logistic efforts required to deliver this treatment to a hospital, it is likely that this will limit its use to higher volume centres. This fits with the general trend in IBD care[9], and may go some way to address variation identified in the care of patients with Crohn's anal fistula, particularly in definitive surgical treatment [10, 11]. This may lead to an indirect reduction in costs in the longer term. *References have been presented, but not replicated here*	Thank you for your comment. See sections 3.4-3.6 and 3.8 on the clinical trial evidence and section 4 on the committee's recommendations for areas of research. See section 3.1 and 3.2 on the committee's consideration on the committee's consideration on the impact of the disease on patients and management of complex perianal fistulas. See section 3.3 of the FAD on the potential implementation of darvadstrocel within the NHS.

Darvadstrocel for treating complex perianal fistulas in Crohn's disease [ID960]: Response to the first ACD

Submitted by Takeda UK Ltd.

Single Technology Appraisal (STA)

National Institute of Health and Care Excellence

Submitted 5th September 2018

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List of Abbreviations

ACD	Appraisal consultation document
DSU	Decision support unit
ERG	Evidence review group
HRQL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAS	Patient access scheme
TSD	Technical support document

1. Executive Summary

Takeda understands that the reason the appraisal consultation document does not recommend darvadstrocel within its marketing authorisation is due to the Committee's uncertainties regarding the clinical data, particularly the long-term outcomes following treatment. The Committee recognised that additional data, relating primarily to long-term outcomes and the natural history of the disease, has the potential to reduce the uncertainty associated with the magnitude of the long-term clinical benefits with darvadstrocel. The ERG broadly agreed with Takeda's base case assumptions in the economic model.

In this response, Takeda provides evidence from the literature and a Delphi panel conducted with UK clinicians to support our base case assumptions regarding long-term relapse used in the submission, and we provide what we consider to be a plausible range of ICERs based on this evidence.

The data obtained from a targeted literature review on long-term relapse rates as presented in this response document has come from studies conducted in both the pre-biologic and post-biologic eras. Takeda would like to emphasise to the Committee the importance of contextualising the evidence associated with long-term relapse, where rates are particularly influenced by the definition of remission, and the maintenance treatment used. This is particularly important in respect of the use of maintenance biologic therapy, which has been shown to reduce the risk of relapse. These factors are continually evolving within clinical practice and as such, long-term evidence from older studies in the literature are likely biased towards reporting higher relapse rates due to less strict definitions of remission, and the inclusion of patients who were treated in the pre-biologic era.

In line with current UK clinical practice, the economic model in the Company Submission assumes that over 80% of patients are treated with maintenance biologic therapy, even when in remission, and this is likely to further reduce the risk of relapse.

Takeda believes that we have demonstrated that darvadstrocel is a much-needed intervention that addresses unmet needs in a patient population with complex perianal fistula in Crohn's Disease who are refractory to antibiotics, immunosuppressants, and/or biologic treatment options for this debilitating disease. The effectiveness of darvadstrocel in this population is considered by UK clinical experts to be clinically meaningful, and the relative treatment benefit observed with darvadstrocel compared with placebo is in line with that of biologic therapies that are considered to have revolutionised the treatment of Crohn's Disease. Takeda also notes the patient expert statements discussing the "*huge benefits*", "*hugely welcome*" and "*life-changing potential*" of darvadstrocel that were included in the committee meeting papers.

Takeda believes that the additional analyses included in this response document support our base case ICER of £20,591/QALY; with a narrow range of plausible ICERs of between £17,068 and £36,235, rather than the higher range specified by the Committee within the ACD. Takeda is optimistic that the steps we have taken in this ACD response can now allow the committee to conclude on the most plausible cost-effectiveness range and recommend darvadstrocel for use within the NHS in England and Wales. With that objective in mind, Takeda remains committed and willing to working constructively with NICE, and if necessary

other stakeholders, to secure a positive outcome from this appraisal, thus allowing access for patients to darvadstrocel in this important indication.

2. Introduction

2.1 Appraisal committee's preliminary recommendations

On the 16th of August 2018, the Appraisal Committee of the National Institute for Health and Care Excellence (NICE) prepared an Appraisal Consultation Document (ACD) summarising the evidence, views and draft recommendations of the committee regarding the use of darvadstrocel for use in the National Health Service (NHS) in England for treating complex perianal fistulas in Crohn's disease. The ACD sets out the draft recommendations made by the committee which currently state that:

'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.'

2.2 Response to the appraisal committee's standard key questions

In this document Takeda have addressed issues raised by the Appraisal Committee, and provided what we think is a fair and balanced response which addresses the uncertainties associated with the long-term outcomes and natural history of perianal fistula in Crohn's disease to estimate what we believe to be the most plausible range of incremental cost-effectiveness ratios (ICERs) for previously treated complex perianal fistulas in adults who have non-active/mildly active luminal Crohn's disease.

As it has been recognised in the ACD, the standard care for complex perianal fistulas in patients with Crohn's disease is surgical intervention and seton placement (Section 3.10 of the ACD) represented by the placebo arm of the ADMIRE-CD trial. Takeda understands the committee's concern that the uncertainty associated with long-term outcomes and the natural history of the disease may result in a wide range of ICERs as discussed in the current ACD (Section 1.6 of the ACD). As a result, the Committee consider that a plausible ICER cannot be determined without better data on these outcomes.

The Committee recognised that additional data collection, relating primarily to long-term outcomes of the current standard of care, and natural history of the disease, has the potential to reduce the uncertainty associated with the magnitude of the long-term clinical benefits with darvadstrocel (Section 3.16 of the ACD). To explore this uncertainty, Takeda have conducted a targeted review of the literature to identify outcomes ≥2-years in patients with perianal fistula in Crohn's disease and a Delphi panel to achieve a consensus across UK clinical experts in relation to long-term recurrence and relapse. These analyses are presented in Appendix 1.

Please find below the responses of Takeda to the questions from the Appraisal Committee listed on page 1 of the ACD.

2.3 Has all of the relevant evidence been taken into account?

Takeda have provided all relevant data currently available. The main clinical evidence to support the case for the clinical and cost-effectiveness of darvadstrocel versus standard of care is the ADMIRE-CD trial. Takeda consider that the Appraisal Committee has taken all relevant data from the original submission and the data from Takeda's response to the ERG questions into account.

To address the uncertainty associated with long-term outcomes and the natural history of perianal fistulae in Crohn's disease, Takeda has conducted a targeted review of the literature and a Delphi panel consisting of views from UK clinical experts (Appendix 1). These analyses are included in response to the Committee's concern associated with the uncertainty encompassed within the ICER estimates. Takeda believe these data support the opinion of clinical experts stated at the appraisal committee meeting that relapse rates would be very low for patients who have achieved remission for two years.

2.4 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Takeda consider that the summaries of clinical effectiveness presented in the ACD are reasonable interpretations of the evidence (Section 3.4 to 3.11). There are a number of issues raised in the ACD relating to the analysis of clinical and cost-effectiveness of darvadstrocel in patients with perianal fistulae in Crohn's disease which we have endeavoured to clarify and address within this document, including the following key issues:

- Treatment benefit of darvadstrocel relative to placebo
- Uncertainty associated with long-term outcomes and the natural history of disease
- Plausibility of the utilities applied in the reference case

Section 2.4.3 presents arguments on why the treatment benefit should not be considered modest in this patient population. Section 2.4.3.3 comments on the clinical uncertainty associated with long-term relapse rates and natural history of perianal fistula(e) in Crohn's disease and address this with evidence from the targeted review and the Delphi Panel. Section 2.4.4 translates these findings into a plausible range of ICERs; Takeda believe that the range of ICERs used for decision making should consider the impact of data available from the literature on long-term relapse rates and anti-TNF use.

Section 2.4.4 details the validation supporting the utilities informing the company's reference case; Takeda believe that these utilities are in line with previous appraisals and the clinical literature.

2.4.1 Discussion on darvadstrocel as a new treatment option (response to Sections 3.1 and 3.2 of the ACD)

Takeda agrees with the committee's comments in Sections 3.1 – 3.2 inclusive of the ACD and would like to highlight the following statements;

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

"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."

"setons are not usually curative, but aim to reduce the risk of abscess formation. Long-term remission rates are relatively low (about 10%)."

"Perianal fistulas are highly debilitating, have a big impact on the person's everyday life and greatly reduce the quality of life"

"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"

2.4.2 Discussion on clinical management and expected use of darvadstrocel (response to Sections 3.3 and 3.4 of the ACD)

2.4.2.1 Clinical Management

In relation to Section 3.3 of the ACD, Takeda agree with the following statements:

"patients should be seen by a multidisciplinary team who are experienced in treating complex perianal fistulas"

"[darvadstrocel] should be used in specialist centres where a multidisciplinary team are available, who could gain appropriate experience in the use of this technology"

"noting the requirements and logistics of administration of darvadstrocel, it would only be used in specialist centres following additional training"

Takeda fully support the Committee's recommendation that the administration of darvadstrocel should be limited to a small number of specialist physicians experienced in the diagnosis and treatment of perianal fistulae in Crohn's disease.

Training will be provided by Takeda to all specialist centres who will be administering darvadstrocel. Many of the UK centres with specialist expertise in the treatment of perianal fistulae are currently working together under the auspices of collaborative groups such as ENIGMA which is a research group specialising in perianal disease. Such expert networks will be leveraged to ensure experience gained in the use of darvadstrocel is quickly shared between centres. The Alofisel global registry will also support identification and sharing of best practice helping to maximise the benefits that darvadstrocel can bring to patients.

2.4.2.2 Expected use of darvadstrocel

Takeda would like to correct the statement (in Section 3.4 of the ACD) that the trial excluded patients "*with one fistula with one single tract.*" The ADMIRE-CD trial only excluded patients

with > 2 internal openings or > 3 external openings, no exclusion criteria specified a minimum number of tracts. This confusion may have resulted from the definition of a complex fistula which stated that patients had to have at least 1 of the following:

- High inter-sphincteric, trans-sphincteric, extra-sphincteric or supra-sphincteric (tract)
- Presence of ≥ 2 external openings (tracts)
- Associated collections

Takeda accept the specific restrictions to certain patient populations suggested by the NICE committee i.e. those patients with >3 fistula tracts or those patients with active proctitis. However, beyond that, we would urge caution and ideally further consultation with clinical experts because we are concerned that limiting the use of darvadstrocel to the identical population studied in the ADMIRE-CD trial could unfairly (and perhaps unintentionally) restrict access to certain patient groups as discussed below:

1. "*CD patients with non-active or mildly active luminal CD defined by a CDAI ≤ 220., diagnosed at least 6 months earlier in accordance with accepted clinical, endoscopic, histological and/or radiological criteria*" The license for darvadstrocel states that it can be used for patients with non-active or mildly active CD however it does not specifically state a CDAI cut-off. Firstly, the use of CDAI is not common in clinical practice for the monitoring of patients with fistulating disease. Secondly, the CDAI score, which was developed for the monitoring of Crohn's disease in general, not for the monitoring of fistulising disease in particular, will not differentiate between local (i.e. rectal) and distant (small bowel) active disease, and clinical feedback strongly suggests that the presence and degree of active inflammation in the rectum is a more important consideration in the treatment of a concomitant fistula than active CD in more distant GI sites. Luminal disease activity is classified in multiple ways in UK clinical practice including clinical assessment, endoscopic assessment and through the use of patient reported outcomes. Specifying one scoring system to be used could mean patients who clinicians would normally consider to be eligible for darvadstrocel could be excluded from receiving treatment.

2. "*Patient who underwent surgery for the fistula other than drainage or seton placement*" UK clinical opinion is that patients will have the best chance of fistula healing if they are provided access to the best medical and surgical treatment options available. If NICE restrict access to darvadstrocel in the manner proposed, then it will not be possible to combine treatment with darvadstrocel with any of the innovative surgical approaches being developed which may prove to be effective in this group of patients. Takeda do not see any rationale such an approach and do not believe it to be in the best interest of patients.

3. *"Patient with a diverting stoma"* Patients with a diverting stoma and ongoing perianal fistulae represent an extremely difficult to treat subgroup of patients with a high level of unmet medical need. Since the presence of a diverting stoma does not alter the fundamental pathology or anatomy of such fistulae, Takeda do not see any reason for denying these patients the opportunity to benefit from darvadstrocel.

4. "*Renal or hepatic impairment*" The regulatory authorities have concluded that despite no formal assessment of darvadstrocel having been undertaken in patients with renal

or haptic impairment, it was not expected that the benefit-risk profile would differ from that observed in patients without renal or hepatic impairment.

5. "*Contraindication to MRI scan (e.g., due to the presence of pacemakers, hip replacements or severe claustrophobia)".* Although MRI imaging constitutes standard of care for the management of perianal fistulae in most UK centres, Takeda do not believe that patients where MRI scanning is contraindicated should be denied the opportunity to benefit from darvadstrocel. In such cases clinical evaluation of the patient's fistula, typically done under anaesthetic, should be sufficient to determine whether a patient is a suitable candidate for darvadstrocel.

Takeda request that the NICE Committee should specify any specific exclusions which restrict the darvadstrocel patient population (e.g. patients with proctitis and those with >3 fistula tracts) rather than stating that it *"should only be used in a population identical to the population in ADMIRE-CD"* (as it currently does in Section 3.4 of the ACD). This would help to avoid any confusion which could result in unnecessary (and perhaps unintended) restrictions to patient access.

2.4.3 Discussion on clinical effectiveness (response to Sections 3.5, 3.6, 3.7, 3.8, 3.9 and 3.10 of the ACD)

2.4.3.1 Magnitude of treatment benefit

Takeda would like to address the following comment: "*While the committee understood the benefit to patients of achieving complete remission, it considered that this additional remission rate is disappointingly modest*." (Pages 9-10 of the ACD). The Committee highlight that treatment with darvadstrocel results in 14.1% more patients achieving CPC remission compared with the placebo arm at 52-weeks. Takeda consider, based on feedback from clinical experts and in the context of complex perianal fistula in Crohn's disease, that this is a clinically relevant benefit that should not be termed '*modest*'.

The increased rate of achieving remission is of huge potential benefit to patients, giving an additional treatment option where limited choices are currently available. The magnitude of benefit from darvadstrocel relative to placebo is also felt by the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) members to be clinically relevant; a recent survey demonstrated that most of the IOIBD participants considered a 15% difference (delta) from placebo for clinical remission and/or endoscopic remission to be clinically relevant.[1]

Additionally, the relative benefit observed with darvadstrocel compared with placebo is in line with clinical trials investigating biologic therapies, which themselves have been considered to have revolutionise the treatment of patients with IBD (e.g. 18% delta with infliximab used in patients with Crohn's Disease[2], 24% delta with adalimumab[3], 7% delta with certolizumab[4] and 12.8% delta with ustekinumab[5]). Therefore, whilst Takeda acknowledge the uncertainties associated with long-term benefits (which are discussed later in this section), we believe the benefit shown in the ADMIRE-CD trial should be considered clinically meaningful in relation to patients and clinicians.

As stated by the British Society of Gastroenterology in their statement to NICE, the most important outcome for patients is sustained remission at 12 months; of patients with combined remission at week 24, a greater proportion of those treated with darvadstrocel versus control had no relapse at week 52 (75.0% vs. 55.9%). 50% and 34% of patients achieved combined remission at week 24 in the darvadstrocel and placebo arms, respectively; this results in twice as many patients achieving sustained remission at week 52 in the darvadstrocel arm (i.e. 75% *x* 50% = 38%) relative to placebo (i.e. 55.9% *x* 34% = 19%), indicating that darvadstrocel both increases the chance of achieving remission *and* increases the chances of a patient sustaining remission.

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

The outcomes from the ADMIRE-CD trial demonstrate that combined remission for both the ITT and mITT populations at week 24 and week 52 show similar benefit with highly significant *p* values, demonstrating the reliability of these data.

There are now several phase I, II and III trials which have demonstrated good outcomes with both autologous and allogenic mesenchymal stem cell therapy in the treatment of perianal fistulae in Crohn's disease.[6] Of those trials that used allogenic stem cells, similar rates of fistula healing have been seen in the intervention arms of a phase IIa trial performed in the Netherlands, with 47%, (n=7/15) patients with healed fistulae at Week 12[7], than that seen in ADMIRE-CD, further supporting these results.

Section 2.4.4 details how Takeda have validated the long-term natural history outcomes within the model.

2.4.3.3 The evidence on the natural history of the disease and outcome of current practice in the UK is limited (Section 3.5 of the ACD)

Takeda understand that the Committee require more robust information on the natural history of the disease to assess the most plausible ICER (page 15 of the ACD). To support this decision-making process, Takeda has conducted a targeted review of the literature and a Delphi Panel to elicit clinical expert consensus.

A clinical systematic literature review was conducted as part of the original NICE submission for darvadstrocel. However, this review was intended to identify clinical trials relevant to the NICE decision problem and, as such, was restricted to patients with complex perianal fistula(e) and evidence from clinical trials. The targeted review now detailed within this Section expands on this evidence base by: (1) including studies reporting complex perianal fistula and those reporting on both complex and simple perianal fistulae in patients with Crohn's disease and (2) imposing no restriction on study type. Additionally, the review is focused on providing evidence on the long-term (defined as ≥2-years) perianal fistula relapse rates. The scope of the review was expanded to consider cohorts with both complex and simple perianal fistula due to the differences in classification of fistula between countries and across time. It was hypothesised that the inclusion of simple fistula may cause improved outcomes to be reported. However, Bouguen et al. (2013)[8] and Haennig et al. (2015)[9] find a non-significant difference in closure rates between complex and simple fistula in multivariate

analyses. Therefore, we do not expect to see a big impact on reported outcomes, particularly in the longer term where fistulae are expected to have 'healed'.

The Delphi Panel elicited expert opinion (n=20) from the first questionnaire and (n=10) from the second questionnaire; clinical experts included gastroenterologists, surgeons and nurses within the UK. Responses from the Delphi Panel in relation to the proportion of patients expected to maintain remission are presented in Appendix 1. These responses indicated a higher rate of relapse than observed in the literature. However, comments collected as part of the Delphi exercise indicated that there were biases arising from differences in remission definition, limited experience and selection biases (for example: surgeons would likely report a high rate of relapse as these healthcare professionals only see patients whose fistula has recurred) when estimating such long-term outcomes. Therefore, the responses to the Delphi Panel are used as supportive information only.

Appendix 1 presents the methodology followed and results associated with both methods. Key findings and interpretation in relation to the decision problem are presented here. Takeda understand the limitations associated with these forms of data generation compared with the "gold-standard" randomised clinical trial. However, in the absence of long-term clinical trial data, Takeda believe that, taken together, these data suggest a plausible upper bound for long-term relapse rates for consideration by the Committee.

Error! Reference source not found. presents all identified data on long-term relapse from 2-years from the targeted review; six studies were identified in the review of which five provide Kaplan-Meier data. Hellers et al. (1980)[10] report a point estimate; 35% of patients who achieved healing experienced relapse within 2.5-years.

