NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Dapagliflozin for the treatment of type 2 diabetes

Submitted by

Bristol-Myers Squibb

and AstraZeneca

Single technology appraisal (STA)

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Abbreviations

ACC	American College of Cardiology
ACE-I	Angiotensin converting enzyme inhibitor
ADA	American Diabetes Association
ADDQoL	Audit of Diabetes-Dependent Quality of Life
AE	Adverse event
AHA	American Heart Association
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
AZ	AstraZeneca
BMI	Body Mass Index
BMS	Bristol-Myers Squibb
CEA	Cost effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CG	Clinical Guideline
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CrCl	Creatinine clearance
CSR	Clinical Study Report
CV	Cardiovascular
DBP	Diastolic blood pressure
DES	Discrete event simulation
DEXA	Dual-Energy X-ray Absorptiometry
DPP-4	Dipeptidyl peptidase-4
DTSQ	Diabetes treatment satisfaction questionnaire
DVLA	Driver and Vehicle Licensing Agency
EASD	European Association for the Study of Diabetes
EC	European Commission
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQOL-5D
ESRD	End-stage renal disease
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GFR	Glomerular filtration rate
GI	Genital Infection
GLP-1	Glucagon-like peptide-1
HbA1c	Glycosylated haemoglobin
HDL	High density lipoprotein
HFS-II	Hypoglycaemia Fear Survey

HR	Hazard ratio
HRQoL	Health-related quality of life
HRU	Health-related utility
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
INS	Insulin
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to treat
IU	International unit
IVRS	Interactive voice recognition service
LDL	Low density lipoprotein
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MET	Metformin
MI	Myocardial infarction
mITT	Modified intention to treat
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIDDM	Non-insulin dependent diabetes mellitus
NMA	Network meta-analysis
NR	Not reported
OAD	Oral antidiabetic drug
OR	Odds ratio
PPG	Post-prandial plasma glucose
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY(s)	Quality-adjusted life year(s)
QD	Once daily
QOF	Quality and Outcomes Framework
RCT(s)	Randomised controlled trial(s)
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT2	Sodium glucose co-transporter 2
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TDDI	Total daily dose of insulin
TZD	Thiazolidinedione

UK	United Kingdom
UKPDS	UK Prospective Diabetes Study
US	United States of America
UTI(s)	Urinary tract infection(s)
wk	weeks
WTP	Willingness-to-pay
XR	Extended release

Executive summary

Burden of Diabetes

Diabetes is a significant health issue; in 2009-10 there were an estimated 3.1 million adults with diabetes in England (NAO, 2012). Diabetes occurs when blood glucose, which can be measured by HbA1c, is not controlled. Lowering HbA1c reduces the risk of complications such as nephropathy, retinopathy, heart attacks and strokes.

Around 90% of people with diabetes have type 2 diabetes (T2DM). There are a number of existing treatment options for T2DM patients and clinical guidelines (NICE CG87) recommend a step-wise approach to treatment, as the disease is progressive over time: start with diet modifications and exercise; progress to monotherapy; then to dual-therapy; then to treatment with insulin.

Unfortunately current therapies have some inherent shortcomings, such as causing weight gain and hypoglycaemia (too low a level of blood sugar). In addition, despite a wide variety of treatment options, a considerable number of people with T2DM continue to fail to meet treatment targets, with over one-third of patients failing to reach an appropriate HbA1c target. Additionally, around half of patients with type 2 diabetes failed to reach NICE recommended blood pressure targets and over three quarters were overweight or obese (National Diabetes Audit 2009-10). These additional cardiovascular (CV) risk factors increase the risk of mortality. A recent National Audit Office report estimates that up to 24,000 people die each year from avoidable causes related to their diabetes (NAO, 2012).

Technology – dapagliflozin 10mg once daily (FORXIGA®)

Dapagliflozin 10mg once daily is the first in a novel class of insulin independent, glucose-lowering medications, the selective sodium-glucose cotransporter 2 (SGLT2 inhibitors). Dapagliflozin is available as a 28-day pack of tablets which can be taken once a day at any time of the day, with or without food.

We consider dapagliflozin to be a highly innovative agent in the treatment of type 2 diabetes for the following reasons:

- Dapagliflozin is a first in a novel class agent. Unlike other therapies it actively removes glucose via the kidney. In contrast, other anti-diabetic agents do not eliminate glucose from the body but promote the uptake of glucose from the circulation by increasing insulin production or by enhancing the body's sensitivity to insulin

- The action of dapagliflozin is insulin independent, meaning it does not rely on underlying beta-cell function to exert its effect. In diabetes, beta-cell function wanes over time and therefore exogenous insulin (insulin injections) is/are eventually required.
- This means that dapagliflozin maintains its efficacy well beyond the initial 6 months investigated in the trials. Data at 2 years will be presented in this

submission for 3 pivotal studies at various stages of the disease (added to metformin, vs placebo and SU comparator, and added to insulin)

- Dapagliflozin can be added to insulin and exerts a clinically meaningful insulin sparing effect while reducing HbA1c and weight.
- Dapagliflozin is associated with weight loss, as a result of the calorie loss induced by glucosuria (glucose excretion), approximately equivalent to 1 hour's brisk walk a day. Other oral agents are often associated with weight gain (thiazolidinedione [TZD] or sulphonylurea [SU]) or are weight neutral (dipeptidyl peptidase-4 [DPP-4] inhibitors)

Dapagliflozin is also associated with moderate blood pressure reductions.

Licence and launch particulars

Dapagliflozin received a positive Committee for Medicinal Products for Human Use (CHMP) opinion on 20 April 2012 for the following indication:

Forxiga is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add on combination therapy

In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

The anticipated launch date of dapagliflozin in the UK is October 2012. The price of dapagliflozin 10mg once daily is £1.31 per day. The price for a 28 day pack of dapagliflozin 10mg tablets is £36.59.

Place in therapy and comparators

In line with the licensed indication and the recommended treatment pathway (NICE CG87), dapagliflozin 10mg once daily can be used in combination with other oral therapies commonly used for the treatment of T2DM. Dapagliflozin could fit into the existing treatment pathway as follows:

1. As a second-line option (dual therapy, add-on to metformin), dapagliflozin can be added to metformin as an alternative treatment option to sulphonylurea, in patients whom sulphonylurea is not appropriate because of the risk of hypoglycaemia, or in whom weight loss is a treatment goal.

2. As a third-line option (add-on to insulin), dapagliflozin can also be added to insulin with or without metformin in those patients who are not adequately controlled on insulin and in whom increasing doses of insulin would result in an increased risk of hypoglycaemia and/or weight gain caused by insulin.

Clinical Evidence

The robust study design and long duration of blinded data collection in the clinical trial programme for dapagliflozin provide a strong evidence base to support its use in the NHS. The trial programme is one of the largest carried out to date, with 32 Phase 2/3 clinical studies completed or ongoing. The entire Phase 3 programme was conducted globally, with 42% of patients coming from European countries. In the Phase 2b and Phase 3 clinical trial programme 4,287 patients were exposed to dapagliflozin and 1,941 to control – a total of 4,009 and 1,682 patient-years, respectively.

Eleven phase 3 double-blind, randomised, controlled clinical trials (which were filed as part of the submission to the European Medicines Agency (EMA) evaluated the efficacy and safety of dapagliflozin in 5,693 patients with T2DM, of whom 3,939 received dapagliflozin. Ten studies had a treatment period of 24 weeks duration, and 5 of these studies had long term extension periods ranging from 24 to 78 weeks (up to a total study duration of 102 weeks). One study had a duration of 52 weeks.

Overview of clinical trial results

<u>Efficacy</u>

- Dapagliflozin resulted in significant and clinically meaningful reductions in HbA1c which are maintained at 2 years.
  - Dapagliflozin 10mg was shown to be superior to placebo and non-inferior to SU (glipizide) with respect to HbA1c reduction.
- Dapagliflozin resulted in significant weight loss when added to metformin. In patients receiving SU or insulin (where weight gain would be expected in both) the addition of dapagliflozin similarly resulted in weight loss. These results were maintained at 2 years.
- Dapagliflozin has the additional benefit of a blood pressure lowering effect.
- Dapagliflozin has a low propensity to cause hypoglycaemia.
  - In a head-to-head study with SU, there were 10 times less hypoglycaemic events with dapagliflozin.
  - When added to insulin, dapagliflozin did not significantly increase the rate of hypoglycaemia.
- Dapagliflozin did not increase mean total daily insulin dose, while insulin requirements increased progressively in the placebo group. Along with the advantages of better glycaemic control and weight loss, dapagliflozin's insulin sparing effect resulted in a 25% difference in daily insulin requirements at 2 years.

Safety

- The adverse events associated with dapagliflozin are consistent with its mechanism of action which causes glucosuria (glucose in the urine) and a mild osmotic diuresis (loss of fluid). Dapagliflozin is associated with a higher incidence of genital tract infections compared to placebo, however infections were mild to moderate and rarely resulted in discontinuation.

- Glucose excretion induced by dapagliflozin is proportional to circulating glucose levels. When glucose levels are lower, glucose excretion is also lower – meaning that dapagliflozin has a low propensity to cause hypoglycaemia.

- In a meta-analysis of 14 phase IIb/phase III clinical trials involving over 6,000 patients where CV events were prospectively and blindly adjudicated by an independent committee dapagliflozin was not associated with an increased risk of cardiovascular events (significant HR 0.67 [95% CI 0.32, 1.10] for a composite of CV death, myocardial infarction [MI] and stroke) (Langkilde et al 2011)

- The overall rates of all malignancies or unspecified tumours were similar between placebo/comparator and dapagliflozin groups. This supports the contention that, based on its mechanism of action and the results of pre-clinical studies, there are no obvious pathways by which dapagliflozin would cause an increase in cancer risk.

Economic Evidence

A cost utility analysis was performed using the same economic model for both the dapagliflozin as an add-on to metformin, and dapagliflozin as an add-on to insulin assessments. The perspective adopted was that of the NHS and Personal Social Services in England and Wales. As is appropriate for a chronic disease and standard in diabetes models a lifetime horizon was adopted consisting of a base case of 40 years.

The model used is a previously developed and validated simulation model run with an MS Excel™ front-end. The model has previously been used in submissions to the Institute and is similar to other established diabetes models. In addition, the model was also subject to extensive validation.

Dual therapy

For patients whose T2DM is not well controlled with metformin alone, cost effectiveness assessments are presented for the combination of dapagliflozin and metformin, compared to:

- sulphonylureas (with metformin)
- TZD (with metformin)

- DPP-4 inhibitors (with metformin)

Add-on to insulin

For patients whose type 2 diabetes is not well controlled with insulin (with or without other oral antidiabetic agents), cost effectiveness assessments are presented for the combination of dapagliflozin and insulin, compared to:

- DPP-4 inhibitors (with insulin)

A range of one-way sensitivity analyses are presented as well as probabilistic sensitivity analysis. In addition, a range of alternative scenario analyses are presented. The base case results for the four comparisons are presented in Table 1 (and in Table 85).

The cost/quality-adjusted life year (QALY) of dapagliflozin and metformin, compared to SU (with metformin) is £2,689. For the comparisons between TZD (with metformin) and DPP-4 inhibitors (with metformin), dapagliflozin (with metformin) dominates, offering improved clinical outcomes at lower cost. The cost/QALY of dapagliflozin and insulin, compared to DPP-4 inhibitors (with insulin) is £4,268. A range of sensitivity and scenarios analyses was also performed. In these analyses, dapagliflozin remained cost effective at conventional thresholds for decision making.

Table 1. Base-case cost-effectiveness results of dapagliflozin 10mg once daily compared to comparator treatments

	Technologies	Incremental			ICER (£)
		Costs (£)	LYG	QALYs	incremental
Add on to metformin	**SU**	-	-	-	-
	dapagliflozin	£ 1,335	0.057	0.496	£ 2,689
	dapagliflozin	– £143	0.029	0.018	Dominant
	DPP-4	-	-	-	
	dapagliflozin	– £ 80	-0.001	0.401	Dominant
	TZD	-	-	-	
Add on to Insulin	**DPP-4**	-	-	-	
	dapagliflozin	£ 538	0.008	0.126	£ 4,268

Abbreviations: DPP-4, dipeptidyl peptidase 4 inhibitor; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; QALYs, Quality-adjusted life years; SU, sulphonylurea; TZD, thiazolidinedione.

Conclusion

- The burden of T2DM remains significant with an estimated £3.9bn spent on diabetes by the NHS in 2009-10 (NAO, 2012).
- While there are numerous treatment options available to T2DM patients, there are also significant unmet clinical needs due to the progressive nature of the disease and the shortcomings of existing therapies.
- Dapagliflozin is the first of a new class of drugs, the SGLT2 inhibitors, which provide a new alternative to existing therapeutic options:
  - Adding dapagliflozin to current treatments provides complementary and sustained HbA1c control
  - In addition, dapagliflozin provides weight loss and blood pressure lowering
  - Furthermore, dapagliflozin has a low propensity to cause hypoglycaemia
  - Dapagliflozin helps treat the diabetic patient as a whole, not just the HbA1c - in line with national standards.
- Dapagliflozin's insulin independent mode-of-action means it is a flexible treatment option for a range of different clinical scenarios in patients whose T2DM is not well-controlled.
- The data presented in this submission confirm that dapagliflozin is a clinically effective and cost effective alternative to existing therapies, either as an add-on therapy to patients not currently controlled on metformin (dual-therapy), or as an add-on to insulin (with or without up to two oral therapies).
- Dapagliflozin is convenient for patients because it is a once-a-day oral medicine that can be taken at any time of the day, with or without food.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Forxiga®; Approved name: dapagliflozin;

Pharmacotherapeutic group: Drugs used in diabetes, Other blood glucose lowering drugs, excluding insulins

ATC code: A10BX09

1.2 What is the principal mechanism of action of the technology?

Dapagliflozin is a novel, first in class drug with an insulin independent mechanism of action which is different and complementary to other anti-diabetic medications. It is a highly potent, selective and reversible inhibitor of the sodium glucose co-transporter 2 (SGLT2). The SGLT2 is selectively expressed in the kidney and is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Despite the presence of an excess of sugar in the blood (hyperglycaemia) in type 2 diabetes, reabsorption of filtered glucose continues. Dapagliflozin improves glycaemic control in patients with T2DM by reducing glucose reabsorption in the kidneys and leading to urinary glucose excretion (glucuresis) and therefore potential weight loss due to excretion of associated calories.

Such glucose excretion is observed after the first dose of dapagliflozin, is continuous over the 24-hour dosing interval, and is sustained for the duration of dapagliflozin treatment. The amount of glucose excreted via the kidney through this mechanism is not only dependent upon the blood glucose concentration but also the kidney's glomerular filtration rate (GFR). Dapagliflozin improves both fasting and post-prandial plasma glucose levels.

In healthy patients, with normal blood glucose concentration, dapagliflozin has a low propensity to cause an abnormal decrease in blood sugar (hypoglycaemia); furthermore, dapagliflozin does not impair normal body glucose production in response to hypoglycaemia. Because dapagliflozin acts independently of insulin secretion and insulin action, it may be used at any stage of type 2 diabetes. Finally, dapagliflozin causes mild increased excretion of urine (diuresis) and as a consequence it is associated with modest reductions in blood pressure.

Interestingly, most oral antidiabetic therapies rely on insulin-secreting cells (β-cell) function for their activity, but because T2DM is characterised by a steady decline in pancreatic β-cell function, the effectiveness of these anti-diabetic agents diminishes over time. In contrast, dapagliflozin does not rely on β-cell function. Furthermore, improvement in the homeostasis model assessment for beta cell (HOMA beta-cell) has been observed in clinical studies with dapagliflozin.

Importantly, the urinary glucose excretion induced by dapagliflozin is associated with calorie loss and associated reduction in body weight. The majority of the weight reduction has been observed to be loss of body fat, including visceral fat rather than lean tissue or fluid loss, as demonstrated by dual X-ray absorptiometry and magnetic resonance imaging.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The application was submitted in December 2010 and the expected approval date is approximately Aug/Sept 2012 following positive CHMP opinion on 19/04/2012.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

The EPAR and final version of the SPC are not available yet and these will be available upon regulatory approval.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

It is anticipated that dapagliflozin will be indicated in adults aged 18 years and older with T2DM to improve glycaemic control as:

<u>Monotherapy</u>

When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

<u>Add-on combination therapy</u>

In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Table 2 summarises all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months.

Please find in Table 111 to Table 131 in Section 9.16 more detailed information on each study.

Table 2. Summary of completed and ongoing studies from which additional evidence is likely to be available in the next 12 months

Study number/ Duration	Subject population	Treatment groups N per group/N treated with dapagliflozin (Dapa)/Total
Phase 2		
MB102008 12 weeks Phase 2	Drug-naïve subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, 10, 20, and 50mg, placebo and metformin extended release (XR) 750/1500 mg 47-59/279/389
MB102009 12 weeks Phase 2	Insulin-dependent subjects with HbA1c ≥7.5% and ≤10.0%	Dapa 10 or 20mg and placebo 23-24/48/71
D1692C00005 12 weeks Phase 2	Japanese subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 1, 2.5, 5, and 10mg and placebo 54-59/225/279
Phase 3		
Add on to metformin		
D1690C00004 52 plus 156 weeks Phase 3	Subjects on metformin >1500mg/day with HbA1c >6.5% and ≤10.0% Non-inferiority vs glipizide	Dapa titrated to 2.5, 5, and 10mg and glipizide titrated to 5, 10, and 20mg 406-408/406/814
D1690C00012 24 plus 78 weeks Phase 3	Subjects on metformin ≥1500 mg/day with HbA1c ≥6.5% and ≤8.5%	Dapa 10mg and placebo 91/91/182
MB102014 24 plus 78 weeks Phase 3 Add-on to metformin	Subjects on metformin ≥1500mg/day with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, and 10mg and placebo 135-137/409/546
Third-line oral add on		
D1690C00010 24 plus 24 weeks Phase 3	Subjects on sitagliptin (with or without metformin) with HbA1c	Dapa 10mg + sitagliptin 100mg QD ± metformin ≥1500mg 226/225/451
Add on to insulin		
D1690C00006 24 plus 24 plus 56 weeks Phase 3	Subjects on insulin ≥30 IU/day ± maximum 2 OAD with HbA1c ≥7.5% and ≤10.5%	Dapa 2.5, 5, and 10mg and placebo 196-212/610/807
Other		
D1690C00005 24 plus 24 weeks Phase 3	Subjects on SU with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, and 10 mg and placebo 146-154/450/596

Study number/ Duration	Subject population	Treatment groups N per group/N treated with dapagliflozin (Dapa)/Total
MB102013 24 plus 78 weeks Phase 3 Monotherapy	Drug-naïve subjects with HbA1c ≥7.0% and ≤10.0% Open treatment group with HbA1c ≥10.1% and ≤12.0%	Dapa 2.5, 5, and 10mg and placebo 64-76/410/485 Dapa 5, 10mg 34-39/73/73
MB102021 24 weeks Phase 3 Initial combination with metformin	Treatment- naïve subjects with HbA1c ≥7.5% and ≤12.0%	Dapa 5mg + metformin XR up to 2000mg, dapa 5mg, and metformin XR up to 2000mg 194-203/397/598
MB102030 24 plus 24 weeks Phase 3	Subjects on pioglitazone with HbA1c ≥7.0% and ≤10.5%	Dapa 5, and 10mg and placebo 139-141/281/420
MB102032 24 weeks Phase 3 Add-on combination therapy with TZD	Drug-naive subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 1, 2.5, and 5mg and placebo 68-74/214/282
MB102029 24 plus 28 plus 52 weeks Phase 3	Subjects with moderate renal impairment (GFR >30 to <60 mL/min/1.73m^2 on a stable anti-diabetic regimen with HbA1c ≥7% and ≤11%	Dapa 5 and 10mg and placebo 83-85/168/252
D1690C00018 24 plus 28 weeks Phase 3	Subjects with cardiovascular disease, hypertension, and HbA1c ≥7.2% and ≤10.5%	Dapa 10mg and placebo 459/455/914
D1690C00019 24 plus 28 weeks Phase 3	Subjects with cardiovascular disease and HbA1c ≥7.2% and ≤10.5%	Dapa 10mg and placebo 482/480/962

Dapa - dapagliflozin; GFR - glomerular filtration rate; HbA1c - glycosylated haemoglobin; IU - International units; OAD - oral antidiabetic drug; SU - sulphonylurea; XR - extended release.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Forxiga (dapagliflozin) has not been launched yet, the launch and availability in the UK is anticipated to be in Q3/2012.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

The application was filed with the EMA via the centralised procedure; the UK is part of this procedure. Positive CHMP Opinion was received on 19 April 2012; upon receiving the European Commission decision, Forxiga will have regulatory approval in the EU member states.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

It is anticipated that the Scottish Medicines Consortium (SMC) will assess dapagliflozin for the treatment of type 2 diabetes in Q3 2012.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 3. Unit costs of technology being appraised

Pharmaceutical formulation	Film-coated tablet
Acquisition cost (excluding VAT)	5mg (28 tablets): £36.59 10mg (28 tablets): £36.59
Method of administration	oral
Doses	5mg (starting dose in patients with severe hepatic impairment), 10mg (standard dose)
Dosing frequency	Once daily
Average length of a course of treatment	Due to the chronic nature of the disease and the stepwise addition of treatments; the duration of treatment is hard to quantify. For dapagliflozin a clear stopping rule would be the development of moderate renal impairment, which is a common feature of patients with diabetes. Although this varies considerably between patients. The UK Prospective Diabetes Study (UKPDS) showed that at 10 years 5% of patients developed macroalbuminuria or worse nephropathy and 24% will develop microalbuminuria after diagnosis (Adler 2003) suggesting that a substantial proportion of patients would no longer be eligible for dapagliflozin at 10 years.
Average cost of a course of treatment	Not applicable (see above)
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable

Dose Adjustments: *Renal impairment* No dosage adjustment is indicated in patients with mild renal impairment. Dapagliflozin is not

recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2).

Hepatic impairment

No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5mg is recommended. If well tolerated, the dose may be increased to 10mg.

Elderly (≥ 65 years)

In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account. Due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended.

Patients at risk for volume depletion, hypotension and/or electrolyte imbalances

Due to its mechanism of action, dapagliflozin increases diuresis associated with a modest decrease in blood pressure, which may be more pronounced in patients with very high blood glucose concentrations. Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness). Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or elderly patients. For patients receiving dapagliflozin, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, and laboratory tests including haematocrit) and electrolytes is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No additional tests or investigations are needed to select patients for dapagliflozin. The economic analysis includes an incremental cost for introducing renal monitoring on initiation of dapagliflozin.

Dapagliflozin can be taken once daily at any time of day with or without food. Tablets are to be swallowed whole.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

<u>Renal function</u>

Monitoring of renal function is recommended:

- prior to initiation of dapagliflozin, and at least yearly thereafter.

- prior to initiation of concomitant medicinal products that may reduce renal function, and periodically thereafter.

- For renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2, dapagliflozin treatment should be discontinued.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

We anticipate that dapagliflozin will mainly be used in combination with metformin when a SU is not appropriate, or in combination with insulin (with or without metformin) when these therapies, together with diet and exercise, are not providing adequate glycaemic control.

1.15 Innovation: SGLT2 inhibition as a novel mechanism of action leading to improved health outcomes

We consider dapagliflozin to be a highly innovative agent in the treatment of T2DM for the following reasons:

- Dapagliflozin is a first-in-class agent. Unlike other therapies it actively removes glucose via the kidney. In contrast, other agents move glucose from the circulation to various compartments (muscle, fat etc,). Therefore it can be seen as a step change in the treatment of diabetes.

The action of dapagliflozin is insulin independent, meaning it does not rely on underlying beta-cell function to exert its effect. In diabetes, beta-cell function wanes over time and therefore exogenous insulin (insulin injections) is/are eventually required.

This means that dapagliflozin maintains its efficacy well beyond the initial 6 months investigated in the trials. Data at 2 years will be presented in this submission for 3 pivotal studies.

- Dapagliflozin can be added to insulin and exerts a clinically meaningful insulin sparing effect while reducing HbA1c and weight.

- Dapagliflozin is associated with weight loss, as a result of the calorie loss induced by glucuresis (glucose excretion). Other oral agents are often associated with weight gain (TZD or SU) or are weight neutral (DPP-4 inhibitors)

Dapagliflozin is also associated with moderate blood pressure reductions.

The aetiology of T2DM is intricate and multifaceted, but virtually all patients contend with both relative insulin deficiency and insulin resistance to varying degrees. The resulting hyperglycaemia can facilitate β-cell failure in the pancreas and worsen insulin resistance, thus triggering a cycle of impaired metabolism and glucotoxicity. Glucotoxicity can

contribute to increased apoptosis of β-cells, causing diminished β-cell mass and thus reduced gene transcription, synthesis and secretion of insulin (Chao and Henry 2010).

The kidney has a key role in regulating glucose levels — by mediating the re-absorption of glucose back into the plasma. This process contributes to the sustained elevated serum glucose levels observed in individuals with diabetes, as they have an increased capacity for renal glucose reabsorption (Farber et al 1951). Inhibiting this glucose re-absorption, thereby allowing its excretion in the urine (glycosuria), is therefore emerging as a potential new approach to the treatment of diabetes.

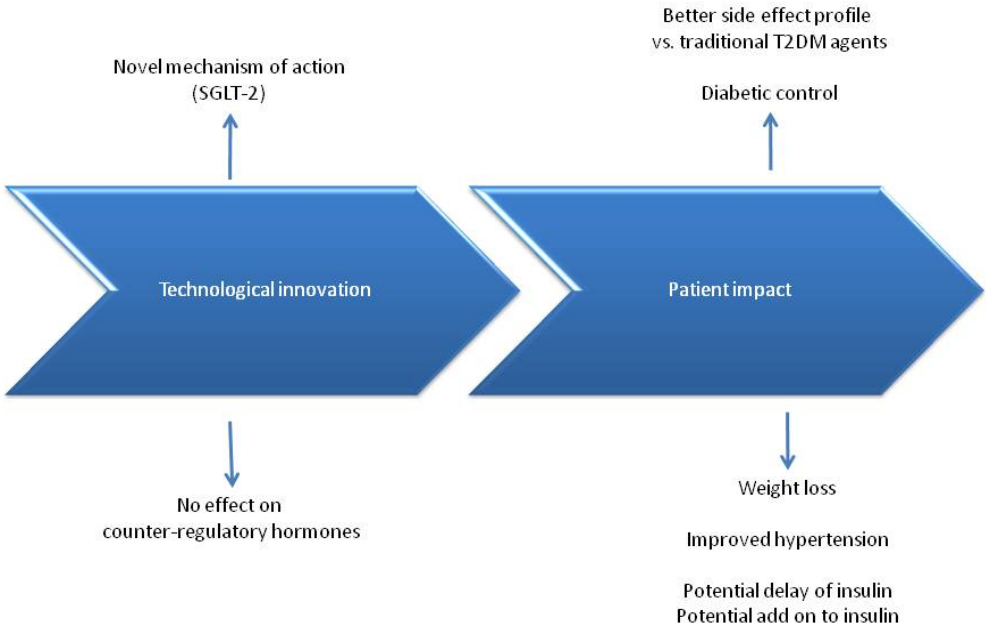
Suppressing glucose reabsorption, through blockade of SGLT, would increase urinary glucose excretion, thereby reducing plasma glucose levels and potentially offering a step change in the therapeutic strategy, without the adverse effects that accompany currently available agents for T2DM.

Dapagliflozin, the most advanced compound in development in the SGLT2 inhibitor class, is a once daily, oral treatment for T2DM. It is approximately 1,200-times more selective for SGLT2 over SGLT1. Thus, SGLT2 offers the most promise as a therapeutic strategy because it is responsible for most of the renal glucose re-absorption and since it is expressed exclusively in the kidney (Chao and Henry 2010). Acute administration of SGLT2 inhibitors to reduce both pre-prandial and postprandial blood glucose, and chronic administration may decrease glucotoxicity (Bakris et al 2009). Inhibition of SGLT2 represents a step change in the treatment of diabetes, as, in contrast to many other current diabetes therapies, SGLT2 inhibitors do not directly influence insulin secretion, thereby utilizing a novel mechanism of action. Therefore, there is a low risk of hypoglycaemia, as these agents selectively target renal glucose transporters, without affecting the counter-regulatory hormones (Wright 2001).

Interestingly, the energy deficit induced by excretion of calories in the urine can lead to weight loss effect, while hypertension may also possibly be concomitantly improved through a slight diuretic-like effect (via glucose induced osmotic diuresis, or a secondary effect via sodium loss).

In summary, increasing urinary glucose excretion with dapagliflozin represents an innovative approach to addressing the challenge of hyperglycaemia, allowing glycaemic control and having the potential to delay initiation of insulin, whilst also having beneficial effects on weight loss and blood pressure.

The innovative nature of dapagliflozin



2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Diabetes mellitus

Diabetes mellitus is a long-term (chronic) metabolic disorder characterised by elevated blood glucose levels (hyperglycaemia) resulting from a lack of the hormone insulin or resistance to its action. There are two main types of diabetes:

Type 1 diabetes is caused by an absolute loss of insulin production and therefore administration of insulin is necessary for survival.

Type 2 diabetes is where there is reduced tissue sensitivity to insulin (known as insulin resistance) as well as a failure of insulin secretion to compensate for this. Type 2 diabetes is often associated with being overweight.

Prevalence

Diabetes mellitus is one of the most common non-communicable diseases (Khatib & Oussama 2006),with approximately 2.8 million people in the UK diagnosed in 2010, the vast majority of whom (around 90%) have type 2 diabetes (NHS, 2011). It is also thought that a further 1 million people may have diabetes - but are not aware and remain undiagnosed (NHS, 2011). T2DM is particularly prevalent in people of African-Caribbean, African, South Asian or Middle-Eastern family origin.

The prevalence of T2DM in the UK is rising due to the increase in obesity, and decrease in physical activity, in the general population (NHS, 2011). Obesity is a very significant problem in patients with T2DM and compounded by the fact that some anti-diabetic medications frequently used in routine clinical practice actually induce weight gain.

In general, an individual is more likely to develop T2DM if; they are overweight or obese, they have a close relative with diabetes, and/or they are over 40 years of age and white, or over 25 years of age and black (NHS, 2011).

Symptoms

In people with untreated T2DM, typical symptoms of hyperglycaemia include thirst, weight loss, fatigue, excessive production of urine (polyuria) and glucose in the urine (glucosuria). Urinary tract infections and genital infections are twice as commonly seen than in patients without diabetes (Boyko et al 2005, Donders 2002). Uncontrolled hyperglycaemia is a more severe symptom which can result in ketoacidosis, which is a medical emergency requiring hospital admission. The patient would present with more severe symptoms as well as signs of dehydration, vomiting, abdominal pain and even loss of consciousness (ketoacidotic coma). Ketoacidosis can be fatal despite modern management (Savage et al 2011).

Complications of diabetes mellitus

If not managed effectively, diabetes can lead to serious, early microvascular complications (Table 4) including kidney failure, blindness, limb amputation, as well as damage to the nervous system, peripheral vasculature and skin (ulcers). Macrovascular complications, including cardiovascular disease, may follow, which can result in myocardial infarction (MI) or stroke.

Due to the vascular effects of T2DM, limb amputations are still very common, the majority of which are preventable (Rightcare, 2011) with proper medical/nursing care and this is despite the availability of modern foot care management and current anti-diabetic medications.

Table 4. Complication prevalence in people with diabetes and the general population

	1 year prevalence (%)	
Complications	People with diabetes	National*
Ketoacidosis	0.48	0.02
Angina	3.13	0.64
Myocardial infarction	0.6	0.16
Cardiac failure	1.58	0.39
Stroke	0.69	0.22
End stage kidney disease treatment	0.38	0.08
Diabetic retinopathy treatments	0.42	0.03
Minor amputation	0.13	0.01
Major amputation	0.07	0.01
* Rates for the whole population of England, including people with diabetes		

Reference: National Diabetes Audit 2009-10, pg 18.

In patients with T2DM life expectancy can be reduced by up to 10 years (National Service Framework, 2001) and mortality rates are up to five times higher than in the general population (Kanters et al 1999). The National Diabetes Audit Mortality Analysis suggests that, each year, up to 24,000 people with diabetes in England die early from causes that could have been avoided through better management of their condition (National Diabetes Audit Mortality Analysis 2007-2008). Overall, the mortality risk for patients with T2DM is 1.6 times higher than the general population (National Diabetes Audit Mortality Analysis 2007-2008).

Treatment

Early diagnosis and effective treatment of diabetes mellitus can minimise the risk of developing serious complications. As diabetes cannot be cured, anti-diabetic treatments aim to keep blood glucose levels as normal as possible, and to control symptoms to prevent health problems developing later in life. T2DM may be controlled initially by eating a healthy diet, losing weight (if overweight) and monitoring blood glucose levels. Blood glucose levels are commonly assessed by measuring glycosylated haemoglobin (HbA1c) levels. The rationale behind this test is that when haemoglobin joins with

glucose in the blood it forms a glycosylated haemoglobin molecule known as HbA1c. The more glucose found in the blood, the higher the HbA1c level.

It is important to realise that T2DM is a progressive condition, meaning that most patients will eventually need to take oral antidiabetic medication. Some existing treatments, such as SUs, used in up to 64% of patients after metformin (CSD Patient Data 2012), or TZDs can cause weight gain, which is an issue especially in patients who are already overweight. This in turn may lead to greater NHS expenditure on weight-loss programmes and/or anti-obesity drugs, indeed the NHS spent £37.1 million on Orlistat in 2011 (IMS BPI/HPI Combined data).

Hypoglycaemia can also be a concern with some medications (especially SUs). This may manifest clinically as major episodes requiring hospitalisation, ambulance call outs or other emergency attention for the resulting complications e.g. falls and fractures, acute confusion and so on. Minor episodes whilst not requiring third party assistance may still result in increased GP or nurse visits or decreased medication compliance (Amiel et al 2008).

As T2DM progresses, the incessant β-cell dysfunction will often ultimately require additional anti-diabetic medication and/or insulin treatment and at increasingly higher doses.

Patients requiring high insulin doses represent a particular treatment challenge and often have uncontrolled glycaemia despite progressive dose increases and are especially prone to insulin related lipotoxicity and weight gain. It is also known that the benefits of some existing anti-diabetic medications reduce over time due to beta-cell failure (Kahn et al 2006).

However, despite the availability of a wide variety of treatment options for T2DM, a considerable proportion of patients have inadequate glycaemic control, with approximately 55% having a HbA1c greater than the NICE recommended target of ≤7.5%, and 6.7% with a high risk HbA1c value of >10% (National Diabetes Audit 2009-10).

2.2 How many patients are assumed to be eligible? How is this figure derived?

In the first full year following a positive NICE recommendation we anticipate dapagliflozin to be prescribed to 6,241 patients, increasing to 105,458 in year 5. These figures are derived from estimates of the prevalence and incidence of T2DM in England and Wales and the proportion of these individuals receiving oral antidiabetic medications and the estimated uptake of dapagliflozin in this population (see Section 7 for further information).

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

There are two NICE Clinical Guidelines specifically concerning the ‘management of Type 2 diabetes’:

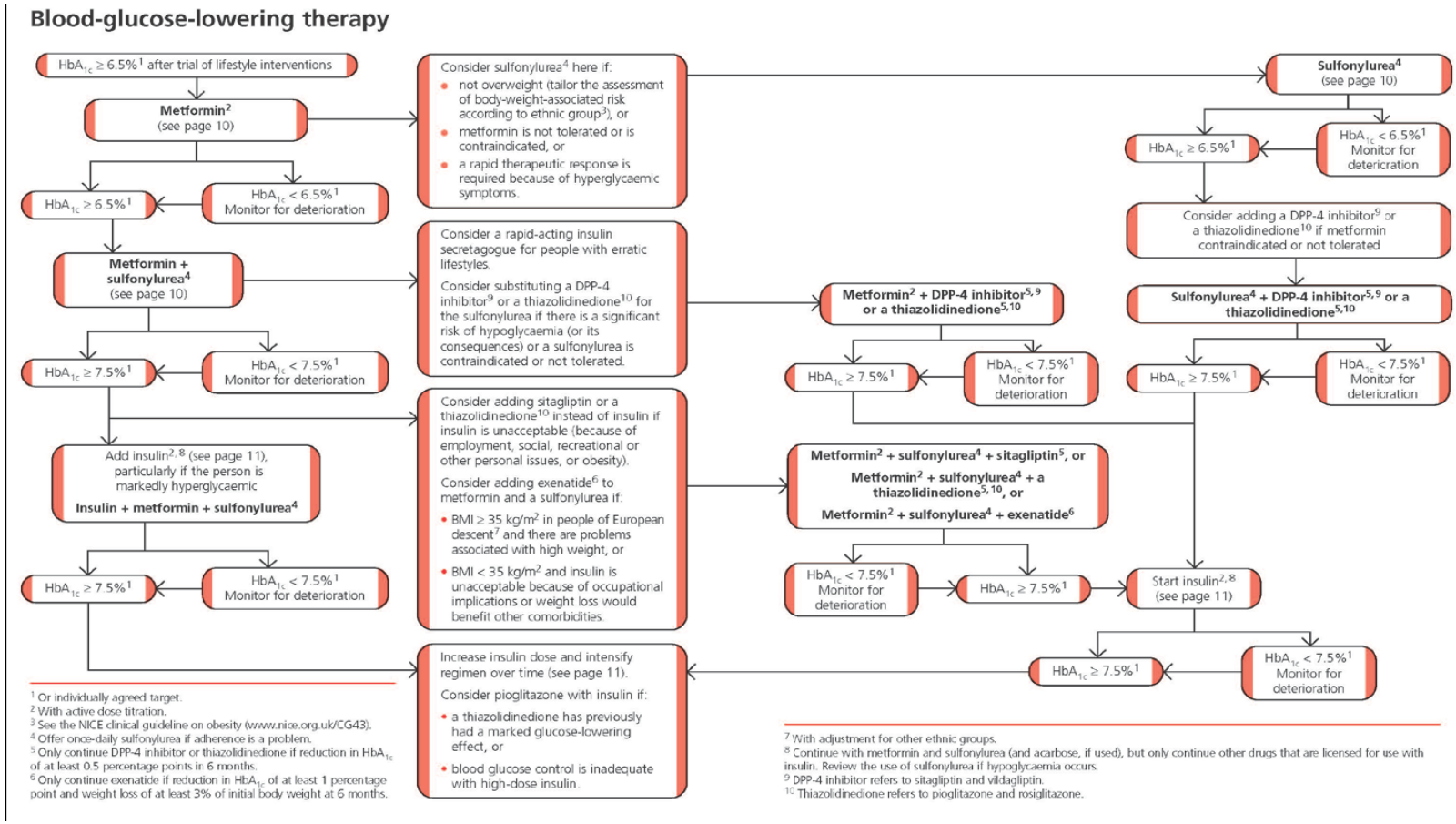
- NICE Clinical Guideline no. 66 (May 2008)
- NICE Clinical Guideline no. 87 (May 2009) which updated the above guideline, and recommended where newer antidiabetic agents can be used.

There are also several NICE Single Technology Appraisals:

- No. 53 (2002): Diabetes (types 1 and 2) - long acting insulin analogues (including insulin glargine)
- No. 203 (2010): Liraglutide for treatment of type 2 diabetes mellitus.
- No. 248 (2012): Diabetes (type 2) - exenatide (prolonged release)

NICE Clinical Guideline 87 is summarised in Figure 1.

Figure 1. Schematic from NICE Clinical Guideline 87



NICE Clinical Guideline no. 87 (2009)

Treatment pathway

Treatment of diabetes is complicated, as shown in Figure 1. In the UK, the vast majority of patients follow the NICE sequence treatment pathway outlined below:

NICE Clinical Guideline 73 (Chronic Kidney Disease)

Around a third of patients with T2DM have moderate or severe renal impairment (Middleton et al 2006). NICE CG 73 presents a comprehensive guide on monitoring renal function. The frequency of testing may be reduced where renal function is stable, but needs to increase where there is rapid deterioration. Table 5 illustrates this.

Table 5. Measurement of eGFR: how often?

Annually in all at risk groups.		
During intercurrent illness and perioperatively in all patients with CKD.		
Exact frequency should depend on the clinical situation. The frequency of testing may be reduced where eGFR levels remain very stable but will need to be increased if there is rapid progression.		
Stage	eGFR range (ml/min/1.73 m^2)	Typical testing frequency
1 and 2	≥ 60 + other evidence of kidney disease	12 monthly
3A and 3B	30–59	6 monthly
4	15–29	3 monthly
5	<15	6 weekly

Reference: NICE Clinical Guideline 73, pg 12.

NICE Multiple Technology Appraisal no. 53 (2002): Diabetes (types 1 and 2) - long acting insulin analogues (including insulin glargine). This can be summarised as:

- Insulin glargine is recommended as a treatment option for people with type 1 diabetes
- Insulin glargine is not recommended for routine use for people with T2DM who require insulin therapy. Insulin glargine treatment should be considered only for those people with T2DM who require insulin therapy and who fall into one of the following categories:
    - Those who require assistance from a carer or healthcare professional to administer their insulin injections.
    - Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes.
    - Those who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs.

