National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Darvadstrocel for treating complex perianal fistula in Crohn's disease

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	British Society of Gastroenterology	Yes. Of great significance as a novel treatment for a disabling complication of Crohn's disease with major associated morbidity, physically and psychologically, with poor outcomes at present	Comment noted. No changes to the scope are needed.
	Merck Sharp & Dohme	Yes	Comment noted. No changes to the scope are needed.
	UK Clinical Pharmacy Association (UKCPA)	This is likely to be an expensive therapy with only 50% response rate and guidance will be very welcome. Fistulae affect patients in a very physical and emotional way and an objective review is appropriate and required	Comment noted. No changes to the scope are needed.
Wording	British Society of Gastroenterology	Yes	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Merck Sharp & Dohme	Yes	Comment noted. No changes to the scope are needed.
	UK Clinical Pharmacy Association (UKCPA)	Disease definitions will have to be clearly defined such as complex vs non complex fistula and mildly active.	Comment noted. The wording of the remit has been amended to remove mildly active. Cx601 will be appraisal within its marketing authorisation
Timing Issues	British Society of Gastroenterology	There is urgent need for new therapies in this area. The key trial has only been published in abstract form to date (Panes et al. A phase III randomised controlled trial of Cx601, expanded allogeneic adipose-derived mesenchymal stem cells (eASC), for complex perianal fistulas in Crohn's disease. J Crohn's Colitis 2016;10 supplement 1:S1)	Comment noted. No changes to the scope are needed.
	Merck Sharp & Dohme	Moderate as it does not address an unmet need	Comment noted. No changes to the scope are needed.
	Takeda UK	[redacted]	Comment noted. No changes to the scope are needed.
	UK Clinical Pharmacy Association (UKCPA)	Appropriate	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft remit	None		

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Society of Gastroenterology	Patients with perianal fistulising disease who fail to respond to medical and surgical therapy will undergo diversion of faecal stream by formation of temporary ileostomy or colostomy. 31%-49% of patients with complex perianal Crohn's will have permament faecal diversion (Mueller et al J GI surgery 2007;11:529. Galandiuk et al. Ann Surgery 2005;241:796). This is usually followed ultimately by proctectomy, as reanastomosis after temporary diversion usually results in gradual reactivation of active perianal disease. In a recent paper this occurred in 14% of all patients with perianal complex fistulising disease (Williamson et al Dis Colon Rectum 1995;38:389). Stomas remain the greatest fear of patients with inflammatory bowel disease. Patients are often reluctant to have proctectomy as there is no possibility of restoring normal gut continuity after this procedure, and poor healing of the perineal wound after proctectomy is a frequent complication (23% of proctectomies in Yamamoto et al Dis Colon Rectum 1999;42:96)	Comment noted. The background information aims to provide a brief overview of the condition and current practice. No changes to the scope are needed.
The technology/ intervention	British Society of Gastroenterology	Yes	Comment noted. No changes to the scope are needed.
Population	British Society of	Disease activity in the rectum (active proctitis) carries a worse outcome for treatment of perianal fistulising disease.	Comment noted. The comment refers to

Section	Consultee/ Commentator	Comments [sic]	Action
	Gastroenterology	NOTE on population: rare to get complex perianal fistulas in context of non-active Crohn's disease. Likewise uncommon in context of mildly active Crohn's disease. Usually there is a burden of luminal inflammation in patients with complex fistulas (which warrants appropriate medical or surgical management). The appropriate population is complex perianal fistulas (without specifying luminal disease)	description of population which has been updated accordingly.
	Takeda UK	We believe that a sub-group that should be discussed are patients for whom the only clinical manifestation of their Crohn's Disease is a perianal fistula. This group do not require any treatment for their Crohns Disease and did particularly well in the Admire clinical trial with no concomitant immunosuppressive or TNF therapy. Cx601 should therefore be considered earlier in the treatment pathway for these patients.	Comment noted. The scope has been updated to include the statement 'If evidence allows patients with perianal-limited disease will be considered'.
	UK Clinical Pharmacy Association (UKCPA)	See above, population group needs to be clearly defined	Comment noted. The comment refers to description of population which has been updated accordingly.
Comparators	British Society of Gastroenterology	Complex perianal fistulising Crohn's is usually managed with joint surgical and medical therapy. The usual algorithm is a combination of surgical (EUA +/- seton insertion) and medical (immunomodulators such as thiopurines or methotrexate) combined with anti-TNF therapy. This combination would be the best comparator	Comment noted. It was noted at the scoping workshop that Cx601 is indicated for the treatment of perianal fistulas and not the underlying Crohn's