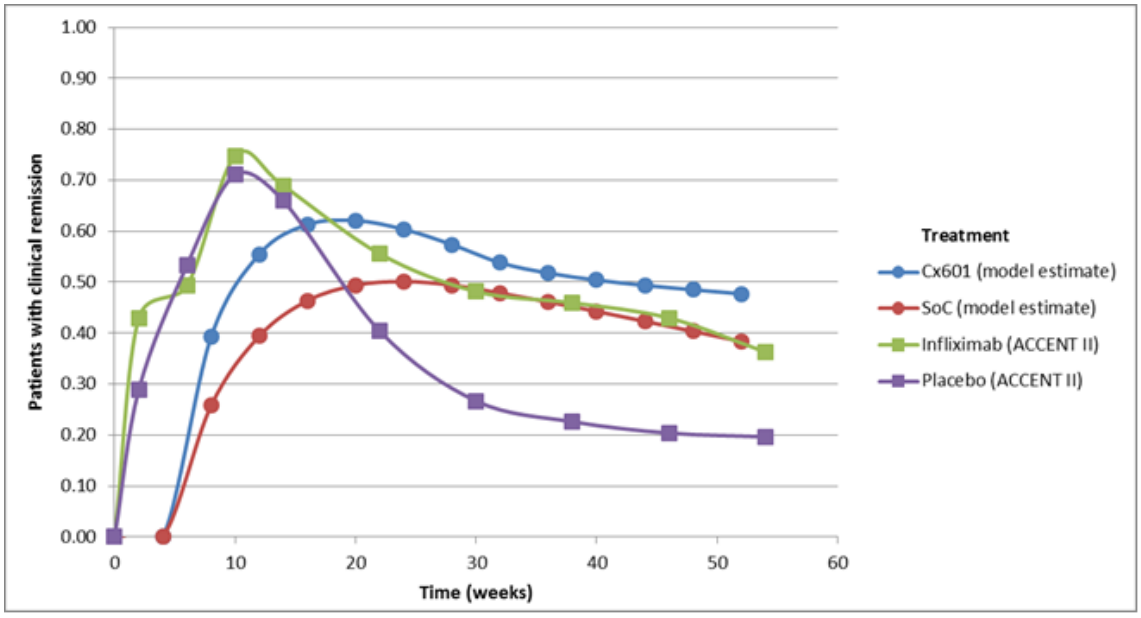
Figure 1:

Figure 1 highlights that there are differences between the short-term outcomes (<2-years) between the ADMIRE-CD trial and the observed data. There are key differences across the ADMIRE-CD trial and between the studies identified in the literature review, including: different definitions of remission, maintenance biologic usage, time points (impacting the clinical management of disease), different populations, countries, and methodologies (retrospective vs. prospective)

The key factor driving the short-term divergence is likely due to the timing of remission assessment and classification. Within the ADMIRE-CD trial, patients could be assessed as in remission and relapse after one visit. Feedback from clinical experts indicates that in clinical practice, patients are classified as in remission across at least two separate visits. The timings related to assessment of remission are less clear within the six identified studies. Only one study reported remission as defined from time of the first fistula closure (Bouguen et al. (2013)[8] Kim et al. (2011)[11] and Haennig et al. (2015)[9] both specified that remission was assessed across a prolonged period: at least 3 months and 4 months, respectively. Gottgens et al. (2015)[12] and Legue et al. (2018)[13] appear to assess outcomes from the point of treatment discontinuation and Hellers et al. (1980)[10] did not provide sufficient detail on remission assessment. Therefore, the relapse rates presented in the literature in the short-term are likely to reflect a subgroup of patients with a more sustained remission than in the ADMIRE-CD trial data. This could account for the rapid relapse rates observed within the first 2-3 months of the ADMIRE-CD trial.

Figure 2 compares the rates of clinical remission between the ADMIRE-CD trial and the ACCENT II trial; this demonstrates that the rates of relapse are aligned with other prospective randomised controlled trials using the same definition of remission and highlight that the differences observed in Figure 2 are likely due to the different definitions.

Figure 2: Rates of clinical remission from ADMIRE-CD and ACCENT II clinical trials



As outcomes are available from the ADMIRE-CD trial up to 2-years, Figure 3 presents all identified data on long-term relapse from 2-years from the targeted review with the objective

of exploring the long-term natural history of perianal fistula in Crohn's disease. Table 1 presents the minimum and maximum relapse rates reported in the identified literature for patients who are in remission at 2-years. These results are compared with the linear rate applied within the model from 2-years for darvadstrocel and placebo in the base case (ICER = £20,591).

Figure 3: Data on 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

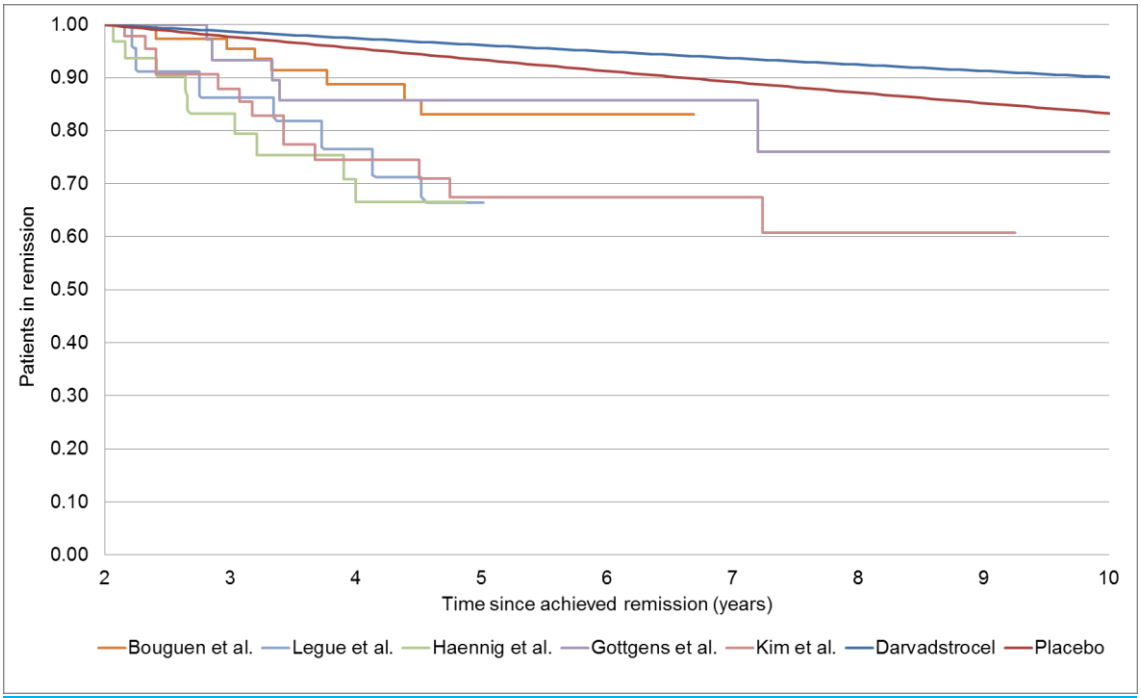


Table 1: Minimum and maximum identified long-term relapse rates for patients in remission at 2-years compared with rates applied in the economic model

	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%

Key factors driving differences in long-term relapse rates are likely due to the definitions of remission and the evolution of clinical management.

The definitions of remission warrant consideration as this directly influences the rate of relapse. The ADMIRE-CD trial uses a much stricter definition of remission than other studies

reported in the literature, as does CPC remission. Therefore, patients with true healing will be identified rapidly and we will likely see a lower relapse rate in these patients. We would expect those who did not achieve true healing to relapse quickly. Simply using a clinical definition of healing, as considered by the majority of identified studies (n=5, Appendix 1), would be expected to result in a steadier decline over time. It is more difficult to achieve radiological healing. However, once patients achieve radiological remission more patients would sustain this. Gottgens et al. (2017)[12] is the only identified study that considers both clinical and radiological healing for defining remission; these data present with a clear "plateau" and most closely reflect the long-term relapse rates applied within the base case model (**Error! Reference source not found.**).

This "plateau" effect is likely to be more apparent the stricter the definition of remission that is used; this is supported by feedback from the clinical experts at the first Committee meeting and responses to the Delphi Panel (Appendix 1). Feedback from the clinical experts at the Committee meeting highlighted that: "*if the fistula is healed and remission is maintained until 2-years, and there is no underlying risk for future relapse, rates are likely to be very low after this time (around 10 to 20%)*" (page 15 of the ACD). Specific comments from the Delphi Panel related to outcomes associated with complete closure indicate that if complete closure is achieved, then the likelihood of relapse is less. The unmet need is related to achieving genuine fistula closure which translates to long-term freedom from fistula and from symptoms. The strict criteria for remission within the ADMIRE-CD trial and the economic model mean that a greater proportion of patients in remission will have genuine fistula closure.

Another difference expected to impact long-term relapse rates is the evolution of clinical management for patients with complex perianal fistula in Crohn's disease. Data identified from the targeted review ranged from 1955 to 2016; it is only from the early 2000s that anti-TNF maintenance therapy has been used in these patients[14, 15] Note that the use of anti-TNF maintenance therapy was high in both arms of ADMIRE-CD. Table 2 presents the anti-TNF therapy use described within the identified literature. Note: studies presented anti-TNF therapy use in differing levels of detail. Therefore, it cannot always be ascertained which therapy was associated with maintenance use.

Table 2: Comparison of anti-TNF use across the identified literature

Study	Anti-TNF use
Bouguen et al. (2013)[8]	Anti-TNF treatment was still on-going for 57% of patients at end of follow-up
Legue et al. (2018)[13]	All patients had discontinued anti-TNF therapy
Haennig et al. (2015)[9]	77% received infliximab following seton drainage. 22% received infliximab as part of other treatments.
Gottgens et al. (2016)[12]	Anti-TNF exposure was 21.2-41.2% in the 2006-2011 era
Kim et al. (2011)[11]	9% received infliximab
Hellers et al. (1980)[10]	Pre-biologics era

The multivariate and univariate analyses conducted within the literature emphasise the positive impact of continued maintenance therapy on sustaining fistula closures. Two papers (Bouguen et al. (2013)[8] and Kim et al. (2011)[11]) provide Kaplan-Meier data for patients

receiving treatment with anti-TNF maintenance therapy compared with those patients that are not receiving this treatment (Appendix 1); these analyses show much improved outcomes for anti-TNF treated patients. Additionally, a letter to the editor published in the Journal of Crohn's and Colitis from St. Marks Hospital within the UK supports these findings; no patients (n=11) with radiologically defined healing were found to relapse who were maintained on biologic therapy as compared to 2/3 (n=6 of 9) of patients who relapsed once biologic therapy was discontinued.[16]

These papers emphasise the improved outcomes experienced with biologic maintenance therapy given whilst a patient with perianal Crohn's Disease is in remission; the ECCO guidelines now recommend continuing biologic therapy in patients with perianal fistula due to these improved outcomes.[17] Clinical practice within the UK reflects this; the Delphi Panel indicates the majority of clinicians would treat patients with biologic maintenance therapy following darvadstrocel and would expect to see improved outcomes associated with this clinical management approach. The UK advisory board informing the treatment mix for the remission health state estimated that >80% of patients would be receiving biologic therapy; this is costed within the economic model. Bouguen et al. (2013)[8] and Gottgens et al. (2016)[12] consider up to 57% and 41% of patients receiving anti-TNF therapy, respectively. Whilst this use is still considerably less than we would expect to see in current UK practice, this represents the highest anti-TNF therapy use across the identified literature and so provides the best comparison of long-term relapse rates for the economic model.

With the stricter definition of remission and the evolved clinical management, Takeda consider that better long-term outcomes following darvadstrocel will be observed in UK clinical practice compared with those identified within the literature. The outcomes presented in Gottgens et al. (2016)[12] provide the best approximation of long-term relapse rates in current clinical practice; the definition of remission and the biologic therapy use best approximate those inputs used within the economic model. Outcomes presented in Bouguen et al. (2013)[8] provide a supportive comparison as the anti-TNF therapy use approximates the inputs used within the economic model. However, this paper considers a looser definition of remission (clinical remission).

Therefore, Takeda believe that the long-term relapse rates applied in the base case of the economic model, and as presented in **Error! Reference source not found.**, provide the best approximation of the "true" underlying relapse rate. Takeda consider that the maximum relapse rates at 5- and 10-years are 16.92% and 24.02%, as defined by Bouguen et al. (2013)[8] and Gottgens et al. (2016).[12] The impact of these relapse rates on the model results are presented in Section 2.4.4.2.

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

Takeda agree that the ongoing ADMIRE-CD II trial may provide further evidence on the clinical effectiveness of darvadstrocel for the treatment of complex perianal fistula in patients with Crohn's disease. However, these data are only expected to be available in 2022, and will be limited to a one-year follow up. A global registry of patients (the INSPIRE registry) is being funded by Takeda as our commitment to provide additional data. The INSPIRE registry is anticipated to collect data on all patients treated with darvadstrocel globally. It will

however take several years to generate a meaningful amount of data on long term outcomes following darvadstrocel treatment.

2.4.3.5 The Company's economic model

The Committee consider the ERG's preferred base case analysis to be appropriate (page 13 of the ACD). Takeda would like to present the argument as to why our submitted base case more accurately reflects the probabilities associated with last-resort surgeries, compared with the ERG's preferred assumptions.

The probability of requiring proctectomy or defunctioning in the base case was derived from Bell et al. (2003)[18] and Mueller et al. (2007)[19],respectively. Although there are issues associated with these sources, which were presented in the original submission dossier and discussed at the first Committee meeting, the resulting probabilities of last-resort surgery were considered conservative estimates. The model predicted ~25% and ~41% experienced defunctioning and proctectomy when these methods were used, respectively. Feedback from clinical experts indicated that these rates were much higher than expected in current clinical practice. As no further data were available, these were applied in the base case as a conservative estimate (lower rates of last-resort surgery reduce the ICER). The ERG provides an alternative way of applying the data from Bell et al. and Mueller et al. within the model. However, this results in ~49% and ~55% experiencing defunctioning and proctectomy across a 40-year time horizon, respectively. This far exceeds clinician's expectations.

Additionally, a review by Pellino and Selvaggi published in 2014[20] suggests that it is those patients with perianal fistulae associated with Crohn's disease who have significant concomitant proctitis and are refractory to medical and surgical therapy who are most likely to undergo last resort surgery. This is in line with UK clinical expert opinion. The Committee stated that if darvadstrocel were recommended then patients with proctitis should be excluded as per the ADMIRE-CD trial (page 7 of the ACD) and Takeda accept this restriction. Therefore, the probability of last-resort surgery in the population being considered in this appraisal is likely less than observed in the general population. The review also states that rates of last-resort surgery, even including patients with proctitis, are between 18 and 20% which are considerably lower than the rates estimated through both Takeda's methods and the ERG's methods.

2.4.4 Discussion on modelling the long-term benefits of darvadstrocel (response to Section 3.16 of the ACD)

Section 2.4.4.1 presents the long-term relapse rates and anti-TNF use from the literature identified within the targeted review. In this Section, scenarios within the economic model explore the impact of these inputs on the ICER. In doing so, Takeda present the clinically plausible range of ICERs: from £17,068 to £36,235. Additionally, given the data presented, we hope to demonstrate to the Committee the clinical implausibility of the log-normal parametric curve for time to CPC relapse data within the economic model.

Please note that all scenarios are presented for validation purposes only, no changes have been made to the base case economic model from the model that was originally submitted (with a 3.5% discount rate for both costs and QALYs).

2.4.4.1 Long-term relapse rates

Results of the targeted literature review and interpretation relative to similarities with the application of the ADMIRE-CD data within the model indicate that maximum long-term relapse rates for the subgroup of patients who are in remission at 2-years are: 16.92% at 5-years and 24.02% at 10-years (based on Bouguen et al. (2013)[8] and Gottgens et al. (2016)[12]).

To align the long-term relapse rates between the model and the literature, the 4-weekly constant relapse rate (applied from 2-years and presented on the "Clinical inputs" sheet) was varied. Note: for simplicity equal long-term relapse rates were assumed across the placebo, salvage therapy and darvadstrocel arms. Therefore, no additional long-term benefit of darvadstrocel vs control was applied after 2-years. This is a pessimistic scenario as the data indicate a trend for improved remission maintenance with darvadstrocel relative to placebo. Assuming equal relapse rates increases the base case ICER from £20,591 to £22,273.

When setting the constant cyclical rate to reflect 16.92% relapse at 5-years, the resultant ICER was £36,235. When setting the rate to reflect 24.02% relapse at 10-years, the resultant ICER was £28,370. When accounting for the relapse rates and reduced anti-TNF use as maintenance therapy across the literature, the ICERs were £29,038 and £17,068, respectively (accounting for 57% and 41% use in the Bouguen et al. (2013)[8] and Gottgens et al. (2016)[12] studies, respectively). Results of the scenarios are presented in Table 3.

Table 3: Scenarios exploring the long-term relapse rates within the economic model

	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%	39.01%	82.22%	£36,235
Scenario 1b	16.92%	39.01%	57%	£29,038
Scenario 2a	9.79%	24.02%	82.22%	£28,370
Scenario 2b	9.79%	24.02%	41%	£17,068

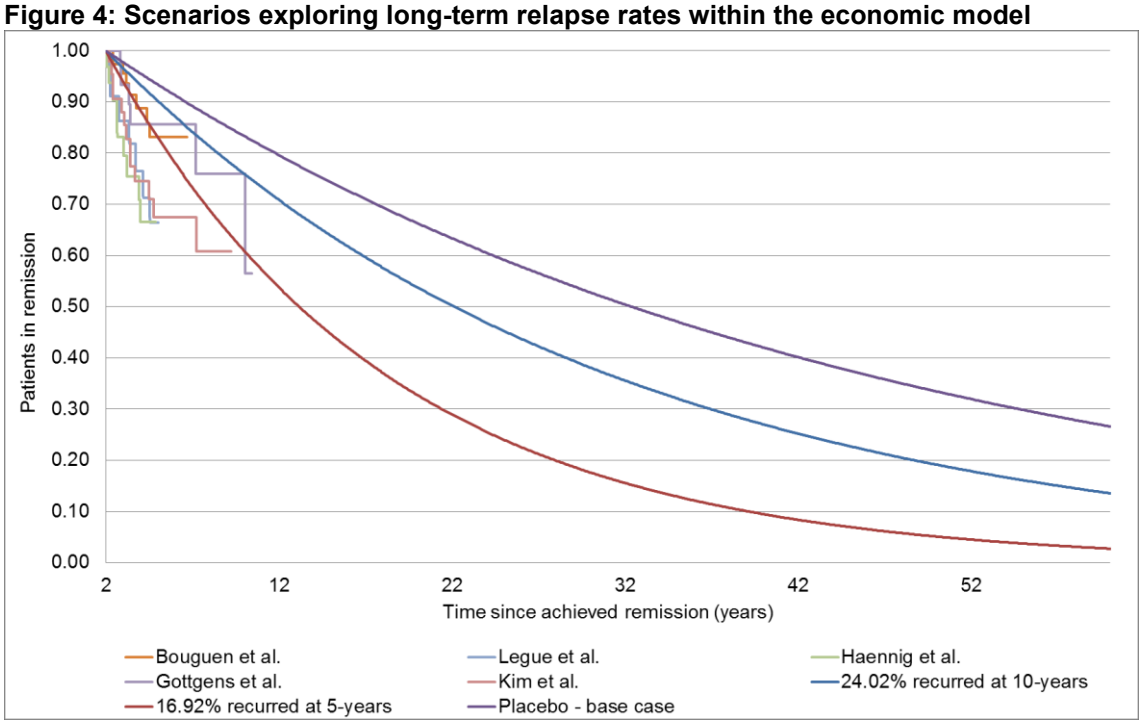
Abbreviations: ICER, incremental cost-effectiveness ratio

The long-term relapse rates applied within the model in each of these two scenarios is presented in Figure 4. It should be noted that, due to the model structure, a constant linear relapse rate is applied from 2-years for the duration of the model time horizon. This simplifying feature means that the "plateau" effect is not accounted for when exploring these scenarios. Consequentially, the modelled relapse rates beyond 10-years are higher than would likely be observed. Feedback from clinical experts, responses to the Delphi Panel and the shape of the Kaplan-Meier curves identified from the literature indicate that for patients who have achieved true fistula closure (clinical and radiological healing) and maintained remission for 10-years, a very small rate of relapse would be expected. This should be

considered when interpreting the ICER estimates of £28,370 and £36,235; inclusion of the "plateau" effect would reduce these estimates.