NICE Single Technology Appraisal no. 203 (2010): Liraglutide for treatment of T2DM can be summarised as:

- Liraglutide 1.2mg daily can be used as part of dual-therapy, in combination with metformin or a SU if either metformin or a SU cannot be taken or tolerated; and a thiazolidinedione or DPP-4 inhibitor cannot be taken or tolerated.

- Liraglutide 1.2mg daily can be used as part of a triple therapy treatment of T2DM when given with two other drugs for diabetes (metformin and either a SU or a thiazolidinedione), if blood glucose levels are still not controlled and other specified criteria are met.

- Liraglutide 1.8mg daily is not recommended by NICE for the treatment of patients with T2DM.

The BMI treatment threshold for use of liraglutide in patients of non-European descent is also adjusted downwards.

NICE Single Technology Appraisal no. 248 (2012): Diabetes (type 2) exenatide (prolonged release). This is summarised below:

Prolonged-release exenatide injections, in combination with other drugs (given as tablets), is recommended as a possible treatment for some patients with T2DM who fall in to one of the following categories:

Those whose blood glucose levels are not under control and are on two other drugs for diabetes, metformin and either a sulphonylurea or a thiazolidinedione **and**:

- body mass index (BMI) is ≥ 35 and have health problems associated with this, **or**

- BMI is ≤ 35, and treatment with insulin would make it much more difficult to do their job or other significant health problems would be helped by weight loss.

Prolonged-release exenatide can be given with one other drug (either metformin or a sulphonylurea) only if:

- they are not able to take either metformin or a SU, **and**

- they are not able to take TZDs **and** DPP-4 inhibitors.

Treatment with prolonged-release exenatide can be continued after 6 months only if tests show it is working well enough.

Only the NICE Clinical Guideline no.87 covers the treatment of any specific subgroups of patients with diabetes.

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The NICE clinical pathway of care for T2DM is described here:

NICE Treatment Pathway

Diet modifications and exercise are initially recommended to manage T2DM.

First-line (Monotherapy)

If the disease progresses, treatment with an antidiabetic drug, usually metformin, is initiated as monotherapy.

Second-line options (Dual-therapy)

If blood glucose control is inadequate with metformin alone, dual-therapy should be started, by adding on a SU.

Third-line option (Insulin)

If blood glucose is still not adequately controlled, insulin is initiated.
The NICE treatment algorithm above includes alternative treatment options at each stage [DPP-4 inhibitors (sitagliptin), TZD (pioglitazone) or glucagon-like peptide-1 (GLP-1) analogue (exenatide)] depending on tolerability/suitability (for e.g. risk of hypoglycaemia and/or weight gain, BMI, risk/benefit of insulinisation).

The only specific patient subgroups addressed in the NICE Clinical Guideline (no. 87) are patients of non-European descent where the BMI threshold for treatment with GLP-1 analogues is adjusted downward, as they are at higher risk of developing T2DM.

Within its licensed indication, dapagliflozin can be used in combination with other oral therapies commonly used for treatment of T2DM.

Dapagliflozin could fit into the existing treatment pathway as follows:

1. As a second-line option (dual therapy, add-on to metformin), dapagliflozin can be added to metformin as an alternative treatment option to SU, in patients whom SU is not appropriate because of the risk of hypoglycaemia, **or in whom weight loss is a treatment goal**.

2. As a third-line option (add-on to insulin), dapagliflozin can also be added to insulin with or without metformin in those patients **who are not adequately controlled on**

insulin and in whom increasing doses of insulin would result in an increased risk of hypoglycaemia and/or weight gain caused by insulin.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Variations in delivery of diabetes care

With the exponential rise in the prevalence of diabetes, a variety of models for the delivery of care have emerged across the UK, with a preference for Primary Care led services. However, the majority of complex patients are managed by Intermediate or Secondary Care, although there is a wide variation in the threshold for referral of patients to Secondary Care.

As a new oral treatment, dapagliflozin widens the options available in the Primary Care setting and so could delay the progression to a third agent (third oral agent, injectable GLP-1 analogue or insulin), which usually requires Secondary Care referral for initiation.

The variations in standards of care of patients with diabetes across the UK include:

- Postcode lottery of care (Department of Health, 2010; Rightcare, 2011)
- Varied access to NICE approved drugs with budgetary prescribing restrictions in primary care (Anekwe, 2011)
- Differing infrastructures of diabetes care and referral to secondary care criteria
- Only half of patients with T2DM are receiving all nine recommended basic key care processes which monitor for treatable risks of diabetes (National Diabetes Audit, 2009-10).

Uncertainty of best practice

Issues with current clinical practice:

- Debate on the ideal HbA1c target (Currie et al 2010) and the best individualised drug treatment approach to this.
    - Balancing HbA1c reduction with risk of hypoglycaemia
    - Balancing drug induced weight gain with HbA1c reduction
- Varied intensity of approach to blood glucose control (Ray et al 2009)**.**

  Although UK diabetes clinical guidelines advise on the treatment steps for the control of blood glucose, they do not advise on the speed the treatment steps should be progressed.

- Differences between Quality and Outcomes Framework targets for HbA1c (QOF, 2010-11) and the HbA1c targets set by NICE Clinical Guideline 87. This results in a

discrepancy between QOF led remuneration of GPs and the targets recommended by clinical guidelines.

- Over 40% of patients are not meeting QOF HbA1c targets (QOF, 2010-11; National Diabetes Audit 2009-10).

In summary, there is a need to individualise patient treatment, taking into account patient preference to meet the specific needs of each patient (risk of hypoglycaemia, weight gain, compliance etc.). Although current clinical guidelines target HbA_1c levels, there is no guide to support individualisation of patient's treatment, with respect to their appropriate HbA_1c level according to their stage of diabetes and treatment level. The guidelines do not set target timelines to encourage clinicians to reach HbA_1c targets/ranges more quickly. The consequence is a clinical inertia, whereby clinicians follow guidelines, but the progression of patients' treatment to reach ideal HbA_1c levels is slow, leaving a majority of patients not 'on target' at any one time. This is occurring in an environment of varied delivery of diabetes care, from the implementation of key monitoring checks to differing referral structures and access to NICE approved diabetes drugs.

2.6 Please identify the main comparator(s) and justify their selection.

Dapagliflozin as a second-line option (dual therapy, add-on to metformin):

The main comparators for dapagliflozin 10mg once-daily in combination with metformin are:

SUs – NICE Clinical Guideline 87 (CG87) recommends SU to be added to metformin when diet and exercise plus metformin fail to reach glycaemic targets.

TZDs – NICE Clinical Guideline 87 (CG87) recommends a TZD when there is significant risk of hypoglycaemia with an SU or an SU is contraindicated or not tolerated.

DPP-4 inhibitors – NICE CG87 recommends DPP-4 inhibitors in patients when there is significant risk of hypoglycaemia with an SU or an SU is contraindicated or not tolerated. A DPP-4 inhibitor may be preferable to a TZD or an SU when weight gain would be an issue.

Dapagliflozin as a third-line option (add-on to insulin):

The main comparators for dapagliflozin 10mg once-daily in combination with insulin are:

TZDs – NICE CG87 recommends pioglitazone with insulin if a TZD has previously had a marked glucose-lowering effect or blood glucose control is inadequate with high dose insulin. Pioglitazone is only licensed in combination with insulin in patients with T2DM for whom metformin is inappropriate because of contraindications or intolerance (Pioglitazone Summary of Product Characteristics, 2011).

DPP-4 inhibitors – There are only two DPP-4 inhibitors (saxagliptin and sitagliptin) licensed for use in combination with insulin (with or without metformin) in patients with T2DM.

At the time of designing the systematic review for this appraisal, none of the GLP-1 analogues were licensed for use in combination with insulin. Therefore GLP-1 analogues are not included as a comparator in the add-on to insulin in this appraisal. Currently the NICE Clinical Guideline 87 does not include the GLP-1, exenatide, in combination with insulin. It is likely that when the Guideline is updated it will consider the positioning of GLP-1s in the treatment pathway.

Sulphonylureas rely on functioning β-cells to boost insulin release. Insulin replacement therapy is generally reserved for patients with long-standing T2DM who have little residual β-cell function. Thus, in practice SUs are often discontinued when insulin is initiated. In addition concomitant use of SU and insulin can lead to greater risk of hypoglycaemia and additional weight gain. Gliclazide, the most commonly used SU in the UK (IMS Health 2012). Gliclazide's SPC recommends discontinuation of gliclazide prior to insulin initiation (Gliclazide Summary of Product Characteristics, 2011). Therefore SUs are not included as a comparator in the add-on to insulin.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Genital infections

Type 2 diabetes is associated with a nearly two fold increased incidence/prevalence of genital infections (Shah & Hux, 2003; Donders 2002). In the short-term, placebo-pooled analysis, patients who had a history of recurrent vulvovaginitis, balanitis and related genital infections, regardless of treatment group, were more likely to have such infections.

Vulvovaginitis, balanitis and related genital infections were reported in 4.8% and 0.9% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (9.7% and 3.4% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection. The most frequently reported infections were vulvovaginal mycotic infections and vaginal infection in females, and balanitis and fungal genital infection in males.

Most genital infections in the clinical trial programme responded to an initial course of antimicrobial treatment and rarely resulted in discontinuation of dapagliflozin (List et al 2011). Standard antimicrobial treatment may be topical antifungals/oral treatments (e.g. miconazole, clotrimazole, or fluconazole) (Grigoriou et al 2006) or antibiotics (e.g. metronidazole or clindamycin) (Sobel, 1997) for fungal or bacterial infections, respectively (British National Formulary, 2012). Some of these treatments are available over the counter.

Urinary Tract Infections

Urinary tract infections (UTIs) are known to be more common in patients with diabetes than in the general population (Sawers et al 1988; Keane et al 1998; Goswami et al 2001), and the rates of UTIs in dapagliflozin treated patients are not dissimilar to those in the T2DM population.

The mechanism of action of dapagliflozin causes glucosuria and increases urine volume, so UTIs and urinary symptoms are not unexpected.

Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo (4.3% versus 3.7%, respectively; see section 4.4). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection (Dapagliflozin Summary of Product Characteristics, 2012).

Pyelonephritis was uncommon and occurred at a similar frequency to control (Dapagliflozin Summary of Product Characteristics, 2012).

Most UTIs in patients treated with dapagliflozin in the clinical trial programme were generally mild to moderate and responded to an initial course of standard treatment (Dapagliflozin Summary of Product Characteristics, 2012) (which is usually a course of antibiotics, such as amoxicillin, trimethoprim or nitrofurantoin) (British National Formulary 2012; SIGN, 2006). Most patients do not have recurrent UTI events.

Hypoglycaemia

The risk of hypoglycaemic events is increased with insulin and SUs. Dapagliflozin has a low incidence of hypoglycaemia compared to SU. When dapagliflozin is added to metformin the rates of minor episodes of hypoglycaemia were low (<4%) and similar to the rates with placebo (Dapagliflozin Summary of Product Characteristics, 2012). However, when added to insulin the proportion of patients who at least one hypoglycaemic event on dapagliflozin 10mg was higher than in the placebo group (53.6% vs. 51.8%) (Wilding et al 2012). The risk of hypoglycaemia can be reduced by lowering the dose of insulin. Events of major hypoglycaemia were rare across the dapagliflozin trials. Minor hypoglycaemia can usually be treated with ingestion of a sugary drink or snack.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Initiation of dapagliflozin is anticipated to be mainly in Primary Care, but may also be commenced in Secondary Care. Dapagliflozin should not require any additional NHS infrastructure to be put in place.

2.9 Does the technology require additional infrastructure to be put in place?

No additional infrastructure is required.

3 Equity and equality

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

The NICE Clinical Guideline 87 (NICE, 2009) states that for patients of non-European descent (African, South Asian or Caribbean), the body mass index (BMI) threshold for treatment with GLP-1 analogues is adjusted downward, as they are at higher risk of developing T2DM. A similar adjustment is recommended for these ethnic groups in the NICE guidance for liraglutide (TA203) and exenatide prolonged release (TA248).

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

None expected.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

A separate economic analysis for South Asian, African or Caribbean patients has not been presented in this submission. However, in view of their increased risk and consequent increased opportunity to gain benefit from treatment at lower BMIs, a lower BMI threshold should still apply.

4 Statement of the decision problem

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	**Dual therapy** Adults with T2DM that is inadequately controlled on monotherapy with either metformin or a SU. **Triple therapy** Adults with T2DM that is inadequately controlled on dual therapy with either of the following: metformin in combination with a SU metformin **or** a SU in combination with a thiazolidinedione, a DPP-4 inhibitor, or a GLP-1 analogue. **Add-on therapy to insulin** Adults with T2DM that is inadequately controlled on monotherapy with insulin or on therapy with insulin and up to two other oral agents.	**Dual therapy** Adults with T2DM that is inadequately controlled on monotherapy with metformin. **Add-on therapy to insulin** Adults with T2DM that is inadequately controlled on monotherapy with insulin or on therapy with insulin and up to two other oral agents.	**Dual therapy** Adults with T2DM that is inadequately controlled on monotherapy with SU will not be considered. Generally, SUs are only recommended if the patient exhibits osmotic symptoms that require rapid control, is not overweight or the patient does not tolerate metformin. **Triple Therapy** Dapagliflozin is currently being studied as third-line add-on to two other oral agents. At the time of submission, the data are not yet available. There are no combination studies with GLP-1 analogues. Dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone.
Intervention	Dapagliflozin (in combination with oral anti-diabetic agents and/or insulin).	Dapagliflozin 10mg once daily (in combination with oral anti-diabetic agents and/or insulin).	
Comparator(s)	**Dual therapy** For the combination of dapagliflozin and metformin, the comparators are: SUs (with metformin) pioglitazone (with metformin) DPP-4 inhibitors (with metformin) GLP-1 analogues (with metformin). For the combination of dapagliflozin and SU, the comparators are:	**Dual therapy** For the combination of dapagliflozin and metformin, we will present comparisons with SUs (with metformin), TZD (with metformin), and DPP-4 inhibitors (with metformin).	**Dual therapy** A comparison with GLP-1 analogues (with metformin) will not be presented because these therapies are recommended by the Institute only where metformin or a SU is not tolerated or contraindicated, and a TZD and a DPP-4 is contraindicated or not tolerated. The proportion of

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	pioglitazone (with a SU) DPP-4 inhibitors (with a SU) GLP-1 analogues (with a SU). **Triple therapy** For the combination of dapagliflozin, metformin and a SU, the comparators are: pioglitazone (with metformin and a SU) DPP-4 inhibitors (with metformin and a SU) GLP-1 analogues (with metformin and a SU) insulin (with metformin and a SU). For the combination of dapagliflozin, metformin and pioglitazone, the comparators are: DPP-4 inhibitors (with metformin and pioglitazone) GLP-1 analogues (with metformin and pioglitazone) insulin (with metformin and pioglitazone). For the use of dapagliflozin in any other triple therapy regimen, the comparator is: insulin (alone or in combination with one or more oral anti-diabetic agents). **Add-on therapy to insulin** One or more oral anti-diabetic agents (in combination with insulin).	**Add-on therapy to insulin** In this setting we will present a comparison of dapagliflozin and insulin with DPP-4 and insulin.	patients in this setting receiving a GLP-1 analogue is less than 5% and therefore these therapies are not considered routine practice in this setting. For the reasons stated in 'Population', the combination of dapagliflozin and SU will not be considered. **Triple therapy** For the reasons stated in 'Population', comparisons of dapagliflozin in the triple therapy setting are not considered.
Outcomes	The outcome measures to be considered include: HbA1c/glycaemic control frequency and severity of episodes of hypoglycaemia calculated cardiovascular risk (including blood pressure and/or	The outcomes measures considered include HbA1c, weight change, total cholesterol, HDL cholesterol, systolic blood pressure and the incidence of ischaemic heart disease, myocardial infarction, congestive heart failure, stroke, blindness, amputation, end-	

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	serum lipids) weight change complications of diabetes e.g. cardiovascular, renal and eye mortality adverse effects of treatment (including genitourinary tract infection) health-related quality of life.	stage renal disease (ESRD), non-CV death. Drug-related outcomes include hypoglycaemic episodes and weight change.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost effectiveness will be expressed in terms of cost per quality-adjusted life year. A lifetime horizon (40 years) will be included in the base case. Shorter modelling time frames will also be included for information. Costs will be considered from an NHS and Personal Social Services perspective.	
Subgroups to be considered	If evidence allows, subgroups based on the following criteria will be considered: body mass index HbA1c duration of diabetes dose of insulin.	• BMI <30 and >30 • Baseline HbA1c	Subgroup analyses for baseline HbA1c and BMI <30 and >30 are included. Dose of insulin and duration of diabetes as subgroup analyses are not presented as they were not undertaken. Other subgroup analyses are not presented as no significant interactions were observed.

Section B – Clinical and cost effectiveness

5 Clinical evidence

Summary

- Dapagliflozin has been well studied in a clinical trial programme including over 6000 patients. The robust study design and long duration of blinded data collection included in this submission provide a strong evidence base to support the use of dapagliflozin.
- Dapagliflozin results in clinically meaningful reductions in HbA1c which are maintained at 2 years.
    - Dapagliflozin 10mg was shown to be superior to placebo and non-inferior to SU (glipizide) with respect to HbA1c reduction.
- Dapagliflozin resulted in significant weight loss when added to metformin. In patients receiving insulin where weight gain would be expected, the addition of dapagliflozin also resulted in weight loss. These results were maintained at 2 years.
- Dapagliflozin has the additional benefit of a blood pressure lowering effect.
- Dapagliflozin has a low propensity to cause hypoglycaemia.
    - In head to head study with SU, there were 10 times less hypoglycaemic events with dapagliflozin.
    - When added to insulin, dapagliflozin did not significantly increase the rate of hypoglycaemia.
- Dapagliflozin did not increase mean total daily insulin dose, but insulin requirements increased progressively in the placebo group. This insulin sparing effect resulted in a relative decrease of 19% decrease in daily insulin requirements at 2 years.
- Dapagliflozin was generally well tolerated. Adverse events of note were genital and urinary tract infections.
    - Genital tract infections were more common with dapagliflozin, but were generally mild to moderate in intensity and responded to standard treatment, with few patients discontinuing.
    - UTIs occurred in a slightly higher proportion of patients on dapagliflozin, but were generally of mild to moderate intensity and responded to standard treatment.

5.1 Identification of studies

A systematic review of the published and unpublished literature was conducted to identify information from randomised clinical trials (RCTs) that presented efficacy and/or safety of anti-diabetic agents, in adults with T2DM mellitus. The search strategy was designed to capture RCTs for three indications of anti-diabetic agents (monotherapy, metformin add-on therapy, and

insulin add-on therapy); however, the results presented here will be limited to metformin add-on and insulin add-on therapy.

The search terms comprised disease terms, a study design filter and drug terms for anti-diabetic agents of relevance to the decision problem. The study design filters used were designed by the Cochrane Collaboration (Higgins and Green, 2011) to identify RCTs using a combination of index and free text terms. Each abstract was assessed by two independent reviewers based on pre-established inclusion and exclusion criteria (see Section 5.2.1).

Detailed search strategies are provided in Section 9.2.2. In summary, the search strategies were executed on May 11, 2011 (and updated in June 2012 [metformin add-on] and July 2012 [insulin add-on]) (see Section 5.7.6.10) in the following databases:

- Medline and Medline In-Process: searched from 1946 until May 11, 2011;
- EMBASE: searched from 1980 until week 17, 2011; and
- CENTRAL (Cochrane Central Register of Controlled Trials): searched from 1991 until 2nd quarter 2011.

Using the Ovid® platform, the searches were run for each database, and then duplicates removed.

In addition, the following 2010 conference proceedings were searched:

- American College of Cardiology (ACC);
- American Diabetes Association (ADA);
- American Heart Association (AHA);
- European Association for the Study of Diabetes (EASD); and
- The Obesity Society.

To identify on-going or unpublished trials, the following sources were searched and cross-referenced with published articles:

- Current Controlled Trials [ISRCTN] (www.controlled-trials.com);
- ClinicalTrials.gov (http://clinicaltrials.gov);
- Clinical Study Results (www.clinicalstudyresults.org); and
- International Clinical Trials Registry Platform [ICTRP] (www.who.int/ictrp).

When completed RCTs could not be identified in the published literature, the manufacturer was contacted for further information.

We identified unpublished trials in the dapagliflozin clinical trial programme by reviewing a list of all on-going and completed BMS/AZ RCTs. The eligibility of each was evaluated according to the criteria in Section 5.2.1, based on published abstracts, records on ClinicalTrials.gov, and if necessary, the full clinical study report (CSR).

The reference lists of included RCTs and systematic reviews published in the three years prior to 2011 (McIntosh et al, 2011; Shyangdan et al, 2010; Waugh et al, 2010) were reviewed to identify additional relevant RCTs.

The rationale for inclusion and exclusion criteria for the search strategy is aligned with that presented in Section 5.2.1. Outcome terms were not included in the search strategy to improve search sensitivity.

5.2 Study selection

5.2.1 Eligibility criteria

Following the retrieval of the search results, eligibility criteria were applied for the selection of studies to be included. Table 6 summarises the inclusion and exclusion criteria that were applied. The criteria were applied in a pre-specified order, and the first applicable reason was applied to each excluded abstract as the responsible reason.

Table 6. Eligibility criteria used in selection of studies

	Description	**Justification**
Inclusion criteria		

Population	Eligible population included studies with:
	• Humans only
	• Adults with T2DM
	  o With inadequate glycaemic control on metformin alone (metformin add-on indication);
	  o With inadequate glycaemic control on insulin with or without oral antidiabetic agents (insulin add-on indication)
		Applicable population with respect to anticipated indication for dapagliflozin

	Description	Justification
Interventions	Licensed agents within all pre-identified drug classes administered at their licensed dose in either United States (US) or Europe. Any of the following drug classes must have been compared to one another or to a placebo/no-intervention arm: • For the metformin add-on indication (as the only anti-diabetic agent added to metformin monotherapy): o SGLT2 inhibitors (dapagliflozin only); o SUs + meglitinides; o DPP-4 inhibitors; o TZDs; o GLP-1 analogues • For insulin add-on indication (with or without other anti-diabetic agents): o SGLT2 inhibitors (dapagliflozin only); o Biguanides; o SUs + meglitinides; o DPP-4 inhibitors; and o TZDs The specific agents and their licensed doses are provided in Table 103 and Table 104.	Comparators of interest in Europe and US. Excluded from the list of agents was the class of glucosidase inhibitors (e.g. acarbose) as it was not considered to be used as conventional agent in Europe.
Outcomes	Studies reporting at least one of the following outcomes of interest As change from baseline or other metric: • HbA1c; systolic blood pressure, weight; fasting blood glucose; high-density lipoprotein; low-density lipoprotein; total cholesterol; triglycerides. As number of events or number of patients with at least one event: • Hypoglycaemia; UTI; genital infection; gastrointestinal event; any adverse event; any serious adverse event.	Outcomes of interest and relevance to decision problem
Study design	RCT of at least 12 weeks duration	Highest level of evidence for evaluating efficacy and safety
Language restrictions	None	To permit the inclusion of all available research of relevance

	Description	Justification
Exclusion criteria		
Population	Study: • Includes animal studies • Evaluates a T2DM adult (≥18 years) population with adequate glycaemic control at baseline • Enrol population restricted to subgroup for which the effect size is not expected to generalize to the population of type 2 diabetics (e.g. renal impairment)	Not applicable to the decision problem
Interventions	Study: • Evaluates agents not of interest for each indication (e.g. alpha-glucosidase inhibitors, or naturopathic or Chinese traditional medicinal agents for any indication; GLP-1 inhibitors for add-on to insulin indication); • Evaluates agents not administered at the licensed dose in Europe or US (see Table 103 and Table 104)	These are not used as conventional treatments in the US and Europe
Outcomes	See inclusion criteria	Not applicable
Study design	• Non-RCTs, observational studies, reviews (systematic or non-systematic), commentaries, post-hoc analyses of subsets of patients enrolled in RCTs; • RCTs published after May 11, 2011; interim or completed CSR available from BMS/AZ after this cut-off date	Cut-off date for search execution
Language restrictions	None	To permit the inclusion of all available research of relevance

Abbreviations: AZ, AstraZeneca; BMS, Bristol-Myers Squibb; CSR, Clinical study report; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; RCT, Randomised controlled trial; SGLT2, Sodium glucose co-transporter 2; T2DM, Type 2 diabetes mellitus; TZD, Thiazolidinediones; US, United States of America

5.2.2 Flow diagram of included and excluded studies

A total of 4270 abstracts were identified from the MEDLINE, EMBASE, and CENTRAL database searches, which was reduced to 2882 after de-duplication.

Among these, 2651 abstracts were excluded; the remaining 231 publications were reviewed using full-text reports. A further 149 full-text reports were excluded at the final screening stage, leaving 82 publications.

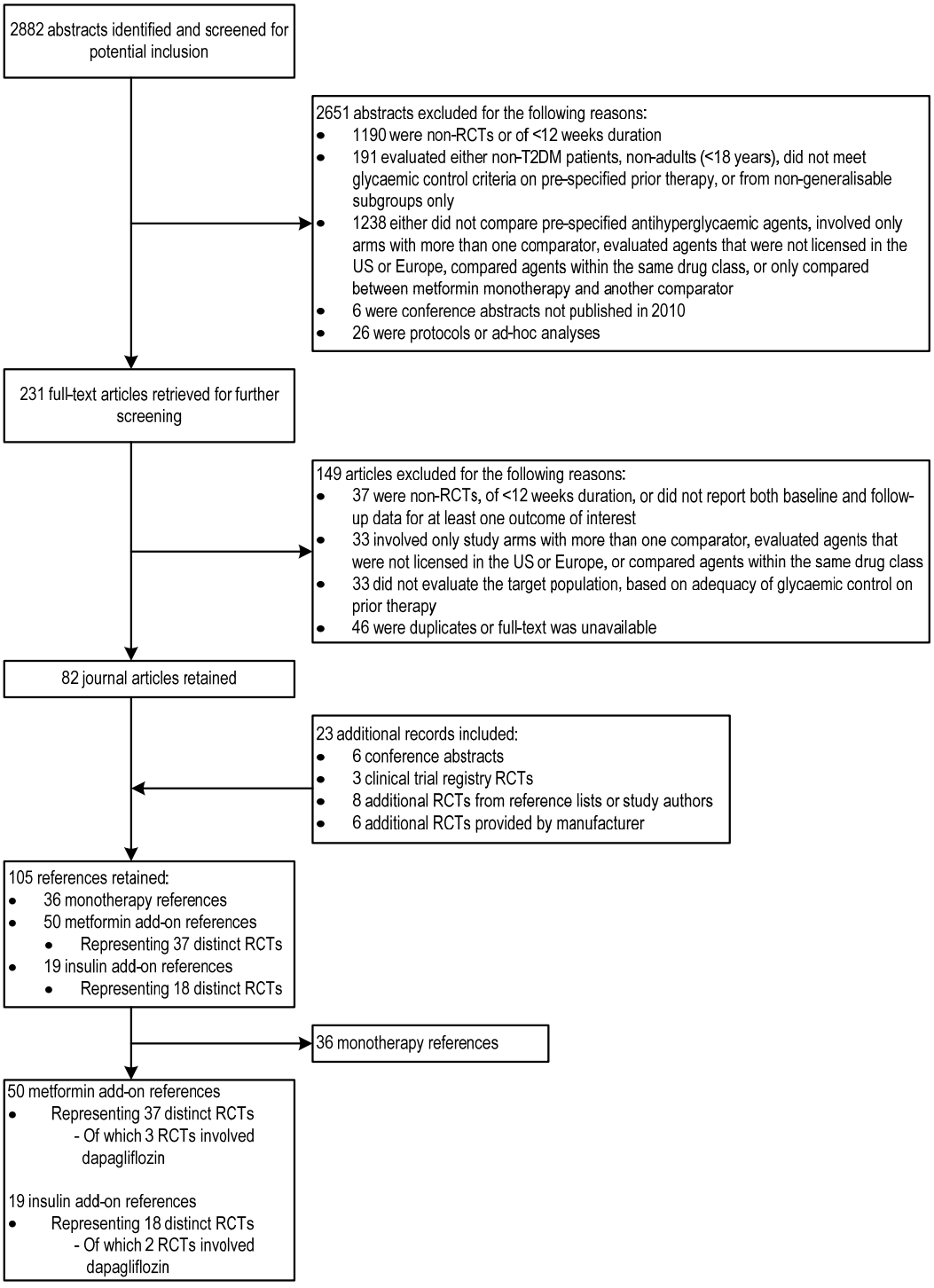
Additional RCTs were identified through a review of conference abstracts, RCT registries, and review of reference lists of included studies and systematic reviews published in the three years prior to 2011 (McIntosh et al, 2011; Shyangdan et al, 2010; Waugh et al, 2010), combining to a

total of 105 publications, of which 50 involved metformin add-on indication and 19 involved an insulin add-on indication, and the remaining 36 involved monotherapy.

The RCTs involving a monotherapy indication were excluded because they are not in the scope of this submission, leaving 50 metformin add-on references, representing 37 distinct RCTs, of which three involved dapagliflozin, as well as 19 insulin add-on references, representing 18 distinct RCTs of which two involved dapagliflozin.

The flowchart in Figure 2 illustrates the study selection process, based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Liberati et al, 2009).

Figure 2. Flow chart of the study selection process



Abbreviations:
RCT, Randomised clinical trial; T2DM, Type 2 diabetes mellitus; US, United States of America

5.2.3 Data sources of identified studies

A complete list of all RCTs that were identified during the systematic review, including contributing data sources, is compiled below. This list includes RCTs that contributed both direct (involving a dapagliflozin 10 mg arm) and indirect evidence (without a dapagliflozin 10 mg arm) to the decision problem.

At the time of search execution, three of the included BMS/AZ RCTs were unpublished, or published only as an abstract. Since the time of search execution, these three RCTs (Bolinder et al 2012; Nauck et al 2011b, Wilding et al 2012) have been published and therefore the references have been added to the list below; although they are not captured in the flow chart in Figure 2, as they were not retrieved as a part of the systematic literature review.

Abstracts from conferences held in 2011 that supplement included dapagliflozin RCTs were also added to the list below. These abstracts are not captured in the flow chart in Figure 2, as they were not retrieved as a part of the systematic literature review.

The RCTs are listed in Table 7 and Table 8 according to four categories:

- Metformin add-on studies involving dapagliflozin;
- Metformin add-on studies not involving dapagliflozin;
- Insulin add-on studies involving dapagliflozin; and
- Insulin add-on studies not involving dapagliflozin.

Table 7. Data sources of identified studies: metformin add-on

Author, Year	Primary Data Source	Supplemental Data Source(s)
Studies involving dapagliflozin		
Duration of study: 18 to 30 weeks (non-SUs)		
Bailey, 2010b	Publication (The Lancet)	Unpublished CSR (BMS, 2010; MB102014 [BMS-512148]) Conference abstract (Bailey et al 2011a; ADA 71st Scientific Sessions; Abstract 988-P)
Bolinder, 2012	Publication (J Clin Endocrinol Metab)	Unpublished CSR (AZ, 2010; D1690C00012)
Duration of study: >30 weeks		
Nauck, 2011b	Publication (Diabetes Care)	Unpublished CSR (AZ, 2010; D1690C00004) Conference abstract (Nauck, 2010; EASD 46th Annual Meeting; Abstract 241) Clinicaltrials.gov website (NCT00660907) Conference abstract (Nauck, 2011; ADA 71st Scientific Sessions; Abstract 40-LB) Conference abstract (Del Prato, 2011; EASD 47th Annual Meeting; Abstract 852)

Author, Year	Primary Data Source	Supplemental Data Source(s)
Studies not involving dapagliflozin		
Duration of study: 12 to 17.9 weeks		
Forst, 2010	Publication (Diabetic Medicine)	Clinicaltrials.gov website (NCT00309608)
Yang, 2011	Publication (Diabetes Obes Metab)	Clinicaltrials.gov website (NCT00614120)
Rosenstock, 2010	Conference abstract (ADA 70th Scientific Sessions; Abstract 77-OR)	No supplemental data sources
Einhorn, 2000	Publication (Clinical Therapeutics)	No supplemental data sources
Feinglos, 2005	Publication (Diabetes Res Clin Pr)	No supplemental data sources
Handayani, 2010	Conference abstract (ADA 70th Scientific Sessions; Abstract 667-P)	No supplemental data sources
Marre, 2002b	Publication (Diabetes Obes Metab)	No supplemental data sources
Duration of study: 18 to 30 weeks (non-SUs)		
DeFronzo, 2009	Publication (Diabetes Care)	Unpublished CSR (BMS, 2010; CV181014) Clinicaltrials.gov website (NCT00121667)
DeFronzo, 2005	Publication (Diabetes Care)	Publication (Blonde, 2006; Diabetes Obes Metab) Publication (Ratner, 2006; Diabetes Obes Metab) Clinicaltrials.gov website (NCT00039013)
Scott, 2008	Publication (Diabetes Obes Metab)	No supplemental data sources
Bosi, 2007	Publication (Diabetes Care)	No supplemental data sources
Raz, 2008	Publication (Curr Med Res Opin)	No supplemental data sources
Bergenstal, 2010a	Publication (The Lancet)	No supplemental data sources
Nauck, 2009	Publication (Diabetes Care)	No supplemental data sources
Taskinen, 2011	Publication (Diabetes Obes Metab)	No supplemental data sources
Bergenstal, 2010b	Conference abstract (ADA 70th Scientific Sessions; Abstract 58-OR)	No supplemental data sources
Kaku, 2009	Publication (Curr Med Res Opin)	No supplemental data sources
Charbonnel, 2006	Publication (Diabetes Care)	No supplemental data sources
Bolli, 2008	Publication (Diabetes Obes Metab)	Publication (Bolli, 2009; Diabetes Obes Metab)
Pratley, 2010	Publication (The Lancet)	Publication (Pratley, 2011; Int J Clin Pract)
Duration of study: 18 to 30 weeks (with SUs)		
Ristic, 2006	Publication (Diabetic Medicine)	Publication (Ristic, 2007; Diabetes Obes Metab)
Arechavaleta, 2011	Publication (Diabetes Obes Metab)	Conference abstract (Goldstein, 2010; EASD 46th Annual Meeting; Abstract 819)
Marre, 2002a	Publication (Diabetic Medicine)	No supplemental data sources

Author, Year	Primary Data Source	Supplemental Data Source(s)
Moses, 1999	Publication (Diabetes Care)	No supplemental data sources
Umpierrez, 2006	Publication (Curr Med Res Opin)	No supplemental data sources
Charpentier, 2001	Publication (Diabetic Medicine)	No supplemental data sources
Papathanassiou, 2009	Publication (Atherosclerosis)	No supplemental data sources
Duration of study: >30 weeks		
Nauck, 2007b	Publication (Diabetes Obes Metab)	Publication (Seck, 2010; Int J Clin Pract)
Goke, 2010	Publication (Int J Clin Pract)	Unpublished CSR (AZ/BMS, 2010; D1680C00001)
Filozof, 2010	Publication (Diabetic Medicine)	No supplemental data sources
Derosa, 2010	Publication (Diabetes Technol Ther)	No supplemental data sources
Salvadeo, 2010	Conference abstract (Salvadeo, 2010; EASD 46th Annual Meeting; Abstract 852)	No supplemental data sources
Matthews, 2005	Publication (Diabetes/Metabolism Research Reviews)	Publication (Charbonnel, 2005b; Diabetologia)
Matthews, 2010	Publication (Diabetes Obes Metab)	Publication (Ferrannini, 2009; Diabetes Obes Metab)

Table 8. Data sources of identified studies: insulin add-on

Author, Year	Primary Data Source	Supplemental Data Source(s)
Studies involving dapagliflozin		
Duration of study: 12 to 17.9 weeks		
Wilding, 2009	Publication (Diabetes Care)	Unpublished CSR (BMS, 2009; MB102009)
Duration of study: 18 to 30 weeks		
Wilding, 2012	Publication (Ann Intern Med)	Unpublished CSR (AZ, 2010; D1690C00006), Wilding 2010b
Studies not involving dapagliflozin		
Duration of study: 12 to 17.9 weeks		
Strowig, 2002	Publication (Diabetes Care)	No supplemental data sources
Schiel, 2008	Publication (Exp Clin Endocr Diab)	No supplemental data sources
Relimpio, 1998	Publication (Diabetic Medicine)	No supplemental data sources
Osei, 1984	Publication (Am J Med)	Publication (Falko, 1985; Am J Med)
Lewitt, 1989	Publication (Diabetes Care)	No supplemental data sources
Mudaliar, 2010	Publication (Diabetes Obes Metab)	No supplemental data sources
Rosenstock, 2002	Publication (Int J Clin Pract)	No supplemental data sources

Author, Year	Primary Data Source	Supplemental Data Source(s)
Asnani, 2006	Publication (Metab Syndr Relat Disord)	No supplemental data sources
Duration of study: 18 to 30 weeks		
Vilsboll, 2010	Publication (Diabetes Obes Metab)	No supplemental data sources
Yilmaz, 2007	Publication (Acta Diabetologica)	No supplemental data sources
Aviles-Santa, 1999	Publication (Ann Intern Med)	No supplemental data sources
Hirsch, 1999	Publication (Diabetes Care)	No supplemental data sources
Mattoo, 2005	Publication (Clinical Therapeutics)	No supplemental data sources
Zib, 2007	Publication (J Invest Med)	No supplemental data sources
Duration of study: >30 weeks		
Hermann, 2001	Publication (Diabetes Obes Metab)	No supplemental data sources
Casner, 1988	Publication (Clin Pharmacol Ther)	No supplemental data sources

5.2.4 Complete list of relevant RCTs

Five RCTs (Table 9 and Table 10) compared the intervention of interest (dapagliflozin 10mg once a day) to either placebo or another anti-diabetic agent of interest. Among these trials, dapagliflozin was administered under two indications:

- As an add-on among patients whose T2DM disease was not well controlled with metformin; and
- As an add-on among patients whose T2DM disease was not well controlled with insulin (with or without other oral antidiabetic agents).

Trial arms involving doses of dapagliflozin that were not administered at the recommended, licensed dose of 10mg once a day are not presented.

The list of relevant RCTs involving the agent of interest (dapagliflozin) is presented in (Table 9 and Table 10). As these are the main dapagliflozin RCTs that will be referenced throughout this document, we have referred to each according to the last two digits of their BMS/AZ trial number (or last one digit where the last two digits fall between 01 and 09) and a 'short study descriptor' (as shown in the first two columns of Table 9 and Table 10), to aid the readability of the submission. 'Study X' will be used to reference these RCTs.

Table 9. List of relevant RCTs (metformin add-on studies)

Trial no.	Short study descriptor	Intervention	Comparator	Population	ClinicalTrials.gov identifier	BMS/AZ identifier	Primary study reference
Study 14†	Add-on to metformin	Dapagliflozin 10mg	Placebo	Type 2 diabetics inadequately controlled on metformin alone	NCT00528879	MB102014	Bailey et al., 2010
Study 12†	Weight loss	Dapagliflozin 10mg	Placebo	Type 2 diabetics inadequately controlled on metformin alone	NCT00855166	D1690C00012	Bolinder et al., 2012
Study 4†	Head to head vs. SU	Dapagliflozin 10mg	Glipizide (a sulphonylurea)	Type 2 diabetics inadequately controlled on metformin alone	NCT00660907	D1690C00004	Nauck et al., 2011a, 2011b

Abbreviations: BMS/AZ, Bristol-Myers Squibb/AstraZeneca; †, Source: Published report and BMS/AZ data on file (clinical study report); SU, sulphonylurea

Table 10. List of relevant RCTs (insulin add-on studies)

Trial no.	Short study descriptor	Intervention	Comparator	Population	ClinicalTrial.gov identifier	BMS/AZ identifier	Primary study reference
Study 6†	Phase 3 Add-on to insulin	Dapagliflozin 10mg	Placebo	Type 2 diabetics inadequately controlled on insulin, with or without oral antidiabetic drugs	NCT00673231	D1690C00006	Wilding et al., 2012)
Study 9†	Phase 2b Add-on to insulin	Dapagliflozin 10mg	Placebo	Type 2 diabetics inadequately controlled on insulin, with or without oral antidiabetic drugs	NCT00357370	MB102009	Wilding et al., 2009

Abbreviations: BMS/AZ, Bristol-Myers Squibb/AstraZeneca; †, Source: Published report and BMS/AZ data on file (clinical study report);

5.2.5 Studies comparing the intervention directly with the appropriate comparator(s) stated in the decision problem

All the studies identified in Table 9 and Table 10 compare the intervention (dapagliflozin) with either a placebo or a comparator of interest.

5.2.6 Studies excluded from further discussion

None of the studies described in Table 9 and Table 10 were excluded from further discussion; however, Study 9 was excluded from the network meta-analysis, for reasons described in Section 5.7.2.1.

