Canagliflozin STA: Janssen response to Clarification Questions

21st November 2013

Section A: Clarification on effectiveness data

Literature review

A1. In section 6.2.2 on page 54 and figure 1 in Amaris 2013, ref 72 (PRISMA flow diagram, page 26), it is stated that 208 citations were identified for data extraction. It is unclear how the 12 potentially relevant canagliflozin RCTs listed in section 6.2.4 on page 56 were selected from these 208 citations. Please clarify how these 12 RCTs were selected and please provide reasons for why others were excluded, along with the number of studies excluded for each reason at this stage.

Of the 12 canagliflozin randomised controlled trials (RCTs), two were discarded as they included patients who received canagliflozin as monotherapy, which is outside the NICE canagliflozin STA scope and one of them is an RCT in an Asian population conducted through all lines of therapy, which was not considered generalisable.

Ten RCTs assessing canagliflozin were provided to Amaris by Janssen and were presented in the cell "additional papers identified through other sources" of the PRISMA diagram. These trials were not selected using the systematic literature review as they were unpublished at the time of the literature search. Therefore they have been included as "additional papers" and were screened and extracted using the same process as all other papers.

A2. In figure 1 in Amaris 2013, ref 72 (PRISMA flow diagram, page 26) the number of references that did not meet the inclusion criteria for the network meta-analysis sums to 123 (in box titled 'Discarded from the NMA as did not meet inclusion criteria'). Please provide a list of these references.

The list of 123 papers discarded from the network meta-analysis (NMA), as well as the reason for exclusion, are provided in Table 6, in the Appendix.

A3. In figure 1 in Amaris 2013, ref 72 (PRISMA flow diagram, page 26) a total of 648 full texts were screened for eligibility, and the total number of references 'discarded as did not meet the inclusion criteria' sums to 434. This should leave 214 publications for inclusion in the narrative review, rather than the 208 publications as specified. Please explain this discrepancy.

Five conference abstracts were included as sensitivity analyses for the NMA but were not described as part of the narrative review (please note that the narrative review was not included as part of the core submission). In addition, one trial that assessed a mixed background (i.e. metformin ± thiazolidinedione [TZD]) was included in a sensitivity analysis for the metformin plus TZD background due to the limited number of trials included in the base case analysis. References of these six studies are reported in Table 7, in the Appendix.

A4. Please provide reference number 57 '*CEGEDIM. Patient Data Report: Diabetes Treatment Combinations - Report AH [JAN2364513_ADH.DN2]. 2013*'.

This reference has now been sent.

Clinical effectiveness

A5. It is stated on page 107 that there were no differences in change in HbA1c over time according to baseline BMI. However, data from the sub-group analyses by baseline BMI have not been reported. Please provide these results.

A sub-group analysis by baseline body BMI (<25, 25 to <30, 30 to <35, and ≥35 kg/m^2) was conducted in a pooled population of placebo-controlled studies and was reported in the Summary of Clinical Efficacy submitted to the EMA. Results of this subgroup analysis by baseline BMI indicate that canagliflozin was similarly effective in lowering HbA1c across the full range of baseline BMI, from individuals with T2DM who are non-overweight/non-obese to individuals with more severe obesity. Clinically sizeable reductions in HbA1c were observed with canagliflozin 300 mg and 100 mg compared to placebo in all BMI subgroups (p<0.001 for all comparisons within each BMI subgroup): -0.75% and -0.71%, respectively, for <25 kg/m^2 subgroup; -0.81% and -0.65%, respectively, for 25 to <30 kg/m^2 subgroup; -0.82 and -0.70, respectively, for 30 to <35 kg/m^2 subgroup; and -0.89% and -0.71%, respectively, for ≥35 kg/m^2 subgroup.

Furthermore, some pre-specified sub-group analyses by baseline BMI (<30 and ≥30 kg/m^2) were conducted in most trials (as presented below).

	DIA3009	DIA3006	DIA3015	DIA3002	DIA3012	DIA3008
Sub-group analysis by	Week 52	Week 52	Week 52	Week 26	Week 26	Week 18
Baseline BMI		✓	✓	✓	✓	✓

The difference in LS mean change in HbA1c from baseline to the primary time point (i.e. 18 weeks for DIA3008 insulin sub-study, 26 weeks for DIA3002, DIA3006 and DIA3012, and 52 weeks for DIA3015) were based on an ANCOVA analysis with baseline BMI group and treatment as fixed effects, and baseline HbA1c as a covariate. The results (placebo/comparator-subtracted LS mean change and 95% confidence intervals [CI]) of these analyses are presented in **Error! Reference source not found.** and **Error! Reference source not found.**.

[redacted]

[redacted]

Trial	Canagliflozin 100mg	Canagliflozin 300mg	Placebo	Active comparator
Dual therapy				
DIA3006 (in combination with MET)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to week 26 in HbA1c (%)				
Baseline BMI of <30kg/m², N				
Mean baseline HbA1c (SD)				
LS Mean change at 26 weeks in HbA1c (SE)				
Difference in LS Mean change minus placebo (95% CI)*				
Baseline BMI of ≥30kg/m², N				
Mean baseline HbA1c (SD)				
LS Mean change at week 26 in HbA1c (SE)				
Difference in LS Mean change minus placebo (95% CI)*				
Triple therapy				
DIA3015 (in combination with MET+SU)				
Change from baseline to week 52 in HbA1c (%)		[redacted]		[redacted]
Baseline BMI of <30kg/m², N				
Mean baseline HbA1c (SD)				
LS Mean change at 52 weeks in HbA1c (SE)				
Difference in LS Mean change minus sitagliptin (95% CI)*				
Baseline BMI of ≥30kg/m², N				
Mean baseline HbA1c (SD)				
LS Mean change at week 52 in HbA1c (SE)				
Difference in LS Mean change minus sitagliptin (95% CI)*				
DIA3002 (in combination with MET+SU)	[redacted]		[redacted]	
Change from baseline to week 26 in HbA1c (%)				
Baseline BMI of <30kg/m², N				
Mean baseline HbA1c (SD)				
LS Mean change at 26 weeks in HbA1c (SE)				
Difference in LS Mean change minus placebo (95% CI)*				
Baseline BMI of ≥30kg/m², N				
Mean baseline HbA1c (SD)				
LS Mean change at week 26 in HbA1c (SE)				
Difference in LS Mean change minus placebo (95% CI)*				

Trial	Canagliflozin 100mg	Canagliflozin 300mg	Placebo	Active comparator
DIA3012 (in combination with MET+TZD)	[redacted]			
Change from baseline to week 26 in HbA1c (%) *Baseline BMI of <30kg/m², N* *Mean baseline HbA1c (SD)* *LS Mean change at 26 weeks in HbA1c (SE)* Difference in LS Mean change minus placebo (95% CI)* *Baseline BMI of ≥30kg/m², N* *Mean baseline HbA1c (SD)* *LS Mean change at week 26 in HbA1c (SE)* Difference in LS Mean change minus placebo (95% CI)*				
DIA3008 insulin sub-study (in combination with MET+SoC)	[redacted]			
Change from baseline to week 18 in HbA1c (%) *Baseline BMI of <30kg/m², N* *Mean baseline HbA1c (SD)* *LS Mean change at 18 weeks in HbA1c (SE)* Difference in LS Mean change minus placebo (95% CI)* *Baseline BMI of ≥30kg/m², N* *Mean baseline HbA1c (SD)* *LS Mean change at week 18 in HbA1c (SE)* Difference in LS Mean change minus placebo (95% CI)*				

DIA3006: CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor Comparator Trial; DIA3015: CANagliflozin Treatment And Trial Analysis - DPP-4 Inhibitor Second Comparator Trial; DIA3002: CANagliflozin Treatment And Trial Analysis - Metformin and Sulphonylurea; DIA3012: CANagliflozin Treatment and Trial Analysis - Metformin and Pioglitazone; DIA3008 insulin sub-study: CANagliflozin cardioVascular Assessment Study (CANVAS insulin sub-study).

CI: confidence interval; Met+: in combination with metformin; SU+: in combination with sulfonylurea; LOCF: last observation carried forward; mITT: modified intent-to-treat; SD: standard deviation; SE: standard error

** Pairwise Comparison are based on ANCOVA with treatment and baseline BMI group as fixed effects, and baseline HbA1c as a covariate.*

*** DIA3008 insulin sub-study population 2 (patients who received ≥30 IU per day alongside standard of care)*

[redacted]

[redacted]

A6. The DIA3008 insulin sub-study compares canagliflozin plus standard of care (SoC) compared with placebo plus SoC in subjects with T2DM.

- Please clarify whether SoC is analogous to other terms used in the submission for this study, such as 'AHA medications'?
- Please clarify whether there is a specific definition of SoC in this study?
- Please provide data showing which AHA medications were being taken in addition to insulin and canagliflozin/placebo in that trial.

