National Institute for Health and Care Excellence

SingleTechnology Appraisal (STA)

Canagliflozin in combination therapy for treating type 2 diabetes

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Association of British Clinical Diabetologists (ABCD) /Royal College of Physicians (RCP)	Our experts wonder whether it is possible to combine this appraisal with that for dapagliflozin - as both ae in the same class ?	Comment noted. To enable NICE to produce timely guidance dapagliflozin has already been appraised No changes to the scope required.
	Boehringer Ingeleheim Ltd / Eli Lilly & Co Ltd	Given that the first in class product (dapagliflozin) is being assessed, it is appropriate that canagliflozin is also assessed.	Comment noted. No changes to the scope required.
	Janssen-Cilag Ltd	No comment.	No changes to the scope required.
	Merck Sharp & Dohme	No comments	No changes to the scope required.

Section	Consultees	Comments	Action
Wording	Association of British Clinical Diabetologists (ABCD) /Royal College of Physicians (RCP)	No comment.	No changes to the scope required.
	AstraZeneca UK Ltd / Bristol-Myers Squibb	Yes, it is appropriately reflected.	Comment noted. No changes to the scope required.
	Janssen-Cilag Ltd	The remit of this future NICE single technology appraisal is appropriate.	Comment noted. No changes to the scope required.
	Merck Sharp & Dohme	No comments	No changes to the scope required.
Timing Issues	Association of British Clinical Diabetologists (ABCD) /Royal College of Physicians (RCP)	No comment.	No changes to the scope required.
	AstraZeneca UK Ltd / Bristol-Myers Squibb	Canagliflozin is second molecule in this class (SGLT-2) to the market , therefore the relative urgency of the guidance is somewhat lessened.	Comment noted. No changes to the scope required.

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	Diabetes Policy Team, Department of Health	There is no specific urgency.	Comment noted. No changes to the scope required.
	Janssen-Cilag Ltd	[redacted]	Comment noted. No changes to the scope required.
	Merck Sharp & Dohme	No comments	No changes to the scope required.
Additional comments on the draft remit	Diabetes Policy Team, Department of Health	The inclusion of a monotherapy study in individuals intolerant of metformin is of some interest, but it is unlikely that this drug would offer such patients additional benefits above those agents already available.	Comment noted. This issue was discussed at the scoping workshop and it was agreed that use in monotherapy would not be considered. The scope has been updated.
	Janssen-Cilag Ltd	No additional comment.	No changes to the scope required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Association of British Clinical Diabetologists (ABCD) /Royal College of Physicians (RCP)	No comment	No changes to the scope required.
	AstraZeneca UK Ltd / Bristol-Myers Squibb	We would suggest further detailing on the epidemiology of T2D, burden of disease and co-mordid conditions.	Comment noted. The background section of the scope provides summary information about the disease area and clinical management. A detailed description of the disease is available in NICE clinical guidelines for type 2 diabetes and is not required in the scope.
	Diabetes Policy Team, Department of Health	This seems reasonable.	Comment noted. No changes to the scope required.
	Janssen-Cilag Ltd	No comment.	No changes to the scope required.
	Merck Sharp & Dohme	No comments	No changes to the scope required.

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The technology/ intervention	Association of British Clinical Diabetologists (ABCD) /Royal College of Physicians (RCP)	Accurate	Comment noted. No changes to the scope required.
	AstraZeneca UK Ltd / Bristol-Myers Squibb	We would like clarification on what dosing schedule the manufacturer is proposing to submit for as the higher dose has been shown to demonstrate higher discontinuation rates in DIA3015 and DIA 3009.	Comment noted. The dose schedule is not part of the scope. This evidence will be considered at the appraisal stage. No changes to the scope required.
	Boehringer Ingeleheim Ltd / Eli Lilly & Co Ltd	Throughout the document, when reference is made to canagliflozin in combination with insulin, it should be clarified at the outset whether this refers to basal or bolus insulin, or both.	Comment noted. This issue was discussed at the scoping workshop. The manufacturer confirmed that in the clinical trials patients on any type of insulin were included. Clinicians did not think it was necessary to specify the type of insulin. Workshop attendees agreed that no changes to the scope were required.
	Diabetes Policy Team, Department of Health	Yes, the description of the agent class is appropriate.	Comment noted. No changes to the scope required.
	Janssen-Cilag	Canagliflozin's mode of action is twofold:	Comment noted. The manufacturer will have the