5.2.7 List of relevant non-RCTs

There is no non-RCT evidence for dapagliflozin. Data from pharmacokinetic and phase 1 studies were identified, but these are not presented as they are not relevant to the decision problem.

5.3 Summary of methodology of relevant RCTs

5.3.1 Summary

The sub-sections below summarise key aspects of the methodology employed in the relevant RCTs involving dapagliflozin 10mg once a day. For each RCT, the following information has been provided:

- Section 5.3.2 (Methods): study location, duration, blinding, randomisation, interventions and outcomes;
- Section 5.3.3 (Participants): inclusion and exclusion criteria for subject selection;
- Section 5.3.4 (Baseline characteristics): baseline demographic characteristics of patients;
- Section 5.3.5 (Outcomes): primary and secondary outcomes;
- Section 5.3.6 (Statistical analyses): the primary hypotheses, sample size estimation and relevant statistical assumptions;
- Section 5.3.7 (Subgroup analyses); and
- Section 5.3.8 (Participant flow): including a CONSORT flowchart of the participants in each RCT

5.3.2 Methods

The methodology of the relevant RCTs is summarised in Table 11 and Table 12.

Table 11. Comparative summary of methodology of the metformin add-on RCTs

Study characteristics	Study 14†,††	Study 12††	Study 4‡,§,††
Location	International, with 80 centres: 30 in the USA, 21 in Canada, 11 in Argentina, 10 in Mexico, 8 in Brazil	Europe, with 40 centres in five countries (Bulgaria, Czech Republic, Hungary, Poland and Sweden)	International, with 95 centres in 10 countries (Argentina, 17 centres; France, 7; Germany 16; Italy, 3; Mexico, 4; The Netherlands, 10; South Africa, 10; Spain, 6; Sweden 10; and United Kingdom 12)
Design	Phase 3 treatment randomised, double-blind, parallel assignment, placebo-controlled safety/efficacy study	Phase 3 treatment randomised, double-blind, parallel assignment, placebo-controlled safety/efficacy study	Phase 3 treatment, randomised, double-blind, parallel assignment, active-controlled non-inferiority study
Duration of study	September 2007 – May 2010 (primary completion date: Nov 2008)	February 2009 – December 2011 (primary completion date: June 2010)	March 2008 – January 2013 (primary completion date: December 2009)
Method of randomisation	Computer-based	Computer-based	Computer-based
Method of blinding (care provider, patient and outcome assessor)	Double-blind (patient and investigator)	Double-blind (patient and investigator)	Double-blind (patient and investigator)
Intervention(s) (n =) and comparator(s) (n =)	Dapagliflozin 10mg od (n=135) compared to placebo (n= 137), in addition to open-label metformin with patients' usual dose.	Dapagliflozin 10mg od (n= 91) compared to placebo (n= 91), in addition to open-label metformin with patients' usual dose.	Dapagliflozin (n= 406, starting 2.5mg od up-titrated to ≤10mg od) compared to glipizide (n= 408, starting 5mg od up-titrated to ≤20mg od). Both in addition to open-label metformin at 1500 to 2500mg daily.
Primary outcomes (including scoring methods and timings of assessments)	Change from baseline in HbA1c (%) [Time frame: at 24 weeks]	Change from baseline in body weight (kg) [Timeframe: at 24 weeks]	Change from baseline in HbA1c (%) [Timeframe: at 52 weeks]

Study characteristics	Study 14†,††	Study 12††	Study 4‡,§,††
Secondary outcomes (including scoring methods and timings of assessments)	Change from baseline in fasting plasma glucose (FPG) concentration [Time frame: at 1 week] Change from baseline in FPG concentration [Time frame: at 24 weeks] Change from baseline in total body weight [Time frame: at 24 weeks] Proportion of patients achieving a therapeutic glycaemic response, defined as HbA1c <7% [Time frame: at 24 weeks] Change from baseline in HbA1c percentage among patients with baseline HbA1c ≥ 9% [Time frame: at 24 weeks]	Change from baseline in waist circumference (cm) [Timeframe: at 24 weeks] Change from baseline in body fat mass measured by Dual Energy X-ray Absorptiometry [Timeframe: at 24 weeks] Proportion of patients with body weight decrease of ≥ 5% [Timeframe: at 24 weeks]	Change in body weight [Timeframe: at 52 weeks] Proportion of patients reporting at least one hypoglycaemic episode [Timeframe: at 52 weeks] Proportion of patients with body weight decrease ≥ 5% from baseline [Timeframe: at 52 weeks]
Duration of follow-up	24 weeks followed by a 78-week extension period	24 weeks followed by a 78-week extension period	52 weeks short-term period followed by two extension period (52 weeks and 104 weeks, respectively)

Abbreviations: FPG, Fasting plasma glucose; HbA1c, Glycosylated haemoglobin; USA, United States of America; †, Although there were four treatment arms (dapagliflozin 2.5mg, 5mg, 10mg and placebo arms) in this RCT, data were only presented from two arms (dapagliflozin 10mg and placebo arms); ‡, Publication (Nauck et al., 2011); §, Up-titration occurred during the first 18 weeks of treatment administration until fasting plasma glucose of <6.1 mmol/L or to the maximum tolerated dose; this dose at end of titration was maintained for a further 34 weeks; †† Source: Published report and BMS/AZ data on file (clinical study report)
od once a day

Table 12. Comparative summary of methodology of the insulin add-on RCTs

Study characteristics	Study 6†,§	Study 9§
Location	International, with 126 centres in 13 countries (USA, Austria, Bulgaria, Canada, Finland, Germany, Hungary, Netherland, Romania, Russian Federation, Slovakia, Spain and United Kingdom)	North America, with 26 centres in total (19 in the United States and 7 in Canada)
Design	Phase 3 treatment randomised, double-blind, parallel assignment, placebo-controlled safety/efficacy study	Phase 2 randomised, double-blind, parallel assignment, placebo-controlled, safety/efficacy pilot study;
Duration of study	April 2008 – November 2009	October 2006 – March 2008
Method of randomisation	Computer-based	An interactive voice response system (IVRS) was used for randomisation; randomisation schedules were generated by study manufacturer
Method of blinding (care provider, patient and outcome assessor)	Double-blind (subject, caregiver, investigator and outcomes assessor)	Double-blind (subject, investigator, and sponsor personnel)
Intervention(s) (n =) and comparator(s) (n =)	Dapagliflozin 10mg (n=194) compared to placebo (n= 193), in addition to unchanged background insulin therapy ± oral antidiabetic agents	Dapagliflozin 10mg (n=24) compared to placebo (n= 23), in addition to open-label therapy with patients on 50% of usual daily insulin dose ± oral antidiabetic agents
Primary outcomes (including scoring methods and timings of assessments)	Change from baseline in HbA1c (%) [Timeframe: at 24 weeks]	Change from baseline in HbA1c percentage (last observation carried forward; LOCF) [Timeframe: at 12 weeks]
Secondary outcomes (including scoring methods and timings of assessments)	Change in body weight from baseline [Timeframe: at week 24] Absolute change in calculated mean daily insulin dose from baseline [Timeframe: at week 24] Proportion of patients with calculated mean daily insulin dose reduction from baseline [Timeframe: at week 24] Change in FPG from baseline [Timeframe: at week 24]	Change in FPG from baseline [Timeframe: at week 12] Proportion of patients achieving a therapeutic glycaemic response (defined as HbA1c <7.5%, ≤ 6.5%; HbA1c decrease from baseline ≥ 0.5%, ≥ 1.0%) Change from baseline in the total daily dose of insulin [Timeframe: at week 12]
Duration of follow-up	24 week short-term period RCT, with two extension periods (24 weeks and 56 weeks, respectively)	12 weeks

Abbreviations: FPG, Fasting plasma glucose; HbA1c, Glycosylated haemoglobin; IVRS, Interactive voice response system; LOCF, Last observation carried forward; TZD, Thiazolidinedione; USA, United States of America; †, Although there were four treatment arms (dapagliflozin 2.5mg, 5mg, 10mg and placebo arms) in this RCT, data were only presented from two arms (dapagliflozin 10mg and placebo arms); § Source: Published report and BMS/AZ data on file (clinical study report); od, once a day

5.3.3 Participants

The inclusion and exclusion criteria for the relevant RCTs are summarised in Table 13.

Table 13. Patient eligibility criteria used in the included RCTs involving dapagliflozin

Inclusion criteria	Exclusion criteria
Metformin add-on RCTs	
Study 14†	
Eligible patients met the following criteria: Aged 18–77 years, had T2DM, with haemoglobin A1c (HbA1c) ranging from 7–10%, C-peptide concentration of 0·34 nmol/L or more, body-mass index of 45 kg/m² or less, and were taking a stable dose of metformin (≥1500mg per day) for at least 8 weeks before enrolment.	Exclusion criteria included: Serum creatinine 133 µmol/L or more for men or 124 µmol/L or more for women (consistent with metformin labelling); urine albumin/ creatinine ratio more than 203·4 mg/mmol, aspartate aminotransferase or alanine aminotransferase more than three times the upper limit of normal, creatine kinase more than three times the upper limit of normal, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with >10% weight loss during the 3 months before enrolment); clinically significant renal, hepatic, haematological, oncological, endocrine, psychiatric, or rheumatic disease; recent cardiovascular event (within 6 months) or New York Heart Association class III or IV congestive heart failure; and systolic blood pressure 180 mmHg or more or diastolic blood pressure 110 mmHg or more
Study 12†	
Eligible patients met the following criteria: Had T2DM; were aged 30 – 75 years for males and 55 – 75 years for females who were postmenopausal for a period of at least five years; on-going treatment with metformin on a stable dose of ≥1500mg daily for at least 12 weeks prior to enrolment; and with inadequate glycaemic control, defined as HbA1c ≥6.5% and ≤8.5%; fasting plasma glucose (FPG) less than or equal to 240 mg/dL (≤13.2 mmol/L); body mass index (BMI) of 25 kg/m^2 or higher; body weight no higher than 120 kg	Exclusion criteria included: Patients with type 1 diabetes; with body weight change >5% within three months prior to enrolment; with renal (kidney) and liver impairment; males under 30 years and perimenopausal women
Study 4†	
Eligible patients met the following criteria: Aged ≥ 18 years with a diagnosis of T2DM; treatment with oral antidiabetic drug therapy including metformin for at least 8 weeks prior to enrolment; inadequately controlled T2DM (HbA1c >6.5% and ≤10%); FPG ≤ 15 mmol/L and C-peptide concentration of ≥ 0.33 nmol/L.	Exclusion criteria included: Diagnosis of type 1 diabetes; treatment with insulin therapy within one year of enrolment; use of weight loss medication within 30 days of enrolment; BMI > 45.0 kg/m^2; and patients with renal (kidney) failure or dysfunction
Insulin add-on RCTs	
Study 6†	
Eligible patients met the following criteria: Age 18 to 80 years, had T2DM; BMI ≤ 45 kg/m^2, inadequate glycaemic control (HbA1c ≥7.5% and ≤10.5%) and were on a stable insulin regimen of at	Exclusion criteria included: Diagnosis of type 1 diabetes; symptoms of poorly controlled diabetes; calculated creatinine clearance less than 50 mL/min per 1.73 m^2; or a measured serum creatinine level greater

Inclusion criteria	Exclusion criteria
least 30 IU (international unit) of injectable insulin per day for at least eight weeks either without any other oral antidiabetic drug or with a stable dose of oral antidiabetic drugs	than 177 µmol/L (> 2 mg/dL) or, if receiving metformin, greater than 133 µmol/L (> 1.5 mg/dL) for men and at least 124 µmol/L (≥1.4 mg/dL) for women; treatment with more than two additional oral antidiabetic drugs; and patients with moderate and severe renal (kidney) failure or dysfunction.
Study 9†	
Eligible patients met the following criteria:	Exclusion criteria included:
Aged 18–75 years; had T2DM; HbA1c ≥7.5% and ≤10.5% and were treated with subcutaneous insulin ≥ 12 weeks prior to enrolment (average daily insulin dose was equivalent to ≥50 units of U100 insulin/day); insulin treatment was stable for at least 6 weeks prior to enrolment	History of type 1 diabetes, aspartate transaminase and/or alanine transaminase >2.5 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, symptoms of severely uncontrolled diabetes, a history of severe hypoglycaemia, and unstable condition or serious CV, renal, or hepatic disease

Abbreviations: BMI, Body mass index; FPG, Fasting plasma glucose;HbA1c, Glycosylated haemoglobin; IU, International unit; †, Source: Published report and BMS/AZ data on file (clinical study report);

5.3.4 Baseline characteristics

Patient characteristics at baseline are summarised in Table 14.

Table 14. Characteristics of participants in the RCTs across randomised groups

Baseline characteristics	Dapagliflozin 10mg arm	Placebo or SU arm
Metformin add-on RCTs		
Study 14‡		
Sample size	135	137
Age (mean (SD) years)	52.7 (9.9)	53.7 (10.3)
Gender (% male)	57	55
Race (%)	White: 89.6; Black/ African American: 3.0; Asian: 0.7; Other: 6.7	White: 90.5; Black/ African American: 1.5; Asian: 2.2; Other: 5.8
Duration of diabetes (mean (SD) years)	6.1 (5.4)	5.8 (5.1)
HbA1c (mean (SD) %)	7.92 (0.82)	8.11 (0.96)
Weight (mean (SD) kg)	86.10 (17.56)	87.85 (19.21)
Body mass index (BMI, mean (SD) kg/m^2)	31.2 (5.1)	31.8 (5.3)
Fasting plasma glucose (FPG, mean (SD) mmol/L)	8.66 (2.15)	9.19 (2.57)
Total cholesterol (mean (SD) mmol/L)	4.8 (1.0)	4.7 (1.2)
LDL (mean (SD) mmol/L)	2.7 (0.9)	2.6 (0.9)
HDL (mean (SD) mmol/L)	1.1 (0.3)	1.1 (0.2)
Triglycerides (mean (SD) mmol/L)	2.2 (1.6)	2.0 (1.2)

Baseline characteristics	Dapagliflozin 10mg arm	Placebo or SU arm
Systolic blood pressure (SBP, (mean (SD) mmHg)	126.0 (15.9)	127.7 (14.6)
Diastolic blood pressure (DBP, (mean (SD) mmHg)	79.0 (10.2)	80.9 (9.0)
Study 12‡		
Sample size	89	91
Age (mean (SD) years)	60.6 (8.16)	60.8 (6.82)
Gender (% male)	55	56
Race (%)	White: 100	White: 100
Duration of diabetes (mean (SD) years)	6.03 (4.53)	5.52 (5.27)
HbA1c (mean (SD) %)	7.19 (0.44)	7.16 (0.53)
Weight (mean (SD) kg)	92.06 (14.1)	90.91 (13.7)
BMI (mean (SD) kg/m^2)	32.06 (3.89)	31.68 (3.89)
FPG, (mean (SD) mmol/L)	8.22 (1.37)	8.30 (1.39)
Total cholesterol (mean (SD) mmol/L)	NR	NR
LDL (mean (SD) mmol/L)	NR	NR
HDL (mean (SD) mmol/L)	NR	NR
Triglycerides (mean (SD) mmol/L)	NR	NR
SBP (mean (SD) mmHg)	135.9 (NR)	133.3 (NR)
DBP (mean (SD) mmHg)	80.6 (NR)	80.4 (NR)
Study 4‡§		
Sample size	400	401
Age (mean (SD) years)	58.1 (9.37)	58.6 (9.80)
Gender (% male)	55	55
Race (%)	White: 81.8; Black/ African American: 6.5; Asian: 6.8; Other: 5.0	White: 80.5; Black/ African American: 6.0; Asian: 8.5; Other: 5.0
Duration of diabetes (mean (SD) years)	6.08 (4.61)	6.55 (5.90)
HbA1c (mean (SD) %)	7.69 (0.86)	7.74 (0.89)
Weight (mean (SD) kg)	88.44 (16.32)	87.60 (16.97)
BMI (mean (SD) kg/m^2)	31.71 (5.10)	31.23 (5.05)
FPG, mean (SD) mmol/L)	9.0 (2.10)	9.10 (2.31)
Total cholesterol (mean (SD) mmol/L)	4.82 (1.08)	4.64 (1.02)
LDL (mean (SD) mmol/L)	2.78 (0.91)	2.55 (0.83)
HDL (mean (SD) mmol/L)	1.17 (0.29)	1.21 (0.32)
Triglycerides (mean (SD) mmol/L)	1.95 (1.12)	1.93 (1.28)

Baseline characteristics	Dapagliflozin 10mg arm	Placebo or SU arm
SBP (mean (SD) mmHg)	132.8 (14.89)	133.8 (14.69)
DBP (mean (SD) mmHg)	80.6 (8.42)	80.6 (8.46)
Insulin add-on RCTs		
Study 6‡		
Sample size	194	193
Age (mean (SD) years)	59.3 (8.75)	58.8 (8.61)
Gender (% male)	45	49
Race (%)	White: 94.8; African American: 2.6; Asian: 1.5; Other: 1.0	White: 96.4; African American: 3.1; Asian: 0; Other: 0.5
Duration of diabetes (mean (SD) years)	14.2 (7.3)	13.5 (7.3)
HbA1c (mean (SD) %)	8.57 (0.82)	8.47 (0.77)
Weight (mean (SD) kg)	94.5 (16.79)	94.5 (19.82)
BMI (mean (SD) kg/m^2)	33.4 (5.06)	33.1 (5.86)
FPG, mean (SD) mmol/L)	9.61 (3.05)	9.47 (3.17)
Total cholesterol (mean (SD) mmol/L) †	4.63 (1.13)	4.66 (1.16)
LDL (mean (SD) mmol/L) †	2.64 (1.00)	2.67 (0.86)
HDL (mean (SD) mmol/L) †	1.21 (0.35)	1.24 (0.39)
Triglycerides (mean (SD) mmol/L) †	1.77 (0.90)	1.80 (1.44)
SBP (mean (SD) mmHg) †	140.6 (16.70)	136.1 (17.17)
DBP (mean (SD) mmHg)	NR	NR
Calculated mean daily insulin dose (mean (SD) IU/day)	78.0 (45.0)	73.7 (42.4)
Study 9‡		
Sample size	24	23
Age (mean (SD) years)	55.7 (9.2)	58.4 (6.5)
Gender (% male)	54.2	69.6
Race (%)	White: 91.7; African American: 4.2; Asian: 4.2; Other: 0	White: 95.7; African American: 0; Asian: 0; Other: 4.3
Duration of diabetes (mean (SD) years)	11.8 (5.8)	13.8 (7.3)
HbA1c (mean (SD) %)	8.4 (0.7)	8.4 (0.9)
Weight (mean (SD) kg)	103.4 (10.2)	101.8 (16.5)
BMI (mean (SD) kg/m^2)	35.5 (3.6)	34.8 (4.6)
FPG, mean (SD) mmol/L)	8.7 (2.2)	9.2 (2.9)
Total cholesterol (mean (SD) mmol/L)	NR	NR-
LDL (mean (SD) mmol/L)	NR	NR

Baseline characteristics	Dapagliflozin 10mg arm	Placebo or SU arm
HDL (mean (SD) mmol/L)	NR	NR
Triglycerides (mean (SD) mmol/L)	NR	NR
SBP (mean (SD) mmHg)	130.7 (14.5)	128.9 (14.0)
DBP (mean (SD) mmHg)	NR	NR
Total daily insulin dose (median (interquartile range) U100/day) ††	93.0 (67.5 – 136.0)	90.0 (70.0 – 136.0)

Abbreviations: BMI, Body mass index; DBP, Diastolic blood pressure; HbA1c, Glycosylated haemoglobin; HDL, High density lipoprotein; IU, International unit; LDL, low density lipoprotein; NR, not reported; SBP, Systolic blood pressure; DBP, diastolic blood pressure; SD, Standard deviation; SU, Sulphonylurea;†, Presented data are from the full analysis set after excluding data post-insulin-up titration; Estimate is presented as a range; ‡, Source: Published report and BMS/AZ data on file (clinical study report); §, Comparator arm is glipizide i.e. a sulphonylurea (not placebo); ††, Before insulin dose reduction on day1 of double-blind period

5.3.5 Outcomes

The primary and secondary clinical outcomes reported in Table 15 are currently used in actual clinical practice to assess response to treatment in T2DM patients. HbA1c, the primary surrogate endpoint used in the clinical trials, is recognised by the CHMP as the most widely accepted measure of overall, long-term blood glucose control (EMA, 2011). It is an accepted surrogate marker for the risk of microvascular diabetic complications. Secondary endpoints included change in fasting plasma glucose (FPG), the proportion of patients reaching target HbA1c, change in body weight, change in blood pressure, change in daily insulin dose, proportion of patients reporting hypoglycaemia, safety and tolerability. These are all clinically relevant outcomes for clinicians and patients alike.

Table 15. Primary and secondary outcomes of the RCTs

Trial no.	Primary outcome(s) and measures	Secondary outcome(s) and measures
Metformin add-on RCTs		
Study 14†	Change from baseline in HbA1c percentage at 24 weeks	Change in FPG concentration and body weight at 24 weeks, change in FPG at 1 week, the proportion of patients achieving glycaemic response; change in HbA1c percentage at week 24 among patients with baseline HbA1c ≥ 9%
Study 12†	Change from baseline in body weight (kg) at 24 weeks	Change from baseline in waist circumference (cm) at 24 weeks; change from baseline in body fat mass measured by Dual Energy X-ray Absorptiometry at 24 weeks; proportion of patients with body weight decrease of ≥ 5% at 24 weeks
Study 4†‡	Change from baseline in HbA1c percentage at 52 weeks	Change in body weight and number of patients reporting hypoglycaemic episodes at 52 weeks

Trial no.	Primary outcome(s) and measures	Secondary outcome(s) and measures
Insulin add-on RCTs		
Study 6†	Change from baseline in HbA1c percentage at 24 weeks	Change in body weight from baseline to week 24; Absolute change in calculated mean daily insulin dose from baseline to week 24; proportion of patients with calculated mean daily insulin dose reduction from baseline to week 24; change in FPG from baseline to week 24
Study 9†	Change from baseline in HbA1c percentage at 12 weeks	Change in FPG from baseline to week 12; proportion of patients achieving a therapeutic glycaemic response (defined as HbA1c <7.5%, ≤ 6.5%; HbA1c decrease from baseline ≥ 0.5%, ≥ 1.0%); and change in the total daily dose of insulin from baseline to week 12

Abbreviations: FPG, Fasting plasma glucose; HbA1c, Glycosylated haemoglobin; †, Source: Published report and BMS/AZ data on file (clinical study report); ‡, Comparator arm is glipizide i.e. a sulphonylurea (not placebo);

5.3.6 Statistical analysis and definition of study groups

The statistical analysis, study group description including the sample size calculation, is described in Table 16.

Table 16. Summary of statistical analyses in RCTs

Trial no.	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Metformin add-on RCTs				
Study 14†	The study was designed to assess the efficacy and safety of dapagliflozin when added to metformin in adult patients with T2DM who are not adequately controlled with metformin alone. It is hypothesised that after 24 weeks of treatment administration, there will be greater mean reduction from baseline in glycosylated haemoglobin achieved with dapagliflozin plus metformin compared to placebo plus metformin	Analyses of continuous outcomes were based on separate analysis of covariance (ANCOVA) models with treatment group as an effect and the baseline value as a covariate (LOCF). As part of the secondary analyses, the comparison of proportions of patients achieving a therapeutic glycaemic response was done with logistic regression based on established methodology, with adjustment for baseline (Zhang et al, 2008; Tsiatis et al, 2008). After adjustment for baseline values and differences in mean changes from baseline at week 24, p values for primary and secondary endpoints were calculated to compare dapagliflozin with placebo. For the primary analysis (change from baseline in HbA1c percentage at week 24), comparisons between each dapagliflozin group and placebo group were done at α=0·019 applying Dunnett's adjustment. If the primary endpoint was significant, changes from baseline in secondary endpoints would be tested sequentially at α=0·05: fasting plasma glucose concentration at week 24, total bodyweight at week 24, proportion of patients with HbA1c less than 7·0% at week 24, HbA1c percentage at week 24 in patients with baseline HbA1c of 9% or more, total bodyweight at week 24 in patients with baseline body-mass index 27 kg/m² or more (In: supplementary web appendix, Bailey, 2010), HbA1c percentage at week 24 in patients with baseline body-mass index 27 kg/m² or more (In supplementary web appendix, Bailey, 2010), fasting plasma glucose concentration at week 1, and proportion of patients achieving HbA1c 6·5% or lower at week 24. No p values were generated for exploratory endpoints. Only summary statistics were reported for safety. Statistical analyses were done with SAS/STAT version 8.2.	With 129 patients per treatment group with post-baseline measurements, there was 90% power to detect a difference in mean of HbA1c of 0·5% between each dapagliflozin treatment group and the placebo group, on the assumption of a standard deviation (SD) of 1·1%.(Buse et al, 2005) If 5% of patients did not have a post-baseline assessment, 544 patients (136 per group) needed to be randomised	The primary efficacy dataset consisted of all randomised patients who received at least one dose of double-blind study medication and who had both a baseline and at least one post-baseline measurement. For rescued patients, measurements obtained after initiation of rescue medication were not included in the efficacy analysis, but were included in the safety analysis. Longitudinal repeated analysis over time including the fixed categorical effects of treatment, week, and treatment-by-week by interaction as well as the continuous fixed co-variance of baseline measurement and baseline measurement – by-week interaction. Rescue was added as an additional effect in this mixed model when the analysis was performed

Trial no.	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
				including data after rescue (main analysis for this endpoint).
Study 12†	The study was designed to compare the efficacy and safety effect of dapagliflozin as add-on therapy to metformin relative to placebo (as add-on therapy to metformin). The hypothesis of the study was that dapagliflozin therapy leads to a decrease in body weight when compared to placebo.	A closed testing procedure was used to control the type I error rate at less than or equal to 0.05 (two-sided) across the primary and three key secondary endpoints. If the primary endpoint was significant at a level $P < 0.05$, then the results of the key secondary endpoints were interpreted using Hochberg's method (Hochberg, 1988). Continuous endpoints were evaluated using ANCOVA, with treatment and sex as fixed effects and baseline value as covariate. Proportions were analysed using logistic regression with adjustment for baseline values and sex as described by Zhang et al. (2008). P values are reported for the primary and key secondary endpoints and confidence intervals with nominal P values for exploratory endpoints. Two analysis sets were defined: the safety analysis set, consisting of all patients who received at least one dose of investigational product, and the full analysis set, consisting of all randomized patients who received at least one dose of investigational product and who had both a baseline and at least one post-baseline efficacy value for at least one efficacy variable. Primary, key secondary and exploratory endpoints were analysed using the full analysis set. For glycaemic variables, observations after initiation of rescue therapy were excluded from the analysis, with these and other missing values for glycaemic and nonglycaemic variables at week 24 replaced using the last observation carried forward (LOCF) method. Safety analyses were performed using descriptive statistics for the safety analysis set. All analyses were performed with SAS® version 8.2.	Sample size calculations were based on 12-week data of body weight change from an earlier study with dapagliflozin,(Zhang et al, 2010) in which the average placebo-corrected change in weight for the 10 mg dapagliflozin group was 1.3 kg at 12 weeks, and the standard deviation across the dapagliflozin doses was 2.6 kg. It was anticipated that data over 24 weeks would demonstrate a greater weight reduction, 2 kg, as well as greater variability. Assuming an approximately 50% increase in variability, a standard deviation of 4.0 kg was selected for this calculation. To detect a difference of 2 kg between the treatment groups, 86 evaluable patients per treatment group were required for 90% power at a two-sided significance level of 0.05. Assuming that 5% of the randomised patients would be excluded from the primary analysis because of missing data (e.g. lost to follow-up), at least 182 patients total needed to be randomised.	The last observation carried forward (LOCF) approach was used for all variables regardless of rescue medication except for glycaemic variables. For glycaemic variables (e.g. HbA1c, FPG), if a subject initiated rescue medication, the last value taken on or before the first rescue dose was used for analysis.

Trial no.	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Study 4†	The primary objective of this study was to demonstrate the non-inferiority of dapagliflozin as add-on therapy to metformin compared to a sulphonylurea (glipizide) as add-on therapy to metformin for the primary outcome variable; change from baseline to week 52 in HbA1c.	A hierarchical closed testing procedure was used to control the type I error rate ≤ 0.05 (two-sided) across the primary and key secondary efficacy variables. The non-inferiority margin δ is determined to be 0.35% (in absolute terms). A difference in HbA1c change from baseline to week 52 between the treatment groups of 0.35% or less is considered clinically equivalent from a medical point of view. Non-inferiority margins of 0.2% - 0.4% for change from baseline HbA1c are commonly used in studies which compare oral antidiabetic agents (Charbonnel et al, 2005a, Nauck et al, 2007a, Nauck et al, 2007b, Pan et al, 2007, Schweizer et al 2007); the non-inferiority margin selected for this study (0.35%) clearly falls within this range. The non-inferiority of the primary variable was tested first (one-sided 0.025 significance level); followed by the key secondary variables (test for superiority of dapagliflozin plus metformin over glipizide plus metformin at a two-sided 0.050 significance level). The primary efficacy variable was analysed with an ANCOVA which was used to derive a least squares estimate of the treatment difference in mean change with the corresponding 2-sided 95% CI. If the upper limit of the 95% CI was <0.35%, then dapagliflozin as add-on therapy to metformin was considered to be non-inferior to glipizide as add-on therapy to metformin. Other continuous key secondary efficacy variables were analysed using an ANCOVA yielding a least squares estimate of the treatment difference in mean change with corresponding p-value and two-sided 95% CI Further, two-sided 95% CI for the mean change within each treatment group were calculated. Comparisons between treatment groups in proportions were performed using the methodology of Zhang et al (2008) and Tsiatis et al (2008) with adjustment for baseline value. Efficacy was evaluated using the full analysis set. The primary efficacy variable was analysed with both the full analysis set and the per-protocol analysis set. The non-inferiority conclusion pertaining to the primary efficacy variable was drawn primarily based on results from the full analysis set. The safety analysis set was used in all summaries of safety data.	To demonstrate non-inferiority of dapagliflozin in comparison with glipizide as add-on therapy to metformin for changes from baseline to week 52 in HbA1c within a non-inferiority margin of 0.35%, assuming a SD of 1.25%, and at a one-sided significance level of 0.025, 280 evaluable patients are needed in each treatment group to provide approximately 90% power (given a true difference of zero between the two treatment groups). Assuming a 5% exclusion rate from the full analysis set, 295 patients per treatment group are needed for the full analysis set. To have adequate patients for the per-protocol population, assuming a 25% exclusion rate from the per-protocol population, 373 patients per treatment group (746 total) were planned for randomisation.	Two analysis sets were defined: the safety analysis set, consisting of all patients who received one or more doses of the investigational product, and the full analysis set, consisting of all randomized patients who received one or more doses of the investigational product and who had a nonmissing baseline and one or more post baseline efficacy value for one or more efficacy variable. Primary, key secondary, and exploratory end points were analyzed using the full analysis set. Missing values at week 52 were replaced using the LOCF method.

Trial no.	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		Discrete variables were summarised by counts, proportions, and corresponding 95% confidence intervals. Comparisons between the treatment groups were performed using two-sided Fisher's exact tests.		
Insulin add-on RCTs				
Study 6†	To evaluate the efficacy and safety of adding dapagliflozin therapy in patients whose T2DM mellitus is inadequately controlled with insulin with or without oral antidiabetic drugs	For continuous variables, a mixed model (using the PROC MIXED procedure in SAS [SAS Institute, Cary, North Carolina]) assessed changes from baseline with fixed effects for treatment group, OAD use, week, baseline value as a covariate, and interactions of week with treatment group and week with the baseline covariate. An unstructured covariance matrix was applied for repeated measures in a patient (Verbeke et al 2000). To probe the validity of the missing-at random assumption underlying the mixed model and to explore the potential effect of informative missing data, missing not at random, a sensitivity analysis was conducted by using pattern-mixture modelling that assumed control-based pattern imputation (Ratitch et al 2011). Categorical variables were analyzed by using the method of Zhang et al (2008), with adjustment for baseline mean daily dose of insulin and OAD use. Patients with missing data were included in these analyses and considered nonresponders. The Kaplan–Meier method was used to analyze time to onset of up-titration for not achieving prespecified glycaemic targets or discontinuation of therapy due to poor glycaemic control. Analysis of differences in proportions of patients experiencing adverse events of interest between the pooled dapagliflozin groups and the placebo group was performed by using Proc-StatXact 4 (Cytel Software, Cambridge, Massachusetts). All other statistical analyses were done with SAS, version 8.2. The frequency of general adverse events and changes in laboratory variables were summarised by using descriptive statistics	Sample sizes were calculated on the basis of anticipated differences in the primary efficacy variable. To detect a difference of 0.5% at a 2-sided significance level of 0.019 between dapagliflozin versus placebo for changes in HbA1c level from baseline to week 24 (assuming an SD of 1.2%), 153 patients per group were needed to provide 90% power. Assuming that 5% of patients would not be evaluable, the randomization target was 161 patients per group (a total of 644). An initial enrolment target of 1610 patients was calculated to account for screening failures. The primary efficacy variable was tested by using the Dunnett method with an α of 0.019 for each pairwise group comparison of dapagliflozin versus placebo (overall α level = 0.05) by using ANCOVA with treatment group and OAD use as fixed effects and baseline value as a covariate in the full analysis set. Data after insulin up-titration were excluded, and	Two analysis sets were defined: the safety set, comprising all randomly assigned patients who received at least 1 dose of study medication, and the full set, comprising all randomly assigned patients who received at least 1 dose of study medication and had a nonmissing baseline value and at least 1 post baseline efficacy value for at least 1 efficacy variable. Efficacy variables were analyzed with the full analysis set. Planned analyses over 48 weeks are reported with data from after insulin up-titration for all variables. Adjusted point estimates and 95% CIs are shown as originally planned. All reported P values are nominal and unadjusted for multiple comparisons.

Trial no.	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
			these and other missing values were replaced by using the LOCF method	
Study 9†	This study was designed with a primary objective of assessing the change from baseline in HbA1c achieved with each dose of dapagliflozin in combination with metformin and/or TZD and insulin therapy versus placebo in combination with metformin and/or TZD, after 12 weeks of oral administration of double-blind therapy.	Analyses for change from baseline in HbA1c, FPG, insulin dose, and total body weight at week 12 (LOCF) were performed using an ANCOVA model with treatment group as effect and baseline value as a covariate. No statistical hypothesis testing was planned for this study designed for exploratory analysis	A sample size target of 22 patients per treatment group permitted the calculation of 95% confidence intervals (CI) for the primary endpoint with a half-width of 0.42% for each treatment group, assuming a 1% standard deviation for the primary endpoint in each of the dapagliflozin and placebo arms. With the same assumption, the half-width of a 95% CI for the difference between any 2 treatment mean changes was estimated to be 0.59%. Assuming that 10% of patients would not have a post-baseline HbA1c measurement prior to up-titration of total daily dose of insulin (TDDI), 25 patients per treatment group (total of 75 patients) were expected to be randomised. However, 71 patients were actually randomised.	The primary efficacy dataset consisted of all randomly assigned patients who took ≥1 dose of double-blind study medication. Analyses of efficacy variables (except change from baseline in insulin dose) excluded data after insulin up-titration.

Abbreviations: ANCOVA, Analysis of covariance; CI, Confidence interval; FPG, Fasting plasma glucose; HbA1c, Glycosylated haemoglobin; ITT, Intention to treat; IU, International unit; LOCF, Last observation carried forward; mITT, Modified intention to treat; OAD, Oral antidiabetic drug; SD, Standard deviation; TDDI, Total daily dose of insulin; T2DM, Type 2 diabetes mellitus; † Source: Published report and BMS/AZ data on file (clinical study report);

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Below are the lists of pre-planned analyses to determine if there were variations in the response of any subgroups to dapagliflozin. However, to add a level of robustness to the findings, these analyses were carried out on pooled data as well some individual studies. Other than baseline HbA1c, not unexpectedly, no significant interactions by subgroup were observed. As the subgroup data, shown below, did not demonstrate any interactions they are described here rather than in the results section.

- Race
    - A treatment by subgroup interaction for race was not observed in the pooled monotherapy/combination therapy group or in any of the other individual studies (BMS, Summary of clinical efficacy, module 2.7.3).
- Ethnicity
    - A treatment by subgroup interaction for ethnicity was not observed in the pooled monotherapy/combination therapy pool. A potential interaction was found in the add-on to TZD study, however, this combination with dapagliflozin is not recommended in the SPC. (Dapagliflozin SPC, June 2012).
- Baseline HbA1c
    - Dapagliflozin treatment was consistently effective across baseline HbA1c subgroups (< 8%, ≥ 8% and < 9%, >9%) and generally resulted in greater HbA1c reductions from baseline in subjects with higher baseline HbA1c (Summary of clinical efficacy, module 2.7.3). This effect was anticipated as similar findings are observed with other diabetes therapies (De Fronzo et al. 2010).
- Age
    - Treatment with dapagliflozin was associated with HbA1c reductions across baseline age subgroups (< 65 years and ≥ 65 years). Efficacy appeared to be greater in the < 65 years of age category. However, a pre-specified analysis was conducted after controlling for baseline eGFR, as renal impairment becomes more common with increasing age and the efficacy of dapagliflozin depends on renal function. The interaction p value was 0.29 for this analysis, suggesting that there was not a systematic difference in efficacy between age groups after controlling for eGFR status (BMS, Summary of clinical efficacy, module 2.7.3).
- Gender
    - A potential interaction in Study 12 was observed with larger HbA1c reductions observed in men than in women, but these results are potentially confounded by different age-related inclusion criteria (≥ 30 and ≤ 75 years for men and ≥ 55 and

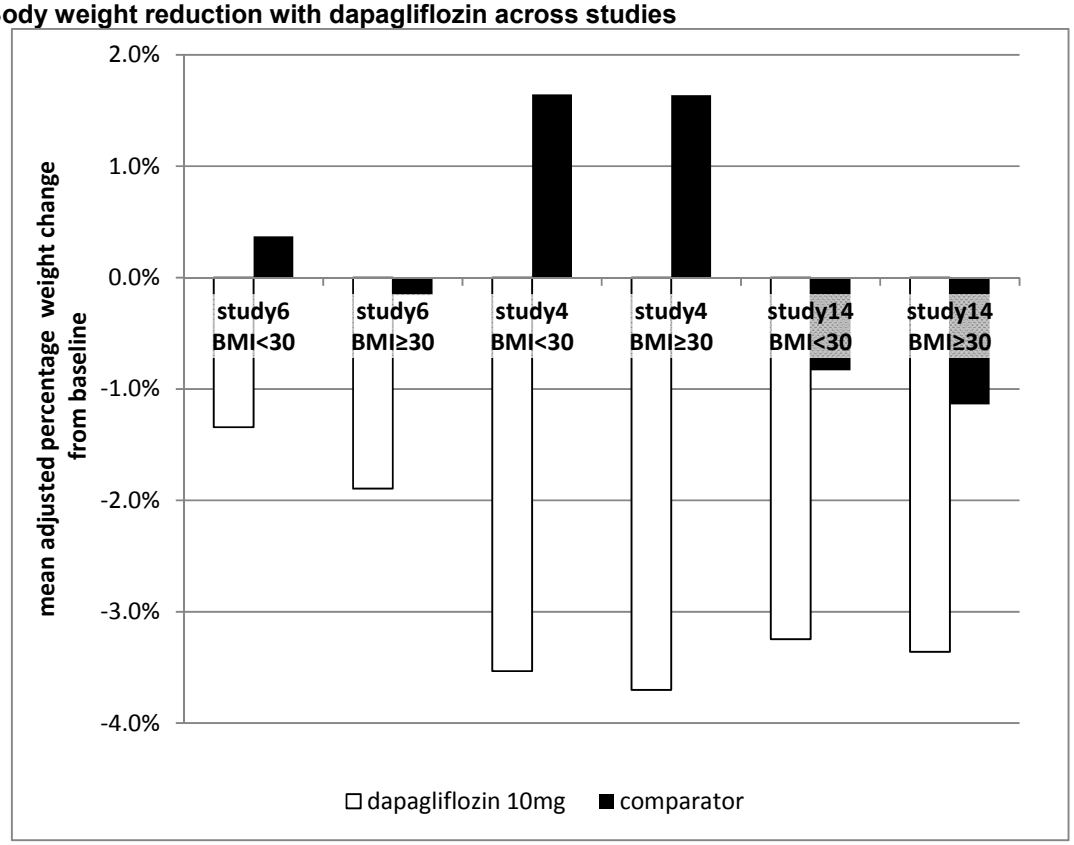
≤ 75 years for women). No treatment by subgroup interaction for gender was observed in any of the other individual studies or the pooled monotherapy/combination therapy group. (BMS, Summary of clinical efficacy, module 2.7.3).

- Gender/age (Female <50y; Female >50y): the female age subgroup, a surrogate indicator of menopausal status, was included as a subgroup in the dapagliflozin programme principally for assessment of safety effects in pre versus post-menopausal women. A potential interaction in which HbA1c reductions appeared greater in the younger subgroup, but this was consistent with the age subgroup analysis above. Treatment by subgroup interaction for this group was not observed for any of the studies.

