Canagliflozin ACD Response

Section 1 Appraisal Committee's preliminary recommendations

We have concerns with these preliminary recommendations.

These are:

1. **SGLT2-inhibitors are not effective in renally impaired patients. NICE should specify that canagliflozin should not be used in patients with moderate renal impairment (eGFR <60).**
2. **There is insufficient consideration as to how the two doses of canagliflozin will be used by health care professionals. We recommend that further economic modelling scenarios whereby 50% of patients receive each dose are carried out to inform the final guidance.**
3. **The canagliflozin economic model inputs regarding moderately renally impaired patients and differences in lipid profiles between dapagliflozin and canagliflozin are inaccurate and require re-modelling.**
4. **Due to lack of stability, the model itself needs to be validated against an established model.**

Further information for each of these points is below:

1. Approximately 30% of type 2 diabetes patients have an eGFR < 60 ml/min/1.73 m^2 (Middleton, 2006) representing a clinically important sub-group. For these patients, the efficacy of canagliflozin in reducing HbA1C is nearly 50% lower (at both doses) than for patients with normal or mild renal function and there are specific safety concerns linked to hypotension and volume depletion for the 300mg dose. This is reflected in the license whereby canagliflozin should not be initiated in patients with an eGFR < 60 ml/min/1.73 m^2 and monitoring is required to ensure that patients whose eGFR falls below 60ml/min/1.73 m^2 only receive the 100 mg dose. Furthermore, the level of efficacy (-0.47% reduction in HbA1C from a pooled analysis of regulatory RCTs, Woo 2013) for the 100 mg dose in patients with an eGFR < 60 ml/min/1.73 m^2 is less than the NICE CG87 criteria of 0.5% HbA1C reduction for continued OAD treatment. Such patients would receive a greater clinical benefit and lower risk of adverse events from an alternative class of treatment, such as DPP4 inhibitors. **Based on the evidence available, we therefore strongly request that NICE specifically states a restriction that canagliflozin should not be used in patients with eGFR <60. A bullet point making this restriction explicit should be added to the recommendations.**
2. We are concerned that the preliminary recommendations do not fully consider the consequences of the SPC dose titration requirements for canagliflozin. As the two doses have a different cost and a different risk-benefit profile, we consider that the proportion of patients likely to use each dose should be considered within the assessment of clinical and cost effectiveness and budget impact of canagliflozin. There is IMS real-world data from the U.S., where canagliflozin was launched in April 2013, demonstrating that approximately 50% of usage is at the 300mg dose (IMS NPA data 5th April 2013-27th December 2013). **We recommend that further economic modelling scenarios whereby 50% of patients receive each dose are carried out to inform the final guidance.**

3. **The canagliflozin economic model inputs regarding moderately renally impaired patients and differences in lipid profiles between dapagliflozin and canagliflozin are inaccurate and require re-modelling:**
   - A specific modelling scenario only including renally impaired patients does not seem to be available, although it is unlikely that canagliflozin will be cost-effective in these patients due to significantly lower efficacy compared with patients with normal to mild renal function. **We ask that this clinically important sub-group of patients is explored in a specific modelling scenario, which if cost-effectiveness is not demonstrated, would support a specific restriction that canagliflozin should not be used in patients with moderate renal impairment (eGFR <60).**
   - The model prescribes that patients discontinuing canagliflozin due to a drop in eGFR are switched to insulin rather than the more clinically appropriate and licensed DPP4 inhibitors. The higher efficacy of insulin compared with DPP4 inhibitors may result in more favourable ICERs for canagliflozin and does not reflect clinical practice whereby patients and physicians aim to delay insulin use for as long as possible. **We ask that a scenario where renally impaired patients are switched to DPP4 inhibitors is run.**
   - The lipid profile of dapagliflozin and canagliflozin differs considerably yet the same lipid profiles for both drugs have been applied in the model. **We request that these differences in lipid profiles are taken into account in the economic modelling.**

4. We are concerned about the lack of stability of the ICERs generated using the ECHO model. We consider the very wide range of ICERs generated for the same drug comparisons to demonstrate a high level of uncertainty in the cost-effectiveness analyses. **Therefore, we request that the results from the ECHO economic model are validated using an alternative validated diabetes model such as the NICE-recommended, type 2 diabetes CORE model.**

References

Middleton RJ et The unrecognized prevalence of chronic kidney disease in diabetes. Nephrol. Dial. Transplant. (January 2006) 21 (1): 88-92.

Woo V et al. Canagliflozin is effective and generally well tolerated in subjects with type 2 diabetes mellitus and stage 3 chronic kidney disease. EASD, September 2013, Barcelona

Section 2 The technology

Section 2.1

Canagliflozin has different selectivity compared to other SGLT2 inhibitors and as this may have implications on efficacy and safety, this should be specifically described in section 2.