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	Ltd	• Canagliflozin inhibits the selective sodium glucose-cotransporter 2 (SGLT2), blocking the reabsorption of filtered glucose from the tubular lumen (back into the bloodstream) and lowering the renal threshold for glucose, resulting in the excretion of excess glucose, thereby directly lowering glucose concentrations in individuals with elevated glucose levels, such as patients with T2DM. This mechanism does not depend upon the action of insulin (ie, is insulin-independent). In addition to lowering glucose in hyperglycaemic patients, the urinary glucose excretion also results in: 1) an osmotic diuresis leading to a reduction in systolic blood pressure and 2) a loss of calories (4 kcalories per gram of carbohydrate, with typical excretion of approximately 100 grams per day in patients with T2DM) and therefore a reduction in body weight. • Canagliflozin is also a low potency inhibitor of the selective sodium glucose-cotransporter 1 (SGLT1), a key gut glucose transport mechanism. At the higher dose (300 mg), high concentrations in the gastrointestinal lumen during drug dissolution prior to drug absorption are likely sufficient to inhibit the SGLT1, thereby reducing the rate of glucose absorption from the intestine, resulting in reduction of postprandial glucose excursions. To the list of regimens studied, the following should be added: • For those on sulphonylurea monotherapy, canagliflozin is being studied as a dual therapy in comparison with placebo.	opportunity to describe the mode of action of cangliflozin in detail in their submission. The scope has been amended to include the additional trial regimen included in this comment.
	Merck Sharp & Dohme	No comments	No changes to the scope required.

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Population	Association of British Clinical Diabetologists (ABCD) /Royal College of Physicians (RCP)	No comment	No changes to the scope required.
	Diabetes Policy Team, Department of Health	It would be important to know: a) how "inadequately controlled" is defined; b) the age distribution of the study population, and; c) whether the ethnicity and gender of the study population reflect the population of England.	Comment noted. This issue was discussed at the scoping workshop. Clinicians did not think it was necessary to define inadequately controlled in this scope because the treatment pathway for the control of blood glucose levels for patients with type 2 diabetes is described in detail in the clinical guidelines CG66 and CG87. At the workshop the manufacturer confirmed that the trials had been carried out across the world including some UK populations. The generalizability of the trial data to the UK population will be considered by the Committee during the course of the appraisal. No changes to the scope required.
	Janssen-Cilag Ltd	No comment.	No changes to the scope required.

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	Merck Sharp & Dohme	We do not believe that the scope should include monotherapy (see our response to the consultation question "Is it apppropriate to include in the scope the use of canagliflozin as monotherapy?")	Comment noted. This issue was discussed at the scoping workshop. The manufacturer confirmed that it was seeking a monotherapy licence, but that this would be limited to people for whom metformin was considered inappropriate due to contraindications or intolerance. Clinicians at the workshop did not consider that canagliflozin would be used as a monotherapy, given the other treatment options available for this population and that its biggest impact on the patient population would be in combination therapy. Workshop attendees also considered the ongoing dapagliflozin appraisal which does not include monotherapy, although it is expected to be within its marketing authorization because it was agreed at the dapagliflozin workshop that an appraisal of dapagliflozin focussed on combination therapy would provide more value to the NHS. Workshop attendees agreed that the appraisal of canagliflozin

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			should in a similar way focus on the use of canagliflozin in combination therapy. The intervention, population and comparators of the scope have been amended to reflect this.
Comparators	Association of British Clinical Diabetologists (ABCD) /Royal College of Physicians (RCP)	The comparators are appropriate. While it is right to include this agent as monotherapy, its biggest area of interest will be as add on therapy (dual or triple). This has been appropriately covered in the appraisal.	Comment noted. This issue was discussed at the scoping workshop. The manufacturer confirmed that it was seeking a monotherapy licence, but that this would be limited to people for whom metformin was considered inappropriate due to contraindications or intolerance. Clinicians at the workshop did not consider that canagliflozin would be used as a monotherapy, given the other treatment options available for this population and that its biggest impact on the patient population would be in combination therapy. . Workshop attendees also considered the ongoing dapagliflozin appraisal which does not include monotherapy, although it is expected to be within its marketing authorization