The long-term relapse rates applied in the model base case (ICER = £20,591) is shown for the placebo arm in Figure 4. As discussed in Section 2.4.3.3, the "true" relapse rates are likely lower than observed in the literature due to stricter definitions of remission and increased anti-TNF use. Additionally, a "plateau" effect would be observed in the long-term which is not reflected in the current application. Therefore, Takeda believe that the base case economic model accurately reflects a plausible reference point.

Figure 4: Scenarios exploring long-term relapse rates within the economic model



For reference, Table 4 displays the proportion of relapses predicted by each parametric curve within the model for the subgroup of patients who have sustained remission for 2-years – using the model reference case (ICER = £20,591). This table emphasises that all other parametric curves within the model over-predict relapse rates beyond 2-years – this is mainly due to the constant rate that is derived from the curve choice and applied within the model from 2-years. When the log-normal curve is selected for time to relapse outcomes within the base case model the ICER increases from £20,591 to £104,398. However, if the constant relapse rates beyond 2-years are set equal to those applied under the Gompertz selection, the ICER is £29,929. This emphasises that the ICER is driven by the long-term relapse rates (rather than curve choices) which has been addressed above.

Table 4: 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%	

2.4.4.2 Long-term remission rates

In the ACD, the Committee consider the generalised gamma parametric curve for extrapolating time to CPC remission within their scenarios exploring the range of ICERs (page 14 of the ACD). This increases the ICER from £20,591 to £30,064. In this Section, we discuss why we believe the Gompertz parametric function has both external and internal validity in both its application and in terms of the derived results.

Takeda acknowledge that the AIC and BIC statistics indicate that the generalised gamma, the Gompertz and the log-normal provide reasonable fits to the data. However, these statistics only inform us on the fit to the observed data. The underlying hazard associated with the generalised gamma is clinically implausible in this setting; extrapolation of this curve assumes all patients would achieve remission over time. Feedback from clinical experts and observed data indicate that a proportion of patients do not achieve remission. Additionally, statistical validation shows that the shape of the empirical hazards does not approximate the generalised gamma and follows (closely) to the Gompertz distribution (as shown in the response to the clarification questions). As highlighted within the ERG report, the empirical hazards remain within the confidence intervals of the Gompertz at all time points; the only parametric curve where this is the case. Additionally, clinical experts believe that the rate of remission will decline to zero over time without a further intervention. Therefore, the Gompertz presents the only statistically and clinically plausible curve choice.

As a result of providing a better statistical fit to the data, the Gompertz model is more accurate in predicting the probability of remission at week-52. The Gompertz predicts 64% and 47% of patients to achieve CPC remission in the darvadstrocel and control arms, respectively (delta of 17%). This is in line with the data from the ADMIRE-CD trial which shows 64% and 48%, respectively (delta of 16%). Conversely, the generalised gamma predicts 59% and 52%, respectively (delta of 7%), further indication that this is not a good fit to the data.

2.4.5 Discussion on the health-related quality of life evidence (response to Section 3.11 and 3.17 of the ACD)

We understand NICE's concerns relating to the lack of EQ-5D data in the ADMIRE-CD trial. However, the vignette study commissioned to estimate utility values for this submission was a robust, methodologically robust study with a significant number of participants (n=835 general public and n=162 patients with Crohn's disease). Therefore, we consider that this vignette study provides reliable estimates of utilities. Additionally, the derived utility estimates

are in line with values used in previous NICE appraisals and with average utility values reported in the literature.

The Committee notes that the ERG's clinical experts considered that the utility values following successful defunctioning (0.567), successful proctectomy (0.564) and in the "mild chronic symptomatic fistulae" health state (0.578) may be underestimated.

Whilst there is no evidence available within the relevant population, there is evidence available within similar populations for proctectomy.

Previous NICE appraisals for biologics in Ulcerative Colitis (UC) have also considered post proctectomy as a health state and this has been associated with utility values between 0.6 and 0.61.[21] The same procedure would be conducted for patients with UC and patients with perianal fistula in Crohn's disease. However, outcomes are often worse for patients with perianal fistula in Crohn's disease; patients with UC would often have a pouch formed and, as UC is limited to the large bowel, proctectomy should fully resolve their symptoms. Comparatively, patients with perianal fistula in Crohn's disease would require a stoma and - as Crohn's disease can occur at any site within the digestive tract (from the mouth to the anus) - proctectomy may not alleviate all symptoms of Crohn's disease. Therefore, we consider that the utility value used in this appraisal in the successful proctectomy health state accurately reflects the quality of life associated with these patients.

Additionally, the average utility predicted by the model for patients with active disease (0.48-0.54) aligns with the literature (0.47) and the responses of patients with perianal fistula in Crohn's disease participating in the vignette study (0.47).

The average utility predicted by the model is calculated by dividing the number of undiscounted QALYs gained within each of the active health states (all of CSF Mild, CSF Severe, Unsuccessful Proctectomy and Unsuccessful Defunctioning, or the non-surgical health states of CSF Mild and CSF severe) by the average time spent in each health state. This gives an average utility predicted by the model for patients with active disease as between 0.48 and 0.54. As discussed in the original submission dossier, the Mahadev study[22] showed that patients with perianal Crohn's disease were willing to trade an average of 5.3-years of life for a cure, this equates to an average utility of 0.47. Some of the patients with Crohn's disease participating in the vignette had a perianal fistula, these patients were asked to rate their current health state and this gave an average utility value of 0.468.

Therefore, the model's prediction of utility for patients with active disease is slightly higher than in the literature and from that reported by patients with Crohn's disease and an active fistula in the vignette study.

Where validation has been possible, the results from the vignette study are shown to be comparable with the literature and patients' feedback. Therefore, we consider that the utility values elicited from the vignette study are an accurate representation of the significant impact that perianal fistula in Crohn's disease has on patients' quality of life. Additionally, within the one-way sensitivity analysis, utility values derived from the vignette study were varied across their reported confidence intervals and showed only a minor impact on the ICER.

2.4.6 Discussion on the most plausible cost-effectiveness range: "The most plausible cost-effectiveness estimate is uncertain, and darvadstrocel is unlikely to be a cost-effective use of NHS resources" (response to Section 3.18 of the ACD)

The Committee considers that the clinical uncertainty associated with the long-term benefit of darvadstrocel and the underlying natural history of the disease could translate into ICERs for darvadstrocel compared with placebo up to £143,131 (with the Department of Health approved patient access scheme, PAS). Based on this, the Committee states that darvadstrocel is not recommended for patients with complex perianal fistula in Crohn's disease.

The company's response to the ACD within this document aims to address the uncertainty associated with long-term relapse rates and the natural history of perianal fistula in Crohn's disease. Exploratory analyses modelling the identified long-term evidence results in an ICER range of £17,068 and £36,235 (including PAS). Takeda consider that the analyses presented to the Committee provide additional validation of the company's base case (ICER of £20,591) and bookend the potential for the residual uncertainty to drive results above an ICER of £36,235.

Takeda believe the exploratory analyses and validation support a case for darvadstrocel to be considered as plausibly cost-effective at willingness to pay threshold of £30,000.

2.5 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

In conclusion, Takeda disagree that the committee's provisional negative recommendation for darvadstrocel is sound and a suitable basis for guidance to the NHS (see Section 1.1 and Section 3.18 of the ACD). Takeda acknowledge the uncertainty associated with long-term outcomes. However, exploratory analyses and validation, as presented within this document, indicate that the uncertainty associated with results could drive the ICER down to £17,068 as well as up to £36,235. Only one scenario results in an ICER above the £30,000 willingness to pay threshold.

Takeda are collecting outcomes through the INSPIRE registry. The INSPIRE registry is a global registry that aims to collect data on all patients treated with darvadstrocel with the intention of ensuring best value is achieved. This is a significant investment by Takeda and highlights the commitment that we, as a company, have for maximising the benefits that darvadstrocel can bring to patients. A steering group has been set up which includes both clinician and pharmacy representation from the UK. With the collaboration that is apparent with the UK community through groups such as ENIGMA (a research group specialising in perianal disease) and the availability of global data on darvadstrocel treated patients, we are confident that clinicians will be able to quickly identify best practice to ensure that the best possible outcomes are achieved with darvadstrocel.

Takeda fully support the Committee's recommendation that the administration of darvadstrocel should be done by a limited number of specialist physicians experienced in the

diagnosis and treatment of conditions for which darvadstrocel is indicated. Training will be provided to all specialist centres, initially this will utilise the expertise gained by European clinical experts through the ADMIRE-CD trial but over time will utilise the expertise gained by UK surgeons and clinicians from early experience centres. Many of the UK specialist centres are currently working together through groups, such as ENIGMA. These networks will be leveraged to ensure experience can be quickly shared across these centres.

Taking all factors into account, Takeda is optimistic that the steps we have taken in this ACD response can reduce the clinical uncertainty felt by the Committee and allow the committee to conclude on the most plausible cost-effectiveness range and recommend darvadstrocel for use within the NHS in England and Wales. Such an outcome would allow patients and the NHS to benefit from timely access to darvadstrocel as a treatment option for complex perianal fistula in Crohn's disease. With that objective in mind, Takeda remains committed and willing to working constructively with NICE, and if necessary other stakeholders, to secure a positive outcome from this appraisal.

3. References

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

Appendix: New evidence analyses in response to the ACD

16 August 2018 for the consideration of the NICE Appraisal Committee

Submitted by Takeda UK Ltd.

Single Technology Appraisal (STA)

National Institute of Health and Care Excellence

Submitted 5th September 2018

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List of Abbreviations

ACD	Appraisal Consultation Document
AiC	Academic in confidence
CPC	Clinical and patient centric
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
N	number
NGT	Nominal group technique
PDAI	Perianal disease activity index
RCT	Randomised controlled trial
TNF	Tumour necrosis factor

1. Introduction

This appendix provides the additional evidence associated with the response to the first Appraisal Consultation Document (ACD, dated August 2018), including:

- Targeted literature review identifying evidence on the long-term outcomes and natural history associated with perianal fistula(e) in Crohn's disease
- A Delphi Panel conducted to elicit expert consensus on the long-term outcomes and natural history associated with perianal fistula(e) in Crohn's disease

This document first outlines the targeted literature review (Section 2.1) and then presents the methodology and results associated with the Delphi Panel (Section 2.2).

2. Updated evidence

Takeda understand that the Committee require more robust information on the natural history of the disease to aid in assessing the most plausible incremental cost-effectiveness ratio (ICER; page 15 of the ACD). To support this decision-making process Takeda has conducted a targeted review of the literature (Section 2.1) and a Delphi Panel (Section 2.2) to elicit expert consensus.

2.1 Targeted literature review

A targeted review was conducted to better understand the evidence available on long-term recurrence rates of perianal fistula in patients with Crohn's disease. A clinical systematic review was conducted as part of the original NICE submission for darvadstrocel. However, this review intended to identify clinical trials relevant to the NICE decision problem and, as such, was restricted to patients with complex perianal fistula(e) and evidence from clinical trials.

The targeted review detailed within this Section expands on this evidence base by: (1) including studies reporting complex perianal fistula and those reporting on both complex and simple perianal fistula and (2) imposing no restriction on study type. Additionally, the review is focused on providing evidence on the long-term (defined as ≥2-years) perianal fistula recurrence rates.

2.1.1 Methods

Searches were conducted in August 2018 and included electronic databases (PubMed and Ovid); screening of reference lists; recommendations from clinical experts; key conference websites and internet searches. Key terms comprising the search strategies used for each of the platforms included: "perianal fistula" and "Crohn's disease" and either "outcome", "recurrence" or "follow-up".

To identify relevant publications explicit inclusion and/or exclusion criteria were applied – presented in Table 1.

Due to the limited data available on long-term recurrence rates and as different grading instruments categorising fistulas as simple and complex in different ways with the ADMIRE-CD definition of a complex fistula being quite broad, the population criteria were expanded to include populations with simple and complex perianal fistula, so long as ≥50% of the population had complex fistula (excluding non-specified fistula). Additionally, study type criteria were expanded to include: clinical trials, retrospective/prospective analyses and retrospective analyses of prospective data. Reviews were excluded from the final body of evidence; however, their reference lists were screened to ensure all relevant studies were identified.

Studies considering treatment with novel medical or surgical procedures were excluded as these interventions are considered irrelevant to UK clinical practice. All other interventions were considered as relevant (e.g. darvadstrocel, anti-tumour necrosis factor (TNF) therapy,

immunosuppressants, surgery and antibiotics). Therefore, studies reporting on these interventions were included.

Table 1: Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	Population with complex perianal fistula in Crohn's disease **or** a population including patients with simple and complex perianal fistula where complex fistula comprise ≥50% N≥25	Population with simple perianal fistula in Crohn's disease only Other fistula subtypes N<25
Intervention	Darvadstrocel Anti-TNF therapy Immunosuppressants Surgery Antibiotics Usual care	Novel medical/surgical therapies
Outcomes	Long-term (≥2-years) recurrence rates associated with perianal fistula	Short term (<2-year) follow-up
Study types	Clinical trials Retrospective/prospective studies	Reviews*
Other	English language only	Non-English studies Insufficient data to determine inclusion/exclusion criteria
*reference lists screened prior to exclusion		

Full-text screening of the identified publications was conducted by two reviewers independently. Papers identified as relevant following this were collated to form the main body of evidence for this review.

2.1.2 Results

Six studies were identified as relevant from the targeted literature review. Table 2 summarises the key characteristics across these studies including: setting; type of analysis; patient population; length of follow-up; definition of remission and definition of recurrence. Studies are presented in order of relevance and applicability of data presented relative to this submission (studies were assessed based on: applicability of population; dates of data collection and analyses implemented for time to recurrence data).

Table 2: Summary of identified papers

Study	Country	Study type	Population	Follow-up	Remission definition	Recurrence definition
Bouguen et al. (2013)[1]	France	Retrospective	Adult patients with documented Crohn's disease at first infliximab infusion N=156 Complex n=128 (82%) Simple n=28 (18%)	1998-2011 Median = 250 weeks (IQR: 124-381)	Clinical assessment: Absence of drainage at any single visit during the follow-up period	Clinical assessment: Presence of fistula opening among patients who experienced fistula closure
Haennig et al. (2014)[2]	France	Retrospective	Patients with perianal Crohn's anorectal or vaginal fistula N=81 Complex n=71 (88%) Simple n=10 (12%)	2000-2010 Median 63.8 months (2-263)	Clinical response: complete closure of the fistula track with no further discharge from the opening(s) on the gentle application of finger pressure on the perianal skin Primary response: complete closure had been sustained for at least four months	Reopening of a former track or the presence of a new fistula after a primary response
Kim et al. (2011)[3]	South Korea	Retrospective analysis of prospective data	Perianal fistula(e) in Crohn's disease [redacted]	[redacted]	[redacted]	[redacted]
Legue et al. (2018)[4]	France	Retrospective analysis of	Patients with Crohn's disease and perianal	1998-2016	Clinical assessment: positive perianal response	Clinical assessment: Perianal relapse defined as recovery of

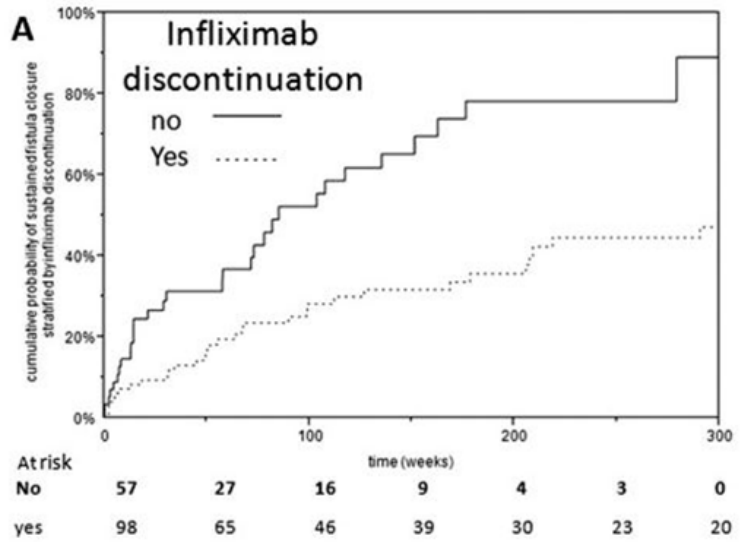
		prospective data	fistulae who achieved a 'positive perianal response' on anti-TNFα therapy and whose anti-TNFα was subsequently stopped N=45 Complex n=28 (62%) Simple n=17 (38%)	Median = 62 months (IQR: 34-106)	as judged by physician	leakage/abscess/need for surgical drainage
Gottgens et al. (2017)[5]	Netherlands	Retrospective analysis of prospective data	Patients with Crohn's disease and perianal fistula(e) N=161 Complex n=39 (24%) Simple n=39 (24%) Unspecified n=83 (52%)	1991-2014	Clinical and radiological assessment	Either a visible new fistula at the same location or the return of symptoms after a symptom-free period
Hellers et al. (1980)[6]	Sweden	Retrospective	Patients with Crohn's disease and anal fistulae N=184	1955-1974 Median 9.4 years (0.5-22.5)	Spontaneous healing of anal fistulae	Reopening of the fistula after primary spontaneous healing
Abbreviations: IQR, interquartile range; N, number; TNF, tumour necrosis factor						

Bouguen et al. (2013)[1] considered a retrospective analysis of 156 patients with documented perianal Crohn's disease from two centres in France. Outcomes were reported from first infliximab infusion; patients discontinued infliximab in the study if they sustained a clinical benefit (n=40), were primary or secondary non-responders which led to switch to adalimumab (n=20), experienced adverse events that led to switch to a TNF-α antagonist (n=10) and for other reasons (n=10). Median duration of follow-up was 250 weeks with an interquartile range (IQR) of 124-381 weeks.

The cumulative probability of first fistula closure was 73% at 5-years and 88% at 10-years, with the probability of achieving sustained fistula closure driven by continued infliximab treatment and short duration of seton drainage. 46% of all patients had sustained complete fistula closure whilst on infliximab, without switching to another biological agent, throughout follow-up.

The cumulative probabilities of first fistula recurrence were 16.6%, 31.3% and 40.1% at 1-, 3- and 5-years, respectively. These data were presented in Kaplan-Meier plots which have been digitised and are presented in Figure 3. When considering the subgroup of patients treated with maintenance infliximab treatment, the cumulative probabilities of first fistula recurrence were: 12% and 36.6% at 1- and 5-years, respectively (Figure 1). No baseline characteristics were associated with fistula recurrence as determined by multivariate analysis (based on a p-value<0.05).

Figure 1: Time to recurrence Kaplan-Meier plots stratified by infliximab discontinuation from Bouguen et al. (2013)



Haennig et al. (2014)[2] considered a retrospective analysis of observational data describing 81 patients with perianal Crohn's anorectal or vaginal fistula from a single centre in France. Outcomes were reported from first referral to the Department of Gastroenterology with perianal Crohn's fistula. Patients were treated with combined seton drainage and infliximab treatment. Before 2003, maintenance therapy with anti-TNFs was not routinely considered (median duration of infliximab treatment of 2.5 months). After 2003, patients were routinely treated with infliximab maintenance therapy. Median follow-up was 63.8 months.

Combined treatment with seton drainage and infliximab treatment resulted in complete fistula closure in 71 patients (87.7%) at a median interval of 12.4 months from the start of treatment. Of these 71 patients, rates of recurrence were 29.2%, 34.9% and 45.8% at 1-, 2- and 3-years, respectively. The fistula was reported to recur at the same location in 72.7% of recurrences and in 27.3% it developed at a new site. These data were presented in Kaplan-Meier plots which have been digitised and are presented in Figure 3. Over 5-years approximately 57% of those experiencing complete closure suffer a recurrence. No risk factors were found to significantly impact fistula recurrence.