Further information on this is as follows:

We believe that canagliflozin should be described as a selective SGLT-2 inhibitor with a low potency for SGLT-1 inhibition. It should be clarified that canagliflozin is not highly selective relative to other SGLT inhibitors. This may have implications when treating patients with canagliflozin regarding

efficacy, but more importantly regarding the safety and adverse event profile of canagliflozin compared with other more selective SGLT2 inhibitors, such as dapagliflozin and empagliflozin.

There is data showing the additional contribution of SGLT-1 to the efficacy of canagliflozin above its effects on the kidney (i.e. SGLT-2 inhibition alone), especially via inhibition of SGLT-1 via the gut (Polidori, 2013). However, this additional SGLT-1 inhibition may also have implications in terms of a higher risk of hypoglycaemia with canagliflozin compared to hypoglycaemia rates observed with the other SGLTs. As glucose excretion by the urine is also accompanied by fluid loss (osmotic), the diuresis may also lead to episodes of hypovolaemia, and dehydration.

Thus, the EPAR for canagliflozin concludes that "some conditions exist in which a starting dose of 100 mg should be used for safety reasons since drop in blood pressure and volume depletion or its sequelae could be more pronounced upon onset of treatment. Therefore, a starting dose of 100 mg is recommended for all patients as a precautionary measure and to simplify posology" (EPAR, section 2.6.2).

References

Canagliflozin EPAR

Polidori D et al, Canagliflozin lowers postprandial glucose and insulin by delaying intestinal glucose absorption in addition to increasing urinary glucose excretion: results of a randomized, placebo-controlled study. Diabetes Care.2013 Aug;36(8):2154-61

Section 3 – The Manufacturer's Submission

1. **SGLT2s are not effective in renally impaired patients. NICE should specify that canagliflozin should not be used in patients with moderate renal impairment (eGFR <60).**
2. **There is insufficient consideration as to how the two doses of canagliflozin will be used by health care professionals. As the two doses have a different cost and a different risk-benefit profile, the proportion of patients likely to use each dose should be fully considered within the assessment of clinical and cost effectiveness and budget impact of canagliflozin. We recommend that further economic modelling scenarios whereby 50% of patients receive each dose are carried out to inform the final guidance.**
3. **The canagliflozin economic model inputs regarding moderately renally impaired patients and differences in lipid profiles between dapagliflozin and canagliflozin are inaccurate and require re-modelling.**
4. **Due to lack of stability, the model itself needs to be validated against an established model.**
5. **The higher odds ratio of hypoglycaemia for canagliflozin compared to dapagliflozin is unlikely to reflect differences in trial outcome definitions and may relate to the different mechanism of actions of these drugs. We request clarification on how this has been approached in the economic modelling.**
6. **There are limitations of the RCT evidence supporting canagliflozin's preliminary recommendations, which should be highlighted further in the ACD.**

Further information on this is as follows:

1. **SGLT2s are not effective in renally impaired patients. NICE should specify that canagliflozin should not be used in patients with moderate renal impairment (eGFR <60).**

Approximately 30% of type 2 diabetes patients have an eGFR < 60 ml/min/1.73 m2 (Middleton, 2006) representing a clinically important sub-group.

For these patients, the efficacy of canagliflozin in reducing HbA1C is nearly 50% lower at both doses than for patients with normal or mild renal function (see figure below) and there are specific safety concerns linked to hypotension and volume depletion for the 300mg dose.

This is reflected in the license, which specifies criteria for the use of canagliflozin in renally impaired patients. Canagliflozin should not be initiated in patients with an eGFR < 60 ml/min/1.73 m^2; patients receiving canagliflozin whose eGFR persistently falls below 60 should be down-titrated from 300 to 100 mg dose or maintained at 100 mg dose. Canagliflozin should be discontinued when eGFR is persistently below 45.