Insulin-based treatment of T2DM patients has to be individualised to address patient needs and many combinations of insulins and standard of care (SoC) are used. Clinical guidelines recommend that T2DM patients initiated on insulin should continue metformin and sulfonylurea (and acarbose, if used), but only continue other drugs that are licensed for use with insulin. The use of sulfonylurea should be reviewed if hypoglycaemia is a concern (NICE submission reference 63).

In DIA3008 insulin sub-study, canagliflozin or placebo was added to insulin concomitantly to standard of care which included:

- No other therapies (i.e. insulin monotherapy)
- Metformin (i.e. insulin + MET)
- Other AHAs (i.e. Insulin + AHAs)

Based on the design of the DIA3008 insulin sub-study study, patients were on a stable background of insulin (alone or with AHAs) for at least 8 weeks prior to screening (NICE submission reference 84). Patients were kept on a stable regimen of their previous AHA regimen from screening through week 18 of the double-blind core treatment phase, unless down-titration was required to manage or avoid hypoglycaemia, or unless glycaemic rescue criteria were met (NICE submission reference 84). It should be noted that investigators were to indicate on a specific electronic case report form (eCRF) whether changes made to the insulin doses constituted glycaemic rescue. The population of patients on insulin mono-therapy or insulin + metformin represents the largest proportion (75%) of patients described in "Population 2" (patients that are on an insulin dose of ≥30 IU/day +/- AHAs) of the DIA3008 Insulin sub-study.

[redacted]

	Placebo	CANA 100 mg	CANA 300 mg	CANA Total	Total
Subjects in the mITT analysis set	[redacted]				
Subjects in the safety analysis set					
mITT subjects on insulin monotherapy					
mITT subjects on insulin + metformin					
mITT subjects on insulin + AHA					
Insulin + Metformin + SU					
Insulin + SU					
Insulin+ other AHAs					

Note: Percentages calculated with the number of subjects in each group as denominator.

Error! Reference source not found. shows the summary of baseline medications for the patients within Population 2 of DIA3008 that received insulin alone, insulin + metformin or insulin + other AHA.

[redacted]

		3008 - Insulin Substudy Population 2 (≥ 30 IU/day)	
		[redacted]	[redacted]
Baseline insulin type (all patients)	Total	[redacted]	[redacted]
	Basal + Bolus	[redacted]	[redacted]
	Basal Alone	[redacted]	[redacted]
	Bolus Alone	[redacted]	[redacted]
	Not specified	[redacted]	[redacted]
AHA category (all patients)	Total	[redacted]	[redacted]
	Insulin + Metformin Alone at Screening	[redacted]	[redacted]
	Insulin Alone at Screening	[redacted]	[redacted]
	Insulin + Other AHA(s) at Screening	[redacted]	[redacted]
Categories of Insulin + other AHA(s) at Screening	*Total*	[redacted]	
	Insulin + Metformin + SU, Urea Derivatives	[redacted]	
	Insulin + Other AHA combination	[redacted]	
	Insulin + SU, Urea Derivatives	[redacted]	

A7. On page 112, in reference to the network meta-analysis, it is stated ***"****According to clinical experts, background therapies are an important treatment effect modifier. Therefore, analyses were conducted by background therapy. Trials assessing treatments on top of a "mixed" background were therefore excluded from the NMA."* Please explain what is meant by 'mixed background'.

"Mixed background" as defined here was used to indicate substantial heterogeneity in background agents taken by trial subjects, in particular in how many agents were being taking (e.g., dual vs. triple therapy). As suggested by the clinical experts, data for dual and triple lines of therapy should probably be handled separately, which was done in the NMA thus making studies that pooled lines of therapies (and for which sub-groups were not reported) inappropriate for inclusion within the NMA.

Otherwise, these trials were described as part of the narrative review (please note that the narrative review was not part of the core submission) but were excluded from the NMA.

A8. On page 112, in reference to the network meta-analysis, it is stated *"Treatments not recommended in the UK (i.e. by NICE or the SMC) were excluded from the NMA (e.g. insulin degludec and liraglutide 1.8 mg)"*. Please provide a list of all treatments which were excluded from the NMA.

A total of three treatments were excluded as they were not recommended (at the time of the analysis) in the UK. These were insulin degludec, liraglutide 1.8mg and lixisenatide.

A9. On page 123 it is stated *"SAS and WinBUGS programs are reported in Appendix 7 in section 10.7.10 (Clinical SRL – Winbugs and SAS programs)".* In the appendix there only appears to be Winbugs code. Please clarify whether the SAS code should have been included here too? If so please provide the SAS code or a summary of what the code does.

SAS programs were prepared for dataset manipulation (preparation of data inputs and imputation of missing data), direct comparisons and heterogeneity assessment. The programs related to direct comparisons and heterogeneity assessment are reported below.

Fixed effects model (direct comparison)

```
proc sql;
create table temp2 as select cc, sum(w_lnOR) as sum_lnOR, sum(w) as sum_w, /*sum(w_lnOR_p)
as sum_lnOR_p,*/ /*Continuity*/
sum(nom) as sum_nom, sum(den) as sum_den,            /*MH estimate*/
sum(pr) as sum_pr, sum(ps_qr) as sum_ps_qr, sum(qs) as sum_qs, sum(r) as sum_r, sum(s) as
sum_s /*MH variance*/
from temp1;
quit;

Data temp3; /* Table with results of the fixed-effects model*/
    set temp2;
    format C1 $80.;
if cc=0 then do;
    C1="Fixed-effects model: inverse variance-weighted method";
            estimate=sum_lnOR/sum_w;
            StdErr=sqrt(1/sum_w);
            SE=round(StdErr,0.01);
    HR=round(exp(estimate),0.001);
    lowerlimit=round(exp(estimate-1.96*StdErr),0.001);
    upperlimit=round(exp(estimate+1.96*StdErr),0.001);
    C2=compress(HR||" ["||lowerlimit||";"||upperlimit||"]");
            trt=&t2;
```

```
            trt2=&t1;
end;
if cc=1 then do;
C1="Fixed-effects model: Mantel-Haenszel's Method";
            estimate=sum_nom/sum_den;
            StdErr=sum_pr/(2*sum_r*sum_r)+sum_ps_qr/(2*sum_r*sum_s)+sum_qs/(2*sum_s*sum_s
);
            HR=round(estimate,0.001);
            SE=round(StdErr,0.01);
    lowerlimit=round(exp(log(estimate)-1.96*StdErr),0.001);
    upperlimit=round(exp(log(estimate)+1.96*StdErr),0.001);
    C2=compress(HR||" ["||lowerlimit||";"||upperlimit||"]");
            trt=&t2;
            trt2=&t1;
end;
keep C1 C2;
run;
```

Heterogeneity assessment

```
%if &nbstudies>1 %then %do;
proc glm data=temp1 outstat=temp6;
    model lnOR=/inverse;
    weight w;
    run;

data temp7; * p-value of the Cochran test;
    set temp6;
    where _source_="ERROR";
    Q=SS;
    C1="pvalue of the Cochran test";
    C2=put(round(1-probchi(Q,DF),0.0001),BEST.);
    keep C1 C2;
    run;

data temp8; * calculation of Isquare;
    set temp6;
    where _source_="ERROR";
    Q=SS;
    C1="Isquare";
    tp=100*(Q-DF)/Q;
    if tp>0 then Isquare=tp;
    else Isquare=0;
    C2=compress(round(Isquare,0.01)||"%");
    keep C1 C2;
    run;
```

Random effects model (direct comparison)

```
data temp9;
    set temp1;
    row=input(Studyname,best5.);
    col=input(Studyname,best5.);
    value=var_lnOR;
    keep row col value;
    run;

ods output SolutionF=temp10;
proc mixed data=temp1 covtest;
    class Studyname;
```

```
    model lnOR=/s cl;
    random Studyname/gdata=temp9 g;
    repeated diag;
    parms / nobound;
    run;

Data temp11; * table with results of random-effects model;
    set temp10;
    C1="Random-effects model";
    HR=round(exp(estimate),0.01);
    lowerlimit=round(exp(estimate-1.96*StdErr),0.01);
    upperlimit=round(exp(estimate+1.96*StdErr),0.01);
    C2=compress(HR||" ["||lowerlimit||";"||upperlimit||"]");
    keep C1 C2;
    run;
```

Section B: Clarification on cost-effectiveness data

B1. In table 33 on page 176 the economic model chooses one comparator within each class of treatment. Please clarify whether other treatments in each class were examined in scenario analyses?

Because the number of simulation results increases proportionately with the number of comparators (and one comparator agent per comparison was associated with approximately 850 sets of simulation results as it was), the submission was limited to one leading member of each drug class. The one exception to this is the GLP-1-a class, where liraglutide data in triple therapy (metformin + SU) and add-on to insulin were not available from the NMA, and so exenatide was selected as the GLP-1-a for comparisons conducted. That is, two different GLP-1 agents were analysed, though only one of them in each line of therapy.