- Baseline BMI

    - Body weight reductions were consistently observed in the dapagliflozin treatment groups across the Phase 3 studies (Figure 3). However, the majority of patients in all studies were overweight or obese and the proportion of normal weight patients in each study was small. The percentage weight loss from baseline observed in dapagliflozin patients with BMI < 30kg/m^2 compared with those with BMI ≥ 30kg/m^2 was similar. Baseline BMI does not appear to have an effect on the proportion of weight lost in dapagliflozin patients.

Figure 3. Body weight reduction with dapagliflozin across studies



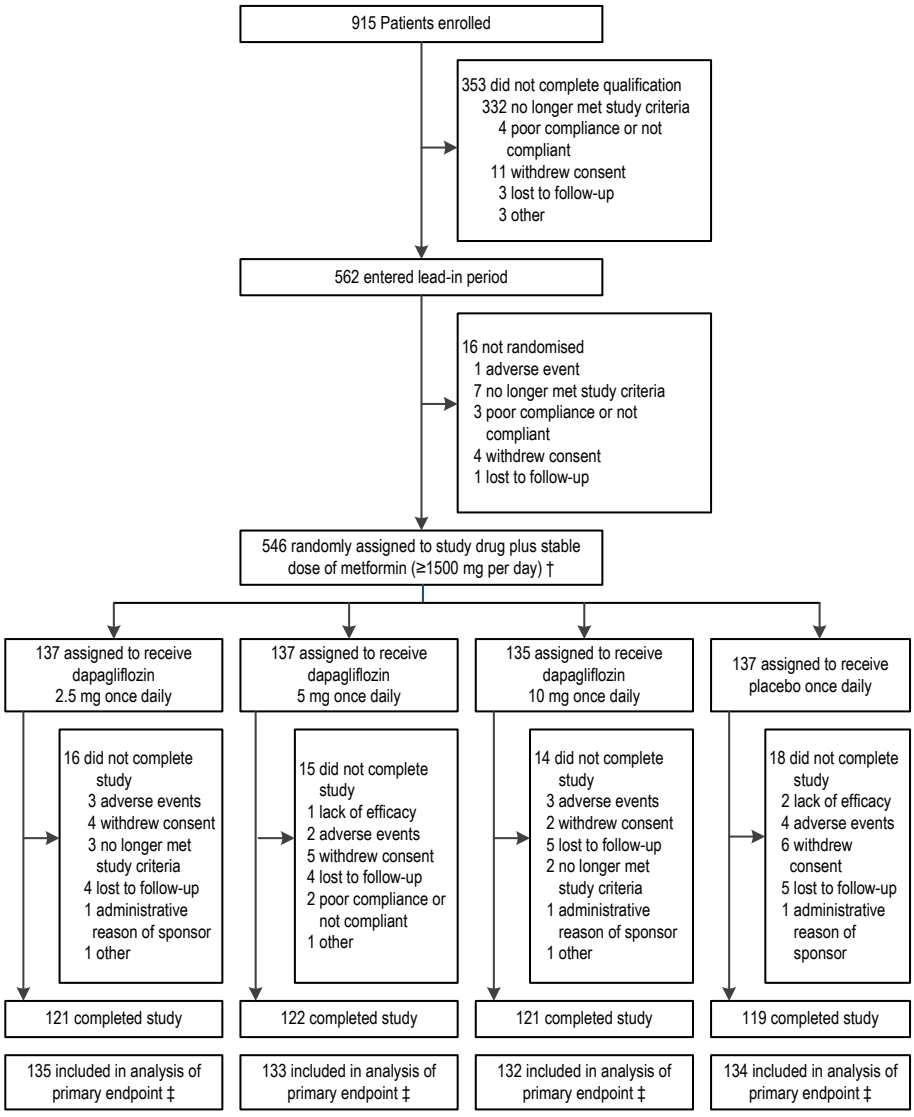
[redacted]

- Geographic Region
    - A treatment by subgroup interaction for geographic region (North America; South America; Europe; Asia/Pacific) was not observed in the pooled monotherapy/combination therapy group or in any of the other individual studies (BMS, Summary of clinical efficacy, module 2.7.3).

5.3.8 Participant flow

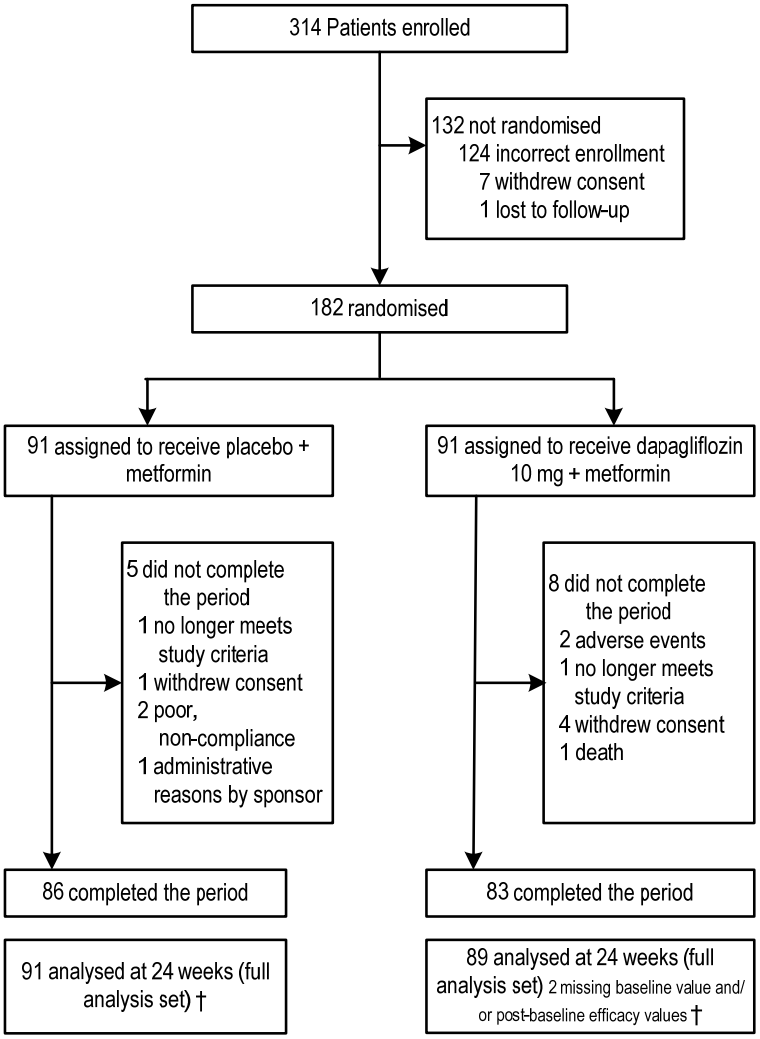
CONSORT flow charts showing the numbers of patients who were eligible to enter the relevant RCTs, and those who were randomised and allocated to each treatment are presented in Figure 4 to Figure 8.

Figure 4. Study 14 trial profile



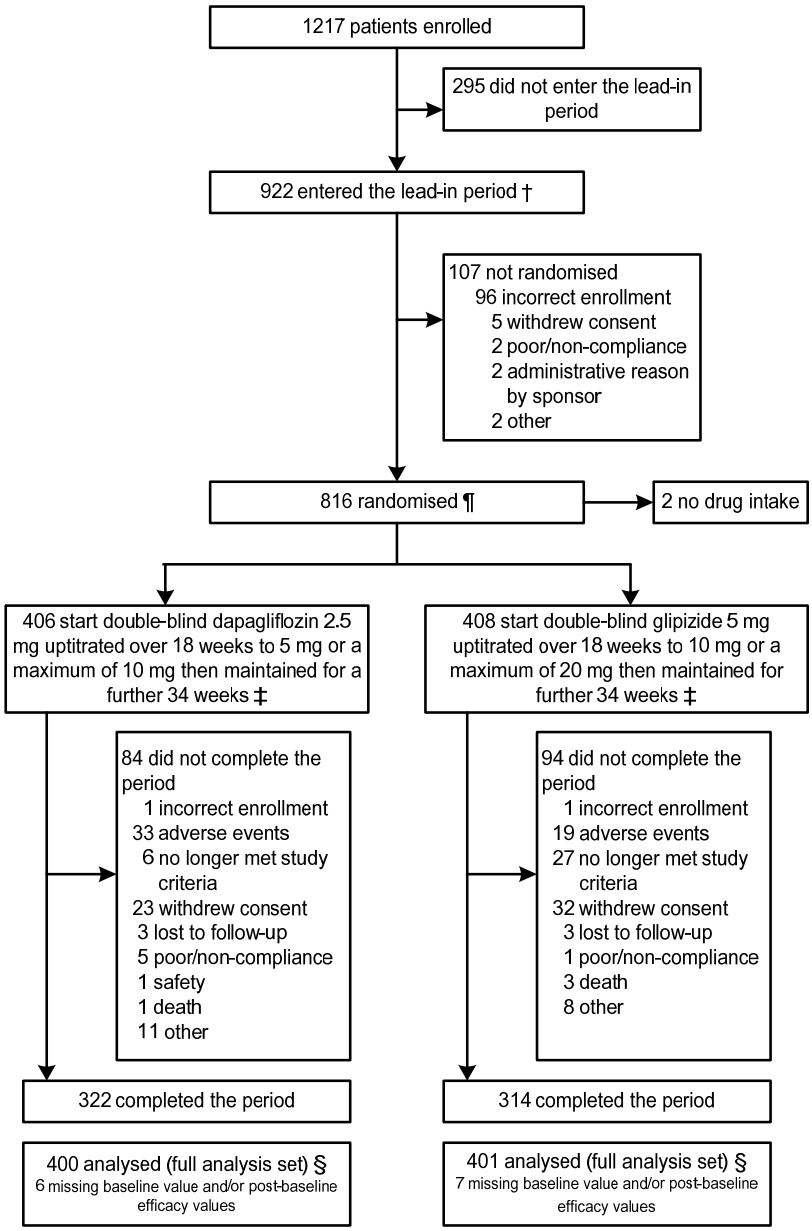
Abbreviations:
†, Random assignment was to three doses of dapagliflozin (2.5 mg, 5 mg, and 10 mg) and placebo i.e. in a 1:1:1:1 ratio, but only the dapagliflozin 10 mg and placebo arms were considered for the benefit assessment;
‡, The primary efficacy dataset consisted of all randomised patients who received at least one dose of double-blind study medication and who had both a baseline and at least one post-baseline measurement

Figure 5. Study 12 trial profile



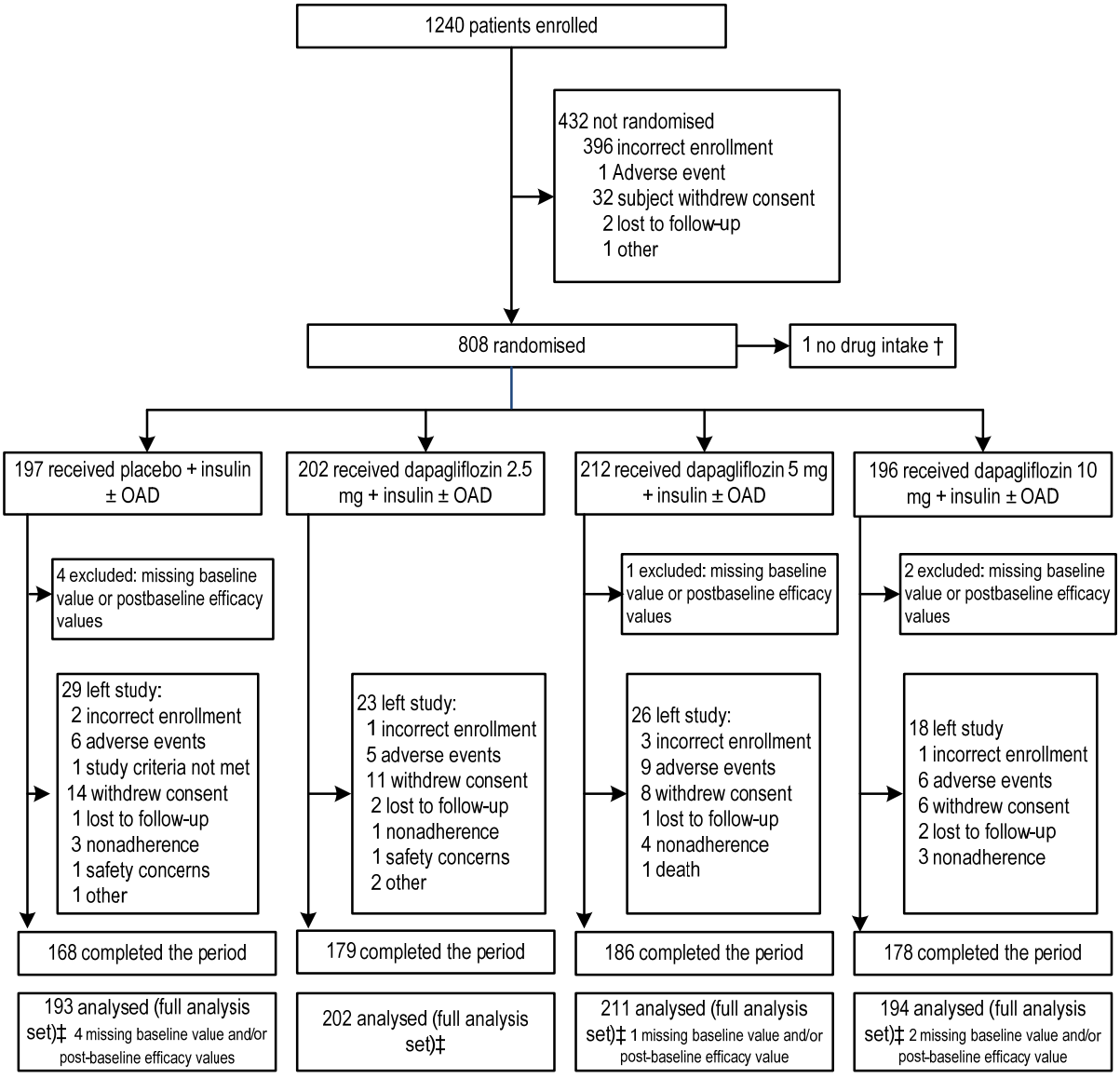
Abbreviations:
†, Full analysis set, consisting of all randomised patients who received at least one dose of investigational product and who had both a baseline and at least one post-baseline efficacy value for at least one efficacy variable

Figure 6. Study 4 trial profile



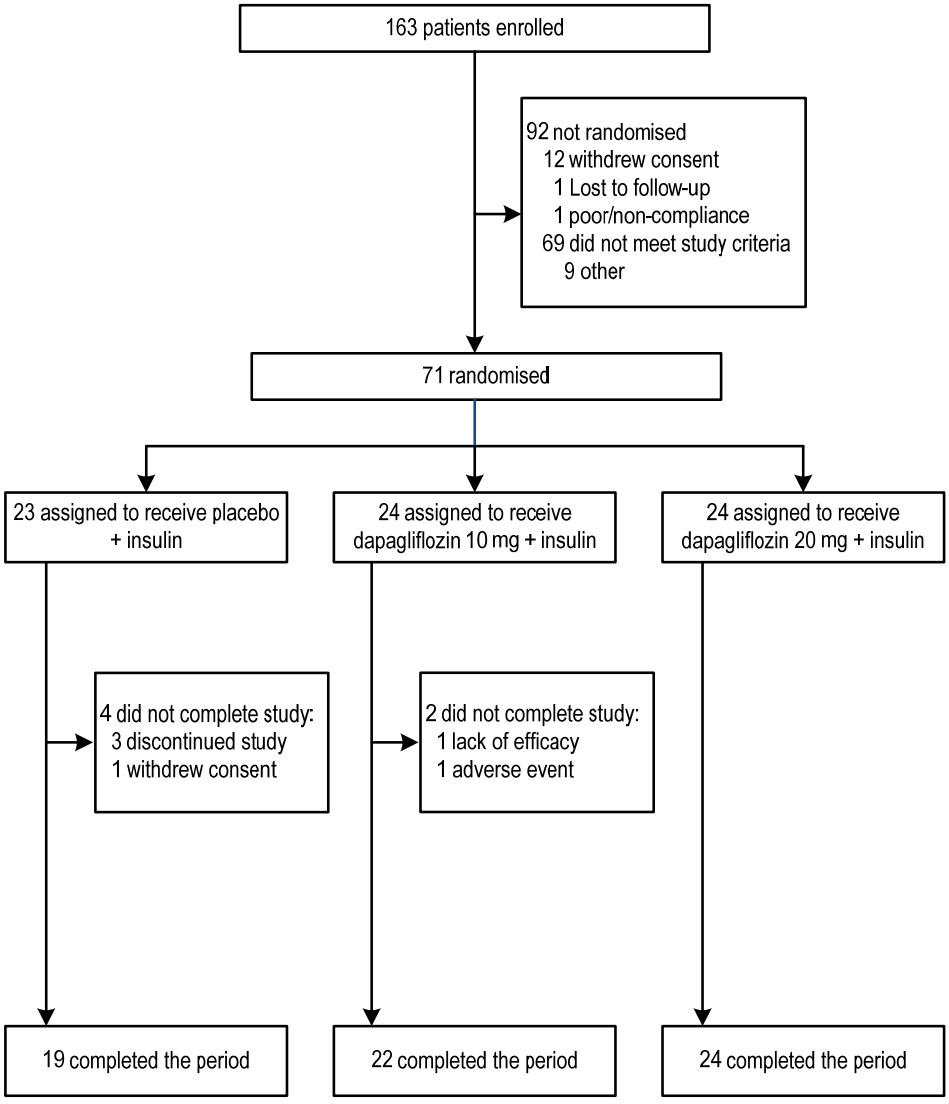
Abbreviations:
†, One patient took no placebo medication but was randomised;
‡, Down titration was permitted in the event of hypoglycaemia;
§, Full analysis set, consisting of all randomised patients who received one or more doses of the investigational product and who had a nonmissing baseline and one or more post baseline efficacy value for one or more efficacy variable;
¶, Patients continue to receive open-label metformin

Figure 7. Study 6 trial profile



Abbreviations:
OAD, Oral antidiabetic drug;
†, This patient received no study medication or post baseline assessments;
‡, Full analysis set, comprising all randomly assigned patients who received at least one dose of study medication and had a nonmissing baseline value and at least one post baseline efficacy value for at least one efficacy variable

Figure 8. Study 9 trial profile



5.4 Critical appraisal of relevant RCTs

5.4.1 Introduction

The five RCTs involving dapagliflozin represented high-quality RCTs. All five RCTs were adequately randomised, concealed, blinded, balanced at baseline and throughout the trial, and had comprehensive reporting. For efficacy analyses, the investigators presented data using a modified intention-to-treat approach (based on the definition of Abraham, 2010). The modifications to the true intention-to-treat principle (all randomised patients) were: i) all randomised patients who took at least one dose of double blind treatment (Study 9), or ii) all randomised patients who received at least one dose of double-blind study medication and who had both a baseline and at least one post-baseline measurement (Study 6, Study 14, Study 4, Study 12). This type of modification is common in trials designed to collect laboratory data from patients over time, and the characteristics of the missing patients are not anticipated to differ across study arms.

A summary of responses to the critical appraisal questions is presented in Table 17.

5.4.2 Complete quality assessment for each RCT.

The complete assessment is presented in Section 9.3, with a summary presented in Table 17, Section 5.4.3.

5.4.3 Tabulation of the responses applied to each of the critical appraisal criteria.

A summary of the critical appraisals of the relevant RCTs (involving dapagliflozin) are presented in Table 17. Detailed quality assessment for each RCT is provided in Section 9.3.

Table 17. Quality assessment results for the RCTs involving the interventional agents

	Metformin add-on RCTs			Insulin add-on RCTs	
Critical appraisal	**Study 14¶**	**Study 12¶**	**Study 4¶**	**Study 6¶**	**Study 9¶**
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No

	Metformin add-on RCTs			Insulin add-on RCTs	
Critical appraisal	**Study 14¶**	**Study 12¶**	**Study 4¶**	**Study 6¶**	**Study 9¶**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	mITT †,§	mITT †,‡,§	mITT †,‡,§	mITT †,‡,§	mITT ††,§

Abbreviations: mITT, Modified intention-to-treat; †, The primary/full analysis dataset consisted of all randomised patients who received at least one dose of study medication and who had a non-missing baseline value and at least one post-baseline measurement; ‡,Authors stated that the intention-to-treat principle is preserved despite the exclusion of patients who took no study medication, as the decision of whether or not to begin treatment during the randomised treatment period could not be influenced by knowledge of the assigned treatment; §, Analysis included a modified intention-to-treat population, as defined by Abraha et al (Abraha, 2010); ¶, Source: Published report and BMS/AZ data on file (clinical study report); ††, The primary efficacy dataset consisted of all randomly assigned patients who took at least one dose of double-blind study medication;

5.5 Results of the relevant RCTs

5.5.1 Results for all relevant outcome measure(s) pertinent to the decision problem.

The results for the outcome pertinent to the decision problem are addressed in the section below; please refer to Section 5.5.3 for details.

5.5.2 Graphical presentation of results

Please refer to Section 5.5.3 for details.

5.5.3 Results

Four outcomes (HbA1c, weight, SBP and hypoglycaemia) were identified as being of greatest relevance to the decision problem, as these are currently used in clinical practice to assess response to treatment in T2DM patients. With the exception of Study 4, a non-inferiority study where the primary end point is based on the on-treatment population, the results of these outcomes from the RCTs involving the intervention of interest are presented on the modified intention to treat (mITT) population under the following sections describing summary findings from the individual RCTs:

- Section 5.5.3.1: Study 14 (Add-on to metformin)
- Section 5.5.3.2: Study 12 (Weight loss)
- Section 5.5.3.3: Study 4 (Head to head vs SU)
- Section 5.5.3.4: Study 6 (Phase 3 Add-on to insulin)
- Section 5.5.3.5: Study 9 (Phase 2 Add-on to insulin)

The study endpoints included: glycaemic endpoints; weight and body composition endpoints; as well as efficacy assessments of blood pressure.

HbA1c

HbA1c is the clinical and regulatory parameter of choice for monitoring longer term glycaemic control. HbA1c was the primary efficacy endpoint for the main studies presented here, except for Study 12 which evaluated changes in weight as the primary endpoint.

Dapagliflozin results in clinically meaningful reductions in HbA1c. Dapagliflozin 10mg was shown to be superior to placebo and non-inferior to sulphonylurea (glipizide) with respect to HbA1c reduction.

Clinical studies in T2DM, where HbA1c was the primary endpoint have shown that dapagliflozin 10mg was consistently associated with statistically and clinically significant reductions in HbA1c. A higher proportion of patients treated with dapagliflozin achieved a therapeutic response of HbA1c <7% compared with those treated with placebo. Dapagliflozin 10 mg also consistently resulted in clinically meaningful reductions of HbA1c of at least 0.5%. The reductions in HbA1c are maintained with long-term treatment. This maintenance of effect is important, as the benefit of some existing anti-diabetic medications reduces over time (Kahn et al 2006). Such beneficial effects are not just limited to improved glycaemic control but also include weight loss and reductions in blood pressure - important co-morbidities in the T2DM diabetes population.

Body weight

More than 85% of patients with T2DM are overweight or obese (CDC 2004) and in addition, treatments for diabetes are commonly associated with an increase in body weight. Patients' efforts to lose weight are often undermined by drug treatments for diabetes that lead to weight gain. Weight loss is a major goal for the most patients with T2DM as it has been shown to improve glycaemic control as well as co-morbid conditions (NHLBI 1998). Dapagliflozin's unique mechanism of action causes the loss of calories due to persistent glucosuria which results in sustained reductions in body weight.

In the placebo controlled studies, the placebo-corrected mean weight reductions over 24 weeks were statistically significant for the 10mg dose of dapagliflozin. Although metformin is associated with weight-loss, dapagliflozin resulted in significant additional weight loss when added to metformin. In patients receiving insulin where weight gain would be expected, the addition of dapagliflozin also resulted in weight loss. [redacted].

The type of weight loss achieved is of clinical importance as total body fat correlates positively with key CV risk factors and most strongly with insulin resistance (Vega et al 2006). Study 12 was designed to investigate weight loss and the type of weight loss. The reduction in total body weight was the primary endpoint. Treatment with dapagliflozin 10mg as add-on to metformin resulted in a statistically significant mean weight reduction of -2.08 kg ($p<0.0001$) compared to placebo plus metformin. The majority of weight loss was attributable to a reduction in total body fat mass, as measured by Dual-Energy X-ray Absorptiometry (DEXA) rather than fluid or lean tissue mass. A further Magnetic Resonance Imaging (MRI) substudy showed that dapagliflozin

induced reductions not only in subcutaneous fat but also in visceral adipose tissue after 24 weeks.

Hypoglycaemia

Dapagliflozin has a low propensity to cause hypoglycaemia. The dapagliflozin studies specifically monitored for incidences of hypoglycaemia. The definition of major hypoglycaemia used in the study programme was a symptomatic episode requiring third party assistance and a plasma glucose value < 3 mmol/L (<54mg/dL). In the dapagliflozin add-on to metformin studies, there was generally a low incidence of hypoglycaemia and no major events. This shows that dapagliflozin can improve glycaemic control in patients who have inadequate control with metformin alone without an increased risk of hypoglycaemia. In Study 4 where dapagliflozin was compared to SU with metformin background therapy, the rate of reported hypoglycaemia was more than 10 times greater with SU (Nauck et al 2011a, 2011b). In Study 6, when dapagliflozin was added to insulin, there was a small increase in reported hypoglycaemia compared to placebo (53.6% vs. 51.8%), but the rate of major hypoglycaemia episodes was low (1.5% vs. 1%) in both arms.

Blood pressure

The evaluation of effects on cardiovascular risk factors is particularly important in T2DM patients, who are at increased risk of CV events. A 10/5 mmHg drop in blood pressure in patients with T2DM achieves a significant reduction in risk of 32% for death related to diabetes, 44% for stroke, 37% for microvascular disease and 56% in heart failure (UKPDS 1998). An isolated systolic blood pressure (SBP) reduction of 12 mmHg has been found to reduce the risk of stroke by 36%, MI or CV death by 17% (SHEP 1991).

Exploratory analyses data in these studies suggest that dapagliflozin has the additional benefit of a blood pressure lowering effect. In Study 14, 38% of dapagliflozin patients who were initially hypertensive achieved a target blood pressure of 130/80 mmHg compared to 9% of placebo patients.

In Study 4, SBP decreased in the dapagliflozin arm compared to a small increase in the SU arm (-4.3 mmHg vs. +0.8 mmHg). A similar change was seen in diastolic blood pressure (-1.6 mmHg vs. -0.4 mmHg). In patients who were initially hypertensive (SBP >140 mmHg) greater reductions were found with dapagliflozin compared to SU (-13 mmHg vs. -8mmHg).

Reductions in Total Daily Dose of insulin required

Endpoints to evaluate changes in insulin requirements as supportive measures of glycaemic efficacy were included in the add-on to insulin studies (Study 6 and Study 9). Dapagliflozin did not increase mean total daily insulin dose, but this requirement increased progressively in the placebo group, resulting in an increased daily insulin dose of 5.65 IU at 24 weeks (Wilding et al 2010a),10.54 IU at 48 weeks (Wilding et al 2012) and 19.17 IU at 104 weeks (BMS CSR Study 6), in the placebo group.

In addition, a fifth of patients treated with dapagliflozin 10 mg had mean daily insulin dose reductions of at least 10% (19.1% of dapagliflozin patients, versus 10.2% of placebo patients at 24 weeks, p = 0.013 for difference (Wilding et al 2012). This difference was maintained through to 2 years (BMS CSR study 6).

5.5.3.1 Key result summary of Study 14 (Add-on to metformin)

- Dapagliflozin (when added on to metformin) significantly reduced HbA1c compared with metformin plus placebo (-0.84% vs. -0.30%), (p value for difference <0.0001) at 24 weeks.
    - Significantly more dapagliflozin patients achieved an HbA1c target of <7% (41% vs. 26%), (p value for difference =0.0062) at 24 weeks.
    - [redacted].
- Some commonly used oral drug treatments (SUs, pioglitazone) are associated with weight gain while newer agents (DPP-4-inhibitors) are weight neutral.
    - Dapagliflozin significantly reduces body weight compared to metformin plus placebo (-2.9kg vs. -0.9kg) at 24 weeks (p value for the difference <0.0001).
    - 22.1% (95% CI 13.5 to 30.6) more patients assigned to dapagliflozin, had total bodyweight reductions of 5% or more compared to metformin plus placebo.
- At 2 years the difference in body weight between the dapagliflozin and placebo arms was maintained (-3.1kg [95% CI -4.24 to -1.96]) demonstrating a sustained clinically meaningful reduction in weight with dapagliflozin.
- Dapagliflozin patients showed a decrease in mean systolic and diastolic blood pressure compared with baseline.
    - 38% of dapagliflozin patients who were initially hypertensive achieved a blood pressure target of 130/80 mmHg compared to 9% of placebo patients (difference vs. placebo 29% [95%CI 13%-44%])

Study 14 is a phase 3, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial, with a 24-week short-term period followed by a 78-week extension period, of 546 adults with T2DM who were receiving daily metformin (≥1500 mg per day) and had inadequate

glycaemic control (Bailey et al 2010). Study patients were randomly assigned to receive one of three doses of dapagliflozin (2·5 mg, n=137; 5 mg, n=137; or 10 mg, n=135) or placebo (n=137) orally once daily. In Table 18, the key results from the placebo and dapagliflozin 10mg arms are presented.

The primary outcome of this RCT was change from baseline in HbA1c percentage at 24 weeks.

The key secondary outcomes were changes in FPG concentration and total bodyweight at week 24, change in fasting plasma glucose concentration at week 1, the proportion of patients achieving a therapeutic glycaemic response (defined as HbA1c <7% at week 24), and change in HbA1c percentage at week 24 for patients with a baseline HbA1c of 9% or more.

The results for the key outcomes of interest relevant to the decision problem are summarised in Table 18.

Table 18. Relevant outcome results from Study 14¶

Outcomes	Dapagliflozin 10mg	Placebo
Glycosylated haemoglobin, HbA1c (%) ¶¶		
Number of patients with week 24 values†††	132	134
Mean baseline value; % (SD)	7.92 (0.82)	8.11 (0.96)
Mean change at 24 weeks; % (95% CI) LOCF	**-0.84 (-0.98, -0.70)**	**-0.30 (-0.44, -0.16)**
Mean difference, compared to placebo (95% CI)	**-0.54 (-0.73, -0.35)**	
p-value compared to placebo	**<0.0001**	
Number of patients with week 102 values†††	57	28
Mean change at 102 weeks; % (95% CI)†† LRM	-0.78 (-0.97, -0.60)	0.02 (-0.20, 0.23)
Mean difference, compared to placebo (95% CI)	-0.80 (-1.08, -0.52)	-
p-value compared to placebo	NR	
Weight (kg)¶¶		
Number of patients with week 24 values†††	133	136
Mean baseline value; kg (SD)	86.3 (17.5)	87.7 (19.2)
Mean change at 24 weeks; kg (95% CI) LOCF	-2.86 (-3.33, -2.39)	-0.89 (-1.35, -0.42)
Mean difference, compared to placebo (95% CI)	-2.0 (-2.8, -1.2)	-
p-value compared to placebo	<0.0001	
Number of patients with week 102 values†††	95	73
Mean change at 102 weeks; kg (95% CI)†† ‡‡, LRM	-1.74 (-2.51, -0.96)	1.36 (0.53, 2.20)
Mean difference, compared to placebo (95% CI)	-3.10 (-4.24, -1.96)	-
p-value compared to placebo	NR	
Seated systolic blood pressure (mmHg)§, ‡‡		
Number of patients with week 24 values†††	122	119

Outcomes	Dapagliflozin 10mg	Placebo
Mean baseline value; mmHg (SD)	126.0 (15.9)	127.7 (14.6)
Mean change at 24 weeks; mmHg (95% CI)‡ LOCF	-5.1 (-7.7, -2.5)	-0.2 (-2.6, 2.2)
Mean difference, compared to placebo (95% CI)	-4.9 (-8.4, 1.4)	-
p-value compared to placebo	NR	
Number of patients with week 102 values†††	94	72
Mean change at 102 weeks; mmHg (95% CI)†† LRM	-0.3 (-3.2, 2.6)	1.5 (-1.6, 4.6)
Mean difference, compared to placebo	-1.8	
p-value compared to placebo	NR	
Seated diastolic blood pressure (mmHg)§, ‡‡		
Number of treated patients with week 24 values†††	122	119
Mean baseline value; mmHg (SD)	79.0 (10.2)	80.9 (9.0)
Mean change at 24 weeks; mmHg (95% CI)‡ LOCF	-1.8 (-3.37, -0.23)	-0.1 (-1.47, 1.27)
Mean difference, compared to placebo	-1.7 (NR)	
p-value compared to placebo	NR	
Number of patients with week 102 values†††	94	72
Mean change at 102 weeks; mmHg (95% CI)†† LRM	-1.2 (-3.16, 0.76)	-1.0 (-2.76, 0.76)
Mean difference, compared to placebo	-0.2	
p-value compared to placebo	NR	
Hypoglycaemia (% with hypoglycaemia)†		
Number of patients in analysis ‡‡‡	135	137
Number of patients with outcome	5	4
% of patients with hypoglycaemia at 24 weeks	3.7	2.9
Odds ratio, relative to placebo	1.3 (0.3, 4.9)	-
p-value compared to placebo	NR	
Number of patients with major hypoglycaemic event at 24 weeks§§	0	0
Number of patients with hypoglycaemia at 102 weeks†	[redacted]	[redacted]
% of patients with hypoglycaemia at 102 weeks†,††,‡‡	[redacted]	[redacted]
Number of patients with major hypoglycaemic event at 102 weeks††,‡‡, §§	[redacted]	[redacted]

Abbreviations: CI, Confidence interval; HbA1c, Glycosylated haemoglobin; LOCF, Last observation carried forward; LRM, Longitudinal Repeated Measures model; NR, Not reported; SD, Standard deviation; SE; Standard error; †, Describes proportion with at least one event of hypoglycaemia; ‡, 95% CI was estimated assuming a normal distribution; §, Refers to seated blood pressure; ¶, Source: Published report and BMS/AZ data on file (clinical study report); †† Extension data; ‡‡, Includes post-rescue data; §§, Major episode defined as a symptomatic episode requiring external (3rd party) assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value < 3mmol/L (<54 mg/dl) and prompt recovery after glucose or glucagon administration; ¶¶, Excludes data after rescue; †††, Number of randomised patients with non-missing baseline and week *t* (LOCF) values; this analysis dataset is consistent with the definition of modified intention to treat (Abraha, 2010); ‡‡‡, Number of patients treated

HbA1c

Reductions in HbA1c percentage after 24 weeks were significantly greater in the dapagliflozin group than in the placebo group. Mean change from baseline at week 24 (LOCF) was -0.84% in the dapagliflozin 10mg group compared with -0.30% in the placebo group ($p<0.0001$). More patients in the dapagliflozin 10mg group (40.6%) achieved a therapeutic response of HbA1c less than 7% at week 24 than patients in the placebo group (25.9%); the difference was significant for the dapagliflozin 10mg group. [redacted]

Weight

At week 24, significant reductions in bodyweight were noted in dapagliflozin groups compared with placebo. Compared with patients assigned to placebo, 22.1% (95% CI 13.5 to 30.6) more patients assigned to dapagliflozin 10 mg, had total bodyweight reductions of 5% or more. [redacted] consistent with the continued loss of calories due to glucosuria. In Study 14, [redacted] in the dapagliflozin treatment groups compared with the placebo group.

Hypoglycaemia

Patients in this trial did not have adequate glycaemic control with metformin alone, and the addition of dapagliflozin for 24 weeks resulted in significant reductions in HbA1c percentage and fasting plasma glucose with no increase in risk of hypoglycaemia compared with placebo. There was a [redacted]

Blood pressure

Patients assigned to dapagliflozin showed a decrease in mean SBP and diastolic blood pressure (DBP); however, there was no increase in the proportion of patients with orthostatic hypotension compared with baseline.

5.5.3.2 Key result summary of Study 12 (Weight loss)

- Obesity, especially visceral/abdominal fat is associated with diabetes, insulin resistance, metabolic syndrome and increased cardiovascular risk.
- The primary endpoint was to determine change in body weight from baseline with dapagliflozin vs. placebo.
  - Dapagliflozin significantly reduced body weight (-2.96kg) compared with placebo (-0.88kg) over 24 weeks.
  - 26.2% more dapagliflozin patients lost ≥5% of their initial body weight.
  - Reduction in fat accounted for two-thirds of the total weight loss observed with dapagliflozin.
  - The reduction of fat mass comprised both subcutaneous and visceral deposits.
- Significant reductions in HbA1c were also noted in the dapagliflozin arm.

Study 12 is a phase 3, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial with a 24-week short-term period followed by a 78-week extension period to evaluate the effect of dapagliflozin in combination with metformin on body weight in adults with T2DM who have inadequate glycaemic control (HbA1c ≥6.5% and ≤8.5%) on metformin therapy (≥1500mg per day) alone (Bolinder et al 2012).

The primary outcome of this RCT was change in body weight from baseline to week 24.

The key secondary outcomes were change in waist circumference, change in body fat mass, and proportion of patients with body weight decrease ≥5% from baseline until week 24.

The results for the key outcomes of interest relevant to the decision problem are summarised in Table 19.

Table 19. Relevant outcome results from Study 12†

Outcomes	Dapagliflozin 10mg	Placebo
Weight (kg) ††		
Number of patients with week 24 values¶¶	89	91
Mean baseline value; kg (SD)	92.06 (14.13)	90.91 (13.72)
Mean change at 24 weeks; kg (95% CI) LOCF	**-2.96 (-3.51, -2.41)**	**-0.88 (-1.43, -0.34)**
Mean difference, compared to placebo (95% CI)	**-2.08 (-2.84, -1.32)**	
p-value compared to placebo	**<0.0001**	
Proportion of patients (X/N)% with body weight decrease from baseline to week 24 of ≥ 5% [95% CI] ‡‡‡	27/89 (30.5% [20.8, 40.2])	4/91 (4.3% [0.0, 8.6])

Outcomes	Dapagliflozin 10mg	Placebo
Difference in proportion of patients with ≥ 5%weight decrease compared to placebo (95% CI)	26.2% (15.5, 36.7)	
p-value compared to placebo	<0.0001	
Number of patients with week 50 values	81	84
Mean change at 50 weeks; kg (95% CI) §§, LRM	-4.39 (-5.31, -3.48)	-2.03 (-2.90, -1.15)
Mean difference, compared to placebo	-2.36	
p-value compared to placebo	NR	
Glycosylated haemoglobin, HbA1c (%)‡‡		
Number of patients with week 24 values¶¶	88	91
Mean baseline value; % (SD)	7.19 (0.44)	7.16 (0.53)
Mean change at 24 weeks; % (95% CI) LOCF	-0.39 (-0.48, -0.29)	-0.10 (-0.20, -0.01)
Mean difference, compared to placebo (95% CI)	-0.28 (-0.42, -0.15)	
p-value compared to placebo	<0.0001	
Number of patients with week 50 values	79	77
Mean change at 50 weeks; % (95% CI) §§, LRM	-0.38 (-0.49, -0.26)	0.02 (-0.10, 0.13)
Mean difference, compared to placebo	-0.40	
p-value compared to placebo	NR	
Seated systolic blood pressure (mmHg)§, ††		
Number of patients with week 24 values¶¶	88	91
Mean baseline value; mmHg (SD)	135.9 (13.92)	133.3 (13.66)
Mean change at 24 weeks; mmHg (95% CI) LOCF	-2.70 (-4.90, -0.60)	0.10 (-2.00, 2.20)
Mean difference, compared to placebo (95% CI)	-2.80 (-5.79, 0.19)	
p-value compared to placebo	0.06	
Number of patients with week 50 values	81	84
Mean change at 50 weeks; mmHg (95% CI) §§, LRM	-1.60 (-5.00, 1.80)	-1.20 (-4.40, 2.50)
Mean difference, compared to placebo	-0.40	
p-value compared to placebo	NR	
Seated diastolic blood pressure (mmHg)§, ††		
Number of patients with week 24 values¶¶	88	91
Mean baseline value; mmHg (SD)	80.6 (8.09)	80.4 (8.25)
Mean change at 24 weeks; mmHg (95% CI) LOCF	-0.7 (-2.1, 0.8)	0.3 (-1.1, 1.7)
Mean difference, compared to placebo (95% CI)	-1.0 (-2.9, 1.0)	
p-value compared to placebo	0.35	
Number of patients with week 50 values	81	84
Mean change at 50 weeks; mmHg (95% CI) §§, LRM	-1.50 (-3.90, 0.90)	-0.20 (-2.40, 2.10)
Mean difference, compared to placebo	-1.3	

Outcomes	Dapagliflozin 10mg	Placebo
p-value compared to placebo	NR	
Hypoglycaemia (% with hypoglycaemia)‡		
Number of patients in analysis †††	91	91
Number of patients with outcome	2	3
% of patients with hypoglycaemia at 24 weeks	2.2	3.3
Odds ratio, compared to placebo	0.66 (0.11, 4.04)	-
p-value compared to placebo	NR	
Number of patients with major hypoglycaemic event at 24 weeks¶	0	0

Abbreviations: CI, Confidence interval; HbA1c, Glycosylated haemoglobin; LOCF, Last observation carried forward; LRM, Longitudinal Repeated Measures model; NR, Not reported; SD, Standard deviation; †, Source: Published report and BMS/AZ data on file (clinical study report); ‡, Describes proportion with at least one event of hypoglycaemia; §, Refers to seated blood pressure; ¶, Major episode defined as a symptomatic episode requiring external (3rd party) assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value < 3mmol/L (<54 mg/dl) and prompt recovery after glucose or glucagon administration; ††, Includes data after rescue; ‡‡, Excludes data after rescue; §§, Extension data; ¶¶, Number of randomised patients with non-missing baseline and week *t* (LOCF) values; this analysis dataset is consistent with the definition of modified intention to treat (Abraha, 2010); †††, Number of patients in safety analysis set, consisting of all patients who received at least one dose of investigational product; ‡‡‡, N is the number of patients in the full analysis set with non-missing baseline values and week 24 (LOCF) values, X is the number of responders

Weight (primary endpoint)

Dapagliflozin treatment in combination with metformin led to a statistically significant and clinically relevant mean reduction in total body weight and total body fat compared to placebo with metformin in patients with T2DM. Dapagliflozin produced a statistically significant weight reduction compared with placebo at 24 weeks; a greater adjusted mean total body weight change of -2.96 kg (95% confidence interval [CI] -3.51 to -2.41) was observed in the dapagliflozin group compared with a change of -0.88 kg (95% CI -1.43 to -0.34) in the placebo group, with a significant difference between groups of-2.08 kg in total body weight (95% CI -2.84 to -1.31; p<0.0001) at 24 weeks. This difference in body weight increased to -2.37kg (95% CI -3.1 to -1.32) at 1 year (BMS CSR Study 12, 1 year).