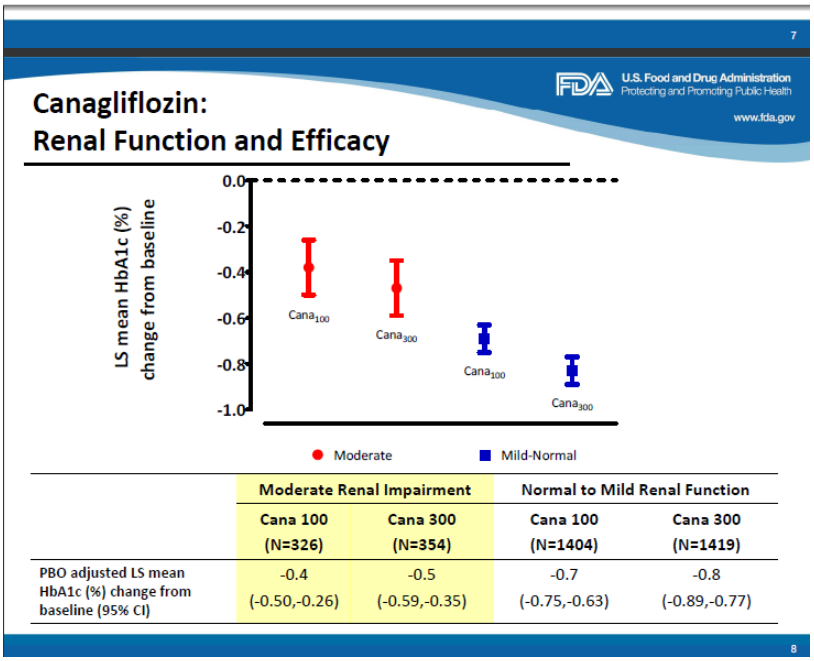
Furthermore, although the 100 mg dose is licensed for patients with an eGFR ≥ 45 and <60, there is evidence from a pooled analysis of canagliflozin regulatory RCTs that patients receiving 100mg canagliflozin mg with an eGFR ≥ 45 and <60 receive limited benefit with a mean HbA1C reduction from baseline of 0.47 % (Woo, 2013). For patients with eGRF in a lower range (≥ 30 and < 50), the mean reduction in HbA1C from baseline was 0.27% in a 52-week randomised controlled trial (Nieto, 2013). This level of efficacy does not meet the criteria of a maintained benefit of HbA1C reduction of 0.5% at 6 months for continued treatment of type 2 diabetes specified in NICE Clinical Guideline 87 for Type 2 diabetes [1].

It is therefore highly likely that for this sub-group of patients, canagliflozin will not be an efficacious option in dual, triple or add onto insulin indications and is therefore unlikely to be cost-effective.

Such patients are likely to receive a greater clinical benefit and lower risk of adverse events from an alternative class of treatment, such as a DPP4-inhibitor. For example, saxagliptin at a dose of 2.5mg in patients with moderate to severe renal impairment shows sustained reductions of -0.73% at 1 year (Nowicki 2011). Furthermore, there is prospective cardiovascular safety evidence for patients with moderate and severe renal impairment treated with saxagliptin from the large cardiovascular outcome trial SAVOR .

We therefore strongly request that NICE recognises the limitations of canagliflozin in patients with renal impairment and specifically states a restriction that canagliflozin should not be used in patients with an eGFR <60. A bullet point making this restriction explicit should be added to the recommendations.

[1] Only continue DPP-4 inhibitor or thiazolidinedione if reduction in HbA_{1c} of at least 0.5 percentage points in 6 months. (NICE Clinical Guideline 87)



	Moderate Renal Impairment		Normal to Mild Renal Function	
	Cana 100 (N=326)	Cana 300 (N=354)	Cana 100 (N=1404)	Cana 300 (N=1419)
PBO adjusted LS mean HbA1c (%) change from baseline (95% CI)	-0.4 (-0.50,-0.26)	-0.5 (-0.59,-0.35)	-0.7 (-0.75,-0.63)	-0.8 (-0.89,-0.77)

FDA Slides for the January 10, 2013 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)

Available at
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm336233.htm

2. **There is insufficient consideration as to how the two doses of canagliflozin will be used by health care professionals. As the two doses have a different cost and a different risk-benefit profile, the proportion of patients likely to use each dose should be fully considered within the assessment of clinical and cost effectiveness and budget impact of canagliflozin. We recommend that further economic modelling scenarios whereby 50% of patients receive each dose are carried out to inform the final guidance.**

Manufacturer's cost-effectiveness results: Section 3.41 (sensitivity analyses): There is IMS data from real-world use of canagliflozin in the US, where canagliflozin was launched in April 2013, regarding dose titration and the percentage of patients receiving the 100 and 300 mg doses, which has not been considered when forming these preliminary recommendations. This data shows that approximately 50% of real-world usage is at the 300mg dose (IMS NPA data 5th April 2013-27th December 2013 [unequalised]). The percentage of patients, which were up-titrated to the 300mg dose is unclear from the current modelling scenario of dose titration and the current scenario is based on clinical specialist opinion rather than real-world data.

Even in the STA report (the submission by the manufacturer page 14) the manufacturers recognise that "it is likely that a higher proportion of patients receiving canagliflozin 100mg as part of a triple therapy or as an add-on to insulin therapy would require tighter glycaemic control and would therefore be switched to canagliflozin 300mg". As such, the estimate of 50% usage at 300mg does not seem unreasonable.

As the two doses have a different cost and a different risk-benefit profile, we consider that the proportion of patients likely to use each dose should be fully considered within the assessment of clinical and cost effectiveness and budget impact of canagliflozin. We recommend that further economic modelling scenarios whereby 50% of patients receive each dose are carried out to inform the final guidance.