While we see little gain in analysing the differences between the DPP-4-i's, both in that sitagliptin is the clear agent of choice and the cost and efficacies are very similar within the class, there are some variations across the SU class. Gliclazide is the most-frequently SU prescribed in the UK (NICE submission reference 150) and a treatment profile was built from available data. One evidence gap was the rate of hypoglycaemic events for gliclazide, and so the glimepiride rate was used. While change in HbA1c, SBP and patient weight can be expected to be consistent between glimepiride and gliclazide, there is some evidence that the rate of hypoglycaemic events is lower for gliclazide (as the modified release (MR) presentation; (1)). Some information about the sensitivity of the modelling results to hypoglycaemic rates was provided in the NICE submission deterministic sensitivity analyses (DSA). Varying hypoglycaemic rates by +/- 20% show little change in the ICER (NICE Appendix , Tables 195 and 197).

In an attempt to find further data on the hypoglycaemic event rate for gliclazide, the publication of the GUIDE trial (1) was re-examined but was again excluded from the NMA for 4 reasons: the trial used a mixed treatment, the duration of 27 weeks did not match with the 52 week basecase NMA, the baseline HbA1c was inclusion criteria are considered broad, and the definition of hypoglycaemia differed from that used in the canagliflozin trial programme. The modelling comparison can be conducted using an ad hoc assumption from the GUIDE trial for hypoglycaemic event rate for gliclazide upon request by NICE, but we would maintain that an estimate of hypoglycaemic events for gliclazide from this this data source would not be robust.

On a separate note, please be aware that there is an error in Figure 43 of the NICE submission. The line showing odds ratios of hypoglycaemic events versus canagliflozin should read glipizide rather than gliclazide.

B2. On page 179 it states for some treatments BMI was estimated by weight using a weighted average of male and female heights in the UK general population.

- Please clarify for which treatments did this estimation occur?
- Please clarify whether this was tested in sensitivity analysis?
- Please clarify what happened if there was neither BMI nor weight data?

When BMI data were unavailable from the NMA, changes in patient body weight were converted to BMI using gender-specific mean heights in the UK population (1.75m for males, 1.613m for females (2)) using the equation below.

$$BMI\ TE = \frac{Treatment\ effect\ in\ kg}{(proportion\ males\ at\ baseline\ x\ 1.75 + (1 - proportion\ males\ at\ baseline) x 1.613)^2}$$

There were six comparisons for which this was necessary: Dapagliflozin and liraglutide 1.2mg in dual therapy (metformin background), exenatide and Insulin LA in triple therapy (metformin + SU background), and sitagliptin and dapagliflozin in add-on to insulin. The details are presented in Cells B4:D13 in the accompanying Excel spreadsheet ("Answer B2.xlsx").

Please note that we identified an inconsistency in the implementation for the dual and triple therapy scenarios. Specifically, we inadvertently used change in the actual BMI reported in the clinical programme for canagliflozin in these simulations rather than the calculated value from the above formula. The values are presented in Cells F4:J29 in the accompanying Excel spreadsheet ("Answer B2.xlsx").

- In dual therapy, the decrease in BMI assigned to canagliflozin was considerably smaller than it would have been using consistent methods for both arms (-0.560 vs. 0.912 kg/m^2 for canagliflozin 100mg; -0.690 vs. -1.042 kg/m^2 for canagliflozin 300mg), thus producing conservative cost-effectiveness estimates (from the standpoint of canagliflozin) for the comparisons against dapagliflozin and liraglutide 1.2mg. We have corrected this and re-run the simulations (Table 3).

- In triple therapy (metformin + SU background), the BMI lowering assigned to canagliflozin was slightly greater than it would have been using consistent methods for arms, which may have resulted in a slight favourable bias to canagliflozin in the cost-effectiveness results (-0.400 vs. -0.358 kg/m^2 for canagliflozin 100mg ; -0.619 vs. -0.576 kg/m^2 for canagliflozin 300mg). The estimates using the corrected values for BMI are largely unchanged (Table 3).

Table 1. Revised basecase ICERs incorporating correct kg to BMI conversion data described in answer to B2.

Comparison	Submitted ICER	Corrected ICER
Dual therapy		
Canagliflozin 100mg vs. dapagliflozin	£8,674	£2,993
Canagliflozin 300mg vs. dapagliflozin	£27,419	£21,626
Canagliflozin 100mg vs. GLP-1-a	£50,005 #	£71,619 #
Canagliflozin 300mg vs. GLP-1-a	£76,214 #	£107,181 #

Triple therapy (Met+SU)		
Canagliflozin 100mg vs. GLP-1-a	Dominating	£265,928 #
Canagliflozin 300mg vs. GLP-1-a	Dominating	Dominating
Canagliflozin 100mg vs. Insulin LA	£263	£183
Canagliflozin 300mg vs. Insulin LA	£607	£671
# Canagliflozin is both cheaper and less effective than GLP-1-a, therefore the ICER is for GLP-1-a ***to replace*** *canagliflozin*		

There were no sensitivity analyses specifically designed to assess the impact of converting patient body weight treatment effect to BMI treatment effects as it was not thought that this would have a material impact on the ICER. As part of routine DSA, however, the differences in the treatment effects (i.e., canagliflozin vs. the comparator) for each of the bio-markers (including BMI) were adjusted by +/- 20% in scenario analysis. These analyses are shown in the NICE submission Appendix 13, Tables 195 to 202. However, to generate a +/- 20% in the BMI (as modelled in the DSA) using the equation detailed above, assuming body weight data was constant and using the canagliflozin 100mg in dual therapy data as an example, the height range explored in the DSA is 1.60m to 1.96m for males and 1.47m to 1.80m for females. That is to say, to achieve a +20% change in BMI, the average height for males/females needs to be changed to 1.60m/1.47m.

As body weight is the numerator of the equation above, varying BMI by +/-20% will generate the same results as varying body weight by +/-20%.

There were two cases for which neither BMI nor body weight treatment effects were available in the NMA. For gliclazide in dual therapy, the BMI change was sourced as the BMI change for glimepiride from the NMA. For sitagliptin in triple therapy (with metformin and TZD background), it was assumed that sitagliptin would not affect BMI and the placebo BMI change from the placebo arm of the 3012 RCT (-0.05 at 26 weeks). The canagliflozin BMI changes were taken from the same trial (-0.91 and -1.26 kg/m^2 at 26 weeks for the 100mg and 300mg doses, respectively).

B3. Please clarify how and why the CODE-2 study for HRQoL data was chosen from the 80 included HRQoL studies reported on page 194.

As evidenced by the 80 HrQoL studies referenced in the submission, there are many estimates of HrQoL for patients with T2DM. These estimates differ in many respects, with some of the most important characteristics being: (i) the methods used to solicit the estimates, (ii) the setting, (iii) the health states encompassed, (iv) any technique used to derive health-state-specific values, and (v) the sample size. CODE-2 was chosen as the base case because it used well-validated techniques (the EQ-5D and the UK tariff) to solicit HrQoL, it is based on patients in the European setting (including the UK as well as Belgium, the Netherlands, Italy, Spain, and Sweden), prevalence data were concomitantly captured for a large number of demographic, clinical, and health history characteristics enabling attribution of disutility to individual health complications using multivariate regression techniques and reducing the risk of the results being confounded, and the sample included more than 4,000 patients with T2DM.

This is detailed further on page 198 of the NICE submission (Table 38). Indeed, CODE-2 disutility weights were used for a number of the input parameters for ECHO-T2DM, reducing the need to mix- and match between different data sources (with the biggest exception that for adverse events) thus increasing the internal validity.

The UKPDS QoL utilities are another multivariate-adjusted set of disutility weights, but they were rejected as they included a smaller sub-set of the health states in the model (introducing the possibility of greater confounding and the need to complement with more

external sources) and they did not include a disutility for the important BMI covariate (whereas CODE-2 does include such a coefficient). As detailed in the NICE submission alternative disutility assumptions were explored for BMI and macrovascular events (modelling scenarios 16, 17 and 19, described in Table 44 of the submission).

B4. On page 175, it is stated that *"The relationship between hypoglycaemic event rate and HbA1c is described by a user-defined hazard ratio for event rates corresponding to each 1% point decrease in HbA1c, defined by the user. In an analysis based on DCCT data, the multivariate regression estimate of the RR was 1.43."* Please confirm whether a hazard ratio or a relative risk (RR) was applied to model the relationship between hypoglycaemic event rate and HbA1c?

The statement is correct. ECHO-T2DM models this relationship as a hazard ratio, i.e. the ratio of the hazard rates associated with two different values of HbA1c value during each annual cycle.

The best available data on the relationship between HbA1c and hypoglycaemic event rates come from the DCCT study (NICE submission reference 149), where multivariate adjustment for confounding factors and a large sample size engender relatively high confidence in the results. Although this study is in Type 1 diabetes, we have not found similar data for T2DM (even of low quality). The statistical estimation methods used by the DCCT analysts did not yield empirical estimates entirely consistent with the structural set-up of ECHO-T2DM, however, as the relationship was estimated as an RR (with the primary difference that the differences are cumulated over the entire study rather than as the instantaneous risk through the study period or some subset of the study period). While the match may be imperfect, we would argue that the implementation is a credible solution.