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			because it was agreed at the dapagliflozin workshop that an appraisal of dapagliflozin focussed on combination therapy would provide more value to the NHS. Workshop attendees agreed that the appraisal of canagliflozin should in a similar way focus on the use of canagliflozin in combination therapy. The intervention, population and comparators of the scope have been amended to reflect this.
	Boehringer Ingeleheim Ltd / Eli Lilly & Co Ltd	Monotherapy: DPP-4 inhibitors and dapagliflozin (subject to NICE appraisal) are also valid comaprators when metformin is inappropriate.	Comment noted. This issue was discussed at the scoping workshop. Workshop attendees agreed that the appraisal of canagliflozin should focus on the use of canagliflozin in combination therapy in a similar way as the dapagliflozin appraisal and to provide value to the NHS. The intervention, population and comparators of the scope have been amended to reflect this.

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	Diabetes Policy Team, Department of Health	Yes, the comparitors seem appropriate.	Comment noted. No changes to the scope required.
	Janssen-Cilag Ltd	No comment.	No changes to the scope required.
	Merck Sharp & Dohme	We do not believe that the scope should include monotherapy (see our response to the consultation question "Is it apppropriate to include in the scope the use of canagliflozin as monotherapy?"). However if it is decided that the use of canagliflozin as monotherapy should remain in the scope, DPP-4 inhibitors and thiazolidinediones should be included as monotherapy comparators.	Comment noted. This issue was discussed at the scoping workshop. The manufacturer confirmed that it was seeking a monotherapy licence, but that this would be limited to people for whom metformin was considered inappropriate due to contraindications or intolerance. Clinicians at the workshop did not consider that canagliflozin would be used as a monotherapy, given the other treatment options available for this population and that its biggest impact on the patient population would be in combination therapy. . Workshop attendees also considered the ongoing dapagliflozin appraisal which does not include monotherapy, although it is expected to be within its marketing authorization

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			because it was agreed at the dapagliflozin workshop that an appraisal of dapagliflozin focussed on combination therapy would provide more value to the NHS. Workshop attendees agreed that the appraisal of canagliflozin should in a similar way focus on the use of canagliflozin in combination therapy. The intervention, population and comparators of the scope have been amended to reflect this.
	MHRA	Only a SU is to be considered as a monotherapy for comparison –three of the DPP-4 inhibitors have a monotherapy indication licensed with the same wording as proposed for canaglifozin (sitagliptin, vildaglitpin and linagliptin, for use in patients who can't take metformin). So whether these are appropriate comparators could be discussed.	Comment noted. This issue was discussed at the scoping workshop. Workshop attendees agreed that the appraisal of canagliflozin should focus on the use of canagliflozin in combination therapy in a similar way as the dapagliflozin appraisal and to provide value to the NHS. The intervention, population and comparators of the scope have been amended to reflect this.

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	Sanofi	Additional comparators beyond "one or more oral agents" should be included for those patients using basal insulin. In the current treatment pathway patients uncontrolled on basal insulin can also add in either bolus (mealtime) insulin or a GLP-1 receptor agonist. Bolus (mealtime) insulin and GLP-1 receptor agonists should therefore be added as comparators in this group. (For inforamtion, exenatide has a licence for use with basal insulin and has recently been approved in this indication by the Scottish Medicines Consortium).	Comment noted. This issue was discussed at the scoping workshop. The comparators in the scope reflect combinations that are recommended by NICE or that are routinely used in clinical practice. . Workshop attendees agreed that the appraisal of canagliflozin should focus on the use of canagliflozin in combination therapy in a similar way as the dapagliflozin appraisal and to provide value to the NHS .No changes to the scope were required.
Outcomes	Association of British Clinical Diabetologists (ABCD) /Royal College of Physicians (RCP)	It will be important to emphasise effects on weight with this agent as this is an important outcome for any new blood glucose lowering agent. Those which promote weight gain or are weight neutral are of most value.	Comment noted. No changes to the scope required.