3. The canagliflozin economic model inputs regarding moderately renally impaired patients and differences in lipid profiles between dapagliflozin and canagliflozin are inaccurate and require re-modelling.

a. The economic modelling approach to renally impaired patients is not entirely clear, but seems to take a less conservative approach to favour canagliflozin:

- A specific modelling scenario only including renally impaired patients does not seem to be available. As stated above in point 1, it is unlikely that canagliflozin will be cost-effective in these patients due to significantly lower efficacy and increased rates of adverse events related to hypoglycaemia, dehydration or hypovolaemia for the 300mg dose compared with patients with normal to mild renal function. **We ask that this clinically important sub-group of patients is explored in a specific modelling scenario, which if cost-effectiveness is not demonstrated, would support a specific restriction that canagliflozin should not be used in patients with moderate renal impairment (eGFR <60).**
- The model prescribes that patients discontinuing canagliflozin due to a drop in eGFR are switched to insulin rather than to the more clinically appropriate and licensed DPP4 inhibitors. The higher efficacy of insulin compared with DPP4 inhibitors may result in more favourable ICERs for canagliflozin and does not reflect clinical practice whereby patients and physicians aim to delay insulin use for as long as possible. There is ample evidence of patient and physician reluctance to initiate insulin (Khunti 2013). **We ask that a scenario where renally impaired patients are switched to DPP4 inhibitors is run; both in the modelling for all patients and in the specific sub-group analysis for renal patients.**
- The base case modelling seems to include a clinically appropriate stopping rule for canagliflozin treatment when eGFR drops below 60 ml/min/1.73m^2, yet this is not reflected in the preliminary recommendations. **We strongly request that NICE specifically states a restriction that canagliflozin should not be used in patients with eGFR <60. A bullet point making this restriction explicit should be added to the recommendations.**

b. We are concerned that the same lipid profiles for canagliflozin and dapagliflozin have been applied in the model (see table 56, page 102 in the evaluation report).

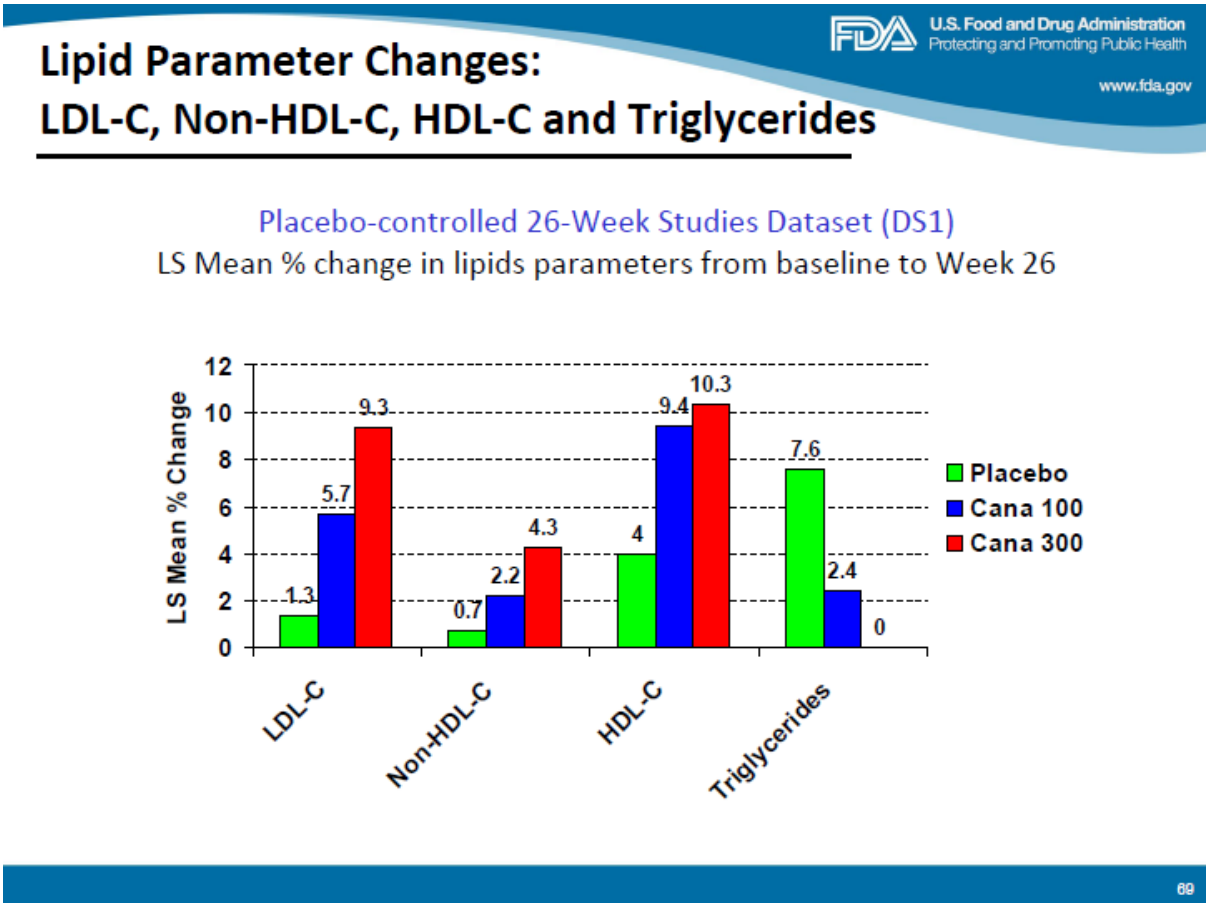
It should be noted that the lipid profile of dapagliflozin and canagliflozin differs considerably. The pooled analyses from the entire dapagliflozin and canagliflozin trial programmes show the much increased levels of LDL-C seen across the canagliflozin program, with rises of 9.3% for canagliflozin 300 mg (see figure 1 below, FDA January 2013) compared to a rise of 2.7% with dapagliflozin 10 mg (see figure 2 below, Hardy 2013). The increase in LDL-C observed with canagliflozin 300mg dose was particularly high in certain indications: up to 13.3% from baseline (Vercruysse, EASD 2013) as add on to metformin and SU or 14.2% from baseline (Langslet EASD 2013) as add on to metformin.