Results specific to T2DM based on a meta-analysis of 82 studies (155 trial arms) were presented at the most recent ISPOR European Congress (3). While the methods used differed from those used in the DCCT analysis, for example the DCCT analysis was estimated using proportional hazards regression on long-term patient-level data and the recent analysis was estimated using log-linear regression on (presumably much shorter) aggregated trial data, exponentiation of the reported coefficients from the new meta-analysis generates roughly comparable hazard ratios that are, in fact, larger (1.95 for non-severe and 2.06 for severe hypoglycaemic events) than the DCCT figures. Differences in the timing of the HbA1c measurement may explain part of the difference (current HbA1c in the DCCT analysis and baseline HbA1c in the new analysis), however, and we interpret the new evidence more as confirmatory of the DCCT estimate used in the model comparisons than as suitable for a new base case.

Because rescue medication leads generally to convergence of HbA1c curves, it is unlikely to be a major driver of the results, but additional comparisons have been run to explore the impact on the ICER of reducing the HR for event rates corresponding to each 1% decrease in HbA1c (Table 4). Comparisons against SU in dual therapy were selected for this analysis as there are likely to be greatest differences between treatment arms in rates of hypoglycaemia in these comparisons, and thus will be most sensitive to the HR assumption tested.

Table 2. Impact on the cost-effectiveness of canagliflozin vs. SU in dual therapy of the HR for hypoglycaemic event rates corresponding with decrease in HbA1c

	ICER Canagliflozin 100mg vs. SU	ICER Canagliflozin 300mg vs. SU
Basecase (Tables 31 and 32 from NICE submission)	£1,537	£4,899
HR reduced by 50%	£1,714	£5,284
HR reduced by 100%	£1,878	£5,469

B5. On page 175, the economic model input data sheet does not appear to contain profiles for some of the dual therapy comparisons shown in table 32. Please provide the profiles for the canagliflozin dual therapy comparisons with TZD, GLP-1-a and dapagliflozin, and the profiles which concern its use as an add-on to insulin (or advise where these are located if already supplied).

Yes, this is correct. With the intention of reducing the burden of files to analyse within the canagliflozin assessment by NICE, the sample spreadsheet submitted with the model was limited to the profiles required to run a subset of key simulations. As offered on the teleconference to NICE and the ERG, the individual input spreadsheets used to run each of the simulation scenarios (which also contain the inputs required by that modelling comparison) can be sent on request.

The spreadsheets for the requested comparisons are the following Excel workbooks which are located in the attached zip file ("Input sheets requested by ERG.zip"):

- Dual therapy
  - Canagliflozin vs. TZD: "CANA vs TZD in DUAL INPUTS 13-11-08.xlsx"
  - Canagliflozin vs. GLP-1-a: "CANA vs GLP in DUAL INPUTS 13-11-08.xlsx"
  - Canagliflozin vs. dapagliflozin: "CANA vs Dapa in DUAL INPUTS 13-11-08.xlsx"
- Add-on to insulin
  - Canagliflozin vs. dapagliflozin: "CANA vs Dapa in ADD-ON INPUTS 13-11-08.xlsx"
  - Canagliflozin vs. DPP-4-i: "CANA vs DPP in ADD-ON INPUTS 13-11-08.xlsx"
  - Canagliflozin vs. GLP-1-a: "CANA vs GLP in ADD-ON INPUTS 13-11-08.xlsx"

B6. On page 273, appendices section 10.7.15, for dual therapy with a metformin background, the submission gives a mean difference versus placebo of -0.63 in HbA1c change at 52 weeks for Cana 100mg QD (table 133). However the economic model input data sheet gives a value of -0.77 versus placebo for 'Fixed First-Year Change in HbA1c (Unrelated to HbA1c at Treatment Start)' for the treatment profile 'NMA DUAL 52WKS (MET BACKGROUND) CANA100 VS. SITA'. (This treatment profile is specified as the intervention arm in the input data spreadsheet.) Other figures given in table 133 are also not the same as those presented for the HbA1c treatment effect in the economic model input data spreadsheet. Please explain why these figures are different?

Yes, this is by design and not an error. The treatment effect sizes reported in the submission are the actual 52-week (in some cases 26-week) therapeutic effects from the NMA and the trials. These figures are net changes, reflecting both the effects of starting a drug treatment and the natural drift in bio-markers.

Because ECHO-T2DM applies upward drift in cycle 1 (separately from the treatment effect), the effect of drift would be double-counted if we did not adjust the treatment effect for the

drift in the first year. Specifically, we subtracted the assumed annual drift for each bio-marker from its NMA treatment effect, so that the patient will have the RCT change from baseline as reported in the NMA at the end of the first cycle (i.e., the annual drift is offset for that initial cycle since it is implicitly included in the treatment effect).

As an example: assuming the HbA1c-lowering in the trial was 1.00 at 52-weeks and we model an upward drift of 0.15 per year. We would assign an HbA1c lowering of 1.15, which after the drift is applied, leads to the net lowering at the end of the cycle of 1.00 seen in the RCT.

B7. On page 277, appendices section 10.7.15, the mean results for the difference in BMI versus placebo presented in table 140 do not agree with figures used in the input data spreadsheet. For example the mean of-0.56 for Cana 100mg QD contrasts with the value of -0.595379183 used in the input data spreadsheet for the 'NMA DUAL 52WKS (MET BACKGROUND) CANA100 VS. SITA' profile. Other figures given in Table 140 are also not the same as those presented for the 'First-Year Change in BMI in Responders' in the economic model input data. Please explain why these figures are different?

As for B6, the annual drift for each bio-marker is offset in the first cycle by subtracting the drift from the baseline figure.

Section C: Clarification on the economic technical guide

C1. Please clarify whether the equation given in the text on page 60 is correct as it does not appear to be correctly specified for a model with time-varying covariates **Xt**.

Yes, the description of the equation is correct. The f_{RR} and the *RR* are extra features that have not been applied in the simulations in the simulations submitted to NICE. These can be considered as 1's for the current modelling purposes (though strictly speaking, the f_{RR} and the *RR* are adjustments that can be applied if desired, e.g., there is some evidence that TZD's may increase the risk for CHF).

The next question is whether the term $1\text{-}\exp(\exp(X_t\beta)\cdot(t^{\rho}\text{- }(t+1)^{\rho}))$ is the correct specification for a model with time-varying covariates (X_t). This is, however, the form that was used in the UKPDS 68 modelling and which we have matched (see the Appendix of Clarke et al. (2004) (NICE reference 133) where the "unconditional probability of an event occurring in the interval t to t+1 is: 1- exp(H(t|xtj)-H(t+1|xtj))."). We have, moreover, exactly matched the predicted probabilities versus the examples included in a spreadsheet provided by Philip Clarke.

C2. Please confirm that the 1000 stochastic draws of parameter values provided by Philip Clarke on page 61 include correlation between parameters.

Yes, the 1,000 stochastic draws of parameter values used boot-strap methods of drawing from with replacement from the patient sample so intra-covariate correlation is contained naturally in the sets of parameter estimates. ECHO-T2DM draws at random from the 1,000 sets of covariates, so this correlation is captured. The covariate values are not drawn individually, which would have required explicit use of a covariance matrix, something which the UKPDS Team has not made publically available.

Note, though, that equivalent sets of parameter values for the new UKPDS equations (UKPDS 82) have not yet been made available (personal communications with Philip Clarke indicate that they have prioritised validation work, but do promise to generate and share the

data). Until then, we naively model no correlation between the parameters in those sensitivities.

C3. Please explain what is shown in table 6 on page 61 as it is not referred to in the text.

Apologies, the description in the technical report is poorly worded. Table 6 describes the format of the relative risk (RR) variable at the end of the equation mentioned in question C1. The "," marker preceding it should be a "*" as this is a multiplicative RR adjustment. This is an optional feature for modelling BMI-related gradients in the risk of macrovascular events. It was programmed for a specific purpose, but it is not a feature that we usually employ (i.e., by setting the RR's to 1) and we did not use it in these simulations submitted to NICE.

The difference between the f_{RR} at the beginning (which should have been followed with a "*" as it is also multiplicative) denotes RR's that the user cannot change (e.g., for use of statins) and the RR represents those that are optional.

In summary, the correct formulation should have been:

$$p = f_{RR} * 1 - \exp\left(\exp(X_t\beta) \cdot (t^{\rho} - (t+1)^{\rho})\right) * RR$$

and the RR at the end of the line should have been properly identified as taking the form in Table 5 (see below). These features were not included in the comparisons presented to NICE.