In addition, a statistically significant and clinically relevant higher proportion of patients in the dapagliflozin group (30.5%), compared to placebo (4.3%), reduced their body weight with at least 5% from baseline to week 24 (LOCF) (p <0.0001) (Bolinder et al 2012). At 1 year this difference is maintained (BMS CSR Study 12, 1 year).

A substudy of patients utilizing magnetic resonance imaging showed that the decrease in body fat mass was partly attributable to a decrease in visceral adipose tissue, which is associated with abnormalities in glucose and lipid metabolism (Gastaldelli et al 2007); an approximately 10% reduction in visceral adipose tissue volume was observed in the dapagliflozin group compared to no significant change in the placebo group at 24 weeks (Bolinder et al 2012).

HbA1c

Change in HbA1c was a pre-specified secondary endpoint in this study. As a consequence of the inclusion criteria, the patients started at a relatively low mean baseline HbA1c of 7.18%, a larger numerical HbA1c decrease of -0.29% compared to placebo was observed in the dapagliflozin 10 mg group (nominal p<0.0001), which was a comparatively modest reduction, but this was anticipated (Bolinder et al 2012).

Hypoglycaemia

As anticipated by its mechanism of action, dapagliflozin was not associated with an increased risk for hypoglycaemia, in line with findings from other studies.

Blood pressure

Numerical mean reductions versus placebo in SBP in the overall population were observed in the dapagliflozin treatment groups (Bolinder et al 2012).

Systolic blood pressure showed a mean decrease from baseline to week 24 (LOCF) in the dapagliflozin group (-2.7 mmHg), whereas there was minimal change (0.1 mmHg) in the placebo group (p >0.06). Diastolic blood pressure showed no meaningful changes in either treatment group and there was no statistical difference between the groups at 24 weeks (Bolinder et al 2012).

In conclusion, this study confirms significant weight loss and improved glycaemic control when dapagliflozin 10 mg once a day is added to metformin in overweight T2DM patients over 24 weeks, consistent with results from other clinical studies of dapagliflozin. Most weight change was accounted for by fat loss. Treatment with dapagliflozin as add-on to metformin over 24 weeks is effective in reducing bodyweight in patients with T2DM who have inadequate glycaemic control on metformin alone. The weight loss was also maintained at 1 year.

5.5.3.3 Key result summary of Study 4 (Head to head vs. SU)

- In the UK, SU is the most commonly prescribed class of drug added to metformin when glycaemic control is lost.
- This study was designed to compare dapagliflozin to SU on a background of metformin.
- This non-inferiority study showed a comparable decrease in HbA1c of dapagliflozin versus SU at 1 year.
- After 18 weeks (i.e. end of maximal titration) the SU patients' HbA1c started to increase and returned towards their pre-randomisation baseline levels by 2 years. The

dapagliflozin patients' HbA1c also increased – however this rate of increase was much slower than the SU arm.

- [redacted] Dapagliflozin patients lost weight in this study, whereas SU patients gained weight. The difference between the 2 arms was 4.66kg at 52 weeks (p<0.0001) and [redacted]
- A third of dapagliflozin patients lost more than 5% of their body weight vs. 2.5% of patients in the SU arm. [redacted]
- Dapagliflozin use was associated with reduced SBP and DBP.
- More patients discontinued study drug due to lack of efficacy in the SU arm than in the dapagliflozin arm (3.6% vs. 0.2%). At 2 years this difference increased to 7.1%. This means that more patients in the SU arm required additional rescue treatment.

Study 4 is a phase 3, multicentre, randomised, double-blind, parallel-group, active-controlled trial with a 52-week short-term period followed by a 52 week extension period to evaluate the efficacy and safety of up-titrated dapagliflozin (2.5mg, 5mg, 10mg, [mean dose 9.2mg]) as add-on therapy to metformin compared with, up-titrated SU (glipizide, 5mg, 10mg, 20mg, [mean dose 16.4mg]) as add-on therapy to metformin in adults with T2DM who have inadequate glycaemic control (HbA1c >6.5% and ≤10.0%) on metformin therapy alone (Nauck et al 2011a, 2011b). The up-titration was done to maintain blinding in the study, however in clinical practice 10mg would be the dapagliflozin licensed starting dose.

The primary outcome of this RCT was change in HbA1c from baseline to week 52.

The key secondary outcomes were absolute change in body weight, and proportion of patients with body weight decrease ≥5% from baseline to week 52, and proportion of patients reporting at least one episode of hypoglycaemia over 52 weeks

The results for the key outcomes of interest relevant to the decision problem are summarised in Table 20.

Table 20. Relevant outcome results from Study 4‡

Outcomes	Dapagliflozin	Sulphonylurea†
Glycosylated haemoglobin, HbA1c (%)		
Number of patients with week 52 values§§	400	401
Mean baseline value; % (SD)	7.69 (0.86)	7.74 (0.89)
Mean change at 52 weeks; % (95% CI) LOCF	**-0.52 (-0.60, -0.44)**	**-0.52 (-0.60, -0.44)**

Outcomes	Dapagliflozin	Sulphonylurea†
Mean difference, compared to sulphonylurea (95% CI)	**0.00 (-0.11, 0.11)**	
p-value compared to sulphonylurea	**<0.0001**	
Number of patients with week 104 values¶¶	233	208
Mean change at 104 weeks; % (95% CI)¶¶, LRM	-0.32 (-0.42, -0.21)	-0.14 (-0.25, -0.03)
Mean difference, compared to sulphonylurea (95% CI)	-0.18 (-0.33, -0.03)	
p-value compared to sulphonylurea	NR	
Weight (kg)		
Number of patients with week 52 values§§	400	401
Mean baseline value; kg (SD)	88.44 (16.32)	87.6 (16.97)
Mean change at 52 weeks; kg (95% CI) LOCF	-3.22 (-3.56, -2.87)	1.44 (1.09, 1.78)
Mean difference, compared to sulphonylurea (95% CI)	-4.65 (-5.14, -4.17)	
p-value compared to sulphonylurea	<0.0001	
Proportion of patients (X/N)% with body weight decrease from baseline to week 52 of ≥ 5% [95% CI] †††	133/400 (33.3% [28.7, 37.9])	10/401 (2.5% [1.0, 4.0])
Difference in proportion of patients with ≥ 5% weight decrease compared to sulphonylurea (95% CI)	30.8% (26.0, 35.7)	
p-value compared to sulphonylurea	NR	
Number of patients with week 104 values¶¶	234	211
Mean change at 104 weeks; kg (95% CI), LRM	-3.70 (-4.16, -3.24)	1.36 (0.88, 1.84)
Mean difference, compared to sulphonylurea (95% CI)	-5.06 (-5.73, -4.40)	
p-value compared to sulphonylurea	NR	
Proportion of patients (X/N)% with body weight decrease from baseline to week 104 of ≥ 5% [95% CI] †††	95/400 (23.8% [19.6, 27.9])	11/401 (2.8% [1.2, 4.4])
Difference in proportion of patients with ≥ 5kg weight decrease compared to sulphonylurea (95% CI)	21.0% (16.5, 25.5)	
p-value compared to sulphonylurea	NR	
Seated systolic blood pressure (mmHg)		
Number of patients with week 52 values§§	400*	401*
Mean baseline value; mmHg (SD)	132.8 (14.89)	133.8 (14.69)
Mean change at 52 weeks; mmHg (95% CI)	-4.3 (-5.4, -3.2)**	0.8 (-0.3, 1.9)**
Mean difference, compared to sulphonylurea (95% CI)	-5.0 (-6.7, -3.4)	
p-value compared to sulphonylurea	<0.0001	
Number of patients with week 104 values¶¶	234	211
Mean change at 104 weeks; mmHg (95% CI), LRM	-2.69 (-4.20, -1.17)	1.20 (-0.38, 2.79)
Mean difference, compared to sulphonylurea (95% CI)	-3.89 (-6.08, -1.69)	
p-value compared to sulphonylurea	NR	
Seated diastolic blood pressure (mmHg)		
Number of patients with week 52 values§§	400*	401*

Outcomes	Dapagliflozin	Sulphonylurea†
Mean baseline value; mmHg (SD)	80.6 (8.42)	80.6 (8.46)
Mean change at 52 weeks; mmHg (95% CI)	-1.6 (-2.3, -0.9)**	-0.4 (-1.1, 0.3)**
Mean difference, compared to sulphonylurea (95% CI)	-1.2 (-2.3, -0.2)	
p-value compared to sulphonylurea	0.02	
Number of patients with week 104 values¶¶	234	211
Mean change at 104 weeks; mmHg (95% CI), LRM	-1.95 (-2.86, -1.05)	-1.51 (-2.45, -0.56)
Mean difference, compared to sulphonylurea (95% CI)	-0.45 (-1.76, 0.86)	
p-value compared to sulphonylurea	NR	
Hypoglycaemia (% with hypoglycaemia)§		
Number of patients in analysis (full analysis set) §§	400	401
Number of patients with outcome	14	162
% of patients with hypoglycaemia at 52 weeks¶	3.5	40.8
Odds ratio, relative to sulphonylurea	0.05 (0.03, 0.10)	-
p-value compared to sulphonylurea	<0.0001	
Number of patients with major hypoglycaemic event at 52 weeks††	0	3
Number of patients with hypoglycaemia at 104 weeks	[redacted]	[redacted]
% of patients with hypoglycaemia at 104 weeks‡‡, §§	[redacted]	[redacted]
Number of patients with major hypoglycaemic event at 104 weeks††	[redacted]	[redacted]

Abbreviations: CI, Confidence interval; HbA1c, Glycosylated haemoglobin; LOCF, Last observation carried forward; LRM, Longitudinal Repeated Measures model; NR, Not reported; SD, Standard deviation; SE; Standard error; †, Therapeutic agent is glipizide; ‡, Source: Published report and BMS/AZ data on file (clinical study report); §, Describes proportion with at least one event of hypoglycaemia; ¶, Data are from full analysis set, in safety analysis set the corresponding values were 3.4 and 39.7 for dapagliflozin and sulphonylurea respectively; ††, Major episode defined as a symptomatic episode requiring external (3rd party) assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value < 3mmol/L (<54 mg/dl) and prompt recovery after glucose or glucagon administration; ‡‡, Full analysis set (Denominators are 400 and 401 patients in the dapagliflozin and glipizide arms respectively; when the safety analysis set consisting of all patients who received one or more doses of the investigational product [denominator 406 and 408 patients respectively] is used, the corresponding proportions are 4.2% and 45.8% respectively); §§, Number of randomised patients with non-missing baseline and week *t* (LOCF) values; this analysis dataset is consistent with the definition of modified intention to treat (Abraha, 2010); ¶¶, Number of randomised patients with non-missing baseline and week 104 values and based on longitudinal repeated measures analyses; †††, N is the number of patients in the full analysis set with non-missing baseline values, X is the number of responders; * Data for sample size are from the full analysis set; corresponding value from the "number of patients with non-missing baseline and Week 52 (LOCF) values in the full analysis set are 399 and 396 for dapagliflozin and glipizide, respectively **, Confidence interval values were estimated from a graph in the study publication

HbA1c

For the primary outcome of this study, the results showed that among metformin-treated patients with inadequate glycaemic control, the addition of dapagliflozin led to the same mean decrease from baseline in % HbA1c (-0.52% in HbA1c at week 52 [LOCF]) compared to

treatment with a SU at 52 weeks. The mean decrease in HbA1c from baseline until 52 weeks (LOCF) was statistically significantly non-inferior in the dapagliflozin group compared to the SU (glipizide) group; with a pre-specified non-inferiority margin of 0.35%). Although the initial drop in HbA1c during the titration period with glipizide was greater than that observed with dapagliflozin, the efficacy of glipizide waned during the maintenance period but that of dapagliflozin remained stable. This resulted in equivalent efficacy at week 52 (Nauck et al 2011a, 2011b).

Interestingly, the study population had relatively low baseline mean HbA1c (~7.7%), but despite this, clinically meaningful reductions of >0.5% were still achieved by both agents (Nauck et al 2011a, 2011b).

Weight

Patients in the dapagliflozin group showed a mean decrease of -3.22 kg in total body weight from baseline to week 52 (LOCF), while in the glipizide group, total body weight increased by 1.44 kg; this difference between the 2 treatments was statistically significant ($p<0.0001$) and clinically meaningful. Additionally, a statistically significant higher proportion of patients in the dapagliflozin group (33.3%), compared to glipizide (2.5%), reduced their body weight by at least 5% from baseline to week 52 (LOCF) ($p<0.0001$).

Hypoglycaemia

In the active comparator Study 4, patients who failed treatment with metformin IR were randomised 1:1 to glipizide 5mg or dapagliflozin 2.5mg, and were up-titrated over 18 weeks to optimal glycaemic effect (FPG <110 mg/dL [6.11 mmol/L]) or to the highest dose tolerated (glipizide 20mg or dapagliflozin 10mg). Thereafter, doses were kept constant with down-titration allowed only in cases of hypoglycaemia. This was the only study utilising a dose titration scheme, which was employed due the risk of hypoglycaemia associated with glipizide.

At the end of the titration period, 87% of patients in the dapagliflozin group had been titrated to the maximum study dose versus 73% in the glipizide group. In total, 0.5% of patients in the dapagliflozin group required down-titration due to hypoglycaemia, versus 5.1% of patients in the glipizide group.

A comparison of hypoglycaemic events between dapagliflozin and glipizide was a secondary efficacy endpoint in Study 4, the active comparator study to glipizide. More than 10-fold fewer patients in the dapagliflozin group (3.5%), compared to the glipizide group (40.8%) experienced at least 1 event of hypoglycaemia over 52 weeks of treatment ($p <0.0001$). A statistically significant and clinically meaningful lower proportion of patients in the dapagliflozin group, compared to glipizide, experienced at least one event of hypoglycaemia over 52 weeks of treatment.

Blood pressure

For SBP a mean decrease from baseline to week 52 (LOCF) in the dapagliflozin group compared to a small mean increase in the glipizide group was reported (Table 20). Dapagliflozin also reduced DBP (Nauck et al 2011a, 2011b).

In conclusion, this head-to-head comparison of dapagliflozin versus glipizide added to metformin in type 2 diabetic patients inadequately controlled with metformin monotherapy demonstrated similar glycaemic efficacy at 52 weeks but markedly divergent effects on weight and hypoglycaemia (Nauck et al 2011a, 2011b). Whereas glipizide treatment led to weight gain and more hypoglycaemic episodes, dapagliflozin produced significant weight loss and significantly fewer hypoglycaemic episodes.

5.5.3.4 Key result summary of Study 6 (Phase 3 add-on to insulin)

- This study demonstrated that dapagliflozin is effective and well tolerated when added to insulin.
- Dapagliflozin when added on to insulin therapy, with or without metformin, significantly reduced HbA1c compared with placebo (-0.90% vs. -0.30%, p value for difference <0.0001) at 24 weeks.
    - This HbA1c benefit of dapagliflozin was sustained at 2 years [redacted]
- Dapagliflozin significantly reduced body weight by 1.69kg compared to placebo (p value <0.0001) at 24 weeks.
    - At 2 years, the weight difference increased to [redacted], mainly due to an increase in weight in the placebo arm.
- Despite a mean baseline of 76 Units of insulin/day, the placebo group needed a continuous and steady up-titration of mean daily insulin dose whereas the dapagliflozin group did not. The % reduction in daily insulin dose vs. placebo was 7.6% at 24 weeks, 11.3% at 48 weeks and increased to [redacted] at 2 years
    - In addition, at 2 years [redacted] of dapagliflozin patients did not require up titration of insulin, compared with [redacted] of patients in the placebo arm.
- Dapagliflozin demonstrated that clinically meaningful changes in HbA1c could be achieved and sustained in a challenging population who have had diabetes for over a decade, as well as reducing daily insulin dose by [redacted] compared to placebo at 2 years, breaking the cycle of ever increasing insulin requirements.

Study 6 is a phase 3, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial with a 24-week short-term period followed by two extension periods (24 weeks and 56 weeks, respectively) to evaluate the efficacy and safety of dapagliflozin as add-on therapy to insulin in adults with T2DM who have inadequate glycaemic control (HbA1c ≥7.5% and ≤10.5%) on insulin therapy alone (Wilding et al 2012). No dose modification of study medications or OADs was allowed during the treatment phase, except to decrease doses of OADs when hypoglycaemia after cessation of insulin therapy was a concern. Daily insulin doses were held constant (within 10% of baseline dose). Up-titration was allowed under predefined conditions. Whilst this does not reflect clinical practice, where treatment to HbA1c target would occur, the design allowed the efficacy of dapagliflozin to be reliably established.

The primary outcome of this RCT was change in HbA1c from baseline to week 24.

The key secondary outcomes were change in body weight from baseline to week 24, absolute change in calculated mean daily insulin dose from baseline to week 24, proportion of patients with calculated mean daily insulin dose reduction from baseline to week 24, and change in fasting plasma glucose (FPG) from baseline to week 24.

The results for the key outcomes of interest relevant to the decision problem are summarised in Table 21.

Table 21. Relevant outcome results from Study 6†

Outcomes	Dapagliflozin 10mg	Placebo
Glycosylated haemoglobin, HbA1c (%)‡‡		
Number of patients with week 24 values §§	192	188
Mean baseline value; % (SD)	8.58 (0.82)	8.46 (0.76)
Mean change at 24 weeks; % (95% CI)	**-0.96 (NR)**	**-0.39 (NR)**
Mean difference, compared to placebo	**-0.57 (-0.72, -0.42)**	
p-value compared to placebo	**<0.001**	
Number of patients with week 48 values	139	89
Mean change at 48 weeks; % (95% CI)	-0.93 (NR)	-0.43 (NR)
Mean difference, compared to placebo at 48 weeks; % (95% CI)	-0.49 (-0.67, -0.32)	
p-value compared to placebo	NR	
Number of patients with week 104 values ¶¶	100	50
Mean change at 104 weeks; % (95% CI)	-0.82 (NR)	-0.27 (NR)
Mean difference at 104 weeks, compared to placebo, LRM	-0.65 (-0.90, -0.41)	
p-value compared to placebo	NR	
Weight (kg)‡‡		

Outcomes	Dapagliflozin 10mg	Placebo
Number of patients with week 24 values §§	192	188
Mean baseline value; kg (SD)	94.63 (16.83)	94.21 (19.49)
Mean change at 24 weeks; kg (95% CI) LOCF	-1.67 (-2.02, -1.31)	0.02 (-0.34, 0.38)
Mean difference, compared to placebo	-1.69 (-2.20, -1.18)	
p-value compared to placebo	<0.0001	
Number of patients with week 48 values	141	89
Mean change at 48 weeks; kg (95% CI)¶	-1.79 (-2.30, -1.29)	-0.18 (-0.77, 0.42)
Number of patients with week 104 values ¶¶	102	50
Mean baseline value; kg (SD)	90.54 (17.67)	88.17 (14.64)
Mean change at 104 weeks; kg (95% CI), LRM	-1.97 (-2.69, -1.26)	0.91 (-0.05, 1.87)
Mean difference, compared to placebo	-2.88 (-4.08, -1.68)	
p-value compared to placebo	NR	
Seated systolic blood pressure (mmHg)		
Number of patients with week 24 values §§	192	186
Mean baseline value; mmHg (SD)	140.6 (16.70)	136.1 (17.17)
Mean change at 24 weeks; mmHg (95% CI)‡‡ LOCF	-6.9 (-8.70, -5.10)	-3.9 (-5.70, -2.10)
Mean difference, compared to placebo	-3.00 (-5.55, -0.45)	
p-value compared to placebo	0.02	
Number of patients with week 48 values	166	156
Mean change at 48 weeks; mmHg (95% CI)	-5.20 (-7.45, -2.95)	-0.20 (-2.78, 2.38)
Number of patients with week 104 values ¶¶	[redacted]	[redacted]
Mean baseline value; mmHg (SD)	[redacted]	[redacted]
Mean change at 104 weeks; mmHg (95% CI)‡‡, LRM	[redacted]	[redacted]
Mean difference, compared to placebo	[redacted]	
p-value compared to placebo	NR	
Seated diastolic blood pressure (mmHg)		
Number of patients with week 24 values §§	192	186
Mean baseline value; mmHg (SD)	79.9 (9.31)	80.0
Mean change at 24 weeks; mmHg (95% CI)‡‡ LOCF	-3.0 (-4.0, -1.9)	-1.9 (-2.9, -0.9)
Mean difference, compared to placebo	-1.1 (-2.5, 0.4)	
p-value compared to placebo	0.15	
Number of patients with week 48 values	166	156
Mean change at 48 weeks; mmHg (95% CI)	-2.9 (-4.17, -1.63)	-1.3 (-2.72, 0.12)
Number of patients with week 104 values ¶¶	[redacted]	[redacted]
Mean baseline value; mmHg (SD)	[redacted]	[redacted]

Outcomes	Dapagliflozin 10mg	Placebo
Mean change at 104 weeks; mmHg (95% CI)‡‡, LRM	[redacted]	[redacted]
Mean difference, compared to placebo	[redacted]	
p-value compared to placebo	NR	
Hypoglycaemia (% with hypoglycaemia) ††		
Number of patients in analysis†††	196	197
Number of patients with outcome at 24 weeks	83	69
% of patients with hypoglycaemia at 24 weeks‡	42.3	35.0
Odds ratio relative to placebo	1.36 (0.91, 2.05)	
p-value compared to placebo	NR	
Number of patients with major hypoglycaemic event at 24 weeks§	1	1
Number of patients with hypoglycaemia at 48 weeks††	105	102
% of patients with hypoglycaemia at 48 weeks	53.6	51.8
Number of patients with major hypoglycaemic event at 48 weeks§	3	2
Number of patients with outcome at 104 weeks ‡‡‡	[redacted]	[redacted]
% of patients with hypoglycaemia at 104 weeks	[redacted]	[redacted]
Calculated mean daily insulin dose (IU/day)		
Number of patients with week 24 values §§	194	191
Mean baseline value; IU/day (SD) ‡‡	77.96 (45.0)	73.96 (42.5)
Mean change at 24 weeks; IU/day (95% CI) ‡‡	-1.16 (-2.99, 0.68)	5.08 (3.23, 6.93)
p-value compared to placebo	<0.0001	
Number of patients with week 48 values	166	157
Mean change at 48 weeks; IU/day (95% CI), LRM	-0.70 (-3.54, 2.13)	10.54 (7.62, 13.46)
Number of patients with week 104 values ¶¶	[redacted]	[redacted]
Mean baseline value; IU/day (SD) §§§	[redacted]	[redacted]
Mean change at 104 weeks; IU/day (95% CI) §§§, LRM	[redacted]	[redacted]
p-value compared to placebo	NR	

Abbreviations: CI, Confidence interval; HbA1c, Glycosylated haemoglobin; IU, International unit; LOCF, Last observation carried forward; LRM, Longitudinal Repeated Measures model; NR, Not reported; SD, Standard deviation; SE; Standard error; †, Source: Published abstract (Wilding et al 2012) and BMS/AZ data on file; ‡, Values exclude data after insulin up-titration, the corresponding values (including data after insulin titration) were 44.9% and 42.1% for dapagliflozin 10mg and placebo arms respectively; §, Major episode defined as a symptomatic episode requiring external (3rd party) assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value < 3mmol/L (<54 mg/dl) and prompt recovery after glucose or glucagon administration; ¶, The presented values excludes data after insulin up-titration, values including data after insulin up-titration are "-1.5 (-2.1, -0.9) and 0.9 (0.3, 1.5)" for dapagliflozin 10mg and the placebo arms, respectively; ††, Describes proportion with at least one event of hypoglycaemia using the safety analysis set and excluding data after insulin up-titration; ‡‡ Excludes data after insulin up-titration; §§, Number of patients in the full analysis set with non-missing baseline and week 24 (LOCF) values and this analysis dataset is consistent with the definition of modified intention to treat (Abraha, 2010) – The full analysis set consists of all randomised patients who received at least one dose of study

medication during the 24-week short-term period, who had a non missing baseline value, and who had a least one post-baseline efficacy value for at least one efficacy variable during the 24-week short-term period; ¶¶, Number of patients in the full analysis set with non-missing baseline and week 104 values and based on longitudinal repeated measures analyses; †††, Safety analysis set consisting of all randomised patients who received at least one dose of study medication,‡‡‡, Includes data after insulin titration, §§§, Includes data after insulin up-titration

The results of this RCT suggests that among patients with T2DM and inadequate glycaemic control on ≥ 30 IU (International unit) injectable insulin per day, the addition of dapagliflozin resulted in significant mean decrease from baseline to week 24 (LOCF) in glycosylated haemoglobin percentage, compared to placebo treated patients. Body weight showed a significant mean decrease from baseline to week 24 (LOCF) in the dapagliflozin group compared to a negligible change in the placebo group (p <0.0001). Dapagliflozin treated patients showed a significantly greater mean reduction from baseline to week 24 in SBP compared to patients receiving a placebo. There were more episodes of hypoglycaemia in the dapagliflozin arm compared to the placebo arm. Calculated mean daily insulin dose showed a slight mean decrease from baseline to week 24 (LOCF) in the dapagliflozin group and a mean increase in the placebo group; the mean change in calculated mean daily insulin dose was statistically significant in the dapagliflozin group relative to placebo.

HbA1c

At 24 weeks there was a significant reduction in HbA1c with dapagliflozin compared to placebo (p<0.0001), which was sustained over 48 weeks[redacted].

Dapagliflozin improved glycaemic control over 24 weeks and maintained efficacy over 48 weeks of treatment[redacted].

Weight

At week 24, modest weight loss compared with baseline was observed in the dapagliflozin groups, while patients in the placebo group did not show any clinically meaningful mean change in body weight. This reduction in body weight was maintained when treatment was continued to 48 weeks, [redacted].

Blood pressure

In the dapagliflozin treatment groups there was a trend towards small decreases in SBP without increased frequency of orthostatic hypotension.

Hypoglycaemia

A higher percentage of patients experienced a hypoglycaemic event on dapagliflozin (42%) than on placebo (35%) at 24 weeks. Over time the rate of hypoglycaemia increased in the placebo arm, perhaps due to the increasing total daily insulin dose, such that the difference at 48 weeks is much smaller (53.6% versus 51.8%), while at 2 years the rate is numerically less in the dapagliflozin arm (60.7% vs 61.9%).. Major episodes of hypoglycaemia were few and evenly distributed among treatment arms; there were no withdrawals due to hypoglycaemia.

Total Daily Dose of Insulin

Protocol-mandated increases in insulin dose were more frequent in placebo-treated versus dapagliflozin-treated patients, resulting in a progressive rise in mean daily insulin dose and weight gain in placebo-treated patients from 24 to 48 weeks. The mean change in calculated mean daily insulin dose was statistically significant with dapagliflozin compared to placebo ($p<0.0001$).

Mean daily insulin dose remained stable in dapagliflozin-treated patients through to week 48. Continuous and steady up-titration of mean daily insulin dose was required in the placebo group but not for any of the dapagliflozin treatment groups. The difference in proportion of patients with a reduction in insulin dose of ≥10% was statistically significant compared to placebo after treatment with 10 mg dapagliflozin.

There was a very small decrease in mean daily insulin dose at week 48 in the dapagliflozin treatment groups compared to baseline (-0.70 IU/day in the dapagliflozin 10 mg group), while a numerical increase of 10.54 IU/day was observed in the placebo group. The daily insulin dose in the placebo group observed at week 24 was nearly doubled numerically at week 48, whereas there did not appear to be a change in the dapagliflozin groups from week 24 to week 48 (Wilding et al 2012).

It is important to realise that in clinical practice where insulin doses are varied to reach glycaemic targets, the insulin-sparing potential of dapagliflozin could be greater, especially in patients on high doses of insulin. In the pilot study (Study 9: see details below) despite the dose of insulin being reduced by 50% the addition of dapagliflozin still resulted in a 0.7% reduction in HbA1c. The SPC for dapagliflozin recommends a reduction in insulin dose when starting insulin and BMS/AZ consider that a 25% decrease in daily insulin dose may be appropriate, especially in those on high doses of insulin. [redacted].

5.5.3.5 Key result summary of Study 9 (Phase 2 Add-on to insulin)

- The study design reduced baseline insulin dose by 50% at study initiation. Despite this, dapagliflozin patients demonstrated greater improvements in HbA1c compared with the placebo arm.
- A greater degree of weight loss was seen in the dapagliflozin patients compared with placebo.

Study 9 is a phase 2, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial to evaluate the efficacy of dapagliflozin in lowering blood glucose in adult patients with T2DM that is inadequately controlled with insulin plus oral antidiabetic agents (Wilding et al 2009).

The primary outcome of this RCT was change in HbA1c from baseline to week 12 (LOCF).

The key secondary outcomes included changes from baseline in FPG and total daily dose of insulin (TDDI), the proportion of patients achieving HbA1c reduction of at least 0.5% from baseline, and the proportion of patients achieving HbA1c <7%. Other outcomes assessed included changes from baseline in total body weight and in postprandial glucose.

The results for the key outcomes of interest relevant to the decision problem are summarised in Table 22.

Table 22. Relevant outcome results from Study 9†

Outcomes	Dapagliflozin 10mg	Placebo
Glycosylated haemoglobin, HbA1c (%) ¶		
Number of patients with week 12 values§	23	19
Mean baseline value; % (SD) ¶	8.39 (0.71)	8.32 (0.78)
Mean change at 12 weeks; % (95% CI) ‡	**-0.61 (-0.87, -0.36)**	**0.09 (-0.19, 0.37)**
Mean difference, compared to placebo	**-0.70 (-1.08, -0.32)**	**-**
p-value compared to placebo	**NR**	
Weight (kg)		
Number of patients with week 12 values§	23	22
Mean baseline value; kg (SD) ¶	102.78 (9.85)	101.29 (16.71)
Mean change from baseline; kg (95% CI) ‡	-4.51 (-5.48, -3.53)	-1.88 (-2.89, -0.88)
Mean difference, compared to placebo	-2.62 (-4.02, -1.22)	-
p-value compared to placebo	NR	

Outcomes	Dapagliflozin 10mg	Placebo
Standing systolic blood pressure (mmHg)		
Number of patients with week 12 values§	22	14
Mean baseline value; mmHg (SD)	124.7 (16.18)	134.6 (14.08)
Mean change from baseline; mmHg (95% CI)	-7.2 (-12.1, -2.3)	2.8 (-4.85, 10.45)
Mean difference, compared to placebo	-10.0 (-19.1, -0.9)	
p-value compared to placebo	NR	
Standing diastolic blood pressure (mmHg)		
Number of patients with week 12 values§	22	14
Mean baseline value; mmHg (SD)	78.4 (10.40)	77.4 (11.17)
Mean change from baseline; mmHg (95% CI)	-1.2 (-4.83, 2.43)	0.3 (-5.29, 5.89)
Mean difference, compared to placebo	-1.5	
p-value compared to placebo	NR	
Hypoglycaemia (% with hypoglycaemia) ††		
Number of patients in analysis	24	23
Number of patients with outcome	7	3
% of patients with hypoglycaemia	29.2	13.0
Odds ratio relative to placebo	2.75 (0.61, 12.29)	
p-value compared to placebo	NR	
Number of patients with major hypoglycaemic event at 12 weeks§§	0	1
Total daily dose of insulin, TDDI (units)¶¶		
Number of patients with week 12 values§	24	22
Mean baseline value; units/day (SD)	52.42 (24.38)	54.14 (27.27)
Mean change from baseline; units/day (95% CI)‡	-1.35 (-6.64, 3.94)	1.69 (-3.83, 7.22)
Mean difference compared to placebo	-3.05 (-10.69, 4.60)	
p-value relative to placebo	NR	

Abbreviations: CI, Confidence interval; HbA1c, Glycosylated haemoglobin; LOCF, Last observation carried forward; NR, Not reported; SD, Standard deviation; TDDI, Total daily dose of insulin; †, Source: Published report and BMS/AZ data on file (Clinical Study Report); ‡, Adjusted change from baseline based on an ANCOVA model with treatment group as an effect and baseline value as a covariate; §, Number of patients with a non-missing baseline and a week 12 LOCF value; ¶, Excludes data after insulin up-titration; ††, Describes total patients with hypoglycaemia; §§, Major hypoglycaemic episode defined as 1) plasma blood glucose value <54 mg/dl, 2) at least one of the following symptoms: confusion/disorientation, abnormal behaviour, or unconsciousness, and 3) external treatment provided; ¶¶, Includes data after insulin up-titration

The results of this 12 week study suggest that the addition of dapagliflozin was more effective than placebo in lowering glucose after 12 weeks in patients with T2DM receiving insulin plus oral antidiabetic agents. Overall, numerically greater mean reductions in total body weight and systolic blood pressure from baseline to week 12 were reported for dapagliflozin relative to placebo; for SBP, a slight mean increase was reported for the placebo group. In both the dapagliflozin and placebo arms, there were no clinically meaningful mean changes from

baseline in TDDI at week 12 (LOCF) and a higher number of patients experiencing hypoglycaemic events were reported for the dapagliflozin group compared to the placebo group.

It should be noted that Study 9 was a phase 2b study of short duration, and consequently only included a small number of patients. The study population was also homogeneous with respect to race. Because of this, extrapolation of the clinical data should be done with caution; the data are presented here for completeness.

HbA1c

Greater mean reductions in HbA1c from baseline at week 12 (LOCF) were achieved with dapagliflozin versus placebo. In the 10mg dapagliflozin group, HbA1c decreased from baseline to week 12 (LOCF), resulting in differences in mean changes versus placebo of -0.71% with 65.2% of patients (in the dapagliflozin group) achieving a decrease from baseline in HbA1c ≥0.5% versus 15.8% in the placebo group. Dapagliflozin 10mg was effective in lowering HbA1c. In spite of a protocol-led reduction in the insulin dose by 50% at baseline, patients in the placebo arm experienced little change in HbA1c, an outcome that likely reflects the relatively severe insulin resistance in the patients and perhaps improved compliance with diet and lifestyle as a result of study participation.

The proportion of patients achieving a therapeutic glycaemic response, defined as HbA1c decrease from baseline ≥ 0.5% at week 12 (LOCF) was greater in the dapagliflozin group compared with the placebo group.

There was no meaningful difference in the proportion of patients achieving therapeutic glycaemic response of HbA1c < 7% or HbA1c ≤ 6.5% at week 12 (LOCF) between the dapagliflozin groups and the placebo group (BMS, CSR Study 9, 12 weeks).

Weight

Treatment with dapagliflozin, with its insulin-independent mechanism of action, was associated with weight loss and with improvements in glycaemic control compared with placebo. Numerically greater mean reductions from baseline in total body weight at week 12 (LOCF) were achieved in the dapagliflozin 10 mg arm (-4.5kg) than in the placebo group (-1.9kg).

Blood pressure

The placebo group experienced a slight increase in blood pressure at week 12, whereas dapagliflozin demonstrated mean improvements in SBP and DBP (-7.2 systolic/-1.2 diastolic mmHg in the 10 mg dapagliflozin group).

Hypoglycaemia

Although the total number of hypoglycaemic events reported was greater with dapagliflozin than with placebo, there were no major hypoglycaemia episodes with dapagliflozin.

Total Daily Dose of Insulin

There was no appreciable change from baseline in TDDI at week 12 (LOCF) across the treatment groups. Four patients in the placebo arm required insulin up-titration, compared with one in the dapagliflozin 10 mg arm

5.6 Meta-analysis

5.6.1 Meta-analysis methods and results

Five RCTs involving dapagliflozin 10mg/day met the systematic review eligibility criteria (Section 5.2.1). In the current section, the relative effect estimates are presented using evidence collected from these five trials involving dapagliflozin compared head-to-head with either placebo or a SU. In Section 5.7, the evidence base is extended to include indirect evidence from other RCTs that met the systematic review eligibility criteria.

The five RCTs involved:

- two different indications (add-on to metformin and add-on to insulin);
- two comparators (placebo and sulphonylurea); and
- three durations of follow-up (12 weeks, 24 weeks, and 52 weeks).

As described in Section 5.7.5, relative effect sizes were stratified by indication and duration of follow up, and relative effect sizes were summarized by drug class. Applying these stratification variables, there was only one RCT in each stratum, with the exception of the metformin add-on indication at 24 weeks. In this stratum there were two RCTs:

- Study 14: The HbA1c inclusion criteria in was 7.0% to 10%, and the mean HbA1c at baseline in the placebo arm was 8.11% (SD = 0.96); and
- Study 12: The HbA1c inclusion criteria in was 6.5% to 8.5%, and the mean HbA1c at baseline in the placebo arm was 7.16% (SD = 0.53).

In the subgroup analysis of Study 14, a potential effect of baseline HbA1c on the treatment effect for the change in HbA1c was identified, with larger relative differences observed among patients with higher baseline HbA1c. In Section 5.7.5, the rationale and methodology for incorporating an adjustment factor in the network meta-analysis (NMA) is described; however, in the pairwise analysis of the RCTs involving dapagliflozin, two RCTs were insufficient for incorporating an empirically estimated adjustment variable. Therefore, the pooled estimates for these two RCTs are not presented in Section 5.6; however, they are presented in Section 5.7.9 for comparison against the results of the NMA and assessment of consistency.

In Section 5.6.2, data are presented graphically using forest plots prepared with STATA version 10.0 (Stata Corporation, Texas, USA); however, no meta-analytic techniques were used to combine data from individual RCTs.

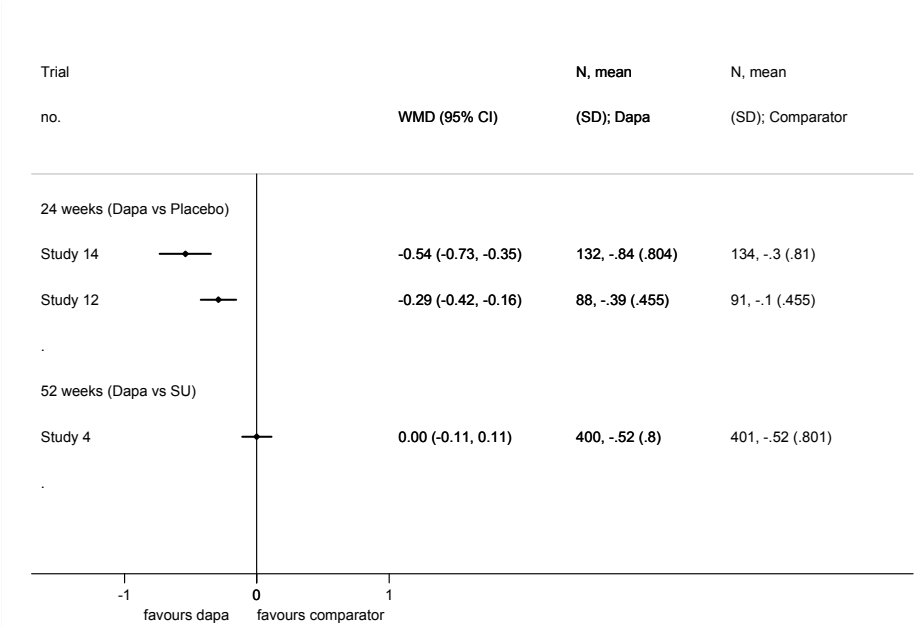
5.6.2 Qualitative overview if meta-analysis inappropriate

The rationale for not presenting pooled estimates for the dapagliflozin RCTs is provided in Section 5.6.1.