This increase in LDL-C was worrying enough for the independent monitoring committee of CANVAS, the canagliflozin cardiovascular safety outcome study, to partially unblind the results and to terminate enrolment in the preplanned extension of the study (FDA Canagliflozin medical review, 2013).

In the interim analysis of CANVAS, a numeric imbalance in major adverse cardiac events (MACE) in the early treatment period of CANVAS between canagliflozin and non-canagliflozin treatment arms was observed (FDA Canagliflozin summary review, 2013). Additionally, a pooled analysis of canagliflozin RCTs showed a HR exceeding 1.0 for fatal/non-fatal stroke for canagliflozin compared to non-canagliflozin treatment arms (see figure 3 below) .

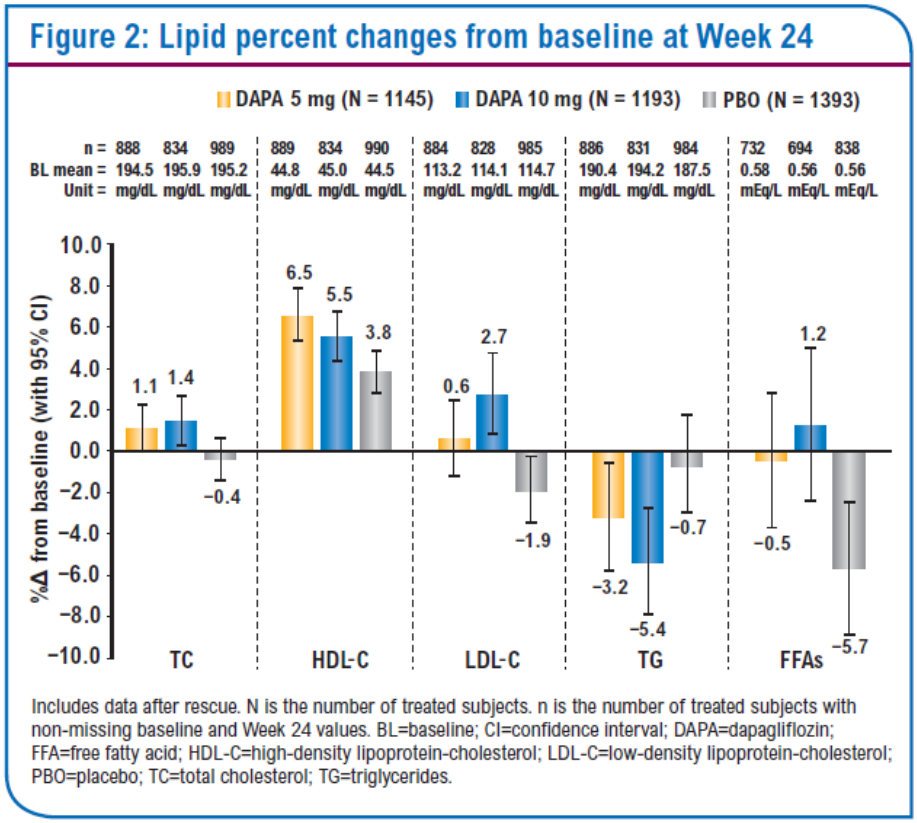
Neither were such large increases in LDL-C nor imbalances in MACE events noted in the overall dapagliflozin programme (see figure 4 below). **Therefore, we request that these differences in lipid profiles are taken into account when modelling the effects of canagliflozin**.