Table 3: Relative risk adjustments

Event	***RR adjustment***
MI	$RR = RR_{\text{MI.obesity}}{}^{max(0,BMI_t-25)}$
IHD	$RR = RR_{\text{IHD.obesity}}{}^{max(0,BMI_t-25)}$
CHF	$RR = RR_{\text{if oedema}}.RR_{\text{agent}}$
Stroke	$RR = RR_{\text{Stroke.obesity}}{}^{max(0,BMI_t-25)}$

References.

1. Schernthaner G, Grimaldi A, Di Mario U, Drzewoski J, Kempler P, Kvapil M, Novials A, Rottiers R, Rutten G, Shaw K. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. European Journal of Clinical Investigation 2004;34, 535-542
2. The Scottish Health Survey 2008. Scotland.gov.uk. 2009-09-28. Retrieved June 2013.
3. McEwan P, Foos V, Grant D, Palmer J, Varol N, Curtis B, Boya K. Predicting the frequency of severe and non-severe hypoglycaemia in insulin treated type-2 diabetes subjects. Poster presented at ISPOR November 2013.

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Table 4. List of papers discarded from the NMA

Title	Authors	Year	Journal	Reason for exclusion
DURAbility of basal versus lispro mix 75/25 insulin efficacy (DURABLE) trial 24-week results: safety and efficacy of insulin lispro mix 75/25 versus insulin glargine added to oral antihyperglycemic drugs in patients with type 2 diabetes	Buse J. B.;Wolffenbuttel B. H.;Herman W. H.;Shemonsky N. K.;Jiang H. H.;Fahrbach J. L., et al.	2009	Diabetes Care	Mixed background
Dose-dependent effects of the once-daily GLP-1 receptor agonist lixisenatide in patients with Type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled trial	Ratner R. E.;Rosenstock J.;Boka G.;Investigators D. R. I. Study	2010	Diabetic Medicine	Time of assessment
Less nocturnal hypoglycemia and better post-dinner glucose control with bedTime of assessment insulin glargine compared with bedTime of assessment NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group	Yki-Jarvinen H.;Dressler A.;Ziemen M.;Group H. O. E. s Study	2000	Diabetes Care	Mixed background
Effect of a peroxisome proliferator-activated receptor-gamma agonist on myocardial blood flow in type 2 diabetes	McMahon G. T.;Plutzky J.;Daher E.;Bhattacharyya T.;Grunberger G.;DiCarli M. F.	2005	Diabetes Care	Time of assessment
Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes.[Erratum appears in Clin Ther. 2006 Nov;28(11):1967]	Philis-Tsimikas A.;Charpentier G.;Clauson P.;Ravn G. M.;Roberts V. L.;Thorsteinsson B.	2006	Clinical Therapeutics	Mixed background
Effect of glibenclamide in insulin-treated diabetic patients with a residual insulin secretion	Mauerhoff T.;Ketelslegers J. M.;Lambert A. E.	1986	Diabete et Metabolisme	Time of assessment
Glyburide decreases insulin requirement, increases beta-cell response to Mixed background meal, and does not affect insulin sensitivity: effects of short- and long-term combined treatment in secondary failure to sulfonylurea	Gutniak M.;Karlander S. G.;Efendic S.	1987	Diabetes Care	Time of assessment
Effects of the combination of insulin and glibenclamide in type 2 (non-insulin-dependent) diabetic patients with secondary failure to oral hypoglycaemic agents	Stenman S.;Groop P. H.;Saloranta C.;Totterman K. J.;Fyhrqvist F.;Groop L.	1988	Diabetologia	Partially published[1]
Effects of combined insulin-sulfonylurea therapy in type II patients	Lewitt M. S.;Yu V. K.;Rennie G. C.;Carter J. N.;Marel G. M.;Yue D. K., et al.	1989	Diabetes Care	Time of assessment
Effects of combination therapy with glyburide and insulin on serum lipid levels in NIDDM patients with secondary sulfonylurea failure	Karlander S. G.;Gutniak M. K. M.;Efendic S.	1991	Diabetes Care	Partially published
Combination insulin and sulfonylurea therapy in insulin-requiring type 2 diabetes mellitus	Feinglos M. N.;Thacker C. R.;Lobaugh B.;Deatkine D. D.;McNeill D. B.;English J. S., et al.	1998	Diabetes Research and Clinical Practice	Time of assessment
The effects of metformin on glycemic control and serum lipids in insulin-treated NIDDM patients with suboptimal metabolic control	Robinson A. C.;Burke J.;Robinson S.;Johnston D. G.;Elkeles R. S.	1998	Diabetes Care	Time of assessment
The lipoprotein profile differs during insulin treatment alone and combination therapy with	Lindstrom T.;Nystrom F. H.;Olsson A.	1999	Diabetic	Time of assessment

[1] Partially published: data available in the publication and/or additional sources were not sufficient to be used as data inputs for the network meta-analysis

Title	Authors	Year	Journal	Reason for exclusion
insulin and sulphonylureas in patients with type 2 diabetes mellitus	G.;Ottosson A. M.;Arnqvist H. J.		Medicine	
Comparison of bedTime of assessment insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial	Yki-Jarvinen H.;Ryysy L.;Nikkila K.;Tulokas T.;Vanamo R.;Heikkila M.	1999	Annals of Internal Medicine	Time of assessment
Combined metformin and insulin therapy for patients with type 2 diabetes mellitus	Ponssen H. H.;Elte J. W.;Lehert P.;Schouten J. P.;Bets D.	2000	Clinical Therapeutics	Partially published
Long-term glycaemic improvement after addition of metformin to insulin in insulin-treated obese type 2 diabetes patients	Hermann L. S.;Kalen J.;Katzman P.;Lager I.;Nilsson A.;Norrhamn O., et al.	2001	Diabetes, Obesity & Metabolism	Time of assessment
Glyburide/metformin combination product is safe and efficacious in patients with type 2 diabetes failing sulphonylurea therapy	Blonde L.;Rosenstock J.;Mooradian A. D.;Piper B. A.;Henry D.	2002		Time of assessment
Improved glycaemic control with metformin-glibenclamide combined tablet therapy (Glucovance) in Type 2 diabetic patients inadequately controlled on metformin	Marre M.;Howlett H.;Lehert P.;Allavoine T.	2002		Time of assessment
Effects of pioglitazone on metabolic control and blood pressure: a randomised study in patients with type 2 diabetes mellitus	Gerber P.;Lubben G.;Heusler S.;Dodo A.	2003	Current Medical Research & Opinion	Mixed background
A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with type 2 diabetes	Massi Benedetti M.;Humburg E.;Dressler A.;Ziemen M.	2003	Hormone & Metabolic Research	Mixed background
The Treat-to-Target Trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients	Riddle M. C.;Rosenstock J.;Gerich J.	2003	Diabetes Care	Mixed background
Addition of pioglitazone or bedTime of assessment insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial	Aljabri K.;Kozak S. E.;Thompson D. M.	2004	American Journal of Medicine	Time of assessment
Effects of two different glibenclamide dose-strengths in the fixed combination with metformin in patients with poorly controlled T2DM: a double blind, prospective, randomised, cross-over clinical trial	Brunetti P.;Pagano G.;Turco C.;Gori M.;Perriello G.	2004	Diabetes, nutrition & metabolism	Time of assessment
GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients	Schernthaner G.;Grimaldi A.;Di Mario U.;Drzewoski J.;Kempler P.;Kvapil M., et al.	2004	European Journal of Clinical Investigation	Mixed background
Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes	Charbonnel B.;Schernthaner G.;Brunetti P.;Matthews D. R.;Urquhart R.;Tan M. H., et al.	2005	Diabetologia	Time of assessment
Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): A	Dormandy J. A.;Charbonnel B.;Eckland D. J.;Erdmann E.;Massi-Benedetti	2005	Lancet	Mixed background