5.6.2.1 Pairwise analysis: HbA1c

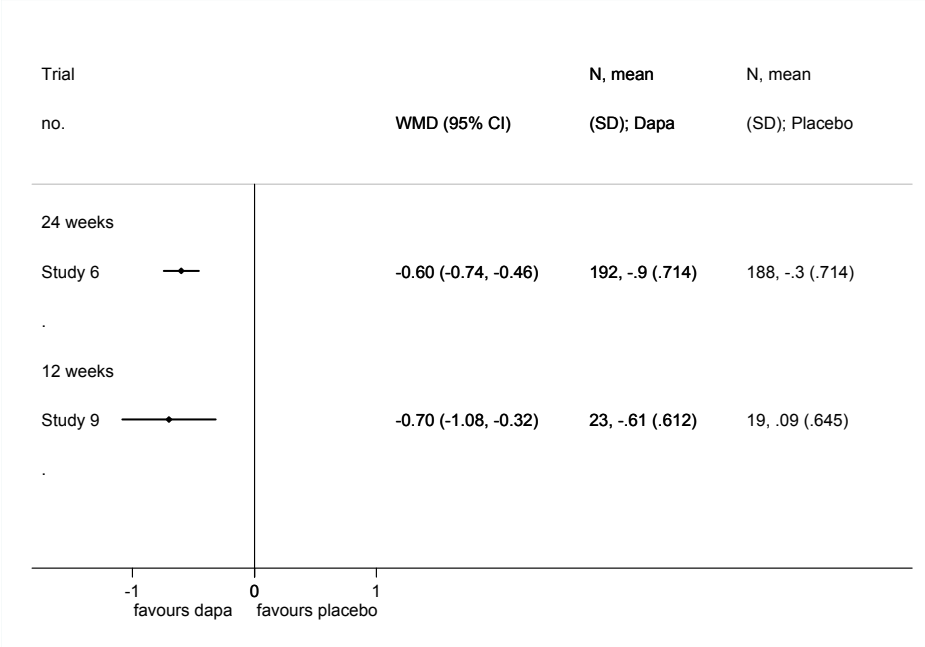
In Section 5.6, data are presented graphically using forest plots prepared with STATA version 10.0 (Stata Corporation, Texas, USA); however, no meta-analytic techniques were used to combine data from individual RCTs.

Figure 9. Mean difference in HbA1c (%) among type 2 diabetic patients treated with dapagliflozin added to metformin compared with patients treated with placebo (Study 14, Study 12) or sulphonylurea (Study 4) added to metformin, at 24 and 52 weeks of follow-up



Abbreviations: CI, Confidence interval; Dapa, Dapagliflozin; HbA1c, glycosylated haemoglobin; N, Sample size; SD, Standard deviation; SU, sulphonylurea; WMD, Weighted mean difference

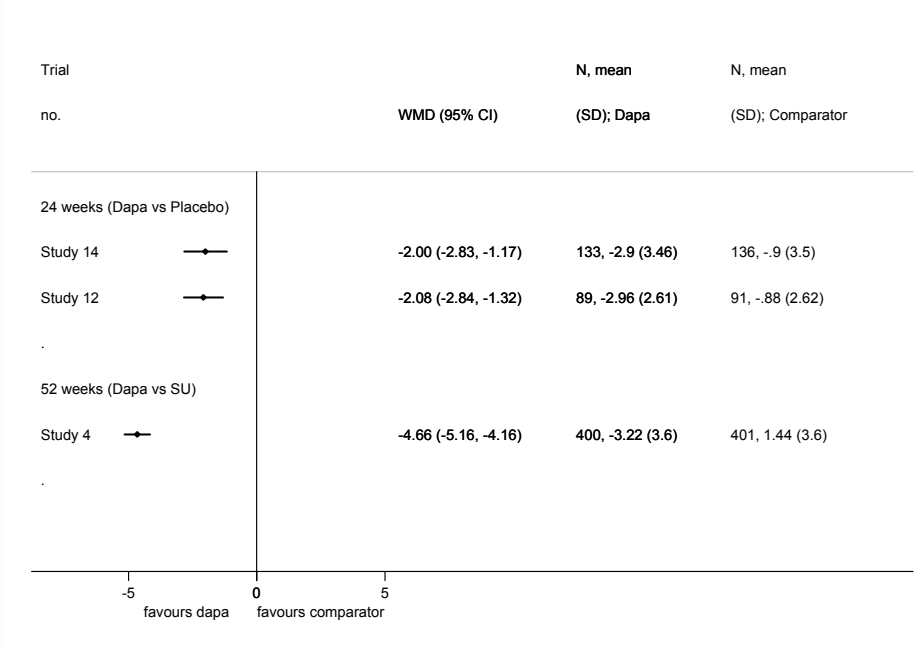
Figure 10. Mean difference in HbA1c (%) among type 2 diabetic patients treated with dapagliflozin added to insulin compared with patients treated with insulin (with or without placebo; with or without other oral antidiabetic agents), at 12 (Study 9) and 24 weeks (Study 6) of follow-up



Abbreviations: CI, Confidence interval; Dapa, Dapagliflozin; HbA1c, glycosylated haemoglobin; N, Sample size; SD, Standard deviation; WMD, Weighted mean difference

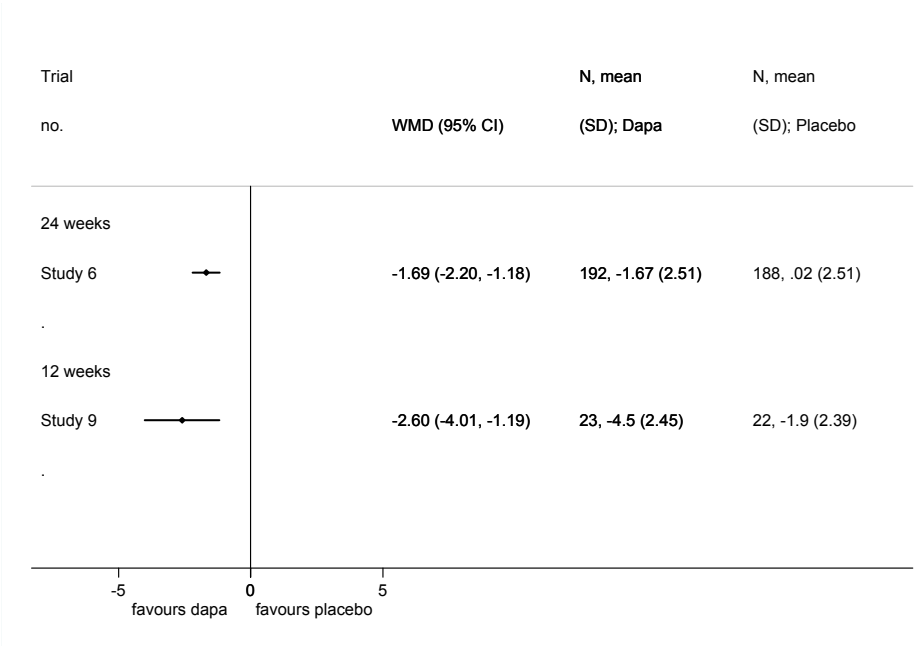
5.6.2.2 Pairwise analysis: Weight

Figure 11. Mean difference in weight (kg) among type 2 diabetic patients treated with dapagliflozin added to metformin compared with patients treated with placebo (Study 14, Study 12) or sulphonylurea (Study 4) added to metformin, at 24 and 52 weeks of follow-up



Abbreviations: CI, Confidence interval; Dapa, Dapagliflozin; N, Sample size; SD, Standard deviation; SU, sulphonylurea; WMD, Weighted mean difference

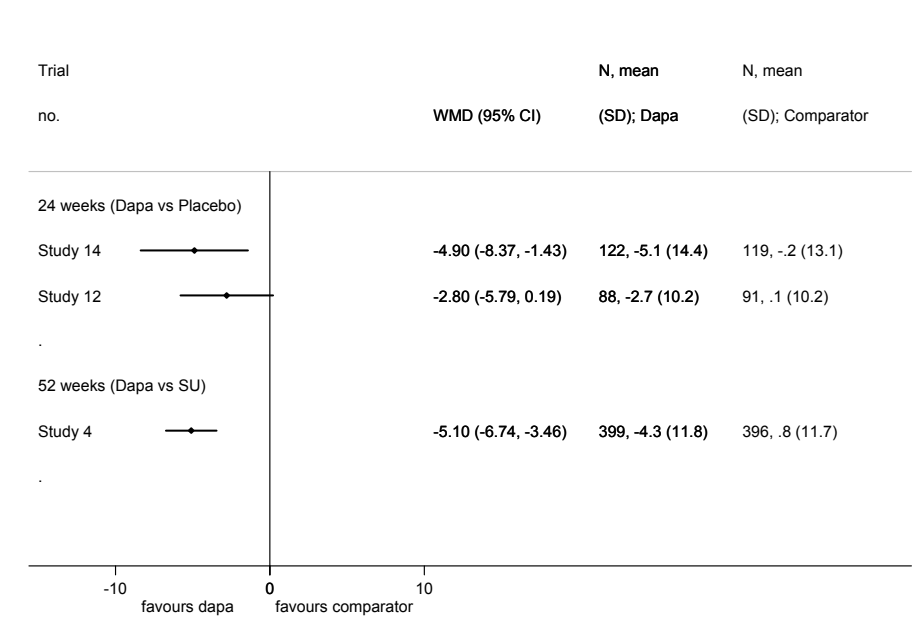
Figure 12. Mean difference in weight (kg) among type 2 diabetic patients treated with dapagliflozin added to insulin compared with patients treated with insulin (with or without placebo; with or without other oral antidiabetic agents), at 12 (Study 9) and 24 weeks (Study 6) of follow-up



Abbreviations: CI, Confidence interval; Dapa, Dapagliflozin; N, Sample size; SD, Standard deviation; WMD, Weighted mean difference

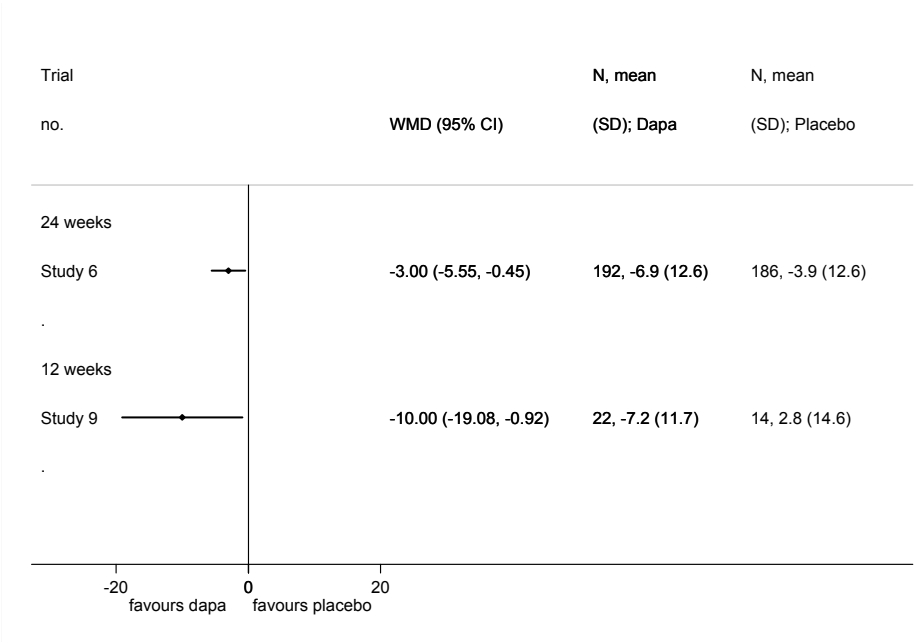
5.6.2.3 Pairwise analysis: Systolic blood pressure

Figure 13. Mean difference in systolic blood pressure (mmHg) among type 2 diabetic patients treated with dapagliflozin added to metformin compared with patients treated with placebo (Study 14, Study 12) or sulphonylurea (Study 4) added to metformin, at 24 and 52 weeks of follow-up



Abbreviations: CI, Confidence interval; Dapa, Dapagliflozin; N, Sample size; SD, Standard deviation; SU, sulphonylurea; WMD, Weighted mean difference

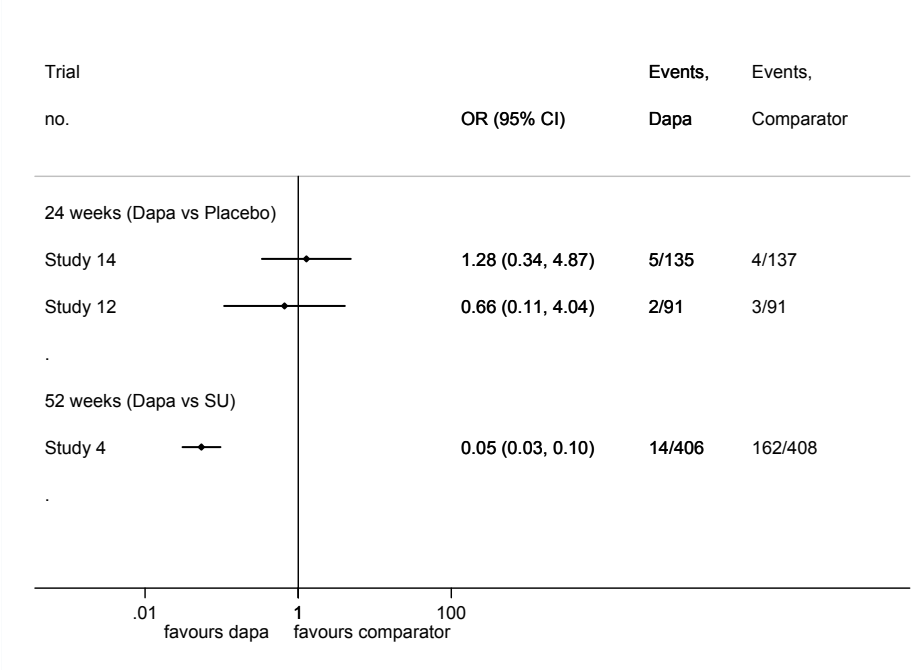
Figure 14. Mean difference in systolic blood pressure (mmHg) among type 2 diabetic patients treated with dapagliflozin added to insulin compared with patients treated with insulin (with or without placebo; with or without other oral antidiabetic agents), at 12 (Study 9) and 24 weeks (Study 6) of follow-up



Abbreviations: CI, Confidence interval; Dapa, Dapagliflozin; N, Sample size; SD, Standard deviation; WMD, Weighted mean difference

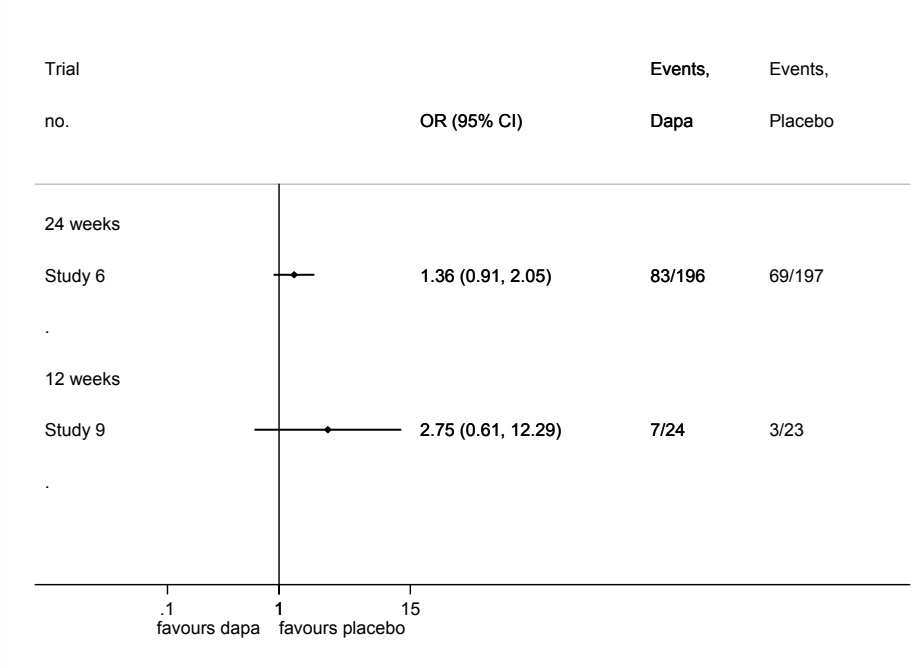
5.6.2.4 Pairwise analysis: Hypoglycaemia

Figure 15. Odds ratio for hypoglycaemia among type 2 diabetic patients treated with dapagliflozin added to metformin compared with patients treated with placebo (Study 14, Study 12) or sulphonylurea (Study 4) added to metformin, at 24 and 52 weeks of follow-up



Abbreviations: CI, Confidence interval; Dapa, Dapagliflozin; OR, Odds ratio; SU, sulphonylurea

Figure 16. Odds ratio for hypoglycaemia among type 2 diabetic patients treated with dapagliflozin added on to insulin compared with patients treated with insulin (with or without placebo; with or without other oral antidiabetic agents), at 12 (Study 9) and 24 weeks (Study 6) of follow-up



Abbreviations: CI, Confidence interval; Dapa, Dapagliflozin; OR, Odds ratio

The network of all relevant RCTs, stratified by indication and by duration of follow-up, and adjusted for baseline HbA1c (where appropriate) is presented in Section 5.7.

5.6.3 Trials excluded from analysis

In Section 5.6, no pairwise meta-analyses of the dapagliflozin RCTs was undertaken. The rationale for this is described in Section 5.6.1. All RCTs that involved dapagliflozin (as presented in Section 5.2.4) were presented in the graphical presentation of results in Section 5.6.

In Section 5.7 (indirect and mixed treatment comparisons), the phase 2 trial (Study 9) was excluded. The reason for excluding this trial is due to the limited duration of follow-up in this trial (12 weeks). The rationale for this exclusion described in Section 5.7.2.2.

5.7 Indirect and mixed treatment comparisons

5.7.1 Identification of studies

The search strategy described in Section 5.1 (with additional details in Section 9.2) was used to identify RCTs involving all anti-diabetic agents relevant to the decision problem.

5.7.2 Study selection, and methodology, quality assessment and results of relevant RCTs

5.7.2.1 Identification of studies

Refer to Section 5.7.1.

5.7.2.2 Study selection

Eligibility criteria and a flow diagram of included and excluded studies can be found in Section 5.2.

To reduce heterogeneity among the RCTs identified in the systematic review, and to improve the generalisability of the NMA estimates, additional eligibility criteria were applied to the RCTs identified in the systematic review, prior to undertaking the NMA.

In the metformin add-on network, the following additional inclusion criteria were applied:

- RCTs were included if they reported outcomes at 24 weeks (+/- six weeks) OR 52 weeks (+/- six weeks) post-baseline.
  - These data were analysed in two separate networks: those of 24 weeks (+/- six weeks) and those of 52 weeks (+/- six weeks), hereinafter referred to as the 24 and 52 week networks.
    - Due to the paucity of available data, SBP was not meta-analysed at 52 weeks.
- The class of SUs was excluded from the 24 week network meta-analyses of HbA1c, weight, and hypoglycaemia (rationale for this decision is provided in Section 5.7.5).
  - SUs were included in the 24 week network for the outcome of systolic blood pressure, given that no estimate was available for this drug class at 52 weeks. Additional considerations were taken before adding this class back in:
    - i) there is little evidence to indicate that there is a J-curve associated with SUs for SBP;
    - ii) the evidence in the 24 week network was sparse, and adding the SU class strengthened that network;
  - 24 week RCTs involving SUs were included in Table 111 and Table 112 to ensure transparency of the impact of their exclusion.
- RCTs involving GLP-1 analogues with intensive diet regimens were excluded (rationale for this decision is provided in Section 5.7.5).
  - Both RCTs were included in a sensitivity analysis to ensure these results were not discarded.
- RCTs of 12 to 17.9 weeks were excluded, due to their relatively short duration and the availability of a sufficient number of longer-duration RCTs.

In the insulin add-on network:

- RCTs were included if they reported outcomes at 24 weeks (+/- eight weeks):
  - SBP was not evaluated at 24 weeks, due to a paucity of data.

- Trial data for dapagliflozin were not available; therefore a 52 week network was not analysed.

- Exclusion of RCTs allowing up-titration of the insulin dose in order to maintain glycaemic control:
  - Several RCTs were designed such that patients were permitted to up-titrate their insulin dose in order to meet glycaemic targets;
  - In Study 6, investigators aimed to maintain a constant dose. This difference represents a source of non-exchangeability across the trials in the network. In studies where insulin was up-titrated in the placebo arm, one might expect better glycaemic control than in studies where it was not;
  - RCTs permitting up-titration of the insulin dose were included in Table 111 and Table 112 to ensure transparency of the impact of their exclusion.
- Exclusion of RCTs comparing metformin with placebo:
  - Although the inclusion criteria for the systematic review included RCTs involving metformin as a comparator, metformin is not a comparator of interest in the UK setting, and therefore was not included in the NMA.
- RCTs of 12 to 15.9 weeks were excluded, due to their relatively short duration and the availability of a sufficient number of longer-duration RCTs. Therefore, Study 9, the phase 2 dapagliflozin RCT, was not included in the NMA.

5.7.2.3 Summary of methodology of relevant RCTs

The design, location, duration, and interventions used in the RCTs included in the indirect comparison are provided in Table 111 to Table 131. Additionally, the inclusion and exclusion criteria are summarised, as are the baseline patient characteristics.

5.7.2.4 Critical appraisal of relevant RCTs

The RCTs that were designed to compare metformin add-on indications were all double-blind, with the exception of one open-label study (Pratley et al 2010), in which oral sitagliptin was compared with subcutaneous liraglutide. All RCTs included in the insulin NMA were double-blind studies.

A summary of key quality characteristics of the included RCTs is presented in Table 111 to Table 131.

5.7.2.5 Results of relevant RCTs

Data were extracted from included RCTs for the following outcomes:

- Mean change in HbA1c (%) from baseline;
- Mean change in weight (kg) from baseline;
- Mean change in SBP (mmHg) from baseline; and
- Proportion of patients experiencing at least one hypoglycaemia episode.

These data are discussed briefly in Section 5.7.4, and details have been provided in Table 111 to Table 131.

5.7.3 Summary of trials used to inform the comparison

A summary of RCTs used to conduct the indirect comparison of agents added on to metformin therapy is provided in Table 23, stratified by duration of follow-up. All investigators reported the mean change in HbA1c from baseline, with fewer investigators reporting the mean change in weight, or SBP from baseline, or the proportion of patients experiencing at least one episode of hypoglycaemia. Graphical depictions of the 24 and 52 week networks for HbA1c, weight, and hypoglycaemia are provided in Figure 17.

Table 23. Randomised clinical trials included in the metformin add-on network meta-analyses, stratified by duration of follow-up and outcomes reported

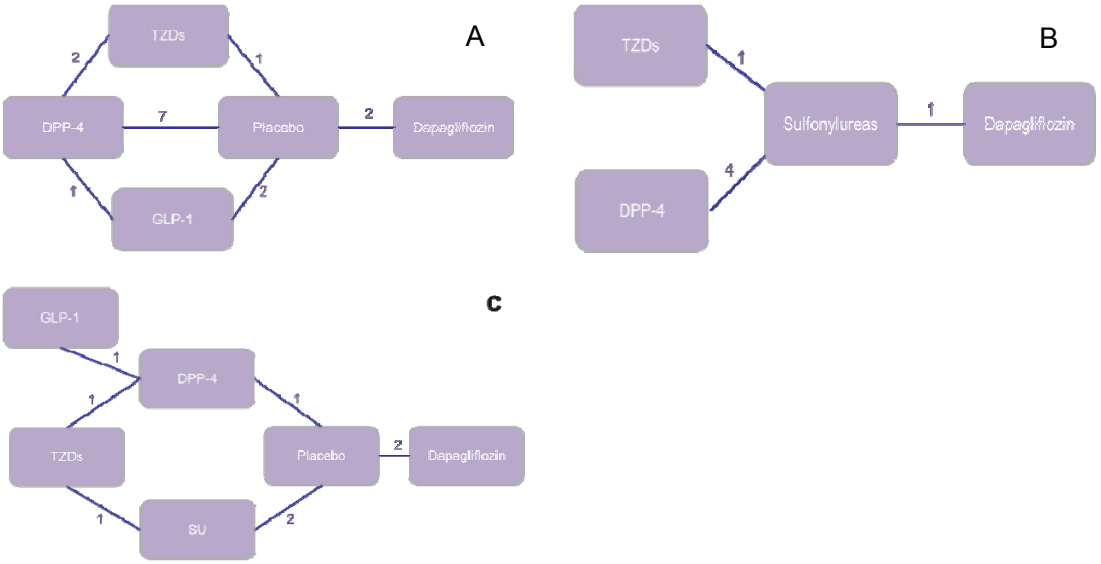
Author	Dapa	DPP-4	GLP-1	TZD	SU	Placebo
24 week network						
Study 14	HbA1c; W; SBP; H					HbA1c; W; SBP; H
Study 12	HbA1c; W; SBP; H					HbA1c; W; SBP; H
Kaku 2009				HbA1c; W; SBP; H		HbA1c; W; SBP; H
Charbonnel, 2006		HbA1c; SBP; H				HbA1c; SBP; H
DeFronzo, 2009		HbA1c; W; SBP; H				HbA1c; W; SBP; H
Raz, 2008		HbA1c; W; H				HbA1c; W; H
Bosi, 2007		HbA1c; W; H				HbA1c; W; H
Taskinen, 2011		HbA1c; W; H				HbA1c; W; H
Scott, 2008		HbA1c; W; H				HbA1c; W; H
Bergenstal, 2010b		HbA1c; W				HbA1c; W
DeFronzo, 2005			HbA1c; W; H			HbA1c; W; H
Bolli, 2008		HbA1c; W; H		HbA1c; W; H		
Bergenstal, 2010a		HbA1c; W; SBP; H		HbA1c; W; SBP; H		
Pratley, 2010		HbA1c; W; SBP; H	HbA1c; W; SBP; H			
Nauck, 2009			HbA1c; W; SBP			HbA1c; W; SBP
24 week network – involving SU – limited to estimates for SBP						
Papathanassiou, 2009				SBP	SBP	

Author	Dapa	DPP-4	GLP-1	TZD	SU	Placebo
Charpentier, 2001					SBP	SBP
52 week network						
Study 4	HbA1c; W; SBP; H				HbA1c; W; SBP; H	
Matthews, 2005				HbA1c; W; SBP; H	HbA1c; W; SBP; H	
Matthews, 2010		HbA1c; W; H			HbA1c; W; H	
Nauck, 2007		HbA1c; W; H			HbA1c; W; H	
Goke, 2010		HbA1c; W; SBP; H			HbA1c; W; SBP; H	
Filozof, 2010		HbA1c; W			HbA1c; W	
52 week network – excluded from main analysis						
Derosa, 2010		HbA1c; W			HbA1c; W	
Salvadeo, 2010		HbA1c			HbA1c	

Abbreviations: Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptiodase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; H, Hypoglycaemia; HbA1c, Glycosylated haemoglobin; SBP, Systolic blood pressure; SU, Sulphonylurea; TZD, Thiazolidinediones; W, weight.

Notes: table indicates the outcome(s) reported for each drug class within each trial.

Figure 17. Network for randomised clinical trials reporting any of HbA1c, weight, or hypoglycaemia (metformin add-on indication)



Abbreviations: Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptiodase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; SU, Sulphonylurea; TZD, Thiazolidinediones;
A) 24 week network; B) 52 week network; C) 24 week metformin add-on network for systolic blood pressure.

In the insulin add-on network, only seven RCTs were identified, and three of these seven were designed to allow up-titration of insulin throughout the study (or requirement of a stable insulin dose was not reported). Therefore, only three RCTs were considered to provide suitable comparisons to Study 6, making a total of four RCTs eligible for the NMA. All four of these RCT reported mean change in HbA1c from baseline mean change in weight from baseline (however, only three reported variance around the mean change in weight from baseline), and the proportion of patients experiencing at least one episode of hypoglycaemia. The mean change in systolic blood pressure from baseline was reported in only two RCTs. A summary is presented in Table 24, and a graphical depiction of all available RCTs, regardless of insulin dose titration, is presented in Figure 18.

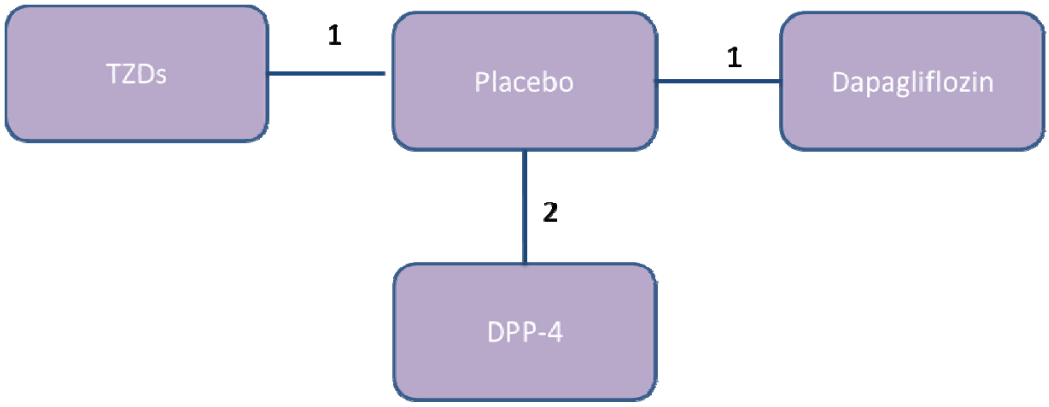
Table 24. Randomised clinical trials included in the insulin add-on network meta-analyses, stratified by duration of follow-up and outcomes reported

Author	Dapagliflozin (10mg)	DPP-4 inhibitor	TZD	Placebo
24 week network – designed to maintain a stable insulin dose				
Vilsboll, 2010		HbA1c; W; H		HbA1c; W; H
Barnett, 2012		HbA1c; W; SBP; H		HbA1c; W; SBP; H
Rosenstock, 2002			HbA1c; W†; H	HbA1c; W†; H
Study 6	HbA1c; W; SBP; H			HbA1c; W; SBP; H
24 week network – permitted up-titration of insulin				
Asnani, 2006			HbA1c	HbA1c
Mattoo, 2005			HbA1c; W; H	HbA1c; W; H
Zib, 2007			HbA1c; W; SBP	HbA1c; W; SBP

Abbreviations: DPP-4, Dipeptidyl peptidase-4 inhibitors; H, Hypoglycaemia; HbA1c, Glycosylated haemoglobin; SBP, Systolic blood pressure; TZD, Thiazolidinediones; W, weight; †, variance not reported and could not be imputed from other trials of the same drug class.

Note: table indicates the outcome(s) reported for each drug class within each trial.

Figure 18. Network for randomised clinical trials reporting any of HbA1c, weight, or hypoglycaemia (insulin add-on indication).



Abbreviations: DPP-4, Dipeptidyl peptidase-4 inhibitors; TZD, Thiazolidinediones;
Note: three additional trials involving TZDs were excluded based on not requiring that the insulin dose remain stable throughout the study period

5.7.4 Summary of the data used in the analysis.

Mean change from baseline for three key clinical outcomes: HbA1c, weight, and systolic blood pressure, are summarised in Table 124 to Table 129. Additionally the proportion of patients experiencing at least one episode of hypoglycaemia is summarised.

Hypoglycaemia was heterogeneously defined across included trials. The definitions provided in Table 130 and Table 131 were made according to standardised definitions, below. Based on the reporting frequency across trials, the meta-analysed data were based on the proportion of patients with at least one hypoglycaemic event, including major and non-major events. The standardised definitions applied in the assessment of each study are:

1) Major (or severe)
    a. Usually defined by unconscious or 3rd party intervention, glucose test value, and/or IV glucose or intramuscular glucagon.
2) Non-major (minor, mild/moderate)
    a. Symptomatic, without requirement for confirmation by glucose test (e.g. self-report)
    b. Symptomatic, with requirement for confirmation by glucose test (e.g. self-report)
    c. Symptomatic or asymptomatic, confirmed via glucose test (e.g. required routine testing, regardless of whether patients had symptoms)
3) Any hypoglycaemic event (where authors do not report major and non-major events separately)
    a. Symptomatic, without requirement for confirmation by glucose test (e.g. self-report)
    b. Symptomatic, with requirement for confirmation by glucose test (e.g. self-report)
    c. Symptomatic or asymptomatic, confirmed via glucose test (e.g. required routine testing, regardless of whether patients had symptoms)
4) Nocturnal
    a. Nocturnal hypoglycaemia was not reported by study authors, and therefore no standardised definition was established.

5.7.5 Indirect/mixed treatment comparison methodology.

Network meta-analysis is a methodology for simultaneously studying the pairwise relative effects of multiple treatments based on a synthesis of both direct and indirect evidence provided by a network of RCTs that compare various subsets of these treatments. In the current analysis, a Bayesian approach was used.

Network stratification

The rationale for considering the relative effect size separately at different time points was because the relative effect size may vary over time. Separate networks were constructed for the two different indications and two different durations of follow up. The final networks were:

1. Metformin add-on at 24 weeks;
2. Metformin add-on at 52 weeks; and
3. Insulin add-on at 24 weeks.

A six week time window around the 24 week and 52 week strata (for metformin) and an eight week window around the 24 week network (for insulin), were selected based on clinical expert opinion. The time windows were defined to include a sufficient number of RCTs for pooling data while reducing the amount of heterogeneity due to duration. In the insulin network, although the permissible time window was widened to 24 +/- eight weeks, the follow-up times in the identified RCTs that met eligibility ranged from 16 to 24 weeks.

The assumption that the relative effect size may vary over time is due to a review of the trajectories for different anti-diabetic agents. The HbA1c trajectory over time for a given anti-diabetic agent may assume a “J-curve” shape (initial drop followed by an upward trend back to baseline), an “inverse hockey stick” shape (initial drop followed by a sustained effect), a slow steady decline over time (linear decline from baseline that does not reach a minimum value over the observed time period), or another shape. Because these trajectories may differ across different anti-diabetic agents, it follows that the relative effect size between agents can differ over time.

Although the trajectory of the change in HbA1c over time associated with antidiabetic agents has been better characterized in the literature than other outcomes such as weight or systolic blood pressure, this principle applies to the other continuous outcome measures considered in the analysis. For consistency, the outcome of hypoglycaemia was analysed using the same stratified approach as the continuous outcomes.

New methods for conducting network meta-analyses have recently emerged for modelling data that are reported at multiple follow-up times (Lu et al 2007). These types of models allow for a ‘borrowing’ of information from the MTC structure and can adjust across different time points.

Although it is technically feasible to apply this approach to the meta-analysis of anti-diabetic agents, the model results are arguably less intuitive. Furthermore, the additional parameterization required to implement this type of analysis would require either a variance structure across time points or an explicitly modelled time effect.

For outcomes where the effect over time is clear (e.g. number of deaths at time t is necessarily less than or equal to number of deaths at time $t+1$), this constraint can be more easily implemented; however, for continuous outcomes such as change in weight, HbA1c, and systolic blood pressure, the relationship over time is unclear.

To avoid making assumptions on constraints, one can fit an unconstrained time-dependent model; however, this is akin to fitting a stratified model, as performed in the original analysis.

Pooling of agents and drug classes

Agents and doses within drug classes were pooled, primarily due to the limited number of RCTs relative to the number of doses and agents. Agents were pooled according to drug class, to produce a class-level estimate of relative efficacy. Pooling of dosages has been done in previous meta-analyses of monotherapy (Bolen et al 2007), metformin add-on (McIntosh et al 2011), and insulin add-on (Goudswaard et al, 2004) indications. Bolen et al (2007) investigated the effect of comparable and non-comparable dosage comparison and did not find an appreciable difference in effect size. The potential impact of bias due to pooling these agents was investigated in sensitivity analyses.

Exclusion of RCTs involving GLP-1 analogues with intensive diet regimens

One RCT (Derosa et al 2010) was identified that involved an intensive diet program (near 600 kcal daily deficit, with a maximum cholesterol content of 300 mg/day and 35 g/day of fibre). A second trial by the same investigator group was identified in abstract form (Salvadeo et al 2010); however, no details of the diet regimen were provided.

The 8kg weight loss observed among subjects receiving exenatide was larger than expected by the study authors, who attributed the finding to the intensive approach to diet and exercise. Because this same intensive approach was not used in other RCTs, where another agent may have been associated with a larger-than-expected weight loss, this element of trial design was considered to be an effect modifier and compromised the consistency of the network. These trials were therefore excluded from the main results, but included in a sensitivity analysis.

Exclusion of SUs from 24 week network

Sulphonylureas were not included in the 24 week network due to unstable effect size at that duration of follow up (between 18 and 30 weeks). The unstable effect size can be attributed to both the observed J-curve effect at shorter durations. Furthermore, titration of SUs may often take up to 18 weeks, leading to further instability and sensitivity of the relative effect sizes to the titration period used across trials.

A summary of the 24 week RCTs involving SUs, as well as longer trials from which interim data at 24 weeks may have been extracted is presented in Section 9.16.

Inclusion of interim data

Interim results from longer trials were only included if a sufficient period of time had passed from the end of the titration period to the time of outcome collection. These interim measurements were reviewed by a clinical team to ensure that the interim data extracted from a RCT of longer duration were not systematically different from endpoint data extracted from a RCT designed with duration of follow-up equal to the interim time point.

Interim data were obtained from two RCTs:

52 week metformin add-on network

- One RCT (Matthews et al 2010) was initially planned to last for up to five years. The scope was re-defined and amended to a two-year design, with a primary endpoint of 'change in HbA1c from baseline to week 104'.
    - Titration period: Glimepiride/matched control could be uptitrated (to a maximum of 6 mg/day) at weeks 4, 8, or any later visit if FPG exceeded 6.2 mmol/L or down-titrated in cases of recurrent hypoglycaemia.
    - Interim estimate: An interim analysis as conducted at week 52, and reported in a separate publication (Ferrannini et al 2009).

24 week insulin add-on network

- One RCT (Hermann et al 2001) was designed as a 52 week RCT. Patients were examined after 3, 6, 9, and 12 months, and had frequent telephone contact with the clinic.
    - Titration period: The dose of metformin was 850mg once daily for 2 weeks and thereafter 850mg twice daily. Placebo tablets were administered similarly.
    - Interim estimate: The mean change in HbA1c was presented graphically at 3, 6, 9, and 12 months.

The 24 week interim data from 52 week RCTs involving sulphonylureas were not included for two reasons:

1) In most 52 week RCTs, there was an 18 week titration period for the sulphonylurea arm, meaning that the relative effect size would be different than the relative effect size estimated from a RCT designed as a 24 week trial, with shorter titration period.
2) SUs were excluded from the 24 week analyses (with the exception of the systolic blood pressure network).

Exclusion of extension data

Open label extensions of RCTs are susceptible to selection bias that may compromise their internal validity (Hemming et al 2008). The extension periods involving dapagliflozin were blinded; however, very few RCTs for other agents involved a blinded extension which limited the availability of long-term comparison data. Therefore, extension data were not included in the NMA.

Handling of missing data

Missing outcome data constituted non-reporting of quantitative results (but qualitative reference of results), non-reporting of variance, reporting of variance for only baseline and final estimates (but not for the difference from baseline), and reporting data only in graphical format. In RCTs where there was missing outcome data, authors were contacted to obtain the missing information. If no response was received, the following steps were undertaken:

For outcomes reported without a measure of variance, standard deviations were imputed by taking a weighted average of the variances from other trials of the same drug class based on the formula (Ma et al 2008):

$$\sigma = \sqrt{\frac{(n_1 - 1)\sigma_1^2 + (n_2 - 1)\sigma_2^2 + ... + (n_K - 1)\sigma_K^2}{n_1 + n_2 + ... + n_K - K}},$$

where K is the number of trial arms for drug class X, σ^2 is the variance (square of the standard deviation), and n is the number of subjects included in that trial arm.

For continuous outcomes for which only baseline and final values were available (no computed difference from baseline), the mean difference was calculated by subtracting the baseline value from the final. The standard error about the mean difference was computed according to the formula:

$$SE_{final-baseline} = \frac{\sqrt{\sigma_{final}^2 + \sigma_{baseline}^2}}{\sqrt{n}},$$

where σ^2 is the variance, and n is the number of subjects included in RCT for that outcome. Authors were contacted to obtain a more precise estimate of SE, given the correlation between baseline and final values. This calculation was only undertaken for one RCT (Derosa et al 2010), which did not form part of the main analysis.