Figure 1: Pooled RCT data for lipid parameter changes observed with canagliflozin



Slide 69, FDA review of efficacy and safety of canagliflozin, EMDAC meeting Jan 13, Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm336233.htm

Figure 2: Pooled RCT data for lipid parameter changes observed with dapagliflozin



Includes data after rescue. N is the number of treated subjects. n is the number of treated subjects with non-missing baseline and Week 24 values. BL=baseline; CI=confidence interval; DAPA=dapagliflozin; FFA=free fatty acid; HDL-C=high-density lipoprotein-cholesterol; LDL-C=low-density lipoprotein-cholesterol; PBO=placebo; TC=total cholesterol; TG=triglycerides.

Hardy et al, poster 1188-P ADA 2013

Figure 3:Pooled RCT data for time to event for fatal/non-fatal stroke observed with canagliflozin

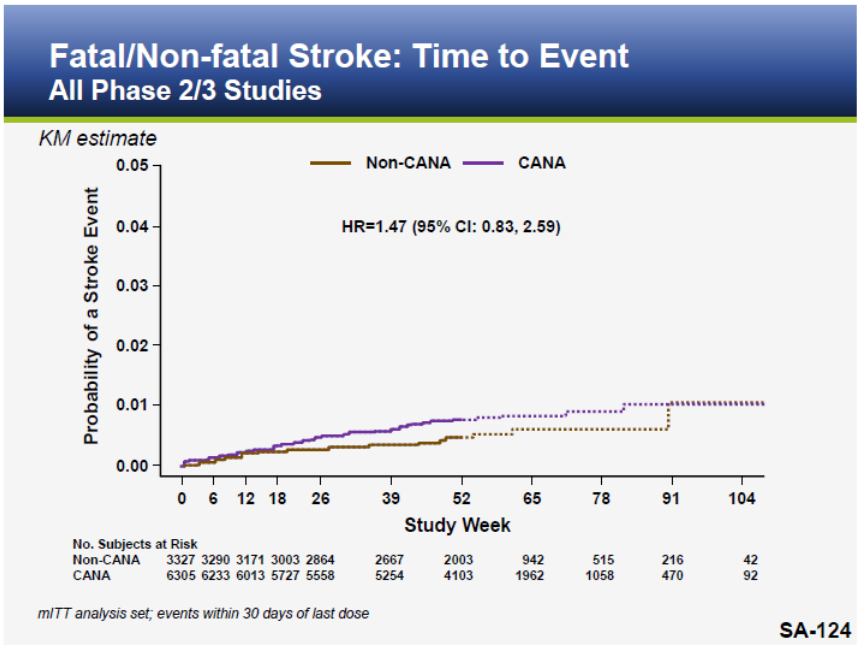
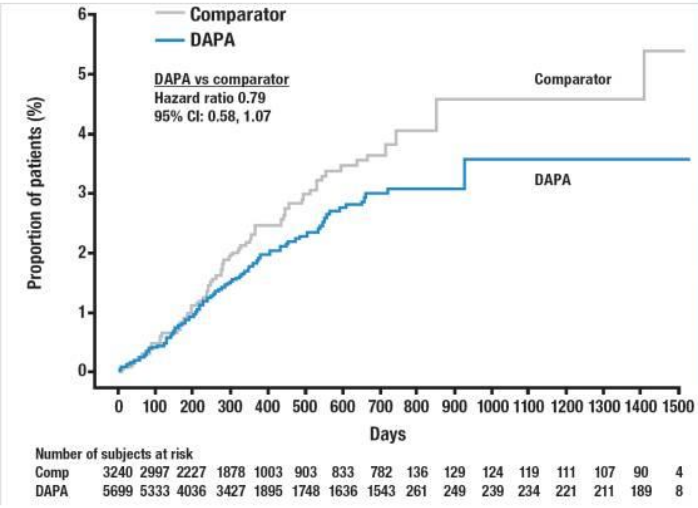


Chart from J&J Backup slides, EMDAC Jan 2013 available at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm336233.htm

Figure 4: Pooled RCT data for major adverse cardiac events observed with dapagliflozin

Summary of Events Contributing to the Primary Composite End Point



	DAPA		Comparator	
	Pts w/event	Incidence rates[a]	Pts w/event	Incidence rates[a]
Total	95	16.2	81	20.6
CV death	20	3.0	18	4.6
MI	30	4.5	33	8.5
Stroke	25	3.8	18	4.6
Unstable angina[b]	26	3.9	20	5.2

[a]Incidence rates=number of subjects with events/1000 patient-years.
[b]Hospitalization for unstable angina.
Pts, patients.

- Secondary composite end point = primary + unplanned coronary revascularization + hospitalization for HF
  - DAPA vs comparator, HR: 0.758; 95% CI, 0.581–0.988

Note: only trials with at least one positively adjudicated event contributed to the analysis.
Cox proportional hazards model and composite event rates are stratified by study. Comp, comparator.