Title	Authors	Year	Journal	Reason for exclusion
randomised controlled trial	M.;Moules I. K., et al.			
Pioglitazone with sulfonylurea: glycemic and lipid effects in Taiwanese type 2 diabetic patients	Tseng C. H.;Huang T. S.	2005	Diabetes Research & Clinical Practice	Time of assessment
Does metformin decrease blood pressure in patients with Type 2 diabetes intensively treated with insulin?	Wulffele M. G.;Kooy A.;Lehert P.;Bets D.;Donker A. J.;Stehouwer C. D.	2005	Diabetic Medicine	Post-hoc analysis / secondary publication
Double-blind, randomized, multicentre study of the efficacy and safety of gliclazide-modified release in the treatment of Chinese type 2 diabetic patients	Lu C. H.;Chang C. C.;Chuang L. M.;Wang C. Y.;Jiang Y. D.;Wu H. P.	2006	Diabetes, Obesity and Metabolism	Mixed background
Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: A randomized trial	Mazzone T.;Meyer P. M.;Feinstein S. B.;Davidson M. H.;Kondos G. T.;D'Agostino, Sr., et al.	2006	Journal of the American Medical Association	Mixed background
Patient-reported outcomes in a trial of exenatide and insulin glargine for the treatment of type 2 diabetes	Secnik Boye K.;Matza L. S.;Oglesby A.;Malley K.;Kim S.;Hayes R. P., et al.	2006	Health & Quality of Life Outcomes	Post-hoc analysis / secondary publication
Effect of glyburide-metformin combination tablet in patients with type 2 diabetes	Chien H. H.;Chang C. T.;Chu N. F.;Hsieh S. H.;Huang Y. Y.;Lee I. T., et al.	2007	Journal of the Chinese Medical Association: JCMA	Time of assessment
Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes	Holman R. R.;Thorne K. I.;Farmer A. J.;Davies M. J.;Keenan J. F.;Paul S., et al.	2007	New England Journal of Medicine	Partially published
Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes	Kim D.;MacConell L.;Zhuang D.;Kothare P. A.;Trautmann M.;Fineman M., et al.	2007	Diabetes Care	Mixed background
A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study	Nauck M. A.;Duran S.;Kim D.;Johns D.;Northrup J.;Festa A., et al.	2007		Time of assessment
Efficacy and treatment satisfaction of once-daily insulin glargine plus one or two oral antidiabetic agents versus continuing preMixed background human insulin in patients with type 2 diabetes previously on long-term conventional insulin therapy: the Switch pilot study	Schiel R.;Müller U. A.	2007		Time of assessment
The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial.[Erratum appears in Ann Intern Med. 2007 Jun 19;146(12):896], [Summary for patients in Ann Intern Med. 2007 Apr 3;146(7):I18; PMID: 17404346]	Zinman B.;Hoogwerf B. J.;Duran Garcia S.;Milton D. R.;Giaconia J. M.;Kim D. D., et al.	2007	Annals of Internal Medicine	Time of assessment

Title	Authors	Year	Journal	Reason for exclusion
Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial	Bretzel R. G.;Nuber U.;Landgraf W.;Owens D. R.;Bradley C.;Linn T.	2008	The Lancet	Mixed background
Differences in effects of insulin glargine or pioglitazone added to oral anti-diabetic therapy in patients with type 2 diabetes. What to add-Insulin glargine or pioglitazone?	Dorkhan M.;Frid A.;Groop L.	2008	Diabetes Research and Clinical Practice	Partially published
Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study	Drucker D. J.;Buse J. B.;Taylor K.;Kendall D. M.;Trautmann M.;Zhuang D., et al.	2008	The Lancet	Mixed background
Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: Results from PROspective pioglitAzone Clinical Trial In macro Vascular Events (PROactive 10)	Wilcox R.;Kupfer S.;Erdmann E.	2008	American Heart Journal	Mixed background
Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)	Buse J. B.;Rosenstock J.;Sesti G.;Schmidt W. E.;Montanya E.;Brett J. H., et al.	2009	The Lancet	Mixed background
Earlier triple therapy with pioglitazone in patients with type 2 diabetes	Charpentier G.;Halimi S.;Investigators F. Pio- Study	2009	Diabetes, Obesity & Metabolism	Mixed background
Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: Results of the helping evaluate exenatide in patients with diabetes compared with long-acting insulin (HEELA) study	Davies M. J.;Donnelly R.;Barnett A. H.;Jones S.;Nicolay C.;Kilcoyne A.	2009	Diabetes, Obesity and Metabolism	Mixed background
Comparison of glycaemic control in patients with Type 2 diabetes on basal insulin and fixed combination oral antidiabetic treatment: results of a pilot study	De Mattia G.;Laurenti O.;Moretti A.	2009	Acta Diabetologica	Time of assessment
Effect of pioglitazone versus insulin glargine on cardiac size, function, and measures of fluid retention in patients with type 2 diabetes	Dorkhan M.;Dencker M.;Stagmo M.;Groop L.	2009	Cardiovascular Diabetology	Mixed background
Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea	Gao Y.;Yoon K. H.;Chuang L. M.;Mohan V.;Ning G.;Shah S., et al.	2009	Diabetes Research & Clinical Practice	Mixed background
Three-year efficacy of complex insulin regimens in type 2 diabetes	Holman R. R.;Farmer A. J.;Davies M. J.;Levy J. C.;Darbyshire J. L.;Keenan J. F., et al.	2009	New England Journal of Medicine	Mixed background
Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus	Kooy A.;De Jager J.;Lehert P.;Bets D.;Wulffele M. G.;Donker A. J. M., et al.	2009	Archives of Internal Medicine	Time of assessment
Effects of initiating insulin and metformin on glycemic control and inflammatory biomarkers among patients with type 2 diabetes: The LANCET randomized trial	Pradhan A. D.;Everett B. M.;Cook N. R.;Rifai N.;Ridker P. M.	2009	JAMA - Journal of the American Medical	Partially published

Title	Authors	Year	Journal	Reason for exclusion
			Association	
Long-term glycaemic effects of pioglitazone compared with placebo as add-on treatment to metformin or sulphonylurea monotherapy in PROactive (PROactive 18)	Scheen A. J.;Tan M. H.;Betteridge D. J.;Birkeland K.;Schmitz O.;Charbonnel B.	2009	Diabetic Medicine	Post-hoc analysis / secondary publication
Long-term glycaemic control with metformin-sulphonylurea-pioglitazone triple therapy in PROactive (PROactive 17)	Scheen A. J.;Tan M. H.;Betteridge D. J.;Birkeland K.;Schmitz O.;Charbonnel B.	2009	Diabetic Medicine	Time of assessment
Comparison of effect of metformin in combination with glimepiride and glibenclamide on glycaemic control in patient with type 2 Diabetes Mellitus	Shimpi R. D.;Patil P. H.;Kuchake V. G.;Ingle P. V.;Surana S. J.;Dighore P. N.	2009	International Journal of PharmTech Research	Time of assessment
A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: Applicability of a novel insulin-independent treatment	Wilding J. P. H.;Norwood P.;T'Joen C.;Bastien A.;List J. F.;Fiedorek F. T.	2009	Diabetes Care	Time of assessment
Initiating insulin therapy in elderly patients with Type 2 diabetes: Efficacy and safety of lispro mix 25 vs. basal insulin combined with oral glucose-lowering agents	Wolffenbuttel B. H. R.;Klaff L. J.;Bhushan R.;Fahrbach J. L.;Jiang H.;Martin S.	2009	Diabetic Medicine	Post-hoc analysis / secondary publication
Twelve weeks treatment with the DPP-4 inhibitor, sitagliptin, prevents degradation of peptide YY and improves glucose and non-glucose induced insulin secretion in patients with type 2 diabetes mellitus	Aaboe K.;Knop F. K.;Vilsboll T.;Deacon C. F.;Holst J. J.;Madsbad S., et al.	2010	Diabetes, Obesity & Metabolism	Time of assessment
DURATION-1: Exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks	Buse J. B.;Drucker D. J.;Taylor K. L.;Kim T.;Walsh B.;Hu H., et al.	2010	Diabetes Care	Partially published
Pioglitazone use in combination with insulin in the prospective pioglitazone clinical trial in macrovascular events study (PROactive19)	Charbonnel B.;DeFronzo R.;Davidson J.;Schmitz O.;Birkeland K.;Pirags V., et al.	2010	Journal of Clinical Endocrinology and Metabolism	Post-hoc analysis / secondary publication
Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial	Diamant M.;van Gaal L.;Stranks S.;Northrup J.;Cao D.;Taylor K., et al.	2010	The Lancet	Mixed background
A randomized, treat-to-target trial comparing insulin lispro protamine suspension and insulin detemir in insulin-naive patients with Type 2 diabetes	Fogelfeld L.;Dharmalingam M.;Robling K.;Jones C.;Swanson D.;Jacober S.	2010	Diabetic Medicine	Mixed background
Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled Type 2 diabetes	Forst T.;Uhlig-Laske B.;Ring A.;Graefe-Mody U.;Friedrich C.;Herbach K., et al.	2010	Diabetic medicine : a journal of the British Diabetic Association	Time of assessment
Pioglitazone in addition to metformin improves erythrocyte deformability in patients with Type 2 diabetes mellitus	Forst T.;Weber M. M.;Lobig M.;Lehmann U.;Muller J.;Hohberg C., et al.	2010	Clinical Science	Post-hoc analysis / secondary publication