Kim et al. (2011)[3] considered a retrospective analysis of 87 prospectively enrolled patients with Crohn's disease and complex perianal fistula. The targeted review identified the abstract only. However, Takeda have contacted the authors of the publication and received the manuscript ahead of publication. Therefore, all information provided detailing Kim et al. (2011) is marked academic in confidence (AiC).

[redacted]

Figure 2:

[redacted]

[redacted]

Legue et al. (2018)[4] considered a retrospective analysis of a prospective database detailing 45 patients with Crohn's disease and perianal fistula(e) who had achieved a positive perianal response on anti-TNF therapy and whose anti-TNF therapy was subsequent stopped. Reasons for drug discontinuation were: sustained clinical remission (n=27), planned isolated infliximab induction treatment (n=3), intolerance (n=7), pregnancy (n=5) and patient preferences (n=3). 53.3% of patients experienced perianal relapse following anti-TNFα discontinuation after a median time of 25.5 months. The cumulative probabilities of perianal relapse at 1-, 2- and 5-years were 23.7%, 35.2% and 55.2%, respectively. These data were presented in a Kaplan-Meier plot which has been digitised and are presented in Figure 3.

Estimates of perianal relapse from this study are likely to be biased for two reasons: (1) the study measured outcomes from time of anti-TNF discontinuation rather than from closure of fistula and (2) no patients received anti-TNF therapy as is standard practice in the UK. These factors are likely to over-estimate long-term perianal relapse outcomes.

Multivariate analyses were not conducted. However, univariate analyses showed that the maintenance of immunosuppressive agents after anti-TNFα discontinuation decreased the risk of perianal relapse.

Gottgens et al. (2017)[5] considered a retrospective analysis of a prospective database detailing 161 patients with Crohn's disease who developed perianal fistula(e). The cumulative probabilities of recurrence at 1-, 5- and 10-years were 10.7%, 25.7% and 36.7%, respectively. These data were presented in a Kaplan-Meier plot which has been digitised and is presented in Figure 3. It should be considered that the number at risk presented in the associated Kaplan-Meier analysis used all patients (n=161) with perianal fistula, it is unclear from the paper whether all patients achieved remission. Therefore, the cumulative probabilities of recurrence in the relevant population (i.e. in patients who are clinically able to be defined as experiencing a recurrence) may differ from those presented within the paper.

Hellers et al. (1980)[6] considered a retrospective analysis of 184 patients with Crohn's disease and anal fistula(e) from 1955 to 1974 with a median follow-up of 9.4 years. The proportion of patients with complex fistula(e) was not reported. Across follow-up, 46.5% of patients had spontaneous healing of anal fistulae and 35% of patients who had achieved healing experienced relapse within 2.5-years. This point estimate is presented for comparison with other identified evidence in Figure 3.

Figure 3: Long-term recurrence rates identified from a targeted review of the literature

2.2 Delphi Panel

Delphi panel methodology was used to elicit expert opinion and achieve a consensus relevant to the long-term outcomes and natural history of patients with complex perianal fistula in Crohn's disease in current UK practice.

The objectives of the Delphi panel were to obtain the opinion and experience of UK clinical experts treating patients with complex perianal fistula in Crohn's disease and in doing so facilitate the Committee in determining a plausible base case ICER and associated range.

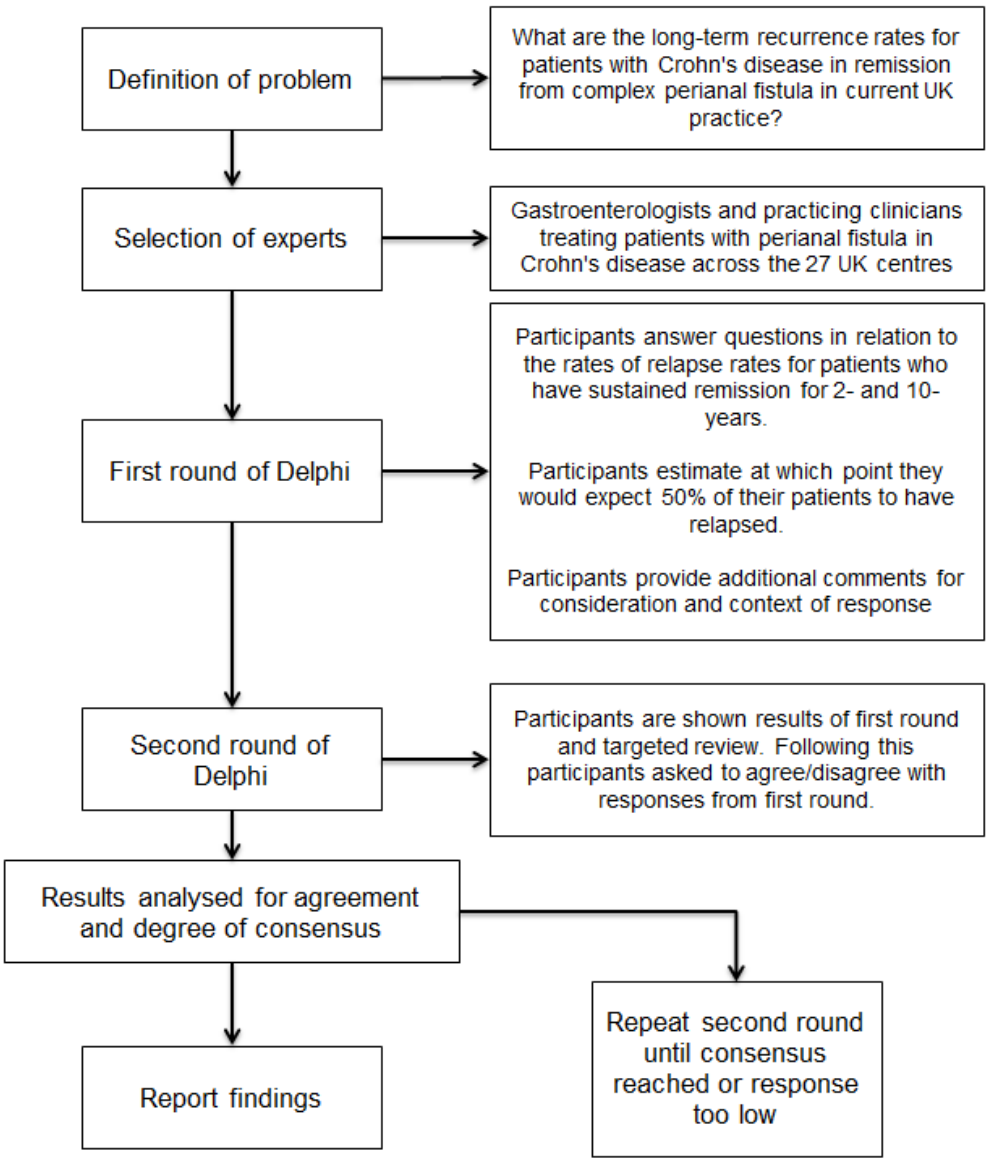
2.2.1 Methods

The Delphi Panel methodology is a scientific method to achieve independent expert consensus.[7] It represents a structured process used to collect knowledge by defining a problem, developing questions for experts to resolve, selecting a panel of experts, employing questionnaires, performing controlled assessment and feedback including qualitative and quantitative analysis, and follow-up (reassessment) using a series of surveys until an accord is established and summarized.

Advantages of the Delphi methodology for this application include: offering a method to address data gaps associated with long-term recurrence rates, ability to reach a consensus quickly in line with NICE timelines and logistical ease which may increase participation thus including a wider range of views and expertise (compared with the nominal group technique (NGT) – another method used to achieve a consensus).

Figure 4 presents a flow diagram of the Delphi Panel process, with each level discussed in more detail below.

Figure 4: Flow diagram of Delphi Panel process



Defining the decision problem

The decision problem was associated with long-term (≥2-years) recurrence rates associated with complex perianal fistula in patients with Crohn's disease.

The patient population of interest was defined as: adults with complex perianal fistula and non-active or mildly active luminal Crohn's disease, who are refractory to at least one of the following treatments: antibiotics, immunosuppressants or induction/maintenance biologics treatment. For the purposes of the data collection, it was assumed that patients would be receiving maintenance treatment with optimised anti-TNF therapy and immunosuppressants. This is in line with where darvadstrocel would be positioned in UK clinical practice. The patient population and the definition of remission and recurrence were detailed to respondents prior to completing the questionnaire (Table 3).

Table 3: Key definitions for participants

	Definition
Population	Adults with complex perianal fistula and non-active or mildly active luminal Crohn's disease, who are refractory to at least one of the following treatments: antibiotics, immunosuppressants or induction/maintenance biologics treatment. The patient population relevant to this survey are receiving maintenance treatment with optimised anti-TNF therapy and immunosuppressants.
Remission	Comprises both clinical remission and patient centred outcomes. It is defined as closure of all external openings as per clinical assessment (as determined by not draining despite gentle finger compression) AND the patient does not experience any pain or discharge, as determined by a score equal to 0 in both pain and discharge dimensions of the PDAI.
Recurrence	Defined as re-opening of any of the treated external openings with active drainage as clinically assessed OR the patient experiencing pain or discharge, as determined by a score ≥1 in either the pain or discharge dimensions of the PDAI.

Abbreviations: PDAI, perianal disease activity index; TNF, tumour necrosis factor

Developing questions for the experts to resolve

The Delphi Panel presented in this document considered two rounds of questionnaires. The questions included in round one were developed based on the key uncertainties identified by the Committee within the NICE submission for darvadstrocel: outcomes were associated with sustained remission and long-term recurrence/relapse rates. Key questions were:

- Of those patients who have maintained remission for 2-years, what proportion of these would you expect to continue in remission for 5- and 10-years?
- Of those patients who have maintained remission for 10-years, what proportion of these would you expect to continue in remission for 20-years and their lifetime?
- At what point would you expect half of your patients to have relapsed with recurrent fistula?

The questionnaire used for round one was developed in paper format and through an online tool (Survey Monkey) prior to being piloted on two participants, including one clinical expert. Following this, minor changes were made, including presentation and wording, before finalisation of the round one questionnaire presented in Appendix 4.1.

The questions included in round two were informed by the response of the first, with the specific objective of achieving a consensus across clinical experts. Similarly, the questionnaire used for round two was developed in paper format and through the online tool prior to being piloted on two participants, including one clinical expert. Appendix 4.2 presents the final questionnaire used in round two. Statements required 75% agreement from the panel to conclude a consensus.

Participants had the opportunity to provide comments at the end of each of the questions in an open-ended style response. Due to infeasibilities related to timing, these comments were not investigated within this Delphi Panel but they are presented within the results.

Selection of a panel of experts

Experts were selected based on identified treating gastroenterologists and surgeons from 27 UK centres known to Takeda to be leaders in providing treatment for complex perianal fistula in Crohn's disease. These 27 centres were identified based on the size of the population they treat; any identified special interest in perianal Crohn's disease; and their involvement in research relating to perianal Crohn's disease. The list of centres was validated through 1:1 discussions with clinical experts in this field. In the email sent out with the link to the Survey Monkey questionnaires we also asked clinicians to forward the invite to participate in the Delphi Panel to any colleagues for whom they felt it would be appropriate.

In total, 68 clinical experts were contacted via email, including: 35 colorectal surgeons and 33 consultant gastroenterologists. Colorectal surgeons were based in London (n=4), Harrow (n=3), Derby (n=3), Greater Manchester (n=3), Glasgow (n=2), Newcastle-upon-Tyne (n=2), Sheffield (n=2), Oxford (n=2), Leeds (n=2), Birmingham (n=2), Luton (n=1), Coventry (n=1), Exeter (n=1), Cambridge (n=1), Nottingham (n=1), Southampton (n=1), Liverpool (n=1), Wales (n=1), Inverness (n=1) and Edinburgh (n=1). Consultant gastroenterologists were based in: London (n=6), Harrow (n=3), Oxford (n=3), Sheffield (n=2), Hull (n=2), Exeter (n=2), Edinburgh (n=2), Liverpool (n=2), Glasgow (n=1), Inverness (n=1), Southampton (n=1), Newcastle-upon-Tyne (n=1), Wales (n=1), Manchester (n=1), Leeds (n=1), Nottingham (n=1) Derby (n=1), Birmingham (n=1) and Cambridge (n=1). All responses presented within this document are anonymised, as specified within the questionnaires.

Employing questionnaires

The link to the first round (via Survey Monkey) was circulated by email to the 68 clinical experts, accompanied by a clear explanation of the objectives of the study and specific instructions for member participation. The link was sent on Monday 20th August and the cut-off for responses was Thursday 23rd August. The short turnaround time was necessitated by the timelines relevant for the NICE ACD response.

A question in round one asked participants for their email address such that they could be identified for participation in round two. However, all respondents chose to skip this question. Therefore, the link to round two (via Survey Monkey) was circulated by email to all 68 clinical experts with the forwarded email from round one. This meant that some clinical experts completing round two may not have completed round one. Similarly, some clinical experts who completed round one may not have completed round two. For this reason, all responses to round one (including those submitted after the cut-off) are included and presented in this response (responses submitted up to Tuesday 4th September). The link to the second round was sent on Friday 31st August and the cut-off for responses was Tuesday 4th September.

Both rounds of questions were expected to take no longer than seven minutes to complete, as predicted by Survey Monkey.

2.2.2 Results

Section 2.2.2.1 presents the responses to round one (n=20, 29% response rate) and Section 2.2.2.2 presents the responses to round two (n=10, 15% response rate). The low response rate is likely due to the short turnaround times, necessitated by the timelines associated with the response to the ACD, and due to the timing of the Delphi Panel (August/September is peak holiday season which has been reflected by a large number of out of office responses).

For this reason, it has been difficult to achieve a meaningful consensus in round two. Therefore, Takeda are continuing to collect responses to both round one and round two beyond the deadline for the ACD response. Following this, if a consensus still hasn't been reached, Takeda will conduct a further round (round three). These results can be sent to NICE following data analysis if required.

2.2.2.1 Responses to Round One

All participants (n=20) agreed to their responses being amalgamated and utilised in this response to the ACD for darvadstrocel. Unfortunately, each participant skipped questions relating to email identification, role information (gastroenterologist, surgeon, nurse or other) and number of patients treated (Q2, Q3 and Q4). This made it difficult to contextualise the responses based on the individual's setting; for example: surgeons are likely to report inflated recurrence rates as these healthcare professionals only see those patients who recur. All participants stated that they had read and understood the definitions relevant to the exercise (Q5, Table 3).

Question 6: *Based on the pre-specified definition of remission (above), of those patients who have maintained remission for 2-years, what proportion of these would you expect to continue in remission for 5-years?*

All participants completed Q6 (n=20). 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%). Four participants considered that >71% of patients would remain in remission for up to 5-years.

Two comments related to the data gap associated with long-term outcomes:

> *Comment 1: "The data on this is poor. A recent systematic review and meta-analysis highlights the problems of heterogeneity in reporting induction and maintenance of remission in this population. Percentages are based on personal experience and opinion."*
>
> *Comment 2: "Once they've been in remission for two years, many will stay there. There is a group who loses response to treatment but they will often have done so before two years. This is not a well-documented group in the evidence and most clinicians have a selection bias in that they will see the patients who lose response more than those who do not. This is my best guess."*

Another comment supported the "plateau" effect after 2-years:

Comment 3: "Critical window is first 12-24months - if can avoid recurrence during this window then should do well long term provided appropriate follow-up"

Two comments did not address long-term recurrence rates but referred to the unmet need related to patients achieving remission in the first instance – this is outside of the scope of the Delphi Panel's objectives:

Comment 4: "don't think a very useful question - the problem is those patients who do not respond"

Comment 5: "Expect loss of response in the majority, because fistula tracks do NOT heal on anti-TNF therapy"

Question 7: *Based on the pre-specified definition of remission (above), of those patients who have maintained remission for 2-years, what proportion of these would you expect to continue in remission for 10-years?*

The majority of participants completed Q7 (n=19), one skipped with the justification there were no data to base their answer on. On average, clinical experts expected 31% of patients who had maintained remission for 2-years to continue in remission for 10-years (range: 0%-80%). One participant considered that >71% of patients would remain in remission for up to 10-years. Five comments were provided to this question; three referred to previous comments to Q6 and two comments emphasised the speculative nature of responses due to the data gap:

Comment 1: "I think the data is poor here in a relapsing and remitting disease. I am basing this on personal experience."

Comment 2: "This is even more speculative than the above for obvious reasons."

Question 8: *Based on the pre-specified definition of remission (above), of those patients who have maintained remission for 10-years, what proportion of these would you expect to continue in remission for 20-years?*

All participants completed Q8 (n=20). On average, clinical experts expected 33% of patients who had maintained remission for 10-years to continue in remission for 20-years (range: 0%-100%). Three participants considered that >71% of patients would remain in remission for up to 20-years. As above, four comments referred to previous comments on lack of data and speculative responses. Two comments referred to the "plateau" effect:

Comment 1: "Maybe I am pessimistic! However, if the small minority of patients who manage 10y in remission are followed, then a higher proportion (up to a third) is likely to remain so for another decade"

Comment 2: "Once they have been in remission for ten years, they may develop a new fistula but the rate of this is not known. I would expect it to be quite small."

Question 9: *Based on the pre-specified definition of remission (above), of those patients who have maintained remission for 10-years, what proportion of these would you expect to continue in remission for a lifetime?*

The majority of participants completed Q9 (n=19), one skipped with the justification that they were unable to comment. 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%). Two participants considered that >71% of patients would remain in remission for a lifetime. As above, three comments referred to previous comments on lack of data and speculative responses. Two comments referred to the "plateau" effect:

> *Comment 1: "Data are almost non-existent, but if there is complete healing of the track, then the likelihood of recurrence is less"*
>
> *Comment 2: "as above - I suspect (don't know) that there is a plateauing of the recurrence curve"*

Finally, one comment referred to the selection bias commented on in an earlier question:

> *Comment 3: "Again, this is unknown and my view is prone to selection basis making me likely to overestimate 'recurrence' or a new fistula"*

Question 10: *Based on the pre-specified definitions of remission and recurrence (above), please mark at which point you would expect half of your patients to have relapsed with recurrent fistula(e). Assume that time 0-years represents start of remission*

The majority of participants completed Q9 (n=19), one skipped the question. On average, respondents expected half of their patients to have relapsed with recurrent fistula(e) after 7-years (range: 1-50).

Question 11: *If you have any additional comments for consideration in addressing the natural history of perianal fistula(e) in Crohn's disease please specify here. Additionally, to support Takeda in providing NICE with a better understanding around anticipated long term outcomes for patients with perianal Crohn's we would be grateful if you could highlight any data, even if this is audit data for small patient cohorts, which examine the long term relapse rates for patients with Crohn's perianal fistula.*

Five comments were provided to this closing question. Two comments emphasised the unmet need with inducing remission rather than maintaining it:

> *Comment 1: "The unmet clinical need is not to maintain remission but to induce remission"*
>
> *Comment 2: "Perianal fistulae are a pain. In Crohn's disease, unless there is complete healing of the track, usually only achieved at present by medical AND surgical therapy, then they frequently recur"*

One comment provided a reference for Legue et al. (2018) which was picked up in our targeted review. One comment discussed a move towards reduced heterogeneity in outcome reporting, thus allowing more meaningful comparisons in the future:

> *Comment 3: "Now that the ACPGBI have published a core outcome set for fistulising perianal CD (Sahnan Gut 2018) there will be reduced heterogeneity in outcome reporting, thereby facilitating more meaningful comparisons between treatments. We*

will then be able to compare outcomes longitudinally and have a more robust idea of how long patients stay in remission following treatment."