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Slide from Langkilde 2013

4. **Due to lack of stability, the model itself needs to be validated against an established model, such as the NICE-recommended CORE model.**
   a. We are concerned about the lack of stability of the ICERs generated using the ECHO model. We consider the very wide range of ICERs generated for the same drug comparisons to demonstrate a high level of uncertainty in the cost-effectiveness analyses. The ERG's exploratory analyses described in section 3.49 of the ACD demonstrated cases where small differences in incremental QALYs could drive a large variation in the ICER compared with the manufacturer's ICER. For example, the ERG exploratory analyses showed an ICER of £100,719 per QALY gained for canagliflozin 100mg versus dapagliflozin in dual therapy compared to an ICER of £8,674 per QALY gained for this comparison from the manufacturer analyses presented in section 3.32. This is a very wide difference in results, which generates concern about the stability of the ECHO model.
   b. In other NICE appraisals of type 2 diabetes treatments (liraglutide: TA203, exenatide: TA248, dapagliflozin:TA288), the CORE model was requested to validate the results presented from manufacturer models. **For consistency in assessing the cost-**

effectiveness of canagliflozin, we therefore request that the CORE model is also used for this appraisal.

c. The ECHO model seems particularly sensitive to changes in HbA1C including HbA1C drift over time with the consequence that the ECHO model may not be as sensitive to other differences between drugs, such as adverse events, as the CORE model. For example, the model does not seem to be sensitive to the difference in hypoglycaemia rate (OR of 3.43-3.65) between dapagliflozin and canagliflozin.

d. The differential HbA1C reduction between the two doses of canagliflozin is limited at a range of 0.09% (insulin sub-study DIA3008) to 0.21% (study DIA3002), yet the monthly cost of the 300 mg dose is £10.79 greater than the cost of the 100 mg dose of canagliflozin. This does not seem to be reflected in the outcomes of the economic modelling where canagliflozin 300mg seems to be more cost-effective than canagliflozin 100mg. As such, this may be a further example of the lack of stability of the model analyses.

5. **The higher odds ratio of hypoglycaemia for canagliflozin compared to dapagliflozin is unlikely to reflect differences in trial outcome definitions and may relate to the different mechanism of actions of these drugs. We request clarification in the ACD on how this has been approached in the economic modelling.**

The manufacturers of canagliflozin explain that the higher odds of hypoglycaemia in a canagliflozin patient versus dapagliflozin (OR of 3.43-3.65) are due to differences in the definition of hypoglycaemia outcomes in the trials. The table below shows the definitions used. As can be seen, total hypoglycaemia reported in the dapagliflozin trials (i.e. considering the event rate for all three outcomes below) is more encompassing than the definition in the canagliflozin trials, where documentation of blood levels was also required, unless a major neurological symptom occurred. The dapagliflozin trials included the “other” category to capture those events where a blood test may not have been available, even in less major cases. However, the threshold was set at a lower level for major hypoglycaemic events, but given that any major symptoms of hypoglycaemia would also contribute to a major event, this lower threshold is unlikely to have changed the results much. Thus, given the narrower definition used in the canagliflozin trial, the differences in hypoglycaemia rates are likely to be even higher.

The increased odds ratio of hypoglycaemia with canagliflozin versus dapagliflozin may be explained by the different mechanism of actions of these drugs. Canagliflozin is not as selective for the SGLT-2 transporter versus SGLT-1 transporter as dapagliflozin or empagliflozin. This may have implications in terms of risk of hypoglycaemia (Nagata, 2013). This is because 90% of glucose reabsorption occurs via SGLT-2 transporters in the kidney and the rest by SGLT-1 transporters. Highly selective inhibition of only SGLT-2 (i.e. with dapagliflozin and empagliflozin) means that some glucose is able to be reabsorbed by the SGLT-1 transporter, thereby reducing the risk of hypoglycaemia. Concurrent SGLT-1 inhibition with canagliflozin would potentially remove this “built-in” safeguard and may explain the higher odds ratios of hypoglycaemia seen with canagliflozin in the NMA.

It is unclear whether this significant OR with cost consequences has been taken into account in the modelling. We therefore request clarification on how this has been approached in the economic modelling.

Dapagliflozin trials	Canagliflozin trials
Major episodes of hypoglycaemia: symptomatic episodes requiring external (3rd party) assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value below 3.0 mmol/L(54 mg/dl) and prompt recovery after glucagon administration.	Documented hypoglycaemic episodes, including biochemically documented episodes (concurrent fingerstick glucose or plasma glucose ≤3·9 mmol/L with or without symptoms) and severe episodes (those needing assistance of another individual or resulting in seizure or loss of consciousness).
Minor episodes of hypoglycaemia – defined as either a symptomatic episode with a capillary or plasma glucose measurement below 3.5 mmol/L (63 mg/dl) regardless of need for external assistance or an asymptomatic capillary or plasmaglucose measurement below 3.5 mmol/L (63 mg/dl), that does not qualify as a major episode.	
Other hypoglycaemia – defined as events suggestive of hypoglycaemia with symptoms that the subject experienced as hypoglycaemia and no confirmative measurement.	