Title	Authors	Year	Journal	Reason for exclusion
Adding liraglutide to oral antidiabetic drug therapy: onset of treatment effects over time of assessment	Gallwitz B.;Vaag A.;Falahati A.;Madsbad S.	2010	International Journal of Clinical Practice	Post-hoc analysis / secondary publication
Effect of exenatide on heart rate and blood pressure in subjects with type 2 diabetes mellitus: a double-blind, placebo-controlled, randomized pilot study	Gill A.;Hoogwerf B. J.;Burger J.;Bruce S.;Macconell L.;Yan P., et al.	2010	Cardiovascular Diabetology	Mixed background
Patient-reported outcomes in patients with type 2 diabetes treated with liraglutide or glimepiride, both as add-on to metformin	Hermansen K.;Kolotkin R. L.;Hammer M.;Zdravkovic M.;Matthews D.	2010		Post-hoc analysis / secondary publication
Improved glycaemic control with minimal hypoglycaemia and no weight change with the once-daily human glucagon-like peptide-1 analogue liraglutide as add-on to sulphonylurea in Japanese patients with type 2 diabetes	Kaku K.;Rasmussen M. F.;Clauson P.;Seino Y.	2010	Diabetes, Obesity & Metabolism	Mixed background
Effects of insulin initiation on patient-reported outcomes in patients with type 2 diabetes: results from the durable trial	Lee L. J.;Fahrbach J. L.;Nelson L. M.;McLeod L. D.;Martin S. A.;Sun P., et al.	2010	Diabetes Research & Clinical Practice	Mixed background
Effects of vildagliptin on glucose control in patients with type 2 diabetes inadequately controlled with a sulphonylurea	Garber A. J.;Foley J. E.;Banerji M. A.;Ebeling P.;Gudbjornsdottir S.;Camisasca R. P., et al.	2008	Diabetes, Obesity and Metabolism	Mixed background
Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study	Matthews D. R.;Dejager S.;Ahren B.;Fonseca V.;Ferrannini E.;Couturier A., et al.	2010		Time of assessment
Effects of intensive insulin therapy alone and with added pioglitazone on renal salt/water balance and fluid compartment shifts in type 2 diabetes	Mudaliar S.;Chang A. R.;Aroda V. R.;Chao E.;Burke P.;Baxi S., et al.	2010	Diabetes, Obesity & Metabolism	Time of assessment
Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study	Seck T.;Nauck M.;Sheng D.;Sunga S.;Davies M. J.;Stein P. P., et al.	2010		Time of assessment
Addition of insulin lispro protamine suspension or insulin glargine to oral type 2 diabetes regimens: a randomized trial	Strojek K.;Shi C.;Carey M. A.;Jacober S. J.	2010	Diabetes, Obesity & Metabolism	Mixed background
Triple oral fixed-dose diabetes polypill versus insulin plus metformin efficacy demonstration study in the treatment of advanced type 2 diabetes (TrIED study-II)	Bell D. S.;Dharmalingam M.;Kumar S.;Sawakhande R. B.	2011		Time of assessment
Weight-related quality of life, health utility, psychological well-being, and satisfaction with exenatide once weekly compared with sitagliptin or pioglitazone after 26 weeks of treatment	Best J. H.;Rubin R. R.;Peyrot M.;Li Y.;Yan P.;Malloy J., et al.	2011	Diabetes Care	Post-hoc analysis / secondary publication
DURATION-5: Exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes	Blevins T.;Pullman J.;Malloy J.;Yan P.;Taylor K.;Schulteis C., et al.	2011	Journal of Clinical Endocrinology	Mixed background

Title	Authors	Year	Journal	Reason for exclusion
			and Metabolism	
Safety and efficacy of saxagliptin in combination with submaximal sulphonylurea versus up-titrated sulphonylurea over 76 weeks	Chacra A. R.;Tan G. H.;Ravichandran S.;List J.;Chen R.;Investigators C. V.	2011	Diabetes & Vascular Disease Research	Time of assessment
Liraglutide improves treatment satisfaction in people with Type 2 diabetes compared with sitagliptin, each as an add on to metformin	Davies M.;Pratley R.;Hammer M.;Thomsen A. B.;Cuddihy R.	2011		Post-hoc analysis / secondary publication
Insulin glargine compared to NPH among insulin-naive, U.S. inner city, ethnic minority type 2 diabetic patients	Hsia S. H.	2011	Diabetes Research & Clinical Practice	Mixed background
Improved glycemic control and reduced bodyweight with exenatide: A double-blind, randomized, phase 3 study in Japanese patients with suboptimally controlled type 2 diabetes over 24 weeks	Kadowaki T.;Namba M.;Imaoka T.;Yamamura A.;Goto W.;Boardman M. K., et al.	2011	Journal of Diabetes Investigation	Mixed background
Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: A prospective 24-week randomized placebo-controlled trial	Lukashevich V.;Schweizer A.;Shao Q.;Groop P. H.;Kothny W.	2011	Diabetes, Obesity and Metabolism	Mixed background
Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment	Newman J.;McGill J. B.;Patel S.;Friedrich C.;Sauce C.;Woerle H. J.	2011		Post-hoc analysis / secondary publication
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	Nowicki M.;Rychlik I.;Haller H.;Warren M.;Suchower L.;Gause-Nilsson I., et al.	2011	International Journal of Clinical Practice	Mixed background
Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment	Nowicki M.;Rychlik I.;Haller H.;Warren M. L.;Suchower L.;Gause-Nilsson I., et al.	2011	Diabetes, Obesity & Metabolism	Mixed background
Addition of sitagliptin to ongoing glimepiride therapy in Japanese patients with type 2 diabetes over 52 weeks leads to improved glycemic control	Tajima N.;Kadowaki T.;Odawara M.;Nishii M.;Taniguchi T.;Ferreira J. C. A.	2011	Diabetology International	Time of assessment
Efficacy of pioglitazone on glycemic control and carotid intima-media thickness in type 2 diabetes patients with inadequate insulin therapy	Yasunari E.;Takeno K.;Funayama H.;Tomioka S.;Tamaki M.;Fujitani Y., et al.	2011	Journal of Diabetes Investigation	Time of assessment
Vildagliptin action on some adipocytokine levels in type 2 diabetic patients: A 12-month, placebo-controlled study	Derosa G.;Ragonesi P. D.;Carbone A.;Fogari E.;D'Angelo A.;Cicero A. F., et al.	2012	Expert Opinion on Pharmacotherapy	Post-hoc analysis / secondary publication
Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target	Diamant M.;van Gaal L.;Stranks	2012	Diabetes Care	Mixed background

Title	Authors	Year	Journal	Reason for exclusion
in patients with type 2 diabetes over 84 weeks	S.;Guerci B.;MacConell L.;Haber H., et al.			
Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial	Gallwitz B.;Guzman J.;Dotta F.;Guerci B.;Simó R.;Basson B. R., et al.	2012		Time of assessment
2-year effi cacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: A randomised, double-blind, non-inferiority trial	Gallwitz B.;Rosenstock J.;Rauch T.;Bhattacharya S.;Patel S.;von Eynatten M., et al.	2012	The Lancet	Time of assessment
Efficacy and Safety Profile of Exenatide Once Weekly Compared With Insulin Once Daily in Japanese Patients With Type 2 Diabetes Treated With Oral Antidiabetes Drug(s): Results From a 26-Week, Randomized, Open-Label, Parallel-Group, Multicenter, Noninferiority Study	Inagaki N.;Atsumi Y.;Oura T.;Saito H.;Imaoka T.	2012	Clinical Therapeutics	Mixed background
The effect of sitagliptin versus glibenclamide on arterial stiffness, blood pressure, lipids, and inflammation in type 2 diabetes mellitus patients	Koren S.;Shemesh-Bar L.;Tirosh A.;Peleg R. K.;Berman S.;Hamad R. A., et al.	2012	Diabetes Technology and Therapeutics	Time of assessment
One-year safety, tolerability and efficacy of vildagliptin in patients with type 2 diabetes and moderate or severe renal impairment	Kothny W.;Shao Q.;Groop P. H.;Lukashevich V.	2012	Diabetes, Obesity and Metabolism	Mixed background
Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin	Ljunggren O.;Bolinder J.;Johansson L.;Wilding J.;Langkilde A. M.;Sjostrom C. D., et al.	2012	Diabetes, Obesity and Metabolism	Time of assessment
Effect of canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, on bacteriuria and urinary tract infection in subjects with type 2 diabetes enrolled in a 12-week, phase 2 study	Nicolle L. E.;Capuano G.;Ways K.;Usiskin K.	2012	Current Medical Research and Opinion	Time of assessment
Reduction of oxidative stress and inflammation by blunting daily acute glucose fluctuations in patients with type 2 diabetes: Role of dipeptidyl peptidase-IV inhibition	Rizzo M. R.;Barbieri M.;Marfella R.;Paolisso G.	2012	Diabetes Care	Time of assessment
Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes	Rosenstock J.;Aggarwal N.;Polidori D.;Zhao Y.;Arbit D.;Usiskin K., et al.	2012	Diabetes Care	Time of assessment
Baseline factors associated with glycemic control and weight loss when exenatide twice daily is added to optimized insulin glargine in patients with type 2 diabetes	Rosenstock J.;Shenouda S. K.;Bergenstal R. M.;Buse J. B.;Glass L. C.;Heilmann C. R., et al.	2012	Diabetes Care	Post-hoc analysis / secondary publication
Efficacy and safety of linagliptin 2.5mg twice daily versus 5mg once daily in patients with type 2 diabetes inadequately controlled on metformin: A randomised, double-blind, placebo-controlled trial	Ross S. A.;Rafeiro E.;Meinicke T.;Toorawa R.;Weber-Born S.;Woerle H. J.	2012	Current Medical Research and Opinion	Time of assessment
Comparing the efficacy and safety profile of sitagliptin versus glimepiride in patients of type 2 diabetes mellitus inadequately controlled with metformin alone	Srivastava S.;Saxena G. N.;Keshwani P.;Gupta R.	2012	Journal of the Association of Physicians of India	Time of assessment