For RCTs reporting outcomes in graphical format, data values were extracted from a digitized format of the graph, and converted to numeric values. Authors were contacted to obtain a more precise estimate.

Treatment*Covariate interaction

When the similarity and consistency assumptions across the network of RCTs are at risk of being violated due to effect modification, including a treatment*covariate interaction term (Cooper et al 2009) can provide an adjustment factor (although this factor is typically based on an aggregate trial level estimate).

In accordance with good practice, a treatment*covariate interaction term was pre-specified based on a previously observed potential for modifying the effect of anti-diabetic agents. Baseline HbA1c was identified as the most important potentially modifying effect, based on previously reported association baseline HbA1c and HbA1c decline from baseline, (DeFronzo et al 2010) and a potential interaction was seen between baseline HbA1c and treatment in Study 14.

Furthermore, HbA1c was used as a stratification variable in a number of the RCTs (Bergenstal et al 2010; Taskinen et al 2011; DeFronzo et al 2005) included in the systematic review, which is a common approach for handling effect modifiers. (Sun et al 2012)

Other potential modifiers of the relative effect such as trial design, demographic, and clinical baseline characteristics, that could be modifiers of the *relative* effect size between comparators were identified, and were considered as covariates in the analysis, but were not implemented due to the limitations that they reduce the degrees of freedom to an NMA and restricts the number of RCTs based on non-reporting of baseline data (including an estimate of variance).

Model selection

Due to the differences in the trial design, trial population and duration of follow-up, variability in the true effect sizes in the included studies was assumed (Borenstein et al 2009). Therefore, the random-effects model was selected a priori over the fixed-effect model; however, fixed-effect models were run to assess the fit of each model.

The deviance information criterion (DIC) was used to compare the fit of the random-effects and fixed-effect models. The *a priori* choice was to use the random-effects over the fixed-effect model. Therefore, the fixed-effect model was selected as the most appropriate model if it offered better model fit (Spiegelhalter et al 2002).

Furthermore, we inspected the posterior distribution of the between studies standard deviation to ensure that it was updated from the prior distribution based on the available evidence. Where the prior distribution dominated, the fixed effect model was selected (Dias et al 2011). Alternate data sources were considered for informing the prior distribution of the between studies standard deviation; however, no suitable sources were identified.

To avoid over-parameterising the model, the adjusted model (based on the covariate*treatment interaction term) was selected based on: a) model fit, b) statistical significance of coefficient, and c) clinically meaningful effect size.

The 24 and 52 week network estimates can be assumed to represent the relative effect at two different time points. The 24 week network estimates were selected based on the larger number of RCTs that reported at 24 weeks compared with 52 weeks. Because sulphonylureas were excluded from the 24 week network (with the exception of the outcome of systolic blood pressure), the relative effect sizes for this class were obtained from the 52 week network.

Analytic approach

Posterior densities were estimated for all unknown model parameters in the NMA using Markov Chain Monte Carlo (MCMC) simulation, as implemented in the software package WinBUGS Version 1.4 (Medical Research Council Biostatistics Unit, Cambridge). Specifically, two MCMC chains were simulated starting from different initial values of select unknown parameters. Each chain contained (at least) 20,000 burn-in iterations followed by (at least) 100,000 update iterations. Convergence was assessed by visualizing the histories of the chains against the iteration number; overlapping histories, that appear to mix with each other, provided an indication of convergence. Inferences were based on the (convergence) posterior distributions of the relevant parameters. The accuracy of the posterior estimates of these parameters was based on calculating the Monte Carlo error for each parameter. As a rule of thumb, the Monte Carlo error for each parameter of interest should be less than about 5% of the sample standard deviation.

Additional technical detail, as well as the WinBUGS code, is provided in Sections 9.14 and 9.15.

5.7.6 Please present the results of the analysis.

Model fit statistics for each of the models are presented in Table 25 and Table 26.

Table 25. Summary of deviance information criterion model fit for all fitted metformin add-on models†

	HbA1c		Weight		SBP		Hypoglycaemia	
	FE	RE	FE	RE	FE	RE	FE	RE
24 weeks								
Unadjusted	64.09	57.79	53.71	50.56‡	28.43	29.43‡	122	122 ‡
Adjusted	71.50	58.08‡	-	-	-	-	-	-
52 weeks								
Unadjusted	44.65	42.83‡	20.12	10.2 ‡	-	-	74	74 ‡
Adjusted	42.72	-40.96	-	-	-	-	-	-

Abbreviations: FE, Fixed-effect model; HbA1c, Glycosylated haemoglobin; RE, Random-effects model; SBP, Systolic blood pressure; †, A model whose deviance information criterion is at least three points lower than that of another model is deemed to have a better fit; ‡, Best model based on *a priori* choice of model (random-effects; adjusted), statistical and clinical significance of model coefficient, model fit, and assessment of the posterior distribution of the between studies variance.

Table 26. Summary of deviance information criterion model fit for all fitted insulin add-on models†

	HbA1c		Weight		SBP		Hypoglycaemia	
	FE	RE	FE	RE	FE	RE	FE	RE
24 weeks								
Unadjusted	15.33	15.78‡	10.36	11.40‡	-	-	13.96	16.29‡
Adjusted	16.19	15.96	-	-	-	-	-	-

Abbreviations: FE, Fixed-effect model; HbA1c, Glycosylated haemoglobin; RE, Random-effects model; SBP, Systolic blood pressure; †, A model whose deviance information criterion is at least three points lower than that of another model is deemed to have a better fit; ‡, Best model based on *a priori* choice of model (random-effects; adjusted),

statistical and clinical significance of model coefficient, model fit, and assessment of the posterior distribution of the between studies variance.

5.7.6.1 HbA1c – metformin add-on

On average, patients who received placebo treatment added on to existing metformin monotherapy did not experience a substantial decrease from their baseline HbA1c value after 24 weeks of treatment (mean = 0.02%; SD = 0.17). Compared with placebo, all drug classes were associated with a significant improvement in HbA1c conditional on a mean baseline HbA1c of 8.16%. The mean baseline HbA1c values in the included RCTs ranged from 7.16% in the placebo arm of the Study 4, to 9.3% in the sitagliptin arm of the RCT of Raz et al (2008).

Based on point estimates alone, dapagliflozin was associated with a significant decline in HbA1c at 24 weeks ([redacted] GLP-1 analogues were associated with the largest decline in HbA1c, compared with placebo [redacted]). The relative difference between dapagliflozin and GLP-1 analogues was toward a greater improvement associated with GLP-1 analogues, although did not result in being statistically significant, based on the indirect estimates [redacted]). Pairwise comparisons with placebo/sulphonylurea are presented Table 27, and pairwise comparisons with dapagliflozin are presented in Table 28.

At 52 weeks, each included RCT involved DPP-4 inhibitors, TZDs or dapagliflozin compared with sulphonylureas. On average, patients receiving sulphonylureas added to metformin experienced a 0.92% decline in HbA1c from baseline (SD 0.47). There was no difference in the decline in HbA1c among patients receiving sulphonylureas and those receiving dapagliflozin, DPP-4 inhibitors, or TZDs (Table 27), and no notable differences between dapagliflozin and any of these agents (Table 28).

Adjusting for baseline HbA1c did not impact the effect estimates, and the co-efficient was small and non-significant. The range of baseline HbA1c in the included RCTs was narrower than in the 24-week network, ranging from 7.3% in both the glimepiride and vildagliptin arms of the RCT by Matthews et al (2010) to 8.7% in the RCT by the same lead author, but involving pioglitazone (Matthews et al 2005). In the study by Derosa et al (2010), which was excluded, the mean baseline HbA1c was 8.9%.

Table 27. Summary of relative effect size of HbA1c change from baseline (%) for all drug classes compared with a common comparator using best fitting model

Comparators	Model type	Weeks	N direct RCTs	Mean Difference (%) (95% CrI)
24 weeks				
DPP-4 vs placebo	Adjusted, Random effects	24	7	-0.75 (-0.89, -0.61)
TZD vs placebo	Adjusted, Random effects	24	1	-0.91 (-1.17, -0.67)
Dapa vs placebo	Adjusted, Random effects	24	2	-0.59 (-0.91, -0.27)
GLP-1 vs placebo	Adjusted, Random effects	24	2†	-0.98 (-1.20, -0.74)
52 weeks				
DPP-4 vs SU	Unadjusted, Random effects	52	4	0.08 (-0.01, 0.16)
TZD vs SU	Unadjusted, Random effects	52	1	0.02 (-0.15, 0.18)
Dapa vs SU	Unadjusted, Random effects	52	1	0.00 (-0.16, 0.16)
GLP-1 vs SU	Unadjusted, Random effects	52	0‡	-

Abbreviations: CrI, Credible interval; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; N, Number; RCT, Randomised clinical trial; SU, Sulphonylureas; TZD, Thiazolidinediones; †, Both studies contained three arms – one placebo arm and two GLP-1 arms (at different doses); ‡, Two trials were excluded in the main analysis but included in sensitivity analysis

Table 28. Summary of relative effect size of HbA1c change from baseline (%) for dapagliflozin compared with comparator agents using best fitting model

Comparators	Model type	Weeks	Mean Difference (95% CrI)
Dapa vs. DPP-4	Adjusted, Random effects	24	0.16 (-0.17, 0.49)
	Unadjusted, Random effects	52	-0.08 (-0.25, 0.10)
Dapa vs TZD	Adjusted, Random effects	24	0.32 (-0.07, 0.73)
	Unadjusted, Random effects	52	-0.02 (-0.24, 0.21)
Dapa vs. GLP-1	Adjusted, Random effects	24	0.38 (-0.04, 0.81)
	Unadjusted, Random effects	52	-
Dapa vs placebo	Adjusted, Random effects	24	-0.59 (-0.91, -0.27)
Dapa vs SU	Unadjusted, Random effects	52	0.00 (-0.16, 0.16)

Abbreviations: CrI, Credible interval; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; SU, Sulphonylureas; TZD, Thiazolidinediones

5.7.6.2 Weight – metformin add-on

On average, a mean weight change of -0.75 kg was observed in the placebo arms of the included RCTs.

Relative to the changes observed in the placebo arms, dapagliflozin was associated with a mean weight loss of [redacted]) during the first 24 weeks of treatment, which was similar to the relative weight loss observed with GLP-1 analogues compared with placebo [redacted] TZDs were associated with a mean weight increase

of [redacted] relative to placebo during the first 24 weeks of treatment. There was no evidence of weight change associated with DPP-4 inhibitors (Table 29).

The estimates generated from the indirect comparison of dapagliflozin with other agents suggested significantly greater weight loss for dapagliflozin-treated patients, compared to those treated with DPP-4 inhibitors, TZDs, or placebo, added on to metformin therapy (Table 30).

Table 29. Summary of relative effect size of weight change from baseline (kg) relative to the reference treatment, for agents added on to metformin therapy

Comparators	Weeks	N direct Estimates	Mean Difference (95% CrI)
24 weeks			
DPP-4 vs placebo	24	6	0.24 (-0.27 , 0.71)
TZD vs placebo	24	1	2.47 (1.64 , 3.37)
Dapa vs placebo	24	2	-2.04 (-3.01 , -1.09)
GLP-1 vs placebo	24	2†	-1.65 (-2.45 , -0.88)
52 weeks			
DPP-4 vs SU	52	4	-1.92 (-3.12, -0.80)
TZD vs SU	52	1‡	-
Dapa vs SU	52	1	-4.67 (-7.03, -2.35)
GLP-1 vs SU	52	-	-

Abbreviations: CrI, Credible interval; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; N, Number; SU, Sulphonylureas; TZD, Thiazolidinediones; †,Both studies contained three arms – one placebo arm and two GLP-1 arms (at different doses); ‡,The authors did not report variance and therefore the estimate was not included in the analysis; All estimates are from random effects models

Table 30. Summary of relative effect size of weight change from baseline (kg) for dapagliflozin relative to each treatment, for agents added on to metformin therapy

Comparators	Weeks	Mean Difference (95% CrI)
Dapa vs. DPP-4	24	-2.28 (-3.36 , -1.17)
	52	-2.74 (-5.35, -0.10)
Dapa vs TZD	24	-4.51 (-5.87 , -3.23)
	52	-
Dapa vs. GLP-1	24	-0.39 (-1.6 , 0.85)
	52	-
Dapa vs placebo	24	-2.04 (-3.01 , -1.09)
Dapa vs SU	52	-4.67 (-7.03, -2.35)

Abbreviations: CrI, Credible interval; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; SU, Sulphonylureas; TZD, Thiazolidinediones; All estimates are from random effects models

5.7.6.3 Systolic blood pressure – metformin add-on

The outcome of systolic blood pressure was analysed at 24 weeks, including the class of sulphonylurea agents in the network.

On average, patients in the placebo arms of this network experienced a reduction of 0.64 mmHg (SD = 0.83) in systolic blood pressure. Dapagliflozin was the only agent associated with a significant decrease in systolic blood pressure relative to placebo ([redacted]) (Table 31).

Given that other agents were similar in efficacy to placebo in reducing systolic blood pressure, the relative effect of dapagliflozin compared with these agents was similar in magnitude to the relative effect of dapagliflozin compared to placebo (Table 32).

Table 31. Summary of relative effect size of systolic blood pressure change from baseline (mmHg) for all drug classes compared with a common comparator

Comparators	N direct estimates	Mean Difference (95% CrI)
DPP-4 vs placebo	1	-0.62 (-3.54, 2.37)
TZD vs placebo	0	-2.12 (-6.32, 2.28)
Dapa vs placebo	2	-3.75 (-6.44, -1.05)
GLP-1 vs placebo	0	-0.76 (-3.32, 1.82)
SU vs placebo†	2	1.52 (-1.09, 4.05)

Abbreviations: CrI, Credible interval; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; SU, Sulphonylureas; TZD, Thiazolidinediones; †, Sulphonylureas included at 24 week analysis All estimates are from random effects models

Table 32. Summary of relative effect size of systolic blood pressure change from baseline (mmHg) for dapagliflozin compared with comparator agents

Comparators	Mean Difference (95% CrI)
Dapa vs. placebo	-3.75 (-6.44, -1.05)
Dapa vs. DPP-4	-3.13 (-7.19, 0.80)
Dapa vs TZD	-1.62 (-6.77, 3.32)
Dapa vs. GLP-1	-2.98 (-6.74, 0.72)
Dapa vs SU	-5.27 (-8.97, -1.56)

Abbreviations: CrI, Credible interval; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; SU, Sulphonylureas; TZD, Thiazolidinediones. All estimates are from random effects models

5.7.6.4 Hypoglycaemia – metformin add-on

In the main analysis, all types of hypoglycaemia (major or non-major) were included. Although the absolute odds of experiencing hypoglycaemia in any arm may have been related to the definition of hypoglycaemia used in the trial, the relative odds (odds ratio) was assumed to be unaffected by the definition.

There was a low risk of hypoglycaemia during the first 24 weeks of add-on therapy to metformin. There were 1386 patients included in the placebo-arms of ten RCTs, and only 35 of these patients experienced one or more hypoglycaemia episodes. The average probability across trials was 2%, or odds of 0.02.

In the 24-week network, the point estimate of the odds of hypoglycaemia for dapagliflozin compared with placebo was toward a slightly increased risk associated with dapagliflozin ([redacted]) (Table 33); however, this was not statistically significantly different. No other drug classes were associated with significantly increased or decreased odds. This finding was consistent in the fixed-effect models (which yielded narrower credible intervals).

Similarly, when dapagliflozin was compared to each of the agents using indirect methods, no comparisons were significantly different.

Although non-significant, the magnitude of the effect size for TZDs relative to placebo was relatively large, in the direction of a protective effect for TZDs. This estimate was generated from a combination of direct and indirect evidence, and these two pieces of evidence were contradictory, with the direct evidence pointing to an increased risk of hypoglycaemia associated with TZDs. This is further explored in Section 5.7.9.

Over the course of 52 weeks, there was additional person-time available for observing hypoglycaemia episodes, meaning that the absolute number of episodes may have increased; however, the relative rate was assumed to remain the same.

In the class of sulphonylureas, the risk of hypoglycaemia was 25%, which calculates to odds of 0.34 (or 1:3). The odds ratio for dapagliflozin added on to metformin compared with metformin plus sulphonylureas was [redacted] indicating reduced odds of experiencing a hypoglycaemia episode associated with dapagliflozin. DPP-4 inhibitors and TZDs were also associated with significantly lower odds of hypoglycaemia than sulphonylureas.

In comparing dapagliflozin with other agents, the only significant difference was between dapagliflozin and sulphonylureas (Table 34).

Table 33. Summary of odds ratio of hypoglycaemia for all comparators compared with a common comparator

Comparators	N direct estimates	Odds Ratio (95% CrI)
24 weeks		
DPP-4 vs placebo	6	0.79 (0.37, 1.53)
TZD vs placebo	1	0.37 (0.03, 1.48)
Dapa vs placebo	2	1.22 (0.28, 3.54)
GLP-1 vs placebo	1†	1.03 (0.36, 2.49)
52 weeks		
DPP-4 vs SU	3	0.09 (0.04, 0.15)
TZD vs SU	1	0.12 (0.02, 0.37)
Dapa vs SU	1	0.06 (0.02, 0.17)
GLP-1 vs SU	0	-

Abbreviations: CrI, Credible interval, Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; SU, Sulphonylureas; TZD, Thiazolidinediones; †, Study contained three arms – one placebo arm and two GLP-1 arms (at different doses) All estimates are from random effects models

Table 34. Summary of odds ratios for hypoglycaemia for dapagliflozin compared with comparator agents

Comparators	Weeks	Odds Ratio (95% CrI)
Dapa vs. DPP-4	24	1.75 (0.31, 5.73)
	52	0.81 (0.18, 2.59)
Dapa vs TZD	24	9.38 (0.43, 51.26)
	52	0.92 (0.09, 3.88)
Dapa vs. GLP-1	24	1.52 (0.22, 5.42)
	52	-
Dapa vs placebo	24	1.22 (0.28, 3.54)
Dapa vs SU	52	0.06 (0.02, 0.17)

Abbreviations: CrI, Credible interval; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; SU, Sulphonylureas; TZD, Thiazolidinediones. All estimates are from random effects models

HbA1c – insulin add-on

The main analysis considered only the comparative effect of dapagliflozin, placebo, and DPP-4 inhibitors, and was restricted to RCTs that employed a similar approach to insulin dosing over the trial period. The RCT involving TZDs was excluded for the main analysis due to the high baseline HbA1c in that trial (9.8%), compared with the baseline HbA1c of the other RCTs in the

network (ranging from 8.5% to 8.7%), and the insufficient amount of available data for estimating a coefficient for a baseline*treatment covariate.

In the three RCTs with baseline HbA1c of 8.5% to 8.7%, the mean change from baseline HbA1c was, on average, -0.21%. Relative to the change in the placebo arm, the addition of dapagliflozin to the existing insulin therapy (with or without other oral antidiabetic agents) resulted in an additional decrease of [redacted]) from baseline.

For the TZD comparison as mentioned above, the result was based on a single TZD study (Rosenstock et al 2002) which contained a baseline HbA1c of 9.8% which is much higher than that for the other three studies included in the NMA (at 8.5%-8.7%).There is evidence to suggest that baseline HbA1c can modify the treatment effect (DeFronzo et al 2010). In the add-on to metformin NMA, a 1% increase in baseline HbA1c was associated with a -0.30% (95% CrL:-0.62 to 0.01) change in relative effect size for active agent relative to placebo. Hence, if this estimate was applied to the add-on to insulin TZD study a correction for a baseline value of 8.5% (.i.e. the value of the dapagliflozin add-on to insulin study) would reduce the relative treatment effect vs placebo to -0.61. This is similar to the dapagliflozin value, as compared to the estimated -1.00% (95% Crl: -1.22 to -0.78) reduction in HbA1c relative to placebo result seen in this analysis.

The summary of relative effect size of mean HbA1c(%) change from baseline relative to the reference treatment, for agents addded on to insulin therapy included 2 direct estimates from 24 week trials of DPP4- vs placebo.The relative effect size for DPP-4 inhibitors, compared with placebo, was also toward an improvement in HbA1c (-0.47%; 95% Crl: -0.62 to -0.31).

The indirect estimates of the relative differences between dapagliflozin and DPP-4, dapagliflozin and TZD and dapagliflozin and placebo were -0.14% (95% Crl: -0.34 to 0.07) 0.40% (0.14, 0.66), and -0.60% (-0.74, -0.46), respectively., (As mentioned above, there is evidence to suggest that baseline HbA1c can modify the treatment effect providing context for the dapaliflozin vs TZD result.

Of the four RCTs that were eligible for meta-analysis, three enrolled a patient population with a mean baseline HbA1 ranging from 8.5% to 8.7%. The fourth RCT, which was the only RCT involving a TZD, included a patient population that had a mean baseline HbA1c of 9.8%. As this was the only RCT involving TZD, the treatment effect could not be disentangled from the effect of baseline HbA1c, and a reliable coefficient could not be estimated from the available evidence. As described in Section 5.7.5, there is evidence to suggest that baseline HbA1c can modify the effect of antidiabetic agents (DeFronzo et al 2010; Bailey et al 2010). This evidence was considered as the basis for an informed prior distribution; as was the posterior distribution of the coefficient in the metformin add-on network (Section 5.7.6.1); however, to ensure transparency of the assumptions, the potential impact of baseline HbA1c on the relative effect size observed in the RCT involving TZDs is instead described below.

The estimated relative difference between the mean change from baseline HbA1c in the TZD and placebo arms was [redacted]). This estimate was based on the RCT

involving TZD, in which the mean baseline HbA1c was 9.8%. In the metformin add-on network (Section 5.7.6.1), the effect of a one percent increase in baseline HbA1c was a [redacted]) change in the relative effect size for an active agent relative to placebo. Applying this estimate to the RCT involving TZDs in the insulin add-on network, one could assume that if the baseline HbA1c in the patient population in the TZD were similar to that of the dapagliflozin trial (mean baseline HbA1c of 8.5%), one would expect to observe a relative difference of approximately -0.61%, rather than the -1.00% observed in the RCT.

5.7.6.5 Weight – insulin add-on

On average, patients in the placebo arms of the included RCTs experienced a minimal weight gain of 0.07kg from baseline. Adding dapagliflozin to the existing insulin therapy (with or without other oral antidiabetic agents) resulted in a statistically significant decrease of [redacted]. No statistically significant difference between DPP-4 inhibitors and placebo was observed (mean difference [redacted]).The indirect estimate of the relative difference between dapagliflozin and DPP-4 was [redacted], suggestive of a statistically significant benefit associated with dapagliflozin .No variance in weight was reported in the TZD vs placebo comparator.

5.7.6.6 Systolic blood pressure – insulin add-on

Only two RCTs reported the relative change in SBP; however, only Study 6 had a regimen that did not involve up-titration of insulin. Therefore, no results could be produced from the NMA for the base case assumptions. The difference between insulin plus dapagliflozin versus insulin plus placebo in Study 6 was statistically significant (mean difference = -2.99 mmHg; 95% CrI: -5.50 to -0.45).

5.7.6.7 Hypoglycaemia – insulin add-on

The definition of hypoglycaemia varied across included RCTs. In the RCT involving dapagliflozin, hypoglycaemia episodes included confirmed and unconfirmed episodes, as well as symptomatic and asymptomatic episodes. In one RCT, (Vilsboll et al 2010) investigators did not require confirmation of episodes, and therefore did not report asymptomatic episodes.

The probability of experiencing at least one hypoglycaemic episode during follow-up was 7.8% in the RCT by Vilsboll et al, and 35.0% in the RCT involving dapagliflozin, likely owing to the difference in definition of outcome. The overall average probability of experiencing at least one episode of hypoglycaemia in the placebo arms was 16.8%.

Relative to no add-on therapy, the direction of the association was toward an increased risk of hypoglycaemia for both dapagliflozin and DPP-4 inhibitors, although no estimate was statistically significant. The summary of the relative odds of experiencing at least one episode of hypoglycemia relative to the reference treatment for agents added on to insulin therapy between DPP-4 vs placebo, TZD vs placebo and dapagliflozin vs placebo were 1.42 (1.00, 2.03), 3.76

(1.74, 8.61) and 1.37 (0.91, 2.06) respectively. TZDs were associated with a significantly increased risk of hypoglycaemia, relative to placebo.

In the indirect comparisons, the odds of hypoglycaemia in the dapagliflozin and DPP-4 inhibitor arms were not significantly different; however, dapagliflozin was associated with significantly lower odds, compared to TZDs The summary of the relative odds of experiencing at least one episode of hypoglycaemia relative to the reference treatment, for agents added on to insulin therapy between dapagliflozin and DPP-4, dapagliflozin and TZD and dapagliflozin and placebo were 0.96 (0.56, 1.65), 0.36 (0.15, 0.87), and 1.37 (0.91, 2.06) respectively.

5.7.6.8 Summary of metformin add-on network results

Relative to DPP-4 inhibitors, dapagliflozin added on to metformin monotherapy demonstrated similar HbA1c control after both 24 weeks and 52 weeks of therapy, with significantly greater weight loss at 24 weeks and 52 weeks. No significant differences were observed in the relative effect on systolic blood pressure or the risk of hypoglycaemia.

A similar trend was observed relative to TZDs. Dapagliflozin offered similar glycaemic control at both 24 and 52 weeks, relative to TZDs, with a significant difference in weight control. No significant differences were observed in the relative effect on systolic blood pressure or the risk of hypoglycaemia.

Non-statistically significant differences were observed between dapagliflozin and the class of GLP-1 analogues, for all outcomes.

The results of the NMA were consistent with the evidence from the head-to-head RCT comparing dapagliflozin with sulphonylureas. The long term effect of dapagliflozin relative to sulphonylureas was for similar glycaemic control, with improved weight control, systolic blood pressure and reduced risk of hypoglycaemia.

5.7.6.9 Summary of insulin add-on network results

Only two main comparisons were made in the insulin add-on network: DPP-4 inhibitors, and TZDs.

The relative effect size of mean HbA1c (%) change from baseline was similar for dapagliflozin relative to DPP-4 inhibitors after 24 weeks of therapy. In the insulin add-on network, dapagliflozin offered improved weight control, and the risk of hypoglycaemia was similar.

The RCT involving TZDs involved a higher baseline HbA1c, causing inconsistency in the network of indirect comparisons between dapagliflozin and TZD, preventing conclusive statements regarding their relative effect from being made.

5.7.6.10 Update to the literature searches

An update of the literature search was performed in June 2012, to identify newly available RCTs involving agents added on to existing metformin or insulin therapy, and applying the same inclusion criteria as the original search. The update involved a re-execution of the MEDLINE,

EMBASE, and CENTRAL search strategy, as well as searching of 2011 ADA and EASD conference proceedings. Registries were searched for the indication of metformin add-on. The relative effect size of newly identified RCTs was compared descriptively with the relative effect sizes for relevant drug class comparisons that were estimated in the original network meta-analyses.

For the metformin add-on indication, four new RCTs were identified, and updated information from two originally included RCTs was identified. The relative effect sizes in the newly identified RCTs were comparable to the original network meta-analysis estimates for the outcomes of HbA1c, weight, systolic blood pressure and hypoglycaemia.

For the insulin add-on indication, one new RCT was identified, which compared a TZD with placebo. The relative effect sizes in the newly identified RCT were comparable to the original network meta-analysis, where reported; however, the study designs in the RCTs involving TZDs differed, leading to challenges in interpretation.

5.7.7 Statistical assessment of heterogeneity

The classical pair-wise meta-analysis frameworks provide tools for estimating the amount of statistical heterogeneity (e.g. Cochran's Q test and the I^2 statistic) and sources of this heterogeneity (meta-regression and subgroup analysis).

Due to the large number of comparators and the relatively small number of RCTs, the analysis of heterogeneity in pairwise comparisons was focussed on pairs of comparators with the most head-to-head evidence. In the 24 and 52 week metformin add-on networks, the comparison between DPP-4 inhibitors and placebo had the largest number of RCTs contributing to the pooled estimate.

In the 24 week network, seven head-to-head RCTs involving DPP-4 inhibitors and placebo contributed to the HbA1c estimate (I^2 =62.9%; p = 0.013), six contributed to the analysis of weight (I^2 =17.3%; p = 0.302), six contributed to the analysis of hypoglycaemia (I^2 =0.0%; p = 0.463), and only one contributed to the analysis of systolic blood pressure.

In the 52 week network, there were four DPP-4 vs. placebo RCTs contributing to the HbA1c estimate (I^2 = 0.0%; p = 0.898); four contributing to the weight estimate (I^2 = 73.8%; p = 0.009); and three contributing to the hypoglycaemia estimate (I^2 = 44.8%; p = 0.163).

In the insulin networks, there were at most two RCTs for any pairwise comparison (DPP-4 inhibitors vs. placebo). No formal assessment of statistical heterogeneity was conducted; however, an assessment of clinical heterogeneity was performed prior to conducting the NMA, which had led to the decision to limit the analysis to RCTs employing a stable dose of insulin.

To understand the source of the heterogeneity, we investigated the potential for effect modification based on baseline HbA1c, as well as the impact of pooling the dose and agent (described in Section 5.7.8).

To account for the observed heterogeneity, we assumed a random-effects framework. We also incorporated a treatment*covariate interaction term. In the analysis of the 24 week HbA1c network, the two DPP-4 inhibitor vs. placebo RCTs that had the largest relative effect size also had the highest baseline HbA1c values. When fitting the adjusted model, the treatment* covariate interaction term for HbA1c was [redacted] meaning that for each unit increase in baseline HbA1c, the magnitude of the effect size, relative to placebo, is increased by -0.30%. Adding the adjustment factor improved the NMA model fit in both the fixed and random effects models.

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

The following sensitivity and exploratory analyses were performed, to assess the relevance of particular trials, or particular assumptions:

- *A priori* choice of random-effects model was tested against a fixed-effect model (5.7.8.1);
- Inclusion of 52 week RCTs involving an intensive diet and exercise regimen (5.7.8.2);
- Pooling of doses and agents (5.7.8.3);
- Use of per-protocol analysis (5.7.8.4); and
- Choice of prior distribution (5.7.8.5).

5.7.8.1 Random-effects model versus fixed-effect model

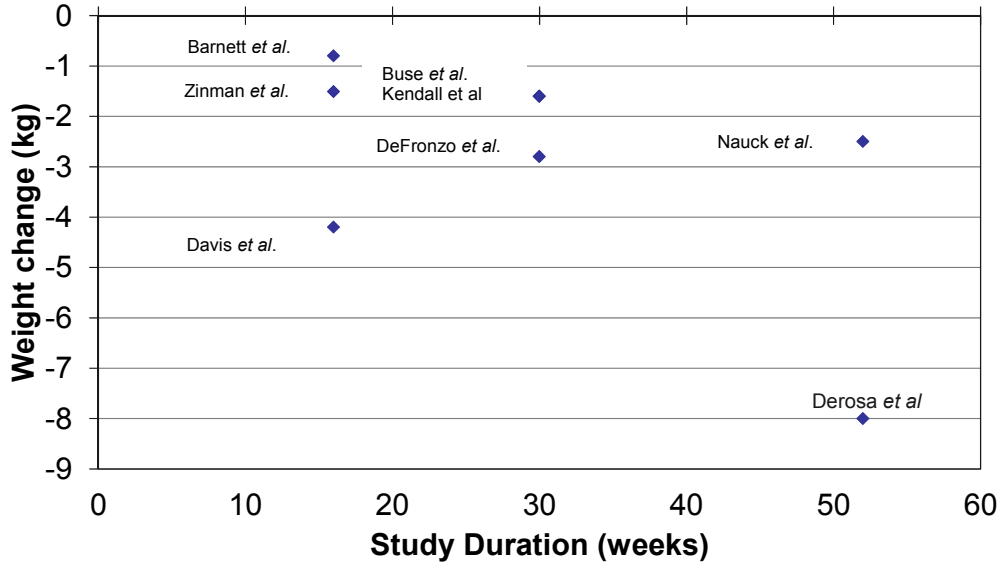
Estimates from both the random-effects and fixed-effect models are presented in Section 5.7.9.

5.7.8.2 Inclusion of RCTs involving an intensive diet and exercise regimen

Weight

The weight loss observed in the study by Derosa et al (2010) was compared with GLP-1 related weight loss observed in other study settings. A plot of weight loss observed in GLP-1 analogue arms from RCTs included in a recent systematic review (Bradley et al 2010) indicates that the weight loss observed in the study by Derosa et al (-8kg) is substantially larger than in other studies, and is not entirely explained by the longer duration of this RCT (Figure 19).

Figure 19. Absolute change in weight from baseline (kg) in 10 µg exenatide arms of randomised trials as reported by Bradley et al, with the addition of the weight change observed by Derosa et al.



Derosa et al (2010) attributed the large drop in weight to the emphasis that the study investigators placed on diet. It has been postulated that the patients on exenatide responded, while those on sulphonylureas did not. A consequence of the mechanism of action for GLP-1 analogues is a slowing of gastric emptying and a feeling of postprandial satiety experienced by those using GLP-1 analogues, resulting in a decrease in food intake and thereby allowing patients receiving GLP-1 analogues to maintain a reduced calorie diet.

Only the RCT by Derosa et al (2010) was excluded from the weight outcome, as weight was not reported by Salvadeo et al (2010). When including the study by Derosa et al (2010), the mean change in weight from baseline was estimated to be [redacted]) in favour of GLP-1 analogues, compared with sulphonylureas.

HbA1c

When including the RCTs by Derosa et al (2010) and Salvadeo et al (2010), the mean change in HbA1c from baseline to 52 weeks post-baseline for GLP-1 analogues added on to metformin treatment, relative to sulphonylureas was estimated to be [redacted] in favour of sulphonylureas.

5.7.8.3 Pooling of doses and agents

The base case analyses involved pooling agents within drug classes due to the otherwise large number of comparator agents compared with a relatively small number of RCTs. The impact of pooling of doses and agents was considered for all outcomes, and systematic reviews comparing individual agents within drug classes were reviewed to establish the evidence base.

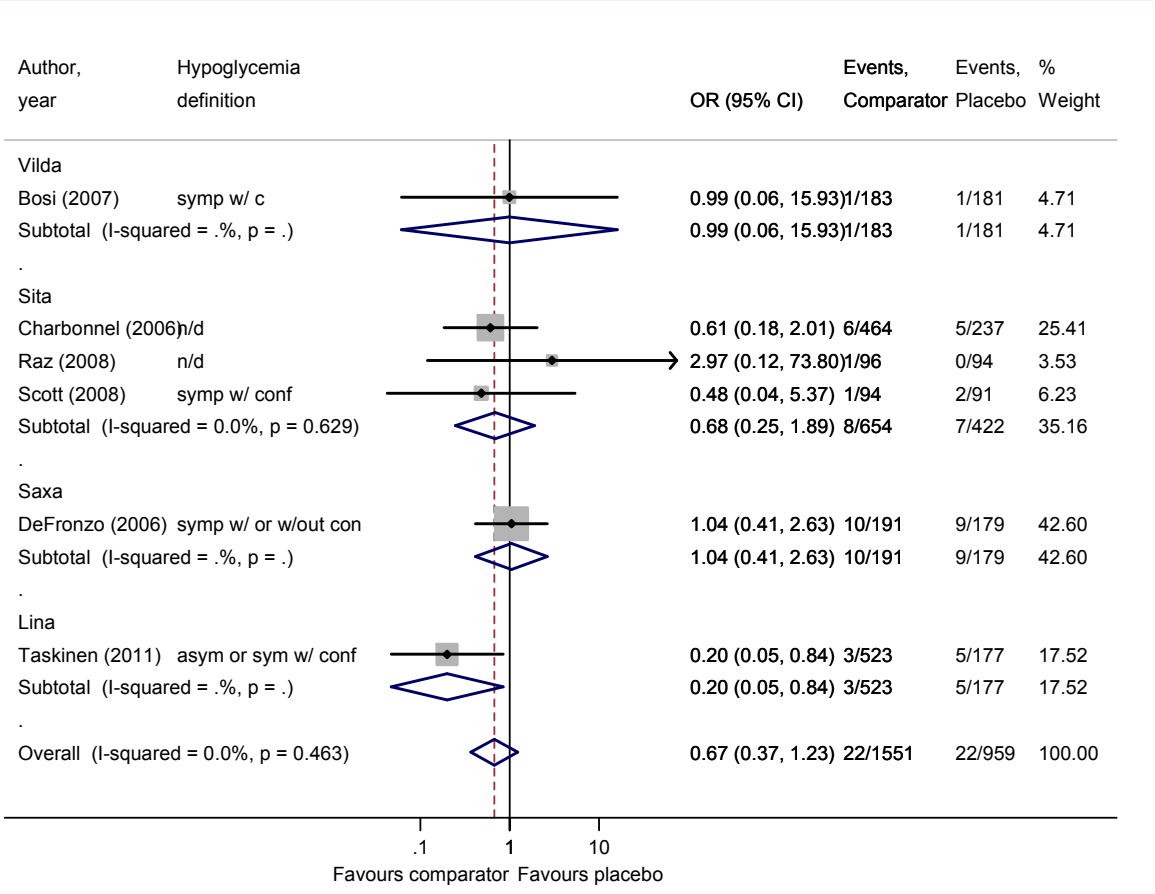
Pooling of DPP-4 inhibitors: hypoglycaemia in 24 week metformin network

The potential bias imposed by pooling doses and agents is presented below for the analysis of hypoglycaemia.

In the 24 week network the relative effect sizes for each of the DPP-4 agents compared with placebo was considered according to the specific agent (Figure 20). Overall, there was no heterogeneity detected across the agents (I^2 = 0.0%; Cochran's Q = 0.463). The point estimates for vildagliptin and saxagliptin were informed by only one trial each but were similar in magnitude, and not statistically different from an odds ratio of one. The pooled effect size for the RCTs involving sitagliptin was non-significant (0.68; 95% CI: 0.25 to 1.89). The trial involving linagliptin was significantly less than one, which was informed by a small number of events.

In a previous meta-analysis of DPP-4 inhibitors, (Fakhoury et al 2010) the relative risk point estimate was estimated to be higher for sitagliptin than for vildagliptin, though not statistically different. In the current analysis, an opposite trend was observed, though these estimates were not statistically different, indicating that the distribution of relative effect versus placebo may be similar for both agents.

Figure 20. Forest plot of the odds ratio of hypoglycaemia network for individual agents within the DPP-4 inhibitor drug class, relative to placebo, using a 24-week random effect model.



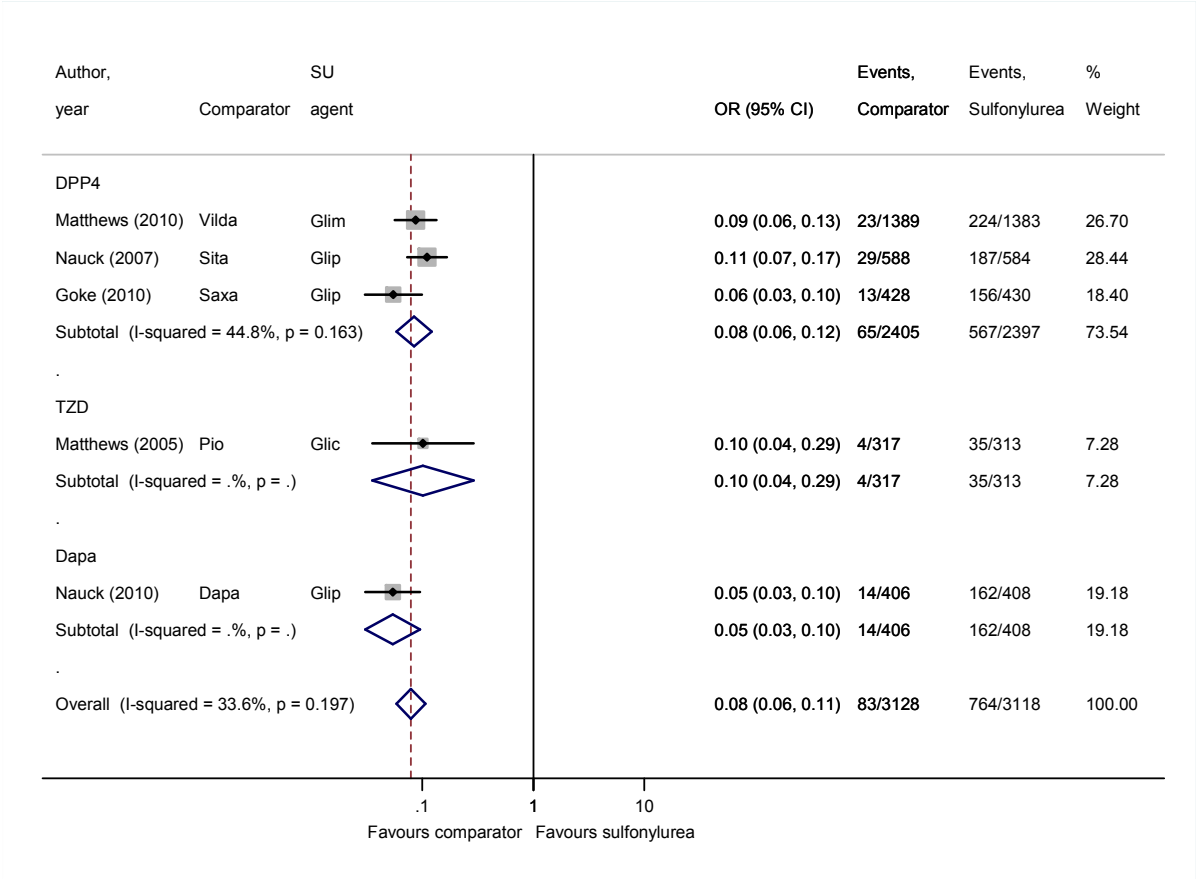
Abbreviations: auth_yr, Author and year; CI, Confidence interval; Lina, Linagliptin; OR, Odds ratio; Saxa, Saxagliptin; Sita, Sitagliptin; symp w/conf, Symptomatic with confirmation; symp w/out conf, Symptomatic without confirmation; Vilda, Vildagliptin; Odds ratio less than 1 favour comparator. The graph is plotted on the log odds scale.