Finally, one comment emphasises the selection bias and the lack of data:

Comment 5: "See my comments above re selection bias and lack of objective data. I expect your data to be very varied because I really don't think we know the answer to this but my view is that if they stay in remission for two years and anti TNF treatment is continued, it is the minority who will recur. Obtaining genuine fistula closure is crucial to long term freedom from fistula and from symptoms and if darvadstrocel helps achieve this, it will be a valuable tool."

2.2.2.2 Responses to Round Two

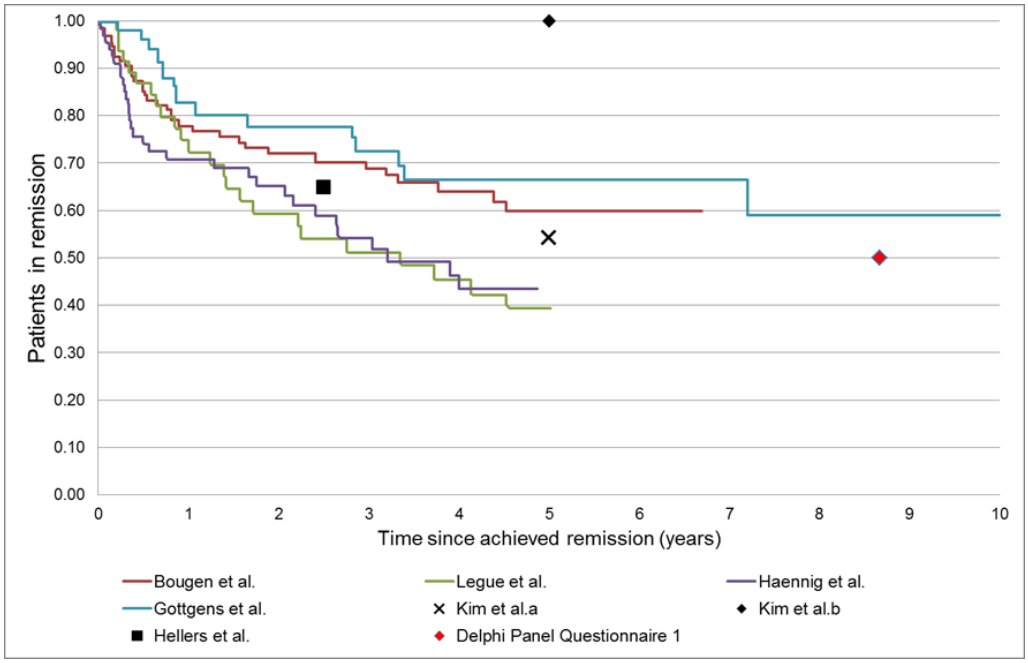
All participants (n=10) agreed to their responses being amalgamated and utilised in this response to the ACD for darvadstrocel.

Question 2:

Figure 5 presents the Kaplan-Meier curves and point estimates detailing long-term (>2-years) recurrence rates identified from the targeted literature review in patients with complex perianal fistula in Crohn's disease. The full references are provided at the end of this survey.

The average result from the first questionnaire estimated that 50% of patients within the UK relapse by an average of ~9-years (answers ranged from 1-50 years) – depicted by a red diamond on the graph below.

Figure 5: Long-term recurrence rates observed in the literature and rates estimated from the first round of Delphi Panel questionnaires



Kim et al.a: all patients

Kim et al.b: patients treated on infliximab maintenance therapy

Given these results, would you consider that it is clinically plausible that 50% of patients will remain in remission up to ~9-years?

Note: the questions sent out as part of round two were designed based on responses to round one. However, due to the overlap between round one and round two – round two was based off all responses to round one as of the original cut-off date (Thursday 23rd August). At this cut-off the median time to relapse was reported to be 9-years. This subsequently reduced to 7-years as the cut-off date was extended to Tuesday 4th September. A consensus was not established to this question: 40% of participants agreed with the statement, 30% disagreed and 30% chose to skip the question. Of those responding, 57% agreed and 43% disagreed.

Two comments refer to the “plateau” effect with reduced long-term recurrence if a fistula is truly closed:

Comment 1: “Major drop off is clearly in 1st 2 years. Beyond that (and with appropriate close follow-up and use of therapies) should be able to maintain remission.”

Comment 2: “Once they have actually healed there fistula I think it is likely they will stay healed. The problem is getting them there. The data on long term remission tend to be in medically treated patients and do not necessarily include patients whose fistulae have actually fully closed, as the medical trials tend to use a weaker definition for healing.”

One comment linked to a “no” response emphasised that they would expect most patients to recur.

Question 3: *Do you agree or disagree with the statement: "The longer a patient is in remission, the less risk of recurrence. In essence a “plateau effect” will likely be observed."*

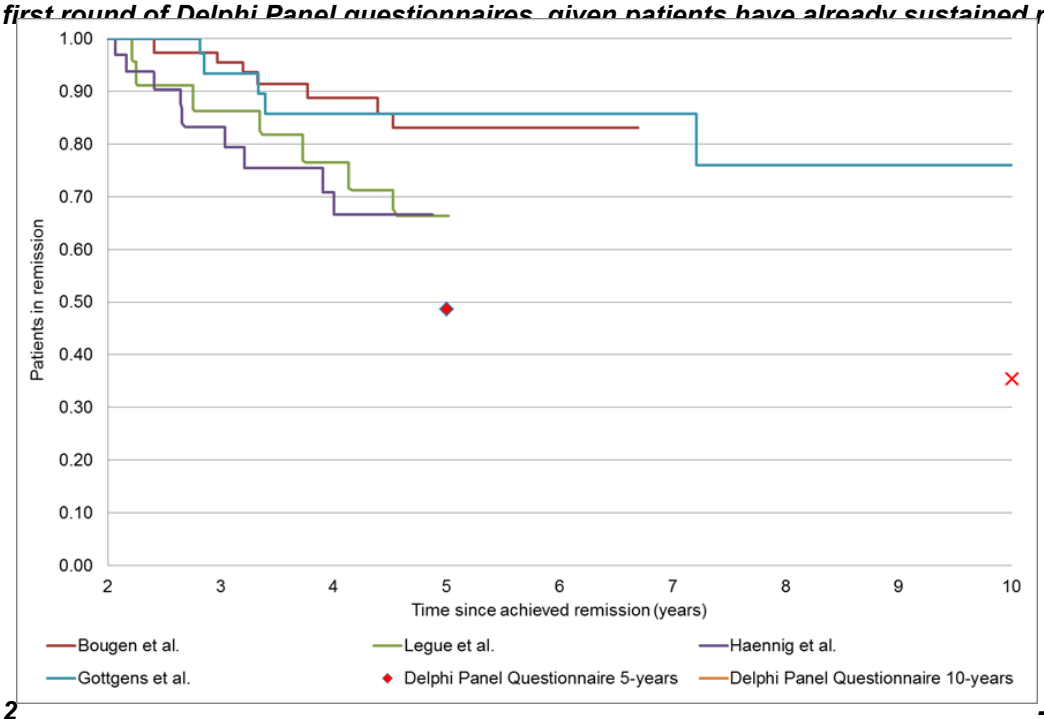
A consensus was established for this question. Of those responding, 100% agreed. However, three participants chose to skip this question.

Question 4: *Figure 6 presents the Kaplan-Meier curves detailing long-term recurrence rates, for patients who remained in remission for 2-years, identified from the targeted literature review in patients with complex perianal fistula in Crohn’s disease. The full references are provided at the end of this survey.*

The average result from the first Delphi Panel questionnaire estimated that ~49% of patients who maintained remission for 2-years would be expected to continue in remission to 5-years (answers ranged from 11-80%) – depicted by a red diamond on the graph below.

The average result from the first questionnaire estimated that ~35% of patients who maintained remission for 2-years would be expected to continue in remission to 10-years (answers ranged from 0-80%) – depicted by a red star on the graph below.

Figure 6: Long-term recurrence rates observed in the literature and rates estimated from the first round of Delphi Panel questionnaires, given patients have already sustained remission for 2-years



Having seen the data from the targeted review and responses from the first Delphi Panel questionnaire: of those patients who have maintained remission for 2-years, what proportion of these would you expect to continue in remission for 5-years?

Note: the questions sent out as part of round two were designed based on an earlier cut-off for responses to round one. Therefore, the estimates shown in Figure 6 may be different from the final cut-off. A consensus was not established for this question. Of those responding: 14% selected 21-30%, 29% selected 31-40%, 29% selected 51-60% and 29% selected 71-80%. Three participants skipped this question. On average, clinical experts expected 51% of patients who had maintained remission for 2-years to continue in remission for 5-years (range: 21%-80%). These estimates are slightly higher than provided in round one, suggesting that clinical experts increased their responses after seeing the literature and the previous responses.

One comment was provided referring to the “plateau” effect:

> *Comment 1: “The plateau is not flat”*

Question 5: *Having seen the data from the targeted review and responses from the first Delphi Panel questionnaire: of those patients who have maintained remission for 2-years, what proportion of these would you expect to continue in remission for 10-years?*

A consensus was not established for this question. Of those responding: 14% selected 0-10%, 14% selected 21-30%, 29% selected 31-40%, 14% selected 41-50% and 29% selected 51-60%. Three participants skipped this question. On average, clinical experts expected 37% of patients who had maintained remission for 2-years to continue in remission for 10-years (range: 0-60%). The average estimate is slightly higher than provided in round

one, suggesting that clinical experts increased their responses after seeing the literature and previous responses.

One comment was provided referring to the “plateau” effect:

> *Comment 1: “Some do enter extended remission”*

Question 6: *Would you continue treatment with anti-TNF therapy (e.g. infliximab maintenance) after a patient had received darvadstrocel?*

A consensus was established for this question. Of those responding: 86% stated they would continue treatment with anti-TNF therapy and 14% stated that they would not. Three participants skipped this question. Three comments were provided:

> *Comment 1: “This is also dependent on their luminal disease. Specifically for their perianal disease yes I would consider a treatment break following a full and informed discussion with the patient”*
>
> *Comment 2: “Until further notice! No evidence base - but they are different treatment modalities and likely to be complementary.”*
>
> *Comment 3: “high risk patients - need to maximise chances of maintaining remission - anti-TNF has independent MOA for helping in this regard.”*

Question 7: *Would you expect improved outcomes in patients who continue maintenance treatment with anti-TNF therapies after darvadstrocel?*

A consensus was established for this question. Of those responding: 86% stated that they would expect improved outcomes in patients who continued with maintenance treatment and 14% indicated that they did not expect such a benefit. Three participants skipped this question. Three comments were provided:

> *Comment 1: “Gut feeling only, I am afraid”*
>
> *Comment 2: “Yes - absolutely!”*
>
> *Comment 3: “At least initially.”*

Question 8: *If you have any additional comments for consideration in addressing the natural history of perianal fistula(e) in Crohn's disease please specify here. Additionally, to support Takeda in providing NICE with a better understanding around anticipated long-term outcomes for patients with perianal Crohn's we would be grateful if you could highlight any data, even if this is audit data for small patient cohorts, which examine the long-term relapse rates for patients with Crohn’s perianal fistula.*

No additional comments were provided to this closing question.

2.2.3 Discussion

To date, the Delphi Panel has achieved a consensus on the “plateau” effect, anti-TNF therapy maintenance use and improved outcomes associated with continued anti-TNF therapy. There is general agreement that the longer a patient stays in remission, the smaller their chance of recurrence. Additionally, the majority of clinical experts would consider some form of maintenance therapy after darvadstrocel administration and they would expect to see improved outcomes as a result of this. These are qualitative outcomes where the participants have agreed with the principles in theory. However, no consensus has been achieved when trying to quantify these results.

The responses to both round one and round two of the Delphi Panel highlight the uncertainty across clinical experts; emphasised by the ranges in responses (some spanning from 0% to 100%). Takeda consider that the comments provided by the participants throughout the Delphi process are particularly informative in describing the uncertainty observed. These comments repeatedly addressed four themes: (1) different definitions of remission, (2) lack of experience related to long-term outcomes, (3) selection bias and (4) lack of data. Interpretation of these comments suggested that some participants responded with over estimates of long-term recurrence.

Comments provided throughout the Delphi Panel process indicate differences between clinical remission and “true” healing of the fistula tract. Comments made in reference to clinical remission suggest high recurrence rates and suspect that the majority will recur. Whereas, comments made in reference to the “true” healing of the fistula tract suggest that many patients will remain in remission and few will recur. Takeda attempted to align the definition of remission across all participants by providing a clear definition of the CPC remission outcome used within the economic model; this definition was repeated at the top of each page of the online questionnaire for round one. However, based on the comments received, it appears that participants based responses on their experience where remission was likely defined with looser criteria, such as clinical remission. Weaker definitions of remission are likely to result in higher recurrence rates, reflected in the comments. Takeda would like to draw the Committee’s attention to the comments that focus particularly on “true” healing of the fistula tract, where recurrence was considered very low over time.

Takeda pre-empted issues relating to experience of treating these patients and the selection bias; in round one questions were included asking each participant to specify their role (gastroenterologist, nurse or surgeon) and how many patients they are exposed to each year. However, all participants chose to skip these questions. Therefore, results could not be contextualised and interpreted for those clinical experts treating few vs. many patients and for those observing long-term follow-up vs. treating with surgery due to a recurrence. For healthcare professionals treating few patients, their long-term experience may not reflect a UK average. Additionally, Takeda would like to emphasise that surgeons completing this Delphi Panel would likely report over-estimated rates of recurrence as these healthcare professionals only see those patients who have recurred as suggested by clinical experts in comments relating to selection bias made throughout the Delphi Panel.

Whilst there is large variation in quantitative results reported, some participants have responded in line with data observed in the literature. Unfortunately, due to lack of information provided on the definitions of remission used and the role of the healthcare professional we cannot draw meaningful interpretations from this. Additional advantages include: responses and comments from up to 30 clinical experts from UK centres, the methodology is robust and has been described in detail and comments are informative in describing the diverging opinions across UK clinical experts.

The main limitation associated with the Delphi Panel was the inability to identify respondents such that the same pool of respondents could be included in round two. Similarly, we could have encouraged a higher response rate by re-sending the questionnaire links had we known who had not yet responded. However, given the uncertainty observed, it is unlikely that a quantitative consensus would be achieved. Instead, the qualitative consensus and comments from the respondents provide a great deal of context for the diverging opinions of healthcare professionals on the topic of long-term recurrence rates in patients with complex perianal fistula in Crohn's disease. This qualitative information is used to validate the outcomes observed within the economic model and described within the main ACD response document.

As stated in Section 2.2.2, Takeda are continuing to collect responses from round one and round two (extended cut-off: Friday 28th September). Following this, Takeda will consider the informative benefits of conducting an additional round (round three). These results can be sent to NICE following data analysis if required.

3. Appendix

3.1 Round one questionnaire

Page title: Introduction

On 16th August 2018, the National Institute for Health and Care Excellence (NICE) published a minded negative recommendation for darvadstrocel for the treatment of perianal fistula in Crohn's disease. This recommendation largely stemmed from the uncertainty associated with the natural history of perianal fistula(e) in Crohn's disease – specifically in terms of long-term recurrence for those achieving remission.

In the absence of the gold-standard randomised controlled trial (RCT) providing such data, Takeda are exploring other avenues of data generation including a Delphi Panel exercise. The Delphi Panel methodology is a scientific, iterative method to achieve independent expert consensus.

We value your clinical expertise in this patient population and thank you for taking the time to complete this Delphi panel exercise. The cut-off for individual responses will be 5pm on Thursday 23rd August (a reminder email will be sent the day before). If you have any questions prior to completing the survey please contact Glynn Owen (email: glynn.owen@takeda.com, contact number: 07818 098396).

1. Takeda UK Ltd will receive your individual responses to this Delphi Panel exercise. These will be anonymised and aggregated for distribution to all survey respondents and utilised to inform a response to NICE. Please confirm that you are happy to proceed in this regard and that your individual and ultimately amalgamated responses will be utilised.

Yes ☐

No ☐

Additional comments:

If no, end of the survey and thank you for participation

Page title: Participant information

Note: Takeda UK Ltd will receive the responses to these questions. However, all data will be anonymised before being shared with survey respondents and NICE.

2. The Delphi Panel technique requires two phases of questionnaires. Therefore, Takeda will keep a list of respondents to the first phase to include in the second phase. Please note provision of an email address is optional. By inputting your email address in this box you are consenting to receive from Takeda UK Ltd, the anonymised and amalgamated results of the survey in which you have chosen to participate. We will keep your email address safe and secure in line with our Privacy Policy (https://www.takeda.com/en-gb/privacy-policy/). You may withdraw your consent to receiving such updates at any time by emailing dataprivacy@takeda.com.

Participant email address:

3. Please select the role that best reflects your position

Gastroenterologist ☐

Surgeon ☐

Nurse ☐

Other (please specify)

4. Approximately how many patients do you treat with perianal fistula in Crohn's disease in the UK each year?

0-10 ☐

11-30 ☐

31-50 ☐

51+ ☐

Additional comments [open ended text box]

Page title: Key definitions

Population for consideration in this exercise is: adults with complex perianal fistula and *non-active or mildly active luminal Crohn's disease*, who are refractory to at least one of the

following treatments: antibiotics, immunosuppressants or biologic treatment. The patient population relevant to this survey are receiving on-going maintenance treatment with *optimised anti-TNF therapy and immunosuppressants*. This is in line with where darvadstrocel would be positioned in UK clinical practice.

Remission comprises both clinical remission and patient centred outcomes. It is defined as closure of all external openings as per clinical assessment (i.e. not draining despite gentle finger compression) AND the patient does not experience any perianal pain or discharge.

Recurrence is defined as re-opening of any of the treated external openings with active drainage as clinically assessed OR the patient experiencing perianal pain or discharge.

5. Have you read the detailed definitions of population, remission and recurrence relevant to this exercise?

Yes ☐

No ☐

If not, repeat definitions

Page title: Long-term recurrence – conditional on time in remission

The following questions all relate to patients who are receiving maintenance treatment with optimised anti-TNF therapy and/or immunosuppressants as per normal clinical practice.

NB: Remission comprises both clinical remission and patient centred outcomes. It is defined as closure of all external openings as per clinical assessment (i.e. not draining despite gentle finger compression) AND the patient does not experience any perianal pain or discharge.

6. Based on the pre-specified definition of remission (above), of those patients who have maintained remission for **2-years**, what proportion of these would you expect to continue in remission for **5-years**?

0-10% ☐

11-20% ☐

21-30% ☐

31-40% ☐

41-50% ☐

51-60% ☐

61-70% ☐

71-80% ☐

81-90% ☐

91-100% ☐

Please provide further details:

7. Based on the pre-specified definition of remission (above), of those patients who have maintained remission for **2-years**, what proportion of these would you expect to continue in remission for **10-years**?

0-10% ☐

11-20% ☐

21-30% ☐

31-40% ☐

41-50% ☐

51-60% ☐

61-70% ☐

71-80% ☐

81-90% ☐

91-100% ☐

Please provide further details:

8. Based on the pre-specified definition of remission (above), of those patients who have maintained remission for **10-years**, what proportion of these would you expect to continue in remission for **20-years**?

0-10% ☐

11-20% ☐

21-30% ☐

31-40% ☐

41-50% ☐

51-60% ☐

61-70% ☐

71-80% ☐

81-90% ☐

91-100% ☐

Please provide further details:

9. Based on the pre-specified definition of remission (above), of those patients who have maintained remission for **10-years**, what proportion of these would you expect to continue in remission for **their lifetime**?

0-10% ☐

11-20% ☐

21-30% ☐

31-40% ☐

41-50% ☐

51-60% ☐

61-70% ☐

71-80% ☐

81-90% ☐

91-100% ☐

Please provide further details:

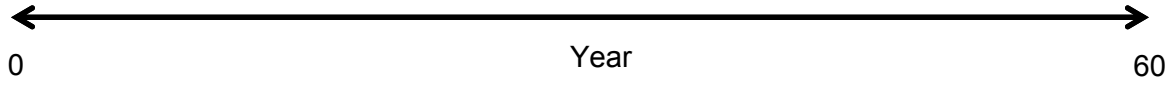
Page title: Duration of remission from baseline

The following questions all relate to patients who are receiving maintenance treatment with optimised anti-TNF therapy and/or immunosuppressants as per normal clinical practice.