Title	Authors	Year	Journal	Reason for exclusion
Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): A randomised, open-label study	Buse J. B.;Nauck M.;Forst T.;Sheu W. H. H.;Shenouda S. K.;Heilmann C. R., et al.	2013	The Lancet	Mixed background
Efficacy of vildagliptin in combination with insulin in patients with type 2 diabetes and severe renal impairment	Lukashevich V.;Schweizer A.;Foley J. E.;Dickinson S.;Groop P. H.;Kothny W.	2013	Vascular Health and Risk Management	Post-hoc analysis / secondary publication
The effect of hydrochloride pioglitazone on urinary 8-hydroxy -deoxyguanosine excretion in type 2 diabetics	Wang Y.;Ye S.;Hu Y.;Zhao L.;Zheng M.	2013	Journal of Diabetes and its Complications	Time of assessment
Combined therapy with insulin lispro Mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy.[Erratum appears in Clin Ther. 2005 Jul;27(7):1112]	Malone J. K.;Kerr L. F.;Campaigne B. N.;Sachson R. A.;Holcombe J. H.;Lispro Mixture-Glargine Study Group	2004	Clinical Therapeutics	Time of assessment
Combined glyburide and insulin therapy in type II diabetes	Reich A.;Abraira C.;Lawrence A. M.	1987	Diabetes research (Edinburgh, Scotland)	Partially published
Sustained efficacy and reduced hypoglycemia during one year of treatment with vildagliptin added to insulin in patients with type 2 diabetes mellitus	Fonseca V.;Baron M.;Shao Q.;Dejager S.	2008	Hormone and metabolic research = Hormon- und Stoffwechselfors chung = Hormones et métabolisme	Time of assessment
A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week, Multicenter Study With a 26-Week Extension, to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus Who Have Moderate Renal Impairment 26-Week Core Double-Blind Period	Janssen		Study report	Mixed background
A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus	Janssen		Study report	Mixed background
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared With Placebo in the Treatment of Older Subjects With Type 2 Diabetes Mellitus Inadequately Controlled on Glucose Lowering Therapy	Janssen		Study report	Mixed background
A Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Versus Sitagliptin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sulphonylurea	Janssen		Study report	Time of assessment

Title	Authors	Year	Journal	Reason for exclusion
Therapy				
Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial	C. J. Bailey, J. L. Gross, D. Hennicken, N. Iqbal, T. A. Mansfield and J. F. List	2013	BMC Medicine	Time of assessment
Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas	M. Davies, S. Heller, S. Sreenan, H. Sapin, O. Adetunji, A. Tahbaz and J. Vora	2013	Diabetes Care	Mixed background
Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial	B. Goke, B. Gallwitz, J. G. Eriksson, A. Hellqvist and I. Gause-Nilsson	2013	International Journal of Clinical Practice	Time of assessment
Linagliptin provides effective, well-tolerated add-on therapy to pre-existing oral antidiabetic therapy over 1year in Japanese patients with type 2 diabetes	N. Inagaki, H. Watada, M. Murai, T. Kagimura, Y. Gong, S. Patel and H. J. Woerle	2013	Diabetes, Obesity & Metabolism	Mixed background
Safety and efficacy of twice-daily exenatide in Taiwanese patients with inadequately controlled type 2 diabetes mellitus	C. H. Lu, T. J. Wu, K. C. Shih, E. Ni, V. Reed, M. Yu, W. H. Sheu and L. M. Chuang	2013	Journal of the Formosan Medical Association	Mixed background
Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study	M. Nauck, A. Frid, K. Hermansen, A. B. Thomsen, M. During, N. Shah, T. Tankova, I. Mitha and D. R. Matthews	2013	Diabetes, Obesity & Metabolism	Time of assessment
Comparative study of sitagliptin with pioglitazone in Japanese type 2 diabetic patients: the COMPASS randomized controlled trial	M. Takihata, A. Nakamura, K. Tajima, T. Inazumi, Y. Komatsu, H. Tamura, S. Yamazaki, Y. Kondo, M. Yamada, M. Kimura and Y. Terauchi	2013	Diabetes, Obesity & Metabolism	Mixed background
Addition of sitagliptin to ongoing metformin monotherapy improves glycemic control in Japanese patients with type 2 diabetes over 52weeks	T. Kadowaki, N. Tajima, M. Odawara, M. Nishii, T. Taniguchi and J. C. A. Ferreira	2013	Journal of Diabetes Investigation	Time of assessment
Efficacy and safety of exenatide once-weekly vs exenatide twice-daily in Asian patients with type 2 diabetes mellitus	L. Ji, Y. Onishi, C. W. Ahn, P. Agarwal, C. W. Chou, H. Haber, K. Guerrettaz and M. K. Boardman	2013	Journal of Diabetes Investigation	Mixed background
Safety of exenatide once weekly for 52weeks in Japanese patients with type 2 diabetes mellitus	Y. Onishi, H. Koshiyama, T. Imaoka, H. Haber, J. Scism-Bacon and M. K. Boardman	2013	Journal of Diabetes Investigation	Mixed background
Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: a randomised controlled trial.[Erratum appears in Int J Clin Pract. 2010 Jan;64(2):277]	Chacra A. R.;Tan G. H.;Apanovitch A.;Ravichandran S.;List J.;Chen R., et al.	2009	International Journal of Clinical Practice	Mixed background
Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control	Kipnes M. S.;Krosnick A.;Rendell M.	2001	American	Mixed background

Title	Authors	Year	Journal	Reason for exclusion
in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study	S.;Egan J. W.;Mathisen A. L.;Schneider R. L.		Journal of Medicine	
Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes	Buse J. B.;Henry R. R.;Han J.;Kim D. D.;Fineman M. S.;Baron A. D.	2004	Diabetes Care	Mixed background
The effect of pioglitazone on the liver: Role of adiponectin	Gastaldelli A.;Miyazaki Y.;Mahankali A.;Berria R.;Pettiti M.;Buzzigoli E., et al.	2006	Diabetes Care	Mixed background

Table 5. List of studies included in sensitivity analyses but not selected for the narrative review

Title	Authors	Year	Journal	Reason for exclusion from the narrative review*
Vildagliptin efficacy and safety in patients with type 2 diabetes inadequately controlled on dual *metformin* plus *sulfonylurea* therapy	Lukashevich V.;Wang M.;Del Prato S.;Araga M.;Kothny W.	2012	Conference: 48th Annual Meeting of the European Association for the Study of Diabetes, EASD 2012 Berlin Germany.	Results published as a conference abstract only
Sitagliptin more effectively improved left ventricular diastolic function compared with bedtime nph insulin as third-line agent in t2dm patients	Nogueira K. C.;Fukui R.;Rocha D. M.;Correia M. R.;Santos R. F.;Furtado M., et al.	2012	Conference: 72nd Scientific Sessions of the American Diabetes Association Philadelphia, PA United States.	Results published as a conference abstract only
Efficacy and safety of *linagliptin* as add-on therapy to basal *insulin* in patients with type 2 diabetes	Yki-Jarvinen H.;Duran-Garcia S.;Pinnetti S.;Bhattacharya S.;Thiemann S.;Patel S., et al.	2012	Conference: 72nd Scientific Sessions of the American Diabetes Association Philadelphia, PA United States.	Results published as a conference abstract only
Long-term safety and efficacy of *linagliptin* as add-on therapy to basal *insulin* in patients with type 2 diabetes: A 52-week randomised, *placebo*controlled trial	Yki-Jarvinen H.;Rosenstock J.;Duran-Garcia S.;Pinnetti S.;Bhattacharya S.;Thiemann S., et al.	2012	Conference: 48th Annual Meeting of the European Association for the Study of Diabetes, EASD 2012 Berlin Germany.	Results published as a conference abstract only
Exenatide vs. *insulin* aspart in patients with type 2 diabetes: Results of a randomised, open-label study	B. Gallwitz, M. Bohmer, T. Segiet, A. Molle, K. Milek, B. Becker, K. Helsberg, H. Petto, N. Peters and O. Bachmann	2010	Conference: 46th Annual Meeting of the European Association for the Study of Diabetes, EASD 2010 Stockholm Sweden.	Results published as a conference abstract only
A placebo-controlled trial of exenatide twice-daily added to thiazolidinediones alone or in combination with metformin	Liutkus J.;Rosas Guzman J.;Norwood P.;Pop L.;Northrup J.;Cao D., et al.	2010	Diabetes, Obesity and Metabolism	Mixed background (met +/- TZD)

* These studies were included in sensitivity analyses only