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	AstraZeneca UK Ltd / Bristol-Myers Squibb	Effect on canagliflozin on blood pressure should be included. LDL levels should also be monitored as part of cardiovacular risk measure especially in light of results from DIA3015 and DIA3009	Comment noted. Following the discussion at the scoping workshop, the outcome 'calculated cardiovascular score' was amended to 'change in cardiovascular risk factors' to clarify that this outcome can included such measures as blood pressure and LDL levels. The outcomes in the scope have been amended.
	Boehringer Ingeleheim Ltd / Eli Lilly & Co Ltd	Please clarify that hypoglycaemia also includes nocturnal hypoglycaemic events.	Comment noted. Clinicians at the workshop did not think it was necessary to specify this explicitly and workshop attendees agreed. No changes to the scope required.
	Diabetes Policy Team, Department of Health	Yes, although more information and how CVD risk is to be calculated should be provided. It is important that an appropriate risk calculator is used, and that the calculator is developed from a population that is representative of the population of people with diabetes in England.	Comment noted. Following the discussion at the scoping workshop, the outcome 'calculated cardiovascular score' was amended to 'change in cardiovascular risk factors' to clarify that this outcome can included such measures as blood pressure and LDL levels. The outcomes in the scope have been amended.

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	Janssen-Cilag Ltd	We are unclear what is meant by calculated cardiovascular risk, can you please clarify?	Comment noted. Following the discussion at the scoping workshop, the outcome 'calculated cardiovascular score' was amended to 'change in cardiovascular risk factors' to clarify that this outcome can included such measures as blood pressure and LDL levels. The outcomes in the scope have been amended.
	Merck Sharp & Dohme	We suggest that the following should be included as additional outcomes: Cancer Decline in eGFR	Comment noted. These outcomes were discussed at the workshop. Attendees did not consider it appropriate to include either 'cancer' or 'decline in eGFR' in the outcomes since if these are related outcomes they would be considered under safety. Data for these outcomes may be included in submissions to NICE as part the adverse effects of treatment outcome. No changes to the scope required.

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	MHRA	The outcome measures are reasonable. We assume that the measure of HbA1c would include specific analyses of the % patients reaching HbA1c target (<7%, <6.5%)	Comment noted. The scope specifies the outcomes without specifying the actual measures to be used. It is expected these will be inline with current UK clinical practice. No changes to the scope required.
Economic analysis	Association of British Clinical Diabetologists (ABCD) /Royal College of Physicians (RCP)	No comment	No changes to the scope required.
	Diabetes Policy Team, Department of Health	Improvements in hard endpoints (CVD events, development of nephropathy or retinopathy) would not be expected to be seen for many years/decades, although one would expect improvements in surrogate markers (HbA1c and body weight) within months.	Comment noted. No changes to the scope required.
	Janssen-Cilag Ltd	No comment.	No changes to the scope required.
	Merck Sharp & Dohme	No comments	No changes to the scope required.
Equality and Diversity	Association of British Clinical Diabetologists (ABCD) /Royal College of Physicians (RCP)	No issues.	No changes to the scope required

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	Janssen-Cilag Ltd	The NICE Clinical Guideline 87 (NICE, 2009) states that for patients of non-European descent (African, South Asian or Caribbean), the body mass index (BMI) threshold for treatment with GLP-1 agonists is adjusted downward, as they are at higher risk of developing type 2 diabetes. A similar adjustment is recommended for these ethnic groups in the NICE guidance for liraglutide (TA203) and exenatide prolonged release (TA248). In view of their increased risk and consequent increased opportunity to gain benefit from treatment at lower BMIs, a lower BMI threshold should still apply to canagliflozin.	Comment noted. This issue was discussed at the workshop. Workshop attendees did not consider that the population for this appraisal depended on body mass index values. It was therefore considered that this is not an equality issue and does not need to be reflected in the scope. No changes to the scope are required.
	Merck Sharp & Dohme	No comments	No changes to the scope required.
Innovation	Association of British Clinical Diabetologists (ABCD) /Royal College of Physicians (RCP)	This is the second in class in an innovative new group of medications for treatment of diabetes. The data could be considered together with the other agent in class, dapagliflozin. The huge potential market for these treatments renders them important to review for economic reasons, if for no other.	Comment noted. The Committee will consider the innovative aspect of canagliflozin during the course of the appraisal. In order for NICE to produce timely guidance dapagliflozin has already been appraised. No changes to the scope required.
	AstraZeneca UK Ltd / Bristol-Myers Squibb	We do not consider this molecule to be innovative.	Comment noted. The Committee will consider the innovative aspect of canagliflozin during the course of the appraisal. No changes to the scope required.