Section	Consultee/ Commentator	Comments [sic]	Action
		Comparators to include; combination therapy with immunomodulators + anti-TNF Faecal stream diversion by formation of colostomy/ileostomy, followed by proctectomy should be included as the end stage treatment if other medical and surgical therapy fails	disease. Cx601 may therefore be used alone or in combination with TNFs indicated for Crohn's disease. The comparators in the scope have been amended.
	Takeda UK	We believe that best supportive care should be considered as a comparator for Cx601. We understand that EUA and seton placement followed by TNF therapy is standard of care. Following this defunctioning stoma is considered to be the treatment of choice, however due to the impact of this intervention for patients it is often delayed requiring long term management of the fistula through repeated surgery (often EUA and seton placement but also including other surgical options eg Plug, LIFT etc). There is no accepted standard of care that defines best supportive care but work is ongoing to identify this.	Comment noted. It was agreed at the scoping workshop that standard care is the appropriate term for surgical treatment and best supportive care is not an appropriate comparator
	UK Clinical Pharmacy Association (UKCPA)	Infliximab is not a direct comparator as it is indicated in moderate to severe disease whereas the intervention addresses a different patient group with non-active or mild disease. Exclude adalimumab as not licenced	Comment noted. It was agreed at the scoping workshop that infliximab and adalimumab should not be included as comparators in the scope. It was agreed that infliximab and adalimumab primarily target the underlying Crohn's disease, not the perianal fistula, and therefore are not

Section	Consultee/ Commentator	Comments [sic]	Action
			appropriate comparators for Cx601.
Outcomes	British Society of Gastroenterology	In addition to the outcomes listed, recurrent abscess requiring surgical drainage is an outcome, and formation of colostomy/ileostomy and proctectomy should be included as outcomes of great significance for patients. Other important outcomes would include subjective measures such as patient-recorded outcome measures (PROMs) and objective measures such as MRI imaging of the pelvis.	Comment noted. It was agreed at the scoping workshop that the outcomes in the scope should include: • closure of fistula • recurrence of fistula • continence • mortality • adverse effects of treatment • health-related quality of life.
	Takeda UK	We understand that no current QoL instrument adequately captures the impact of perianal fistula and as such current efforts are underway to develop such an instrument. Takeda UK are currently exploring approaches to develop utilities for this appraisal including mapping (time permitting) and vignettes.	Comment noted. No changes to the scope are needed.
	UK Clinical Pharmacy Association (UKCPA)	Needs to include/consider recurrence rate of fistula if possible (data most likely not available) as this a chronic condition.	Comment noted. It was agreed at the scoping workshop that the comparators should include 'closure of

Section	Consultee/ Commentator	Comments [sic]	Action
			fistula and 'recurrence of fistula'.
Economic analysis	UK Clinical Pharmacy Association (UKCPA)	IBD affects physical and mental health which will be difficult to evaluate in the economic analysis as patients are differently affected by the recurrent disease	Comment noted. No changes to the scope are needed.
Equality and Diversity	British Society of Gastroenterology	This disease has significant implications for women of child-bearing age, as active perianal disease usually precludes vaginal delivery, and pelvic surgery often results in impairment of fecundity and/or delays in women becoming pregnant. This is an important group to consider. Surgery and complex perianal disease is a common reason for women to choose not to become pregnant (Factors associated with voluntary childlessness in women with IBD. Selinger C, Ghorayeb J, Madill J. British Society of Gastroenterology annual meeting abstract PWE-008)	Comment noted. It was agreed at the scoping workshop that this treatment if effective may be beneficial in women of childbearing age.
	UK Clinical Pharmacy Association (UKCPA)	Are all religious groups able to receive this treatment?	Comment noted. NICE is aware that the people from some religious groups may decline this treatment if recommended.
Other considerations	None		-
Innovation	British Society of Gastroenterology	Yes. Highly innovative and has the possibility of altering treatments of this complication of Crohn's significantly. It is a condition which has high physical and psychological morbidity	Comment noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Impact on fecundity will not be measured in QALY calculations, and a successful treatment is likely to improve fecundity in both women and men. Data on this is only available from long-term population-based studies, with very little related to specific treatments.	
	Merck Sharp & Dohme	No, this medication is not a step change in the management of the condition	Comment noted. No changes to the scope are needed.
Questions for consultation	British Society of Gastroenterology	Have all relevant comparators for Cx601 been included in the scope? Which treatments are considered to be established clinical practice in the NHS for treating complex perianal fistula in non-active or mildly active luminal Crohn's disease? Yes, apart from diverting stoma and proctectomy as discussed above Is adalimumab used for treating complex perianal fistula in non-active or mildly active luminal Crohn's disease in England? Yes. Probably used as much as infliximab, and patient preference (sub-cutaneous vs intravenous) is taken into account. Patients failing infliximab are often offered adalimumab. What types of surgery are used for treating complex perianal fistula in non-active or mildly active luminal Crohn's disease? Covered adequately, if diverting stoma, and proctectomy included as detailed above	Comments noted. If evidence allows patients with perianal – limited disease will be considered as a subgroup

Section	Consultee/ Commentator	Comments [sic]	Action
		Is best supportive care an appropriate comparator? If so, how should it be defined? See above Are the outcomes listed appropriate? Yes Are there any subgroups of people in whom Cx601 is expected to be more clinically effective and cost effective or other groups that should be examined separately? As discussed above: active proctitis makes surgical treatment outcomes worse Where do you consider Cx601 will fit into the existing NICE pathway Crohn's disease? Until further data available, will be used after EUA +/-seton insertion with combined immunomodulators plus anti-TNF therapy has failed, and in fistulae not amenable to fistulotomy, and where early defunctioning stoma is not required. (In the future, it may be more logical to use this local therapy at the time of initial EUA, when normal treatment would be to insert setons, and then commence anti-TNF therapy, but further data is needed to show if this approach would produce better results.)	

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	None	-	-

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Abbvie