NB1: Remission comprises both clinical remission and patient centred outcomes. It is defined as closure of all external openings as per clinical assessment (i.e. not draining despite gentle finger compression) AND the patient does not experience any perianal pain or discharge.

NB2: Recurrence is defined as re-opening of any of the treated external openings with active drainage as clinically assessed OR the patient experiencing perianal pain or discharge.

10. Based on the pre-specified definitions of remission and recurrence (above), please mark at which point you would expect half of your patients to have relapsed with recurrent fistula(e). Assume that time 0-years represents start of remission.



Page title: Additional comments

11. If you have any additional comments for consideration in addressing the natural history of perianal fistula(e) in Crohn's disease please specify here. Additionally, to support Takeda in providing NICE with a better understanding around anticipated long term outcomes for patients with perianal Crohn's we would be grateful if you could highlight any data, even if this is audit data for small patient cohorts, which examine the long term relapse rates for patients with Crohn's perianal fistula.

Comments:

Page title: Thank you for completing this Delphi Panel survey

If you have any questions please contact Glynn Owen (email: glynn.owen@takeda.com, contact number: 07818 098396)

3.2 Round two questionnaire

Page title: Introduction

On 16th August 2018, the National Institute for Health and Care Excellence (NICE) published a minded negative recommendation for darvadstrocel for the treatment of perianal fistula in Crohn's disease. This recommendation largely stemmed from the uncertainty associated with the natural history of perianal fistula(e) in Crohn's disease – specifically in terms of long-term recurrence for those achieving remission.

In the absence of the gold-standard randomised controlled trial (RCT) providing such data, Takeda are exploring other avenues of data generation including a Delphi Panel exercise.

This survey represents the second (of two) questionnaires aiming to achieve a consensus across clinical expertise in this patient population. If you missed the first questionnaire and would like to take part please follow this link: https://www.surveymonkey.com/r/6NBGH56. The aggregated responses from respondents (n=13) of the first questionnaire are presented within this survey. Note, if you wish to change your response to the first questionnaire please contact Glynn Owen (contact details below).

Thank you for taking the time to complete this exercise.

The cut-off for individual responses will be 5pm on **Monday 3rd September**. If you have any questions prior to completing the survey please contact Glynn Owen (email: glynn.owen@takeda.com, contact number: 07818 098396).

1. Takeda UK Ltd will receive your individual responses to this Delphi Panel exercise. These will be anonymised and aggregated for distribution to all survey respondents and utilised to inform a response to NICE. Please confirm that you are happy to proceed in this regard and that your individual and ultimately amalgamated responses will be utilised.

Yes ☐

No ☐

Additional comments:

If no, end of the survey and thank you for participation

Page title: Recurrence rates from the literature and clinical expert feedback

Alongside this Delphi Panel exercise, Takeda UK have conducted a targeted review of the literature to identify the evidence available for long-term (≥2-years) fistula recurrence rates in patients with complex perianal fistula in Crohn's disease. This review highlighted the limited evidence base with only six studies identified. Takeda UK use the results of this literature review and the feedback from the first Delphi Panel survey to attempt to reach a consensus in this questionnaire.

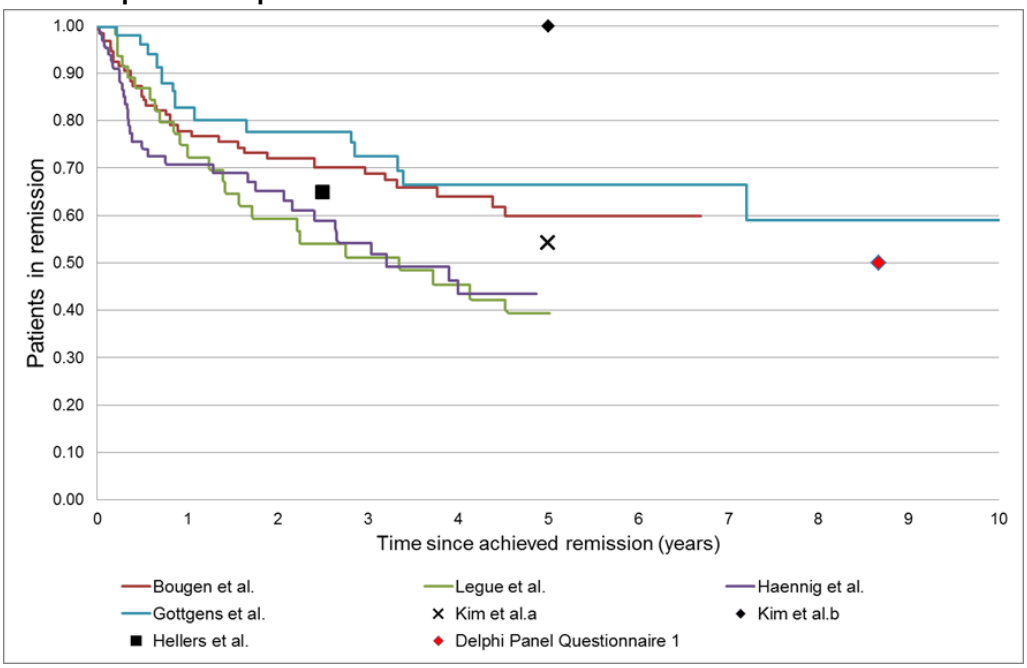
Due to the uncertainty associated in this area a quantitative consensus is likely to be difficult to achieve – therefore, please provide as much qualitative information as you can to the following questions. Again, thank you for your time in helping us address this evidence gap.

2.
3.
4.

5. *Figure 5* presents the Kaplan-Meier curves and point estimates detailing long-term (>2-years) recurrence rates identified from the targeted literature review in patients with complex perianal fistula in Crohn's disease. The full references are provided at the end of this survey.

   The average result from the first questionnaire estimated that 50% of patients within the UK relapse by an average of ~9-years (answers ranged from 1-50 years) – depicted by a red diamond on the graph below.

Figure 7: Long-term recurrence rates observed in the literature and rates estimated from the first round of Delphi Panel questionnaires



Kim et al.a: all patients
Kim et al.b: patients treated on infliximab maintenance therapy

Given these results, would you consider that it is clinically plausible that 50% of patients will remain in remission up to ~9-years?

Yes ☐

No ☐

Additional comments:

6. Do you agree or disagree with the statement: “The longer a patient is in remission, the less risk of recurrence. In essence a “plateau effect” will likely be observed.”

Agree ☐

Disagree ☐

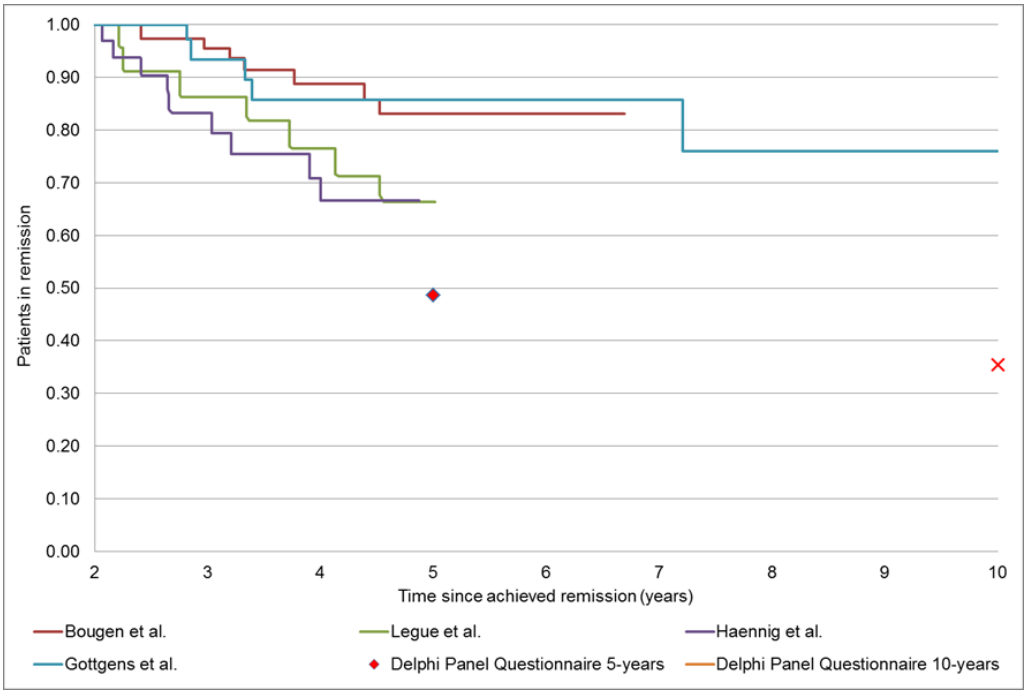
Additional comments:

7. Figure 6 presents the Kaplan-Meier curves detailing long-term recurrence rates, for patients who remained in remission for 2-years, identified from the targeted literature review in patients with complex perianal fistula in Crohn’s disease. The full references are provided at the end of this survey.

   The average result from the first Delphi Panel questionnaire estimated that ~49% of patients who maintained remission for 2-years would be expected to continue in remission to 5-years (answers ranged from 11-80%) – depicted by a red diamond on the graph below.

   The average result from the first questionnaire estimated that ~35% of patients who maintained remission for 2-years would be expected to continue in remission to 10-years (answers ranged from 0-80%) – depicted by a red star on the graph below.

   Figure 8: Long-term recurrence rates observed in the literature and rates estimated from the first round of Delphi Panel questionnaires, given patients have already sustained remission for 2-years



Having seen the data from the targeted review and responses from the first Delphi Panel questionnaire: of those patients who have maintained remission for 2-years, what proportion of these would you expect to continue in remission for 5-years?

0-10% ☐

11-20% ☐

21-30% ☐

31-40% ☐

41-50% ☐

51-60% ☐

61-70% ☐

71-80% ☐

81-90% ☐

91-100% ☐

Please provide further details:

8. Having seen the data from the targeted review and responses from the first Delphi Panel questionnaire: of those patients who have maintained remission for 2-years, what proportion of these would you expect to continue in remission for 10-years?

0-10% ☐

11-20% ☐

21-30% ☐

31-40% ☐

41-50% ☐

51-60% ☐

61-70% ☐

71-80% ☐

81-90% ☐

91-100% ☐

Please provide further details:

Page title: Clinical management

9. Would you continue treatment with anti-TNF therapy (e.g. infliximab maintenance) after a patient had received darvadstrocel?

Yes ☐

No ☐

Additional comments:

10. Would you expect improved outcomes in patients who continue maintenance treatment with anti-TNF therapies after darvadstrocel?

Yes ☐

No ☐

Additional comments:

Page title: Additional comments

11. If you have any additional comments for consideration in addressing the natural history of perianal fistula(e) in Crohn's disease please specify here. Additionally, to support Takeda in providing NICE with a better understanding around anticipated long-term outcomes for patients with perianal Crohn's we would be grateful if you could highlight any data, even if this is audit data for small patient cohorts, which examine the long-term relapse rates for patients with Crohn's perianal fistula.

Comments:

Page title: Thank you for completing this Delphi Panel survey

If you have any questions please contact Glynn Owen (email: glynn.owen@takeda.com, contact number: 07818 098396)

4. References

1. Bouguen G, Siproudhis L, Gizard E, et al. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. Clin Gastroenterol Hepatol. 2013;11(8):975-81 e1-4.

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3. Kim J KS, Park K, Jung H, Song I, editor Are combined medical and surgical treatments optimal therapy for complex perianal fistula in Crohn's disease? 6th congress of European Crohn's and Colitis Organisation; 2011; Dublin.

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6. Hellers G BO, Ewerth S, Holmström B. Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease. Gut. 1980;21(6):525-7.

7. O H. Analysis of the Future: The Delphi Method. The RAND Corporation. 1967;P-3558.

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 05/09/2018 **email:** NICE DOCS

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**British Society of Gastroenterology**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 05/09/2018 **email:** NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I think that the NICE committee have made a fair assessment of the data and whilst we are excited about the prospect of a new treatment for this group of patients with a difficult condition, I would agree that the available data (from a single clinical trial) does suggest a modest treatment effect. The cost of the medicine is relative high and I acknowledge that the cost effective estimates are very variable. I have one or two comments to make:
2	In section 3.10 – I would disagree that the standard of care in the UK is solely surgical intervention. The standard of care is a multidisciplinary approach including both medical and surgical treatments.
3	Study population - I think that the study population is as similar to UK populations as in many other clinical trials and I do not accept that this is a major reason not to accept the data.
4	We would support the use of the medicine in further clinical trials and that these should be done in the UK to gain some relevant experience.
5	I acknowledge and support the fact that the medicine will be reviewed again when further data is available.

Insert extra rows as needed

Checklist for submitting comments

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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

NICE National Institute for Health and Care Excellence

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Crohn's and Colitis UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1.1	We are very disappointed that the Committee has chosen not to recommend this innovative stem cell treatment. Perianal fistulas in people with Crohn's disease are associated with pain, discharge and considerable morbidity rates (including sphincter and perineal tissue destruction), negatively impacting on a person's quality of life and ultimately their life outcomes. Our position remains that darvadstrocel should be made available on the NHS, given the limited availability of effective treatment options currently offered, the significant unmet need identified within this patient population, and the strength of evidence demonstrating the severely debilitating nature of perianal fistulas. If upheld, this decision is likely to leave groups of patients with no or limited effective medical treatment options and very low quality of life. *"My mother suffered with fistulas for many years; in the last few years of her life they became more chronic and numerous. She suffered constant pain, which was at times so excruciating she could barely stand. These waves of intense pain could come at any time, making her wary of going out. Eventually she had to have district nurses visit the house every day to change her dressings. About 2 years ago she developed cancer within one of the fistulas. Doctors concluded that it was untreatable: surgery was ruled out because they would have had to remove such a large area (one leg and buttock), radiotherapy was ruled out because the affected area was too large and chemotherapy wasn't possible because the surrounding tissue was too badly damaged. My mum sadly passed away about a month ago (in her late sixties) from the cancer after a lifetime of pain and discomfort".* Furthermore, the introduction of **this innovative therapy has the potential not just to introduce a specific healing option for patients, but to raise the standards and expertise** of healthcare professionals – across the multidisciplinary team - in treating this condition. We would strongly encourage the Committee to revisit their decision.
1.1	We wish to draw the Committee's attention to the fact that darvadstrocel significantly increases the chances of remission in one year in comparison to the placebo group. This is likely to have far-reaching effects for people affected both mentally and physically. *"I can't say it enough that having Crohn's in this way is greatly debilitating both physically and mentally. Having been very headstrong prior to my diagnoses, the result of how I've had to live since as left me a different person. This drug might not work in every case but offers patients some hope and a new alternative."*
3.1	We are very concerned that the current recommendation does not accurately reflect the physically and emotionally debilitating impact of existing surgical options felt by patients, particularly in comparison to the approach offered by darvadstrocel. Furthermore, we would ask the Committee to place more emphasis, when coming to a final decision, on evidence that indicates it is more often the case that patients will face **multiple interventions, of limited efficacy, over many years** with current treatment options.

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Consultation on the appraisal consultation document – deadline for comments 5pm on 05/09/2018 **email:** NICE DOCS

	"I've suffered with Crohn's…for nearly 10 years, and I just want my life back! *I haven't had any partners since this due to the sheer embarrassing state of my body with setons left in place…. I don't see setons as fixing the problem other than patching it up.* *The current level of treatment can only be described as not good enough… with the prospect of reoccurring abscesses and more time spent in A&E using surgeons time... I've had too many visits for abscess surgery than I care to remember in the same spot that has been causing trouble for years. There is a great need for this treatment".* As demonstrated by evidence submitted by patients, seton surgery: • Can negatively impact on a person's quality of life; setons are reported by patients to be painful, intrusive and uncomfortable affecting self-esteem, sexual activity and everyday functions such as riding a bike or walking. • Impact on daily life/routine- for example changing (needing assistance to change) daily dressings and maintenance. • Risk continued symptoms and faecal incontinence. • May involve numerous surgeries to drain or reposition the seton. • The success of the intervention (efficacy and comfort) is dependent on the experience of the surgeon (which currently varies). • There are the associated risks of (multiple) surgery. Furthermore**, we do not consider that the decision document accurately describes** proctectomy and defunctioning surgery from the patient perspective: • Multiple surgical treatments are usually required to achieve healing, with a median of six procedures for complex fistulas and median of three for simple fistulas (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4188928/) • These are life-changing interventions which: • impact on a person's daily life of surgery, such as managing a stoma/wounds that do not heal, • can impact self-esteem, sexual relationships and **reduce fecundity,** • are stigmatising interventions, • carry the associated risks of surgery, • bring the associated costs of further surgery, lifetime costs of stoma nursing support and appliances. **In comparison to having to manage and/or live with setons and/or ostomy, this new treatment offers a much more manageable and attractive alternative to current treatment options. We feel strongly that the final recommendation does not reflect this.** We would also welcome further consideration by the Committee of the fact that immunosuppressants and antibiotics are ongoing treatments and have associated risks such as cancer, infection and antibiotic resistance (as well resources and costs associated with their prescribing and monitoring).
3.2	See above. We are concerned that the current recommendation may not take account of the physically and emotionally debilitating impact of existing surgical options in comparison to the approach offered by darvadstrocel. We are disappointed that the final recommendation does not give more consideration to the evidence offered detailing the impact that this condition has on sexual relationships, pregnancy rates and the impact of current treatment options on fecundity.
3.19	A number of equalities issues were raised in evidence and discussed by the Committee such as: - sexual relationships - pregnancy

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	- fecundity 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.