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	Diabetes Policy Team, Department of Health	The innovation is that this is a new class of agent with a very different mechanism of action to anything else in existance. Its mechanism of action would also suggest that there may be additional benefits in terms of wieght loss. At present, the only licensed agents that are associated with significant weight loss in people with diabetes are GLP-1 agonists, and these are injectable therapies. The availability of an agent that improves glycaemic control, and is associated with significant weight loss, is appealing.	Comment noted. The Committee will consider the innovative aspect of canagliflozin during the course of the appraisal. No changes to the scope required.
	Janssen-Cilag Ltd	We consider that canagliflozin's mode of action is innovative as it is an insulin-independent mechanism and as such, unlike some other therapeutic options, canagliflozin's clinical utility remains even as pancreatic function declines over the course of the disease. The urinary glucose excretion resulting from SGLT2 inhibition not only lowers plasma glucose, but also results in: 1) an osmotic diuresis leading to a reduction in systolic blood pressure and 2) a loss of calories and therefore a reduction in body weight.	Comment noted. The Committee will consider the innovative aspect of canagliflozin during the course of the appraisal. No changes to the scope required.
	Merck Sharp & Dohme	The benefit of canagliflozin on the underlying components of diabetes (insulin resistance, beta cell function and hepatic glucose output) is unknown. Therefore we do not believe canagliflozin can be considered as innovative.	Comment noted. The Committee will consider the innovative aspect of canagliflozin during the course of the appraisal. No changes to the scope required.
Other			

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considerations	Boehringer Ingeleheim Ltd / Eli Lilly & Co Ltd	Canagliflozin is the second in class DPP-4 inhibitor, the first in class product (dapagliflozin) will be appraised by NICE in early 2013. It is important that the appraisal of canagliflozin is demonstrably consistent with that of dapagliflozin in terms of the application of the guidance to the final scope(s). In addition, should dapagliflozin be recommended by NICE in 2013, it is plausible that this could amend the scope for the canagliflozin appraisal in some of the various comparisons to, for example, "only in populations where a SGLT-2 inhibitor is already deemed appropriate". In this case, the comparator would be restricted to dapagliflozin only.	Comment noted. Dapagliflozin has been included in the scope as a comparator in combination therapy subject to the recommendations from TA 288.
	Janssen-Cilag Ltd	No comment.	No changes to the scope required.
	Merck Sharp & Dohme	We suggest that a subgroup based on renal function should also be considered (for example, it will be important to consider patients with eGFR <30).	Comment noted. At the scoping workshop the manufacturer confirmed that canagliflozin is not likely to be licensed for use in people who have severe renal impariment. Attendees did not consider this an approprirate subgroup. No changes to the scope required.

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	MHRA	In this section, additional subgroup analyses might be considered in the elderly and in patients with varying degree of renal impairment – renal function significantly affects the efficacy for dapaglifozin. For any indirect comparison to dapaglifozin, the baseline GFR would therefore have to be compared, (as well as the as the baseline HbA1c and response in the placebo group, of course)	Comment noted. At the scoping workshop the manufacturer confirmed that canagliflozin is not likely to be licensed for use in people who have severe renal impariment. Attendees did not agree that it was appropriate to consider subgroups based on age or renal impairment for this technology. No changes to the scope required.
Questions for consultation	AstraZeneca UK Ltd / Bristol-Myers Squibb	1. It is not the best use of limited NICE resources to appraise canagliflozin as monotherapy as it is difficult to see how it could displace metformin. 2. We would challenge whether pioglitazone is an appropriate comparator in light of the declining usage and MHRA warnings. 3. We have no further comments to make concerning innovation and equality	Comment noted. This issue was discussed at the scoping workshop. The manufacturer confirmed that it was seeking a monotherapy licence, but that this would be limited to people for whom metformin was considered inappropriate due to contraindications or intolerance. Clinicians at the workshop did not consider that canagliflozin would be used as a monotherapy, given the other treatment options available for this population and that its biggest impact on the patient population would be in combination therapy. Workshop attendees also considered the ongoing