6. There are limitations of the RCT evidence supporting canagliflozin's preliminary recommendations, which should be highlighted further in the ACD.

- The manufacturer's submission Section 3.2 of the ACD: The canagliflozin trials did not include a dose titration regimen and rather assessed the two doses separately; thus the trial data does not reflect how canagliflozin will be used in real-world practice. We recommend that further real world practice based economic modelling scenarios are carried out to inform the final guidance, as described above.
- ERG's comments on the manufacturer's clinical-effectiveness evidence section 3.25: We note the ERG's comment regarding the manufacturer's clinical-effectiveness section that the per-protocol analyses did not show superiority for canagliflozin 300mg in the two dual therapy trials unlike the modified intention to treat analyses. This is an unusual sequence of analysis as in non-inferiority trials, typically the initial analysis would be conducted in the PP population and only then conducted in the ITT population once a significant result was demonstrated in the PP population. We ask for consideration of why these results differ by analysis and whether this is driven by unequal discontinuations across the treatment arms.
- The manufacturer's submission Section 3.2 of the ACD : The add onto insulin data for canagliflozin is limited to a sub-group analysis of the CANVAS study including patients with a history or at high risk of CV disease. Whilst we appreciate that most diabetes patients requiring insulin will have CV risk factors, there will be a spectrum of risk in these patients. As such, the CANVAS study is unlikely to be generalisable to patients with lower CV risk. Additionally, only 18-week data is currently available for this population.

References

FDA Canagliflozin Medical Review
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204042Orig1s000MedR.pdf

FDA Canagliflozin Summary Review
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204042Orig1s000SumR.pdf

Hardy E et al. Dapagliflozin effects on lipid profile of patients with type 2 diabetes mellitus. 73rd ADA Meeting, Chicago June 21st-25th 2013

Khunti et al Clinical Inertia in People With Type 2 Diabetes: A retrospective cohort study of more than 80,000 people. Diabetes Care vol. 36 no. 11; 3411-3417 November 2013

Langkilde A M et al Cardiovascular Safety of the SGLT2 Inhibitor Dapagliflozin: Meta-Analysis With > 6000 Patient-Years Exposure AHA Dallas 2013

Middleton RJ et The unrecognized prevalence of chronic kidney disease in diabetes. Nephrol. Dial. Transplant. (January 2006) 21 (1): 88-92.

Nieto J et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes mellitus and chronic kidney disease over 52 weeks. EASD, September 2013, Barcelona.

Nagata et al American Journal of Physiology Selective SGLT2 inhibition by tofogliflozin reduces renal glucose reabsorption under hyperglycemic but not under hypo- or euglycemic conditions in rats. American Journal of Physiology - Endocrinology and Metabolism Vol.304no.E414-E423 15 February 2013

NICE CG87 Quick reference guide: The management of type 2 diabetes, May 2009

Nowicki et al. Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study International Journal of Clinical Practice Volume 65, Issue 12 Pages 1207–1322 December 2011

Woo V et al. Canagliflozin is effective and generally well tolerated in subjects with type 2 diabetes mellitus and stage 3 chronic kidney disease. EASD, September 2013, Barcelona

Vercruysse F et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes mellitus inadequately controlled with metformin plus sulphonyluera over 52 weeks. EASD, September 2013, Barcelona.

Section 4 Consideration of the evidence

1. **Due to lack of stability, the model itself needs to be validated against an established model, such as the NICE-recommended CORE model.**

We are concerned about the lack of stability of the ICERs generated using the ECHO model. We consider the very wide range of ICERs generated for the same drug comparisons to demonstrate a high level of uncertainty in the cost-effectiveness analyses. In other NICE appraisals of type 2 diabetes treatments, the CORE model was requested to validate the results presented from manufacturer models. For consistency in assessing the cost-effectiveness of canagliflozin, we

therefore request that the CORE model is also used for this appraisal. Please see section 3 for further detail concerning the rationale for this request.

2. **Whilst we appreciate that dapagliflozin was not considered a comparator to canagliflozin in triple therapy, as to date it has not been recommended in triple therapy by NICE TA 288, we clarify that a triple therapy RCT for dapagliflozin (in combination with metformin plus a sulphonylurea) is now available.**

This RCT demonstrates:

- A clinically relevant decrease in HbA1c of -0.86% with dapagliflozin vs. -0.17% for placebo (p value for difference <0.0001) at 24 weeks
- Significant weight loss of -2.65 kg with dapagliflozin vs -0.58 kg for placebo (p <0.0001) at 24 weeks (Matthei, 2013)

References

Matthaei. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulphonylurea. 2013. Presented at the 49th Annual Meeting of the EASD, September 2013.