Insert extra rows as needed

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

NICE National Institute for Health and Care Excellence

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	School of Health and Related Research, University of Sheffield
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Typographical error In Section 3.15, it is stated that "The company presented a base-case cost-effectiveness estimate of £21,685 per quality-adjusted life year (QALY) gained (incremental costs £21,811; incremental QALYs 1.01), 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." These numbers are inconsistent with the company's base case cost-effectiveness estimate in which a 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. Please amend the numbers to be consistent with the company's response to clarification question B7. "The company presented a base-case cost-effectiveness estimate of £20,591 per quality-adjusted life year (QALY) gained (incremental costs £21,639; incremental QALYs 1.05)…" These numbers are using the deterministic ICER, they will be slightly different if you want to report the probabilistic ICER.
2	Inaccuracy and unclear text In Section 3.15, it is stated that "adjusting the probabilities of moving to the proctectomy and defunctioning surgery health states in the model, based on the available evidence from St Mark's study". It should also be noted that the data used to inform the transition to the defunctioning surgery was from the Mueller *et al* prospective cohort study and the transition to the proctectomy state was from the Bell *et* al prospective cohort study. Neither of these studies related to the St Mark's study data presented as part of the company's submission. Also whilst the sentence is otherwise accurate, it is unclear what the ERG did. I recommend the following text to replace the existing text "the probabilities of moving to the proctectomy and defunctioning surgery health states in the model, were adjusted so that the model predictions matched the evidence from the Mueller *et al* and Bell *et al* studies"
3	Potentially misleading text In section 3.17 it is stated that "In a conservative scenario analysis, 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." Conservative could imply that the ERG though that this scenario analysis was a lower bound on the effect of this factor on the ICER. This is not the case, as the ERG report (page 105) explicitly states "This scenario should be interpreted with caution, as it is intended only to inform the direction and maximum magnitude of any changes in the ICER due to the possible under prediction of utility in these three health states. For this reason, it is not incorporated in the ERG's preferred base." I recommend the following text "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 magnitude of any changes in the ICER due to the possible under prediction of utility in these three health states"
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant
Organisation	
Location	England
Conflict	I have received speaker fee from Takeda but not for the product discussed
Notes	
Comments on the ACD:	
I am concerned about the negative review as this is a viable treatment option for patients with refractory perianal Crohn's disease. Several of these patients end up with a permanent end stoma	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Other
Conflict	
Notes	

Comments on the ACD:

Hello, having read the recent reports that this drug is not to be authorised is great disappointment to me. I've suffered in this area of Crohns for 10 years since I was 20. As a gay male this is absolutely torturing me. There is a great need for developments to specifically treat perianal fistulas and to read that this isn't going to be authorised has killed any hope I had. Surgery has failed as an option for me. Immunosuppressants haven't worked. The success stories of this drug speak for them selves. I'm desperate for this to be become legalised. The easiest way of putting is by putting your self in the shoes of someone that has this specific condition. It's had impact on my confidence. I'm too embarrassed of my body to meet anyone. When I first heard of this drug I thought amazing, and now hearing that for economic concerns has really made me feel let down. Can't this even be given privately at cost? All I can say is whoever has made the decision not to authorise probably hasn't met anyone with this area of Crohns. I strongly urge you to reconsider your opinion on this. This has been the only thing keeping me sane and positive. I can't face more years with no treatment developments. Please reconsider and think how this impacts people with perianal fistulas. There is no other way of getting rid of mine due to how it passes the anal muscles. If I have surgery I could run a risk of incontinence. Therefore this been less evasive sounded like the perfect treatment. My consultants in Leeds even said the same. Before I heard of the trials for this I even considered taking my own life I was that depressed about my health. This drug would give me the chance to get my life back! Even consider as a private treatment. Please reconsider and think the benefits outweigh the reoccurring hospital visits and surgery. The cost would surely level out. I have puss the drains by my back end and a seton stitch. There is a need for this I can't stress this enough. I moved to Kuwait for work and was hoping by January 2019 this would be available. Please take into account my situation or please call me to discuss.
Kind Regards
[redacted]

I can't stress enough how much this new innovative treatment is needed. I can't have surgery on my fistula due to the complexity of where it lies across the schincter muscles and infusion treatments have failed me. This to me is the only thing keeping me positive that an actual tailored non evasive treatment to help cure the fistula. I have had this ongoing for ten years almost and cannot stress enough how much my anxiety levels have raised as a result. I can't meet anyone sexually, my confidence is at an all time low. I've had re-occurring absesses several times and this treatment would potentially put an end to years of suffering. I used to be a very head strong person. This complication of crohns has ruined my personal relationships and is almost on the edge of ruining my career. I've considered suicide many times and cannot face more years without no cure for the fistula. I'm desperate. The medicine might be expensive but the results I've heard are extremely positive. The time I've spent in hospital, failed infusion treatments which aren't specifically designed to treat fistulas have failed me. Please consider the people who can't tolerate infusions or where surgery isn't an option. I'm desperate need this

Name	[redacted]
Role	NHS Professional
Other role	Consultant Gastroenterologist and IBD Service Lead
Organisation	[redacted]
Location	England
Conflict	I have received research / educational grants, and honoraria within the previous 3 years from Abbvie, Gilead, GSK, Janssen, MSD, Novartis, Pfizer, Sandoz, Takeda.
Notes	

Comments on the ACD:

The committee have rightly questioned the relevance of an approximately 15% difference from the sham-surgery arm. I think it is worth pointing out that this population of patients really do currently lack good alternative treatment options beyond surgical interventions that lack a solid evidence base and that have poor published success rates that have tended to further decline in subsequent case series.

The long term outcome of fistula tracts that have healed will be critical to determine the benefit of this intervention. The committee have rightly commented that there is much uncertainty in this area, but I would agree with the expert advice that the committee has been given suggesting that relapse is generally an early phenomenon noted in the first 1-2 years and that, whilst relapse can occur after this time, it is less common. There is some support for this in the published literature - see for example the survival curve in figure 4 from the relatively large case series presented by Bouguen et al Clin Gastroenterol Hepatol. 2013.

The effectiveness of the present therapy in achieving fistula healing to by a robust assessment method at 1 year has been proven, with some data available beyond the first year. It would seem to me that we have a therapy that has the potential to achieve fistula closure by one of the more stringent definitions used in clinical trials of late, to at least the timepoint when most fistula recurrence would have been expected, and that we have effective therapies (anti-TNF) for preventing relapse/new fistula formation (see eg ACCENT-II trial).

This is not to say that there is much room in the literature for more information and longer term studies. But it is unrealistic to expect some of the sorts of really long term followup studies to be available - and indeed such studies are often flawed by the time they do get published since standards of care and available medications move on. I feel we should be cautious about denying a patient group with a condition that currently lacks effective treatments access to a treatment of proven benefit in this context.

Name	[redacted]
Role	NHS Professional
Other role	Gastroenterology Registrar & IBD Clinical Research Fellow
Organisation	
Location	England
Conflict	IISR grant on which I am named as a sub-investigator has been supplied for a research project regarding vedolizumab.
Notes	
Comments on the ACD:	
I have been through the useful slides and appraisal document in its entirety. They both make a great deal of sense to me and I am in agreement with the vast majority. I was also slightly surprised by the costs of a single course of Darvadstrocel, although I am led to believe that the NHS would pay an undisclosed but reduced price, to be agreed with Takeda. This also seems entirely appropriate.	

Name	[redacted]
Role	NHS Professional
Other role	Consultant Gastroenterologist
Organisation	
Location	England
Conflict	I have received speaker fees from Takeda Pharma for vedolizumab and darvadstrocel.
Notes	

Comments on the ACD:

This is a massively important issue for patients with Crohn's disease. Patient involvement exercises undertaken to underpin research activity has indicated that the debility caused is significant, underreported and symptoms that are reported are under-appreciated by clinicians. Existing treatments have a high rate of primary and secondary failure.

The difference between Darvadstrocel and standard care in the trial by Panes was statistically significant and clinically important - particularly given Comment 1 above, and limited options for therapy. This was a group who had already failed available treatments and where the intervention proved superior to optimised standard care where great attention to preparing the fistula track had been taken. Given the debility experienced, and failed alternative therapies, options for patients here include a defunctioning stoma (which is usually not reversed) or proctectomy - both life altering surgeries.

The data suggests that fistula closure is likely to be sustained - obviously important in reducing debility.

Clearly longer term results beyond the currently available studies are not available to determine subsequent relapse rates. It is certainly possible that having achieved fistula closure for intervals of 12-24 months, that this might be sustained. It shoudl be remembered that loss of response occurs regularly with antiTNF agents, and as a result patients may require repeated examinations under anaesthetic, drainage of sepsis and seton insertion, followed by further antiTNF or switch of agents if antidrug antibodies develop.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Gastroenterologist
Organisation	
Location	England
Conflict	
Notes	

Comments on the ACD:

This is a careful and well conducted appraisal. The only comments I would make are

1) this is a very difficult clinical problem representing possibly the greatest unmet need in the management of complex Crohn's disease. Current treatments are unsatisfactory

2) The reasoning in section 3.10 does not make sense: if placebo response in the ADMIRE CD in a nonUK trial population is higher than expected in a UK population, then this makes it more likely that the IMP would have a greater effect in a UK population, not less.

3) The economics are difficult to refute - but it would be very useful to have this agent available for selected patients.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Gastroenterologist
Organisation	
Location	England
Conflict	I was paid to attend a Takeda advisory board meeting in autumn 2017 in London on a different product
Notes	
Comments on the ACD:	
I agree with the committee findings. This is an exciting new treatment for patients whose illness is often difficult to treat and debilitating. However given the concerns re long term outcomes, apllicability to uk population together with cost and logistical issues , I agree that we should wait for data from the next study before approving use .	

Name	[redacted]
Role	NHS Professional
Other role	Consultant Nurse IBD
Organisation	[redacted]
Location	England
Conflict	
Notes	

Comments on the ACD:

The RCN Inflammatory Bowel Disease Network Grouphave concerns that a new treatment for perianal Crohn's disease, a disease area of significant unmet need, has been given an unfavourable review.

Perianal disease has a massive impact upon the mental health, quality of life, psychosocial well-being, as well as having a significant symptom burden including perianal pain, abscesses, faecal incontinence and drainage of blood and pus via the external wounds. The impact upon patients lifestyle and relationships is immeasurable. Perianal Crohn's disease patients have very much been the â€˜poor relations in terms of positive medical care improvements. Alofisel very much offers a shift change to redress this balance in a cohort of predominantly young people whose luminal disease is well managed, but they continue to endure the complications of a devastating disease. Current treatment results in repeated perianal surgeries which are painful, intrusive and potentially destructive to continence mechanisms. Repeated abscesses also risk faecal continence, the impact of which cannot and should not be underestimated.

As the EMA license is for patients with complex perianal fistulae who have mildly or inactive luminal disease, and the complexity of the surgical administration will dictate the treatment will be reserved for highly specialised centres and candidates will be carefully selected, treatment outcomes are likely to be very good. Ongoing research into producing acellular matrix to provide scaffolding for stem cells to stay and proliferate is likely to maximise benefits to a wider patient group going forward.

We feel it is unfair to deny patients potential relief from a dreadful disease because the long-term efficacy data is not yet available. It offers an alternative treatment option for people with significant, debilitating disease.

[redacted], on behalf of the RCN IBD Network Group

Name	[redacted]
Role	NHS Professional
Other role	Consultant Surgeon with an interest in IBD and advanced proctology
Organisation	
Location	England
Conflict	I am a member of the INSPIRE group which is an international registry of stem cell treatment in perianal Crohn's disease. This group is funded by Takeda although it is independent in its actions. I have no shares or other financial interest in Takeda or this technology itself.
Notes	

Comments on the ACD:

Thank you for consulting on this issue. Perianal Crohn's disease is an area of huge unmet need internationally, identified in several publications and by the James Lind Alliance priority setting exercise as a priority for research and clinical advance. The scale of morbidity, symptoms and impact on quality of life of this condition can be enormous and I've no doubt that patients and charities such as CCUK will have made contact with you to make that point. I can certainly echo it, as I operate on these patients regularly to try to keep their symptoms under control as best I can and in some cases, ultimately, to defunction or even remove the rectum entirely. The principle medical treatments have limited efficacy. They certainly help a good number of patients and induce improvement and even sometimes 'remission', although the definition of this in the medical treatment trials tend to be fairly loose, being based entirely on symptoms and the appearance of the external opening which tends to fluctuate over time in some patients anyway. We desperately need a treatment which actually closes fistulae, with deep tissue healing of the tracts, and does so in a greater proportion of patients. The potential for stem cells is that they may do just that, providing robust healing of fistulae in a group of patients. The ADMIRE-CD study certainly raises the possibility of sustained remission in a group of patients much larger than in the comparator group. The delta of 15% is significant given the morbidity that patients face and also because the comparator group has what is probably an elevated success rate initially thanks to the closure of the IO which probably gives an early benefit before the rates of remission fall away to those we would expect from medical treatment alone as time goes on (at 1 and 2 years, for example), when they represent the true current clinical picture, and the delta at this point is larger as a result. We very much want to be able to offer this to patients who have not benefitted from the advanced medical treatments (e.g. anti-TNF agents) currently available and who will head, in some cases, towards a permanent stoma. The evidence for long term healing is scant but it is my view that in those patients in whom we do see genuine deep tissue remission, it is likely that that remission will persist. The disappointing rates we often see are, in my view, related to a much looser definition of remission which is therefore more likely to ebb away, and to a selection bias that most clinicians with an interest in this area see, since the patients who do well tend to vanish from our clinics into those of the IBD nurses etc. If stem cells can produce robust fistula closure, it may well be the case that this persists in the longer term in which case it would be a very powerful resource in refractory disease. Many thanks for considering this agent.

Name	[redacted]
Role	NHS Professional
Other role	Clinical Research Fellow
Organisation	
Location	England
Conflict	I received payment as a member of the advisory board for this drug, but have received no other payments related to this product. My research has been funded by the Bowel Disease Research Foundation and a Royal College of Surgeons of England/Crohn's and Colitis UK Research Fellowship.
Notes	

Comments on the ACD:

Thank you for the opportunity to respond to this consultation document.I comment on this as a surgical registrar with an IBD interest, and as I have just completed my thesis on this subject.

THE EVIDENCE BASE

One of the key considerations of this new treatment is where it sits in the evidence base. As you will be aware, the treatment of Crohn's anal fistula is a multi-modal approach combining medicine and surgery [1]. Thanks to the many medical trials in the field, we can identify drugs to use in the induction and maintenance of clinical response or remission[2]. Unfortunately the surgical literature is underdeveloped; it is based on retrospective studies of poorly defined cohorts, with poorly defined outcomes [3].

In comparison, we are presented with a randomised trial, with a well defined cohort, intervention and outcomes for darvadstrocel [4]. This means that we have a high level evidence for this treatment, if not a large volume as for other treatments. Despite this, the reported benefits from the RCT report outcomes which compare favourably to those reported elsewhere in the literature. The inclusion criteria used in this trial are not overly restrictive when compared to others reported in the literature [5, 6].

The limited evidence in the field is recognised by the panel and by clinicians [7]. A recommendation from NICE to encourage research into quality of life, stratification and robust outcomes measurement would be helpful when proposing research to funders.

THE CLINICAL NEED

This treatment is the potentially the most significant innovation in the field since the ACCENT II trial [8], and is much needed a field with significant clinical need. We have cared for patients who would fit the criteria for darvadstrocel, but are facing the near to mid-term prospect of stoma formation/protectomy. This group of patients is typically young and economically active. They are keen to avoid the either of these interventions for their own quality of life and mental wellbeing, as well as to minimise their economic well being and risk of losing their jobs.

LOCATION OF CARE SERVICES

Given both the cost, and the logistic efforts required to deliver this treatment to a hospital, it is likely that this will limit its use to higher volume centres. This fits with the general trend in IBD care[9], and may go some way to address variation identified in the care of patients with Crohn's anal fistula, particularly in definitive surgical treatment [10, 11]. This may lead to an indirect reduction in costs in the longer term.

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Darvadstrocel for treating complex perianal fistula in Crohn's disease: ERG critique of the company's response to the first ACD.

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Date completed	Date completed (14/09/2018)

1 Scope of the critique

Due to time constraints imposed by the date of receipt of the ACD responses and the scheduled committee meeting date, the ERG have focused on critiquing the company's additional scenario analyses conducted in response to the ACD.(1) A lack of critique of other areas of the company's response to the ACD should not necessarily be taken to mean that the ERG agrees with these aspects of the company's ACD response.

2 The company's new scenario analyses

2.1 Identification of relevant studies

The company conducted new searches to identify data non-RCT data from clinical trials and observational studies (retrospective or prospective) recurrence rates on the long term (>2 years) for people with perianal fistulae who received darvadstrocel or standard care. It should be noted that standard care for second line treatment complex perianal fistulae is highly heterogeneous, see page 17 of the ERG report.(2) The company found six observational studies in their searches which they considered to be potentially relevant to this decision problem. The company used only the Bouguen(3) and Gottgens(4) studies to inform the scenario analyses provided in response to the ACD. Both of these studies predate the ADMIRE-CD trial, and consequently do not include people who have received darvadstrocel. Full details of the revised searches are provided in the company's response to the ACD.(1)

2.2 Applicability of the cohort study populations to the ADMIRE-CD population

The ERG assessed whether the study populations of Bouguen *et al.*(3) and Gottgens *et al*.(4) were sufficiently similar to the ADMIRE-CD study population to inform the plausible long term relapse rates in the standard care arm of the company's submitted economic model. The details of the populations recruited into each study are provided in Table 1.

The ERG identified four key differences between the ADMIRE-CD study(5, 6) and the Bouguen (3) and Gottgens (4) studies. Firstly, the ERG has concerns about whether the types of fistulea are consistent across the studies. The patients recruited into the ADMIRE-CD study had a complex perianal fistulae which was refractory to at least one conventional treatment (antibiotic, immunosupresant, anti-TNF), whereas the population in the Bouguen *et al*.(3) study was a mixture of people with simple (17.9%) and complex fistulae and the population in Gottgens *et al*.(4) study was a mixture of people with simple (24.2%) and complex (24.2%, the remaining 51.6% of people had an unknown fistula severity). The ERG note that this leads to two key differences between the populations in ADMIRE-CD study and these observational studies. Firstly, the Bouguen (3) and Gottgens (4) studies are a mixture of people with a simple and complex fistulae and secondly it is unclear what proportion of the fistulae in the

Bouguen (3) and Gottgens (4) studies were refractory to first line treatment. Secondly, the ERG has concerns that cohorts are not comparable with respect to their age. The mean age at which people were recruited into the ADMIRE-CD trial was 38 years old, this compares to 27.8 years in Bouguen *et al.* (3) (24 years median age at diagnosis and 3.8 years median Crohn's disease duration) and 46.4 years in Gottgens *et al (4)* (37.7 mean age at Crohn's disease diagnosis and 8.7 year mean duration of Crohn's disease). Consequently there are substantial differences in the age of the populations included in the different studies. Thirdly, the studies examine people with fistulising Crohn's disease over very different time periods. The ADMIRE-CD study included data on people recruited between 2012 and 2015, which compares to data collected between 1998 and 2011 in Bouguen *et al*.(3) and data collected on people diagnosed between 1991–2011 in Gottgens *et al*.(4) (subgroup analyses were conducted for people were diagnosed between 1991–1998, 1999–2005, and 2006–2011). As the Bouguen *et al*.(3) and Gottgens *et al*.(4) were conducted in different time periods compared ADMIRE-CD, it is unclear whether the long term relapse rates in these populations would applicable to the ADMIRE-CD population. Finally, the definitions of the recurrence differ across the studies. In the ADMIRE-CD study was based upon no longer being in the clinical and patient centric (CPC) definition of remission, in Bouguen *et al*.(3) recurrence was defined using clinical assessment and in Gottgens *et al*. remission was defined as a new visible fistula at the same sight or a return of symptoms. Given the differences in the definition of remission, it is unclear how relevant the time to relapse curves in these studies are for informing the long term extrapolation of the time to relapse curve from the ADMIRE-CD study.

The ERG believes that there is significant heterogeneity in terms of the people recruited, the definition of remission and care received between the standard care arm of ADMIRE-CD and the Gottgens (4) and Bouguen (3) studies. Consequently, it is unclear whether this evidence is relevant for informing plausible long term extrapolations of the standard care arm of ADMIRE-CD. Furthermore, as darvadstrocel is not used in either of the long term studies, the ERG believe that these studies do not provide any new information on the plausibility of the extrapolation of the darvadstrocel arm of the ADMIRE-CD trial.