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			dapagliflozin appraisal which does not include monotherapy, although it is expected to be within its marketing authorization, because it was agreed at the dapagliflozin workshop that an appraisal of dapagliflozin focussed on combination therapy would provide more value to the NHS. Workshop attendees agreed that the appraisal of canagliflozin should in a similar way focus on the use of canagliflozin in combination therapy. The intervention, population and comparators of the scope have been amended to reflect this.

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	Janssen-Cilag Ltd	Janssen does not believe that a separate appraisal of canagliflozin as an add-on therapy to insulin population would be necessary.	Comment noted. This issue was discussed at the scoping workshop. Attendees agreed that the monotherapy should be removed from the scope and that the appraisal of canagliflozin as combination therapy (including as an add-on therapy to insulin) was appropriate for the STA process. The intervention, population and comparators of the scope have been amended to reflect this.
	Merck Sharp & Dohme	In response to the consultation question "Is it apppropriate to include in the scope the use of canagliflozin as monotherapy?": To ensure consistency with the technology appraisal for dapagliflozin which is currently underway (ID427), we do not believe that the use of canagliflozin for monotherapy should be included in the scope for the proposed technology appraisal. Dapagliflozin, like canagliflozin, has been studied in clinical trials as monotherapy. Despite this the final scope for ID427 did not include use of dapagliflozin for monotherapy. Consequently we suggest the same population restrictions should apply to canagliflozin. In response to the consultaion question "Have the most appropriate comparators for canagliflozin for the treatment of type 2 diabetes been included in the scope? Are the comparators listed routinely used in clinical practice?":	Comment noted. At the workshop, the manufacturer confirmed that it was seeking a monotherapy licence, but that this would be limited to people for whom metformin was considered inappropriate due to contraindications or intolerance. Clinicians at the workshop did not consider that canagliflozin would be used as a monotherapy, given the other treatment options available for this population and that its biggest impact on the patient population would be in combination therapy. Workshop attendees also

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		We agree that all comparators listed are appropriate, providing their usage is in line with the recommendations as stated in the prevailing NICE guidance documents, as listed below: CG66/87:Type 2 diabetes - the management of type 2 diabetes TA203:Liraglutide for the treatment of type 2 diabetes mellitus TA 248: Exanatide prolonged release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes	considered the ongoing dapagliflozin appraisal which does not include monotherapy, although it is expected to be within its marketing authorization because it was agreed at the dapagliflozin workshop that an appraisal of dapagliflozin focussed on combination therapy would provide more value to the NHS. Workshop attendees agreed that the appraisal of canagliflozin should in a similar way focus on the use of canagliflozin in combination therapy. The intervention, population and comparators of the scope have been amended to reflect this.
		In response to the consultation question "Are the subgroups suggested in 'other considerations' appropriate? Are there any more subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?: We suggest it is also important for NICE to consider any subgroups of people in whom the technology may be less clinically and cost effective. Based on the	At the scoping workshop the manufacturer confirmed that canagliflozin is not likely to be licensed for use in people who have severe renal impariment. Attendees did not agree that it was appropriate to consider