Table 1: The study populations of ADMIRE-CD(5, 6), Bouguen *et al*.(3) and Gottgens *et al*.(4)

Study	**Location (sites)**	**Design**	**Population**	**Intervention**	**Comparator**	**Primary outcome measures**	**Duration**	**Remission definition**
Panes et al. 2016, 2018(5, 6) ADMIRE-CD (NCT01541579; Cx601-0302) Funded by: TiGenix	49 sites in 8 countries (Austria, Belgium, France, Germany, Italy, the Netherlands, Spain and Israel)	Phase III, randomised, double-blind, parallel group, placebo controlled trial (n=212, 2012 to 2015)	Patients (aged ≥ 18 years) with complex perianal fistulising CD who are refractory to conventional (antibiotics, immunosuppressants) or biological treatment strategies	Darvadstrocel (24 mL containing 120 million expanded allogeneic adipose-derived stem cells) given as a single intralesional injection[a] and standard of care (n=107)	Placebo (24 mL saline solution) given as a single intralesional injection and standard of care (n=105)	Combined remission (clinical and MRI) at 24 weeks[b]	Active treatment consists of one administration of darvadstrocel, follow-up extended from 24 weeks to 52 weeks and then to 104 weeks[c]	The fistula was draining after gentle finger compression or the patient experienced any pain or discharge (defined as a patient scoring 1 or more in either of the pain or discharge sections of the Perianal Disease Activity Index [PDAI] scale
Bouguen et al. 2013(3)	2 referral centres in France	Retrospective observational cohort study (people treated between, 1998 to 2011)	Consecutive patients (age > 18 years) with documented perianal CD at first infliximab infusion (17.9% had simple fistula; 62% had seton drainage; 56% concomitant	NA	NA	Fistula closure, recurrence of perianal CD, recurrence of abscess after	250 weeks	The presence of fistula opening (determined by clinical assessment) among patients who

Study	Location (sites)	Design	Population	Intervention	Comparator	Primary outcome measures	Duration	Remission definition
			immunosuppressants; median age of diagnosis, 24 years; median CD disease duration, 3.8 years) and an established diagnosis of CD based on clinical, biological, radiological, endoscopic and/or histological evidence (n=156)			infliximab initiation and sustained fistula closure		had experienced fistula closure
Gottgens et al. 2017(4)	Inflammatory Bowel Disease South-Limburg registry, Netherlands	Cohort registry (people diagnosed between 1991 to 2011, with follow up data until 2014)	CD patients with and without perianal (PF) or rectovaginal fistulas (RVF) between 1991 to 2011 (mean age of diagnosis, 37.7; mean duration 8.7 years; anti-TNF exposure in 2011, 41.2%) n=1162 (CD with primary PF, n=161 [24.2% Simple; 24.2% complex; 51.6% unknown]; 82.6% treated with antibiotics; 61.5% underwent surgery for PF; anti-TNF between 2006 to 2011, 54% most in combination	NA	NA	Incidence of PF in CD patients over the past two decades	20 years	Either a visible new fistula at the same location, or the return of symptoms (the exact definition of symptoms is unclear) after a symptom-free period.

Study	Location (sites)	Design	Population	Intervention	Comparator	Primary outcome measures	Duration	Remission definition
			with immuno-modulator)					

CD, Crohn's disease; MRI, magnetic resonance imaging; PF, perianal fistula; RVF, rectovaginal fistulas; anti-TNF, anti - tumor necrosis factor

[a] The administration procedure involved the injection of darvadstrocel (or placebo) into the tissues surrounding the tract. Four vials (6mL each) containing approximately 30 million cells were shipped to the hospital for use by the surgeon on the day they were received. The content of two vials (60 million cells) was injected into the fistula walls along the length of the fistula tract and two vials (60 million cells) injected around the internal opening during an Examination Under Anaesthesia. This procedure was done by specialist physicians experienced in the diagnosis and treatment of conditions for which darvadstrocel is indicated.

[b] Defined as the clinical assessment of closure of all treated external openings that were draining at baseline, and the absence of collections > 2 cm of the treated perianal fistula in at least two of three dimensions, confirmed by masked central magnetic resonance imaging. Clinical assessment of closure was defined as the absence of draining despite gentle finger compression.

[c] Following a series of protocol amendments, the follow-up period was extended to 52 weeks (October 2012) and then to 104 weeks (December 2014

2.3 Comparison of the Kaplan-Meier curves and numbers at risk in the ADMIRE-CD(5, 6), Bouguen et al.(3) and Gottgens et al.(4) studies

The Kaplan Meier curves for the ADMIRE-CD(5, 6), Bouguen *et al*.(3),and Gottgens *et al.(4)* are presented in Figure 1. It is clear that in the ADMIRE-CD study that people in both the standard care and darvadstrocel relapsed at a greater rate than those people recruited into the Bouguen (3) and Gottgens (4) studies. Given the large differences in the initial rates of remission between the studies, the ERG believe that this may be indicative that the data in the Gottgens and Bouguen studies is not suitable for estimating the long term rate of remission after two years in the ADMIRE-CD population.

The numbers at risk over time, for each of the studies are presented in

Table 2. It should be noted that only 4 people remained at risk of having a recurrence in the Gottgens (4) study 10 years after their fistula went into remission and 26 people remained at risk of recurrence in the Bouguen (3) study 250 weeks (approximately 5 years).

Figure 1: A comparison of the Kaplan Meier curves of ADMIRE-CD(5, 6), Bouguen *et al*.(3),and Gottgens *et al*.(4)

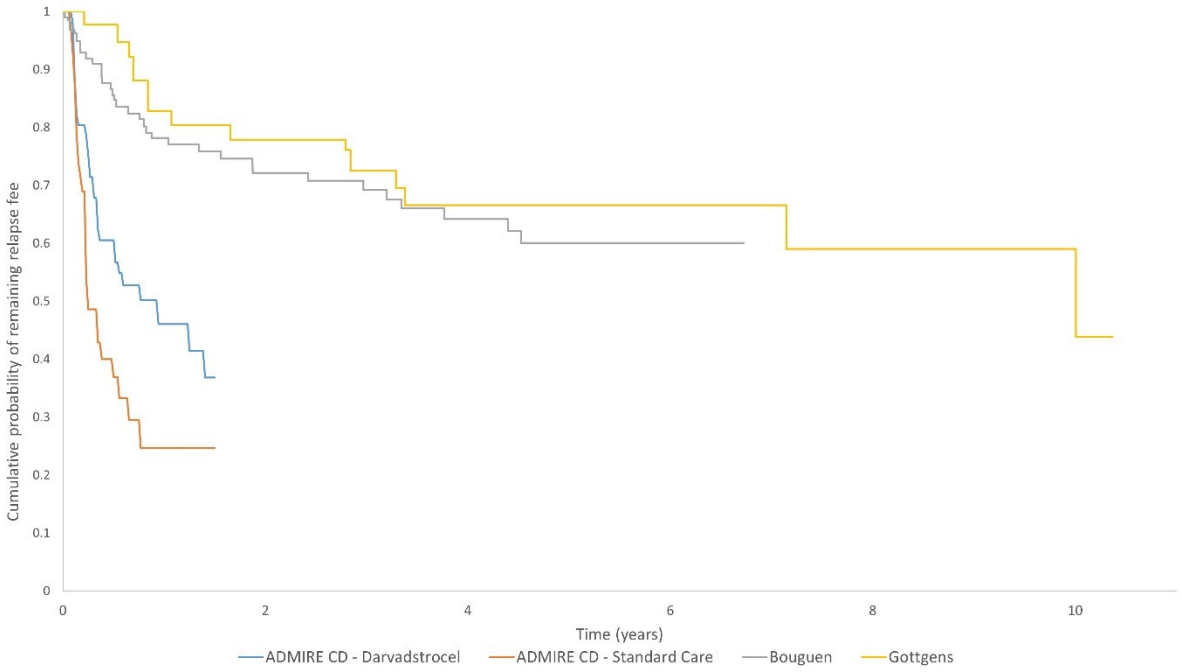


Table 2: A comparison of the numbers at risk over time the ADMIRE-CD(5, 6), Bouguen *et al*.(3) and Gottgens *et al*.(4) studies

Time (years)	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**
ADMIRE–CD, darvadstrocel	[redacted]	[redacted]	[redacted]	[redacted]	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
ADMIRE–CD, standard care	[redacted]	[redacted]	[redacted]	[redacted]	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Gottgens	46	*NR*	*NR*	*NR*	31	*NR*	20	*NR*	14	*NR*	6	4
Time (weeks)	**0**	**25**	**50**	**75**	**100**	**150**	**200**	**250**	**300**	**350**	**400**	**500**
Bouguen *et al*	108	*NR*	72	*NR*	56	47	35	26	20	11	*NR*	*NR*
NR – not reported												

2.4 Estimation of the long term remission rates

It was unclear exactly how the company estimated the long term relapse rates. The ERG replicated the company's process by digitising Figure 4 in Bouguen (3) and Figure 1b, 2006-2011 era in Gottgens (4). The ERG estimated the probability of relapsing between year 2 and year 5, conditional on being in remission at 2 years using the 2 and 5 year time points of the digitised time to event curve given in Bouguen (3). We also estimated the probability of relapsing between year 2 and year 10, conditional on being in remission at 2 years using the 2 and 10 year time points of the digitised time to event curve given in Gottgens (4). Using this approach the ERG estimated that the probability of relapsing between year 2 and year 5, conditional on being in remission at 2 years was 0.1674 (compares to 0.1692 in the companies response to the ACD(1)) and the probability of relapsing between year 2 and year 10, conditional on being in remission at 2 years was 0.2404 (compares to 0.2402 in the companies response to the ACD(1)). Given the similarity of the numbers estimated by the ERG and the company, the ERG considers that it is likely that the company followed this approach, rather than fitting an exponential curve to their digitised data.

The ERG has concerns about estimating the long term probabilities of relapse in this way, as fitting an exponential curve would weight the data given by the Kaplan-Meier by the numbers at risk at each time point. Using only the simple proportions remaining relapse free to calculate the probability is problematic as the long term follow up points have very low numbers at risk (see Table 2). In Gottgens (4) 31 people were at risk of relapse at the two year time point, 20 at 4 years and 14 at 6 years, but only 4 people were at risk at the 10 year time point in the 2006-2011 era curve in Figure 1b. In Bouguen (3), 56 people were at risk at the 100 week time point (approximately 2 years) but only 26 people were at

risk at the 250 week time point (approximately 5 years) in Figure 4. Consequently, fitting an exponential curve to this digitised data could produce a substantially different estimate than those provided by the company in their response to the ACD.

2.5 Curve extrapolations used in the scenario analyses

The extrapolations used the Gompertz function for the first two years in both sets of analyses. After two years, in scenario analysis S1, both arms were extrapolated at a constant rate so that of people who had not relapsed at two years, 16.92% of them would have relapsed after five years. After two years, in scenario analysis S2, both arms were extrapolated at a constant rate so that of people who had not relapsed at two years, 24.02% of them would have relapsed after ten years. These probabilities were assumed to apply equally in the darvadstrocel and standard care arms.

As these probabilities only apply to those people who have not relapsed at two years, the actual risk of relapse is lower in the whole population as a substantial proportion of this population will relapse before two years after they achieve remission of their fistula. For clarity the ERG have produced the extrapolations used in these scenario analyses over a 10 year time horizon for the whole population who achieve a remission of their fistula. The cumulative probability of relapse in both model arms and scenario analysis S1 over a 10 year time horizon is provided in Figure 1 and the cumulative probability of relapse in both model arms and scenario analysis S2 over a 10 year time horizon is provided in Figure 2. The first two years of these curves follow the Gompertz distribution and the subsequent years have a rate of relapse as described in the paragraph above. The graphs show that the relative benefit of darvadstrocel compared to standard care appears to slightly diminish over the model time horizon. However, the ERG considers that the treatment effect is still mostly maintained in both sets of scenario analyses over a 10 year horizon.

The company compares the long term rates of remission for each of the fitted parametric curves to the evidence from the literature in Table 4 of their response to the ACD.(1) This Table shows that the Gopertz curve predicts a remission rate after two years that is in line with the lower end of the literature estimates. Whereas all of the other curves predict a much higher rate. However it should be noted that whether this comparison is valid and useful depends upon whether the estimated long term rates from the literature are reliable estimates of the long term relapse rate in the ADMIRE-CD population. The ERG does not believe that this is not necessarily a useful comparison to make (see Section 4)

Figure 2: The long term extrapolations used for the darvadstrocel and standard care arms in Scenario analysis S1

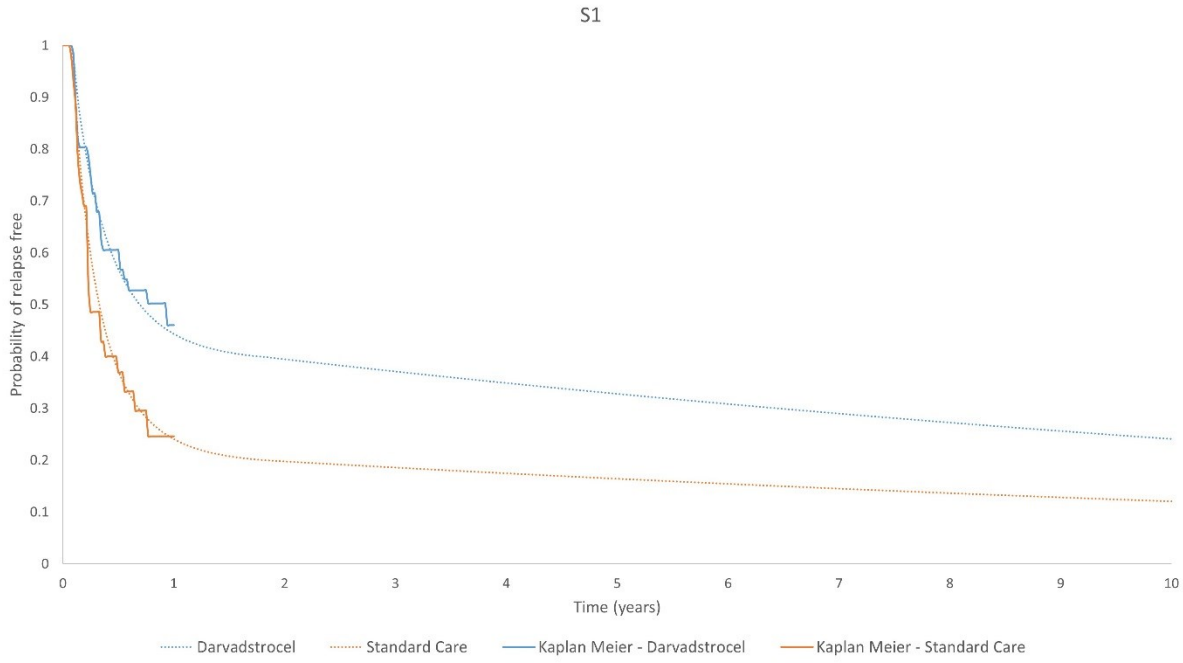
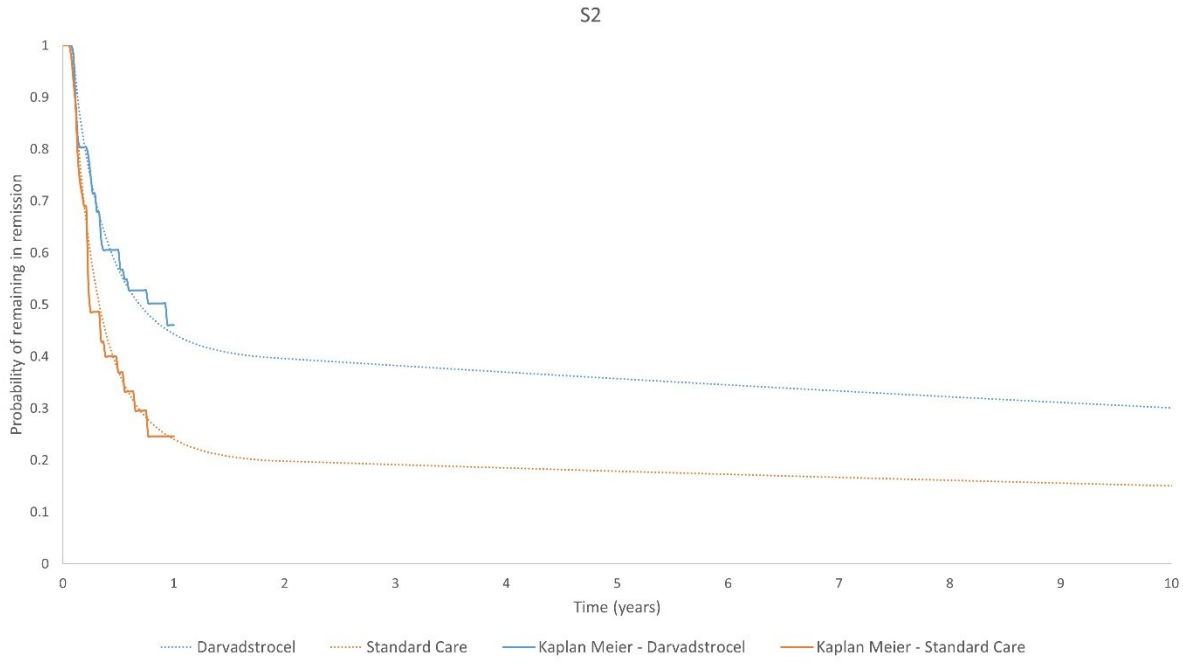


Figure 3: The long term extrapolations used for the darvadstrocel and standard care arms in Scenario analysis S2



3 The company's revised scenario analysis

3.1 Implementation of the scenario analyses

The company's response to the ACD had sparse details on how the revised scenario analyses were implemented. As the response did not contain the adapted models which gave the scenario analysis results, the ERG verified these analyses by attempting to replicate them in the company's base case model. The steps that the ERG undertook to implement these analyses were:

Step 1 – the time to relapse curves were estimated up until 10 years,

Step 2 – the probability that someone would relapse at 5 years, given that they were relapse free at 2 years and the probability that someone would relapse at 5 years, given that they were relapse free at 2 years were calculated

Step 3 – the rate of relapse after two years in the standard care arm and salvage therapy arm were set equal to the rate of relapse after two years in darvadstrocel arm.

Step 4 – the rate of relapse after two years was calibrated so that:

a) the probability that someone would relapse at 5 years, given that they were relapse free at 2 years was equal to 0.1692 (Scenario 1a)
b) the probability that someone would relapse at 10 years, given that they were relapse free at 2 years was equal to 0.2402 (Scenario 2a)

Due to time constraints, the ERG were unable to identify how the anti-TNF use was altered to produce the results given in scenarios 1b or 2b. Consequently the results of these analyses were not verified by the ERG. It should be noted that assuming lower anti-TNF usage doesn't match current practice, even if it was reflective of usage in the cohorts that inform the extrapolation. As such, it is unclear to the ERG how relevant these scenarios are to understanding the cost-effectiveness of darvadstrocel in this indication.

The ERG was able to reproduce the company's reported ICERs for scenarios 1a and 2a with only very minor differences between the ERG's replicated ICER and the company's reported ICER. The ERG are satisfied that the company implemented the new scenario analyses without any errors which would have a significant impact on the estimated ICER.

Table 3: A table comparing the company's revised analyses, the ERGs validation of these analyses in the company's base case model and the application of the company's revised scenario analyses to the ERG's base case economic model

	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 (£ per 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

3.2 Replication of the company's scenario analyses in the ERG base case model

As the committee was minded to accept the ERG's amendments to the company's model in the ACD (7), the ERG have replicated scenario analyses 1a and 2a in the ERG's preferred base case model. When these scenario analyses are applied to the ERG base case model the ICER does increase compared to when using the company's model (Scenario 1a £40,900 in the ERG's base case v £36,235 in the company's base case and Scenario 2a £31,925 in the ERG's base case v £28,370 in the company's base case).

4 Conclusions

The company's analysis of the relapse rates in each of the parametric curves and the relapse rates in the literature shows that the Gompertz is at the lower end of 5 and 10 year recurrence rates predicted by literature but the others all predict much higher rates.(1) However the ERG has three key concerns with comparing the relapse rates in the literature to those extrapolated from the ADMIRE-CD study.

The first key concern is that the ERG considers that there is substantial heterogeneity between the Bouguen (3), Gottgens(4) and ADMIRE-CD(5, 6) studies, consequently the relevance of the estimated long term probabilities of a fistula relapsing to this decision problem is unclear. Secondly, the ERG considers that the way in which the estimated long term probabilities of a fistula relapsing is likely to be unreliable. Finally, the ERG believes that the new evidence submitted does not provide any

additional information on the long term effectiveness of darvadstrocel. Consequently the ERG believes that the uncertainty around whether the darvadstrocel would result in considered at the original appraisal committee meeting has not been substantially reduced.

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