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		clincial data for canagliflozin and its mode of action, it is likely that this drug will be less effective in patients with renal insufficiency. As the product licence for canagliflozin has not yet been granted, it is unclear whether the licence will include restrictions on the use of canagliflozin in patients with renal insufficiency. Nevertheless we feel it appropriate to raise this point at this time for NICE's consideration.	subgroups based on age or renal impairment for this technology. No changes to the scope required.
		In response to the consultation question "NICE intends to appraise this technology as a single technology appraisal. Would it be more appropriate to appraise the add-on therapy to insulin separately?": We do not think that it would be appropriate to appraise the add-on therapy to insulin separately. Additionally, we would like to raise the wider issue concerning inconsistencies in the appriasal routes decided by NICE for different drugs indicated for the treatment of type 2 diabetes. In August 2012, NICE's Guidance Executive released a proposal for consultation concerning TA203 (Liraglutide for the treatment of type 2 diabetes mellitus) and TA248 (Exanatide prolonged release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes) (Ref 1). This document recommended that both should be reviewed within the on-going update of CG87. The GE proposal stated that it was unfair to preserve the funding direction for two products in the GLP-1 class, when it does not apply to others in the class. The GE proposal also stated that consideration of the most clinically and cost effective positions for these treatments is best considered in the context of the entire treatment pathway, and this can only be assessed in the context of a clinical guideline. With the GE proposal concerning TA203 and TA248 in mind, we question the rationale for NICE's decision to appraise SGLT-2 inhibitors under their own	This issue was discussed at the scoping workshop. Attendees agreed that the monotherapy should be removed from the scope and that the appraisal of canagliflozin as combination therapy (including as an add-on therapy to insulin) was appropriate for the STA process. The SGLT-2s are a new class of drugs and have not been included in the update of the existing guideline. In order to produce timely guidance they are being appraised as single technology appraisals.

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		individual technology appraisals. This is at odds with the GE's rationale for TA203 and TA248, as well as NICE's position on DPP-4 inhibitors, none of which have been reviewed by the TA route (including those licensed after publication of CG87). Additionally, the GE proposal appears to acknowledge the commercial advantage (preservaton of funding direction) gained by technologies which have a TA when compared to those which have been appraised and included as part of the clinical guideline (CG87); however this is not restricted to a within-class advantage. The commercial advantage applies across classes, and therefore the issue needs to be considered more widely. Ref 1: Guidance Executive - TA203 Diabetes (type 2) - liraglutide: appendix B proposal paper "Review of TA203; Liraglutide for the treatment of type 2 diabetes mellitus, and TA248; Exenatide prolonged release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes" – August 2012. Available at: http://guidance.nice.org.uk/TA203/ReviewProposal (accessed 26 September 2012)	
	MHRA	One question asked is whether it is appropriate to include in the scope the use of canagliflozin as monotherapy- presumably yes, as it may be as effective as a SU in patients who can't take metformin, and might be more favourable in terms of weight gain	Comment noted. At the workshop, the manufacturer confirmed that it was seeking a monotherapy licence, but that this would be limited to people for whom metformin was considered inappropriate due to contraindications or intolerance. Clinicians at the workshop did not consider that canagliflozin would be used as a monotherapy, given the

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			other treatment options available for this population and that its biggest impact on the patient population would be in combination therapy. Workshop attendees also considered the ongoing dapagliflozin appraisal which does not include monotherapy, although it is expected to be within its marketing authorization because it was agreed at the dapagliflozin workshop that an appraisal of dapagliflozin focussed on combination therapy would provide more value to the NHS. Workshop attendees agreed that the appraisal of canagliflozin should in a similar way focus on the use of canagliflozin in combination therapy. The intervention, population and comparators of the scope have been amended to reflect this
Additional comments on the draft scope.	Janssen-Cilag Ltd	No comment.	No changes to the scope required.

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

Eli Lilly and Company Ltd.
Pfizer Ltd.
The Royal College of Nursing

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Canagliflozin for treating type 2 diabetes

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1	Healthier Weight Centres	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria has been removed from the matrix of consultees and commentators.
2	Insulin Pump Therapy (INPUT)	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria has been removed from the matrix of consultees and commentators.

3	Insulin Pumpers UK	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria has been removed from the matrix of consultees and commentators.
4	Independent Age	Independent Age		Removed	This organisation has asked not to be included in matrices relating to clinical issues. They are a charity that focuses largely on a more social than a medical model of care.
5	National Obesity Forum	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria has been removed from the matrix of consultees and commentators.

6	Weight Concern	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria has been removed from the matrix of consultees and commentators.
7	UK Health Forum	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria has been removed from the matrix of consultees and commentators.