Pooling of sulphonylureas: hypoglycaemia in 52 week metformin network

A similar approach was used to investigate the impact of pooling drug classes at 52 weeks (Figure 21). Given that there were different agents within the common comparator of sulphonylureas, the forest plot is presented with the comparator agent as well as the type of sulphonylurea. Within the comparisons with DPP-4 inhibitors, the point estimates were of similar magnitude, with saxagliptin carrying the lowest risk, compared with glipizide (OR: 0.06; 95% CI: 0.03 to 0.10). Sitagliptin was also compared with glipizide (OR: 0.11; 95% CI: 0.07 to 0.17). The point estimate was not significantly different from the saxagliptin estimate. The vildagliptin odds ratio (OR: 0.09; 95% CI: 0.06 to 0.13) was the same as the overall class average, and lay between the sitagliptin and saxagliptin estimates.

In a meta-analysis comparing different sulphonylurea agents, (Gangji et al 2007) few significant differences were identified between glibenclamide (glyburide in the US) and other sulphonylureas, although the point estimates were toward a reduced risk associated with glibenclamide. The other agents were not compared directly; however, when compared with glibenclamide, the RCTs involving gliclazide and glipizide had a similar relative risks, ranging from a RR of 2.23 (95% CI: 1.08 to 4.59) to 3.58 (95% CI: 0.77 to 16.76). The RCTs comparing glimepiride with glibenclamide had lower relative risks, ranging from an RR of 1.34 (95% CI: 0.90 to 1.71) to 1.42 (95% CI: 0.94 to 2.13). No RCTs included in the network involved glibenclamide. Only one RCT (Matthews et al 2010) involved glimepiride and the relative effect size was similar to the others within the class of DPP-4 agents, as described above. Therefore, the bias introduced by pooling agents and doses is expected to be minimal.

Figure 21. Forest plot of the odds ratio of hypoglycaemia network for individual agents relative to sulphonylureas, using a 52 week random-effects model.



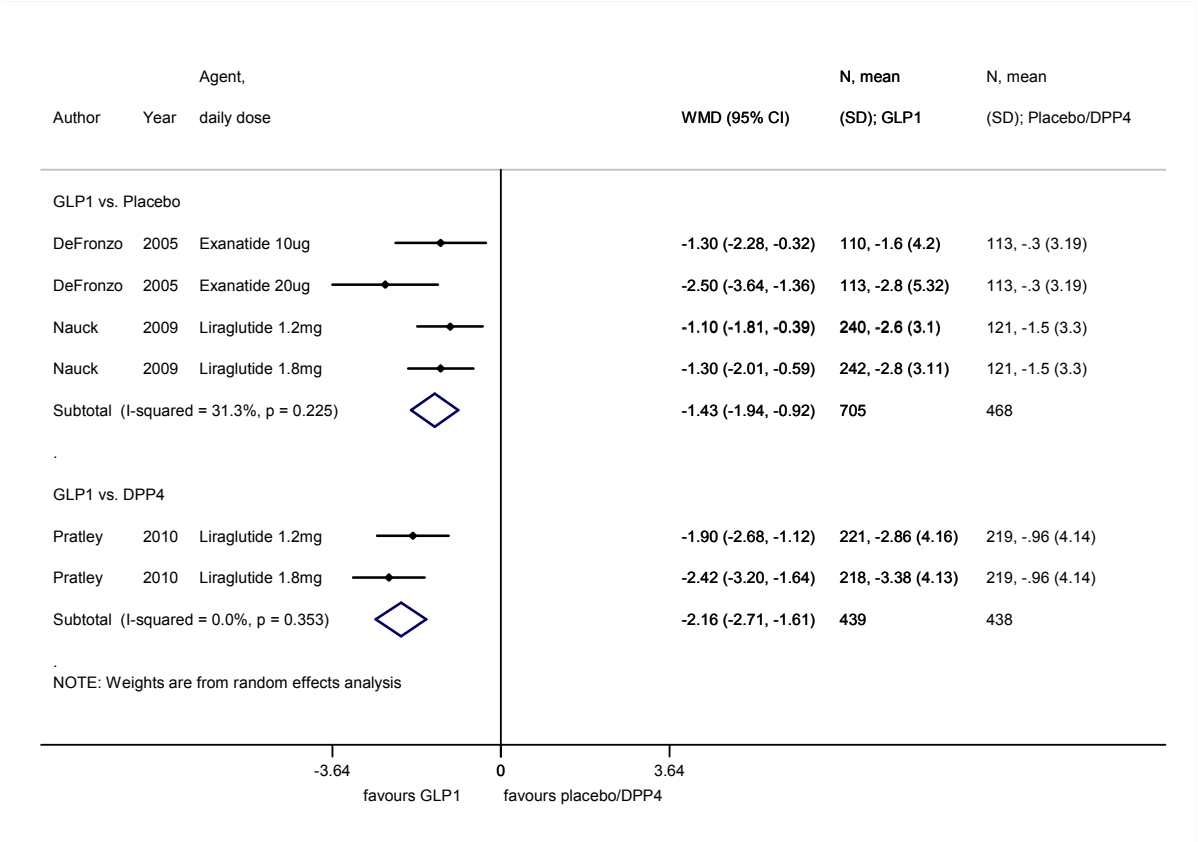
Abbreviations: Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptiodase-4 inhibitors; Glic, Gliclazide; Glim, Glimepiride; Glip, Glipizide; OR, Odds ratio; Pio, Pioglitazone; Saxa, Saxagliptin; Sita, Sitagliptin; TZD, Thiazolidinediones; Vilda, Vildagliptin; Odds ratio less than 1 favour comparator. The graph is plotted on the log odds scale

Pooling of GLP-1 analogues: weight change in 24 week metformin network

The relative effect size for each of the agents and doses within the class of GLP-1 analogues is presented in Figure 22. In both RCTs involving liraglutide, the magnitude of weight loss was consistently larger in the 1.8mg liraglutide arm compared with the 1.2mg liraglutide arm, although this difference was not clinically meaningful. Similarly, the higher dose of exenatide resulted in a larger weight loss than the lower dose.

In the NMA, the data reported by Nauck et al (2009) and DeFronzo et al (2005) provided a direct estimate comparing GLP-1 analogues with placebo, whereas the evidence comparing GLP-1 analogues with DPP-4 inhibitors from Pratley et al (2010) was incorporated through the indirect network of evidence.

Figure 22. Forest plot of the mean change in weight from baseline for individual agents within the GLP-1 analogue drug class, relative to placebo or DPP-4 inhibitors, using a 24 week random effect model.



5.7.8.4 Inclusion of per-protocol analyses

In the 52 week network, several of the contributing studies were designed as non-inferiority studies, and implemented a per-protocol analysis. A table highlighting the trial population used in the analysis of HbA1c is presented in Table 35. In the comparisons with TZDs and dapagliflozin, an intention-to-treat (ITT) approach was used. Among the four trials comparing DPP-4 inhibitors with SUs, only one used ITT; the other three used per-protocol. Matthews et al and Filozof et al noted that the ITT results were similar in magnitude, and Nauck et al stated that the ITT analysis confirmed the per-protocol results. There were more discontinuations due to lack of efficacy in the DPP-4 inhibitor arms of the RCTs by Filozof et al, Nauck et al, and Matthews et al, meaning that if these patients were included in the analysis, the ITT estimate would have been slightly more favourable towards SUs. The study by Goke et al was reported using ITT analysis, and indeed it has the largest effect size (0.09%; 95% CI -0.02 to 0.20). The per-protocol estimate for that same RCT was 0.06% (95% CI: -0.05 to 0.16).

If we were to assume a 0.03% difference between the per-protocol and ITT estimates, we anticipate that the relative effect size for DPP-4 inhibitors versus SUs, which was 0.08% (95%

CrI: 0.01, 0.16) based on three RCTs that were designed as per-protocol and one that was designed as ITT, might have been 0.03 higher, at 0.11%. The implication for the relative difference between dapagliflozin and DPP-4 inhibitors might have been a relative difference of -0.11% rather than -0.08%.

Table 35. Population used in the analysis of glycosylated haemoglobin at 52 weeks among patients with T2DM inadequately controlled on metformin monotherapy

Author, Year	Intervention	N	Trial population used in analysis
Nauck (-04), 2010	Dapagliflozin	801	ITT (full analysis set)*
Matthews, 2005	Pioglitazone	630	ITT
Matthews, 2010	Vildagliptin	2190	Per-protocol; ITT results “similar”
Nauck, 2007	Sitagliptin	1135	Per-protocol
Goke, 2010	Saxagliptin	846	ITT; per-protocol also reported
Filozof, 2010	Vildagliptin	779	Per-protocol; ITT results “comparable”

Abbreviations: ITT, Intention to treat; HbA1c, glycosylated haemoglobin; N, Sample size

5.7.8.5 Choice of prior distribution

The choice of prior distribution on the between-studies standard deviation in the main analysis was selected based on the possible range of values for the continuous outcome measurements, and was set to U (0,2) for all outcomes, although the prior was updated to U (0,4) for the outcome of weight at 52 weeks based on an assessment of the posterior distribution. For the continuous outcomes, the rationale for this choice was:

- It is plausible to assume that these mean changes could range from -3 to +3.
- The difference between arms could therefore range from -6 to +6
- Assuming a normal distribution where this range captures 99.7% of all values, one sixth of this range would represent one standard deviation
- Therefore, one can assume that one standard deviation might be 2
- Based on this reasoning, a Uniform (0,2) was for the standard deviation of the random effects.

Each outcome was re-fitted using a U (0,4) and U (0,6) prior on the random-effects between studies standard deviation. For each outcome, the point estimates and widths of the credible intervals were robust to the choice of prior, and the upper bound of the 95% CrI for the posterior inference on the between studies standard deviation was well below the upper bound for any of the prior distributions, and did not change for the different prior assumptions. The results of the sensitivity analysis for HbA1c are presented in Table 36 and Table 37.

Table 36. Relative treatment effects for all pairwise comparisons fitted to the 24-week HbA1c data (change from baseline, %), using different choices of prior for the between-study standard deviation

Treatment Comparison	Random-Effects Network Meta-Analysis Model					
	Uniform(0,2)		Uniform(0,4)		Uniform(0,6)	
	MD	95% CrI	MD	95% CrI	MD	95% CrI
DPP-4 vs. Placebo	-0.72	(-0.88, -0.57)	-0.72	(-0.88, -0.57)	-0.72	(-0.88, -0.57)
GLP1 vs. Placebo	-1.02	(-1.27, -0.75)	-1.02	(-1.27, -0.75)	-1.02	(-1.28, -0.75)
TZD vs. Placebo	-0.91	(-1.19, -0.63)	-0.90	(-1.20, -0.63)	-0.91	(-1.20, -0.63)
DAPA vs. Placebo	-0.40	(-0.71, -0.11)	-0.41	(-0.71, -0.11)	-0.40	(-0.71, -0.10)
GLP1 vs. DPP-4	-0.30	(-0.56, -0.02)	-0.30	(-0.56, -0.02)	-0.30	(-0.57, -0.01)
TZD vs. DPP-4	-0.19	(-0.45, 0.07)	-0.19	(-0.46, 0.07)	-0.19	(-0.45, 0.07)
DAPA vs. DPP-4	0.31	(-0.02, 0.66)	0.31	(-0.02, 0.65)	0.31	(-0.03, 0.65)
TZD vs. GLP1	0.11	(-0.27, 0.47)	0.11	(-0.26, 0.46)	0.11	(-0.26, 0.47)
DAPA vs. GLP1	0.61	(0.21, 1.00)	0.61	(0.21, 1.00)	0.61	(0.21, 1.01)
DAPA vs. TZD	0.50	(0.10, 0.91)	0.50	(0.09, 0.91)	0.50	(0.09, 0.92)

Abbreviations: CrI, Credible interval; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; MD, Mean difference; SU, Sulphonylureas; TZD, Thiazolidinediones. Note: Relative treatment effects are expressed as mean differences (MD) and are not adjusted for baseline HbA1c

Table 37. Posterior inference on the between-study standard deviation parameter in the random-effects NMA model fitted to the 24-week HbA1c data (change from baseline, %), obtained by using different choices of prior for the between-study standard deviation

Choice of Prior for the Between-Study Standard Deviation	Posterior Inference on the Between-Study Standard Deviation		
	Posterior Mean	Posterior Median	95% CrI
Uniform(0,2)	0.18	0.17	(0.07, 0.34)
Uniform(0,4)	0.18	0.17	(0.07, 0.35)
Uniform(0,6)	0.18	0.17	(0.07, 0.34)

Abbreviations: CrI, Credible interval;

5.7.9 Heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Consistency of the evidence was explored for outcomes that contained closed loops, and that showed inconsistency between the direct evidence and the estimates generated from the NMA. To understand the source of the discrepancy, we used the Bucher method (Bucher et al 1997) to construct simple indirect networks using three comparators. We compared the three estimates: i) from the direct head-to-head evidence; ii) from the simple indirect estimates generated from the Bucher method; and iii) from the NMA model. We reviewed these with a clinical team to evaluate face validity, and generated a hypothesis as to the more likely direction of effect.

The 52-week metformin add-on network, and the 24 week insulin add-on networks were star-shaped, involving no closed loops. The pairwise estimates generated from the unadjusted

random-effects NMA were similar in magnitude to the pooled estimates generated from the unadjusted random-effects classical pairwise meta-analysis (Table 17 to Table 20).

There are several factors contributing to differences in the estimates generated from the classical pairwise framework compared with the Bayesian approach. Two key factors involve the ways in which the data contribute to these two different analyses. First, in the NMA, the between studies standard deviation was calculated from all trials in the network, whereas in each pairwise comparison, only data from RCTs comparing the two relevant agents are included. Second, in the adjusted analysis, it was assumed that the impact of baseline HbA1c on the relative difference between active treatments and placebo (or sulphonylurea in the 52 week metformin add-on network) was constant across all active treatments. Therefore, in the NMA, all RCTs involving the common comparator contributed data to the estimate of the treatment*covariate interaction term. An adjusted analysis was not performed in the classical pairwise analysis due to a limited number of RCTs.

In the 24-week metformin add-on network, there were several closed loops. Across the four key outcomes, there was only one inconsistency between the direct and indirect estimates, leading to a different direction of association.

In analysing the relative odds of experiencing at least one hypoglycaemia episode in the 24 week metformin add-on network, the relative effect size for TZD versus placebo [redacted]) was lower than anticipated based on the head to head evidence from the study by Kaku et al (2009). In this RCT, there was one event among 83 patients in the pioglitazone arm, and no events among the 86 patients in the placebo arm. Using a frequentist framework, the direct head to head estimate resulted in an odds ratio of 3.15 (95% CI 0.13 to 78.32), which was non-significant but in the direction of an increased risk associated with TZDs. Omitting the direct estimate of TZD vs. placebo, the indirect evidence generated from the closed loop of DPP-4 vs. placebo and DPP-4 vs. TZD resulted in an odds ratio of [redacted], indicating a decreased risk of hypoglycaemia associated with TZDs. This decreased risk was further informed by indirect evidence in the closed loop involving GLP-1, DPP-4, TZDs and placebo, ultimately resulting in an overall odds ratio of [redacted]).

A summary of the estimates generated from the metformin add-on NMA (including the random-effects, fixed-effect, and for HbA1c the unadjusted and adjusted estimates) compared with each individual trial estimate, with 95% CIs and with the pooled estimate generated using a classical pairwise meta-analysis approach and a random-effects model, is presented in Table **38** to Table 41.

Table 38. Consistency of evidence in the glycosylated haemoglobin (%) network of trials enrolling patients with T2DM, inadequately controlled on metformin monotherapy

		Mean difference (NMA) Mean difference % (95% CrI)		Individual trial estimates and pairwise meta-analysis Mean difference %	
Comparison	Model type	Fixed Effect	Random Effects	Author, Year	Relative effect (95% CI)
24 week data					
DPP-4 vs placebo	Unadjusted	-0.69 (-0.75, -0.62)	-0.72 (-0.88, -0.57)	Bosi, 2007 Charbonnel, 2006 Raz, 2008 Scott, 2008 Bergenstal, 2010b DeFronzo, 2009 Taskinen, 2011 Pooled WMD†	-1.10 (-1.38, -0.82) -0.65 (-0.80, -0.50) -1.00 (-1.55, -0.45) -0.51 (-0.70, -0.32) -0.79 (-0.98, -0.60) -0.82 (-1.01, -0.63) -0.64 (-0.78, -0.50) -0.74 (-0.87, -0.61)
	Adjusted	-0.73 (-0.80, -0.66)	-0.75 (-0.89, -0.61)		
TZD vs placebo	Unadjusted	-0.85 (-0.98, -0.72)	-0.91 (-1.19, -0.63)	Kaku, 2009	-0.92 (-1.18, -0.66)
	Adjusted	-0.85 (-0.98, -0.72)	-0.91 (-1.17, -0.67)	Pooled WMD†	-0.92 (-1.18, -0.66)
Dapa vs placebo	Unadjusted	-0.37 (-0.48, -0.26)	-0.40 (-0.71, -0.11)	Study 14 Study 12	-0.54 (-0.73, -0.35) -0.29 (-0.42, -0.16)
	Adjusted	-0.59 (-0.76, -0.41)	-0.59 (-0.91, -0.27)	Pooled WMD†	-0.40 (-0.65, -0.16)
GLP1 vs placebo	Unadjusted	-1.04 (-1.17, -0.92)	-1.02 (-1.27, -0.75)	Nauck, 2009 DeFronzo, 2005	-1.08 (-1.35, -0.80)‡ -0.70 (-0.98, -0.42)§
	Adjusted	-1.00 (-1.13, -0.87)	-0.98 (-1.20, -0.74)	Pooled WMD†	-0.89 (-1.25, -0.52)
52 week data					
DPP-4 vs SU	Unadjusted	0.08 (0.04, 0.13)	0.08 (0.01, 0.16)	Nauck, 2007	0.05 (-0.08, 0.18)

Comparison	Model type	Mean difference (NMA) Mean difference % (95% CrI) Fixed Effect	Random Effects	Individual trial estimates and pairwise meta-analysis Mean difference % Author, Year	Relative effect (95% CI)
	Adjusted	0.07 (-0.02, 0.16)	0.08 (-0.12, 0.43)	Filozof, 2010 Goke,2010 Matthews, 2010 Pooled WMD†	0.04 (-0.13, 0.21) 0.09 (-0.02, 0.2) 0.09 (0.04, 0.15) 0.08 (0.04, 0.13)
TZD vs SU	Unadjusted	0.02 (-0.09, 0.13)	0.02 (-0.15, 0.18)	Matthews, 2005	0.02 (-0.09, 0.13)
	Adjusted	0.03 (-0.10, 0.17)	0.03 (-0.22, 0.29)	Pooled WMD†	0.02 (-0.09, 0.13)
Dapa vs SU	Unadjusted	0.00 (-0.11, 0.11)	0.00 (-0.16, 0.16)	Study 4	0.00 (-0.11, 0.11)
	Adjusted	-0.01 (-0.13, 0.11)	0.00 (-0.22, 0.26)	Pooled WMD†	0.00 (-0.11, 0.11)
GLP1 vs SU	Unadjusted	-	-		-
	Adjusted	-	-	-	

Abbreviations: CI, Confidence interval; CrI, Credible interval; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; HbA1c, glycosylated haemoglobin ; SU, Sulphonylureas; TZD, Thiazolidinediones; WMD, Weighted mean difference; †, Random-effects model; ‡, 1.2 and 1.8 mg arms were pooled in this estimate; §,10 and 20 mcg arms were pooled in this estimate. Estimates in bold font represent the best estimate based on an assessment of *a priori* model choice, statistical and clinical significance of model coefficient, model fit, and assessment of the posterior distribution of the between studies variance.

Table 39. Consistency of evidence in the weight (kg) network of trials enrolling patients with T2DM inadequately controlled on metformin monotherapy

Comparison	Model type	Mean difference (NMA) Mean difference (kg) Fixed Effect (95% CrI)	Mean difference (NMA) Mean difference (kg) Random Effects (95% CrI)	Individual trial estimates and pairwise meta-analysis Author, Year	Individual trial estimates and pairwise meta-analysis Mean difference (kg) Relative effect (95% CI)
24 week data					
DPP-4 vs placebo	Unadjusted	0.33 (0.07, 0.59)	**0.32 (-0.14, 0.78)**	Bosi, 2007	1.20 (0.37, 2.03)
				Raz, 2008	0.00 (-0.80, 0.80)
				Scott, 2008	0.40 (-0.15, 0.95)
				DeFronzo, 2009	0.05 (-0.57, 0.67)
				Bergenstal, 2010b	0.40 (-0.47, 1.26)
				Taskinen, 2011	0.10 (-0.70, 0.90)
				Pooled WMD†	**0.33 (0.01, 0.66)**
TZD vs placebo	Unadjusted	2.37 (1.88, 2.84)	**2.52 (1.73, 3.40)**	Kaku, 2009	2.15 (1.40, 2.90)
				Pooled WMD†	**2.15 (1.40, 2.90)**
Dapa vs placebo	Unadjusted	-2.04 (-2.60, -1.48)	**-2.04 (-2.93, -1.14)**	Study 14	-2.00 (-2.83, -1.17)
				Study 12	-2.08 (-2.84, -1.32)
				Pooled WMD†	**-2.04 (-2.61, -1.48)**
GLP1 vs placebo	Unadjusted	-1.59 (-2.01, -1.17)	**-1.62 (-2.34, -0.91)**	DeFronzo, 2005	-1.91 (-2.98, -0.84)
				Nauck, 2009	-1.2 (-1.91, -0.49)
				Pooled WMD†	**-1.44 (-2.09, -0.78)**
52 week data					
DPP-4 vs SU	Unadjusted	-1.81 (-2.03, -1.59)	**-1.92 (-3.12, -0.80)**	Nauck, 2007	-2.6 (-3.43, -1.77)
				Filozof, 2010	-1.28 (-1.73, -0.83)
				Goke,2010	-2.20 (-2.67, -1.73)
				Matthews, 2010	-1.79 (-2.11, -1.47)

Comparison	Model type	Mean difference (NMA) Mean difference (kg)		Individual trial estimates and pairwise meta-analysis Mean difference (kg)	
		Fixed Effect (95% CrI)	Random Effects (95% CrI)	Author, Year	Relative effect (95% CI)
				Pooled WMD†	**-1.90 (-2.36, -1.43)**
TZD vs SU	Unadjusted	-	**-**	-	**-**
Dapa vs SU	Unadjusted	-4.66 (-5.16, -4.17)	**-4.67 (-7.03, -2.35)**	Study 4	-4.66 (-5.16, -4.16)
				Pooled WMD†	**-4.66 (-5.16, -4.16)**
GLP1 vs SU	Unadjusted	-	**-**		

Abbreviations: CI, Confidence interval; CrI, Credible interval; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; SU, Sulphonylureas; TZD, Thiazolidinediones; WMD, Weighted mean difference; †, Random-effects model. Estimates in **bold** font represent the best estimate based on an assessment of *a priori* model choice, model fit, and assessment of the posterior distribution of the between studies variance

Table 40. Consistency of evidence in the systolic blood pressure (mmHg) network of trials enrolling patients with T2DM inadequately controlled on metformin monotherapy

Comparison	Model type	Mean difference (NMA) Mean difference (mmHg) Fixed Effect (95% CrI)	Mean difference (NMA) Mean difference (mmHg) Random Effects (95% CrI)	Individual trial estimates and pairwise meta-analysis Author, Year	Individual trial estimates and pairwise meta-analysis Mean difference (mmHg) Relative effect (95% CI)
24 week data					
DPP-4 vs placebo	Unadjusted	-0.77 (-3.17, 1.62)	**-0.62 (-3.54, 2.37)**	DeFronzo, 2009	-0.10 (-3.85, 3.65)
				Pooled WMD†	**-0.10 (-3.85, 3.65)**
SU vs placebo	Unadjusted	1.61 (-0.48, 3.69)	**1.52 (-1.09, 4.05)**	Charpentier, 2001	0.51 (-2.98, 4.00)
				Nauck, 2009	2.20 (-1.52, 5.92)
				Pooled WMD†	**1.30 (-1.24, 3.85)**
Dapa vs placebo	Unadjusted	-3.7 (-5.95, -1.42)	**-3.75 (-6.44, -1.05)**	Study 12	-2.8 (-5.79, 0.19)
				Study 14	-4.9 (-8.37, -1.43)
				Pooled WMD†	**-3.70 (-5.96, -1.43)**
GLP1 vs placebo	Unadjusted	-0.82 (-2.79, 1.17)	**-0.76 (-3.32, 1.82)**	Nauck, 2009	-0.75 (-3.7, 2.2)
				Pooled WMD†	**-0.75 (-3.7, 2.2)**

Abbreviations: CI, Confidence interval; CrI, Credible interval; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; SU, Sulphonylureas; TZD, Thiazolidinediones; WMD, Weighted mean difference; †, Random-effects model. Estimates in bold font represent the best estimate based on an assessment of *a priori* model choice, model fit, and assessment of the posterior distribution of the between studies variance.

Table 41. Consistency of evidence in the hypoglycaemia network of trials enrolling patients with T2DM inadequately controlled on metformin monotherapy

Comparison	Model type	Odds ratio (NMA)		Individual trial odds ratios and pairwise meta-analysis	
		Fixed Effect (95% CrI)	Random Effects (95% CrI)	Author, Year	Relative effect (95% CI)
24 week data					
DPP-4 vs placebo	Unadjusted	0.76 (0.42, 1.27)	**0.79 (0.37, 1.53)**	Charbonnel, 2006 Bosi, 2007 Raz, 2008 Scott, 2008 DeFronzo, 2009 Taskinen, 2011 **Pooled WMD†**	0.61 (0.18, 2.01) 0.99 (0.06, 15.93) 2.97 (0.12, 73.80) 0.48 (0.04, 5.37) 1.04 (0.41, 2.63) 0.2 (0.05, 0.84) **0.67 (0.37, 1.23)**
TZD vs placebo	Unadjusted	0.31 (0.03, 1.06)	**0.37 (0.03, 1.48)**	Kaku, 2009 **Pooled WMD†**	3.15 (0.13, 78.32) **3.15 (0.13, 78.32)**
Dapa vs placebo	Unadjusted	1.18 (0.31, 3.06)	**1.22 (0.28, 3.54)**	Study 14 Study 12 **Pooled WMD†**	1.28 (0.34, 4.87) 0.66 (0.11, 4.04) **1.01 (0.35, 2.97)**
GLP1 vs placebo	Unadjusted	0.96 (0.45, 1.85)	**1.03 (0.36, 2.49)**	DeFronzo, 2005 **Pooled WMD†**	0.93 (0.33, 2.57) **0.93 (0.33, 2.57)**
52 week data					
DPP-4 vs SU	Unadjusted	0.09 (0.06, 0.11)	**0.09 (0.04, 0.15)**	Nauck, 2007 Goke,2010 Matthews, 2010	0.11 (0.07, 0.17) 0.06 (0.03, 0.10) 0.09 (0.06, 0.14)

Comparison	Model type	Odds ratio (NMA)		Individual trial odds ratios and pairwise meta-analysis	
		Fixed Effect (95% CrI)	Random Effects (95% CrI)	Author, Year	Relative effect (95% CI)
				Pooled WMD†	**0.09 (0.06, 0.12)**
TZD vs SU	Unadjusted	0.10 (0.03, 0.24)	**0.12 (0.02, 0.37)**	Matthews, 2005	0.10 (0.04, 0.29)
				Pooled WMD†	**0.10 (0.04, 0.29)**
Dapa vs SU	Unadjusted	0.05 (0.03, 0.09)	**0.06 (0.02, 0.17)**	Study 4	0.05 (0.03, 0.10)
				Pooled WMD†	**0.05 (0.03, 0.10)**
GLP1 vs SU	Unadjusted	-	**-**	-	**-**

Abbreviations: CI, Confidence interval; CrI, Credible interval; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; SU, Sulphonylureas; TZD, Thiazolidinediones; WMD, Weighted mean difference; †, Random-effects model. Estimates in **bold** font represent the best estimate based on an assessment of *a priori* model choice, model fit, and assessment of the posterior distribution of the between studies variance.

HbA1C

The consistency of evidence in the glycosylated haemoglobin (%) network of trials enrolling patients with T2DM, inadequately controlled on insulin therapy with or without oral anti-diabetic agents compared with each individual trial estimates and pooled weighted mean difference is described as follows:For DPP4-vs placebo, unadjusted fixed effect model -**0.47 (**CrI **-0.62, -0.31)** unadjusted random effects model was -0.49 (-2.75, 1.86). The adjusted‡ fixed effect result -1.81 (CrI -4.39, 1.06) and adjusted random effect was -2.21 (CrI -27.72, 22.58). This compared with the individual trial estimates and pairwise meta-analysis cited in Vilsboll et al 2010 with a relative effect of -0.60 (95% CI -0.88, -0.32) and Barnett et al 2012 with relative effect of -0.41(95% CI -0.58, -0.24). The pooled weighted mean difference for these two trials relative effect for DPP-4 vs placebo was **-0.46 (-0.61, -0.32).**

The TZD vs placebo result, , likely driven by the high baseline HbA1c value described in Section 5.7.6.5, the unadjusted fixed effect mean difference was -**1.00 (95% CrI -1.22, -0.78)** the unadjusted random effects mean difference was -1.00 (95% CrI -4.38, 2.47). The adjusted fixed effect mean difference was 4.47 (-7.12, 15.02) and adjusted random effects mean difference was 6.10 (95% CrI -9816, 112.50). This compared with the individual trial estimate in the Rosenstock et al 2002 trial mean difference in relative effect of -1.00 (95% CI -1.22, -0.78), which was the same as the pooled weighted mean difference of **-1.00 (95% CI -1.22, -0.78).**

In the dapa vs placebo unadjusted fixed effect mean difference was **-0.60 (95% CrI** -**0.74, -0.46)** and unadjusted random effect mean difference was -0.60 (-4.03, 2.74). The adjusted fixed effect mean difference was -2.52 (-6.21, 1.55) and adjusted random effect mean difference was -3.10 (95% CrI -40.83, 33.64). This compared with the individual trial estimate in Study 06 mean difference in relative effect of -0.60 (95% CI -0.74, -0.46) and the same for the pooled weighted mean difference.

Estimates in **bold** font represent the best estimate based on an assessment of *a priori* model choice, statistical and clinical significance of model coefficient, model fit, and assessment of the posterior distribution of the between studies variance. ‡ conditioned on a baseline HbA1c of 8.9%, with adjustment co-efficient of -5.87 (95% CrI: -17.14, 6.56) (fixed effect) and -7.63 (95% CrI: -122.0, 104.4) (random effects).

Weight

The consistency of evidence in the weight (kg) network of trials enrolling patients with T2DM inadequately controlled on insulin therapy with or without oral antidiabetic agents compared with each individual trial estimates and pooled weighted mean differerence is described as follows: For DPP4- vs placebo the unadjusted fixed effect mean difference in kg was **0.12 (95% CI -0.26, 0.49)** and unadjusted random effects mean difference in kg was 0.10 (95% CrI -1.34, 1.52). This compared with the individual trial estimate cited by Vilsboll et al 2010 with a relative effect of 0.00 (95% CI -0.55, 0.55) and Barnett et al 2012 wtih a relative effect of 0.21 (95% CI -0.30, 0.72). The pooled weighted mean difference for these two trials was **-0.12 (95% CI -0.26, 0.49)**.

In the dapagliflozin vs placebo comparison, the unadjusted fixed effect mean difference in kg was -1**.69 (95% CrI -2.20, -1.19)** and unadjusted random effects mean difference was -1.68 (95% CrI -3.69, 0.36). This compared with the individual trial estimate in Study 06 mean differencein kg relative effect of -1.69 (95% CI -2.20, -1.18) with the pooled weighted mean difference **of 1.69 (95% CI -2.20, -1.18)**.

Estimates **in bold** represent the best estimate based on an assessment of *a priori* model choice, model fit, and assessment of the posterior distribution of the between studies variance.

Systolic blood pressure

The consistency of evidence in the SBP (mm/Hg) network of trials enrolling patients with T2DM inadequately controlled on insulin therapy wtih or without oral antidiabetic agents can be described as follows: no SBP NMA was conducted for the 24-week add-on to insulin network for DPP-4 vs placebo or dapagliflozin vs placebo. The indivdual trial estimate for DPP-4 vs placebo cited in Barnett et al 2012 showed a mean difference in relative effect of SBP reduction in mm/Hg of -0.50 (95% CI -3.61, 2.61) wtih a similar pooled weighted mean difference of **-0.50 (95% CI -3.61, -2.61)**. The individual trial estimate in Study 06 for SBP mean difference relative effect was -3.00 (95% CI -5.55, -0.45) with pooled weighted mean difference the same at **-3.00 (95% CI -5.55, -0.45)**.

Estimates in **bold** font represent the best estimate based on an assessment of a priori model choice, model fit, and assessment of the posterior distribution of the between studies variance.

Hypoglycaemia

The consistency of evidence in the hypoglycaemia network of trials enrolling patients with T2DM inadequately controlled on insulin therapy with or without oral antidiabetic agens can be described as follows: the odds ratio of DPP-4 vs placebo unadjusted fixed effect model was **1.42 (95% CrI 1.00, 2.03)** and unadjusted random effects **1.42 (95% CrI 0.26, 7.74)**. This compared with the individual trial odds ratio and pairwise meta-analysis cited in Visboll et al 2012 of 2.16 (95% CI 1.30, 3.59) and Barnett et al 2012 of 0.91 (95% CI 0.56, 1.49). The pooled weighted mean difference was **1.40 (95% CI 0.99, 1.99)**. In the TZD vs placebo unadjusted fixed effects odds ratio was 3.75 (95% CrI 1.74, 8.61) and the unadjusted random effects odds ratio was 3.80 (95% CrI 0.33, 45.65). This compared with the individual trial odds ratio from Rosenstock et al 2002 of 3.61 (95% CI 1.66, 7.85) and the same pooled weighted mean difference of **3.61 (95% CI 1.66, 7.85)**. In the dapagliflozin vs placebo unadjusted fixed effect odds raio was 1.37 (95% CrI 0.91, 2.06) and unadjusted random effects odds ratio of 1.36 (95% CrI 0.12, 15.15). This compared with the individual trial odds ratio in Study 6 of 1.36 (95% CI 0.91, 2.05) and the pooled weighted mean difference of **1.36 (95% CI 0.91, 2.05)**.

Estimates in **bold** font represent the best estimate based on an assessment of a priori model choice, model fit, and assessment of the posterior distribution of the between studies variance.

5.8 Non-RCT evidence

Summary

- Non-RCT evidence was not considered based on pre-defined eligibility criteria used for the selection of studies

Summary of methodology of relevant non-RCTs

Not applicable.

Critical appraisal of relevant non-RCTs

Not applicable.

Results of relevant non-RCTs

Not applicable.

5.9 Adverse events

Summary

- The adverse events (AEs) associated with dapagliflozin are consistent with its mechanism of action which causes glucosuria (glucose in the urine) and a mild osmotic diuresis (loss of fluid). As such events of urinary tract infections (UTIs), genital infections (GIs) and volume depletion were actively sought for in the trial programme.
    - GIs were reported in a higher proportion of patients treated with dapagliflozin compared with control. Most were reported in the first 24 weeks and the majority were mild to moderate in intensity and responded to initial standard treatment and were not recurrent. Few events of GI resulted in discontinuation.
    - UTIs were reported in a slightly higher proportion of patients treated with dapagliflozin than with control. The majority were non serious, mild to moderate in intensity, and generally responded to conventional treatment. Few resulted in discontinuation. Kidney infections or pyelonephritis were reported infrequently and were balanced across both groups.
- Glucose excretion induced by dapagliflozin is proportional to circulating glucose levels. When glucose levels are low, glucose excretion is also low and therefore dapagliflozin has a low propensity to cause hypoglycaemia.
    - When dapagliflozin is added to metformin (itself associated with low risk of hypoglycaemia) no additional risk is observed compared with placebo.
    - When dapagliflozin is added to insulin (itself associated with a high risk of hypoglycaemia), a higher overall frequency of hypoglycaemia was reported for both placebo- and dapagliflozin-treated patients, with higher rates among dapagliflozin-treated patients compared with placebo-treated patients.
- The overall rates of all cancers in both placebo and dapagliflozin arms were balanced. From the mechansim of action and the pre-clinical studies of dapagliflozin, there are no obvious pathways which would cause an increase in cancer risk. In addition there were too few events of bladder or breast cancer to establish causality.

5.9.1 Trials designed to primarily assess safety

None of the RCTs involving the interventional agent were designed primarily to assess safety outcomes; as such no additional information is provided for this sub-section.

Summary of methodology of trials designed to primarily assess safety

Not applicable.

Critical appraisal of trials designed to primarily assess safety

Not applicable.

Results of trials designed to primarily assess safety

Not applicable.

5.9.2 Details of all important adverse events for each intervention group

Overall, dapagliflozin was generally well tolerated during the initial study periods and extension phases in patients with T2DM. Side effects associated with dapagliflozin administration (such as GIs, UTIs, dysuria, and pollakiuria, [excessive frequent urination]) would be expected considering that dapagliflozin promotes glucosuria and increases urine volume. The safety profile of dapagliflozin was generally similar for both the short-term and long-term periods. Most AEs were reported in similar proportions of patients treated with dapagliflozin and control.

The most common AEs (≥ 2%) in the dapagliflozin 10 mg group (in descending order of frequency) were nasopharyngitis, back pain, headache, diarrhoea, upper respiratory tract infection, UTI, dyslipidaemia, nausea, hypertension, influenza, pollakiuria and dysuria. Of these AEs, pollakiuria and dysuria were the only AEs more commonly reported (> 1% difference) in the dapagliflozin 10 mg group compared with placebo.

Most AEs were mild or moderate in intensity and resolved while continuing treatment. Few serious adverse events (SAEs) or AEs led to discontinuation of study drug and were balanced across treatment groups. Death was infrequent in all treatment groups.

Information on AEs and SAEs of note in the overall study programme are discussed below.

Hypoglycaemia

The mechanism of action and clinical experience suggest that dapagliflozin as monotherapy has a low risk of hypoglycaemia. The proportions of dapagliflozin-treated patients with events of hypoglycaemia were low and comparable with placebo in the monotherapy pool. In studies where dapagliflozin was used in combination with stable antidiabetic background therapy known to be associated with the development of hypoglycaemia [for example add-on to insulin (Study 6)], a higher overall frequency of hypoglycaemia was reported for both placebo- and dapagliflozin-treated patients, with non-significantly higher rates among dapagliflozin-treated patients compared with placebo-treated patients at 48 weeks. At 2 years, the placebo arm results in numerically higher hypoglycaemia rates. The majority of hypoglycaemia episodes were minor. Major episodes of hypoglycaemia were rare and balanced across all treatment groups. When dapagliflozin was studied as a direct comparison to SU, dapagliflozin plus metformin had a ten-fold reduction of patients with hypoglycaemia compared with SU plus metformin. In all populations, few patients discontinued study treatment due to a hypoglycaemic event.

Genital and Urinary Tract infections

For completeness, the safety profile from 12 randomised placebo controlled trials (all clinical data Phase 2 and Phase 3 – 1393 in placebo group and 1193 in the dapagliflozin 10 mg group) are presented. The subsequent tables present data from the individual trials pertinent to the submission.

Genital Infections

GIs were considered events of special interest in the dapagliflozin development program given that, due to its mechanism of action, dapagliflozin causes glucosuria and that these infections are known to be more common in diabetic patients than in the general population (Donders et al 2002). Events of GI were reported in a higher proportion of patients treated with dapagliflozin compared with control. In all treatment groups, most events (first event) of GI were reported in the first 24 weeks. The majority of events of GI were non serious, mild to moderate in intensity and responded to initial standard treatment and were not recurrent. Few events of GI resulted in discontinuation.

Urinary Tract Infections

UTIs were considered events of special interest in the dapagliflozin development program due to dapagliflozin's mechanism of action which causes glucosuria, and that these infections are known to be more common in diabetic patients than in the general population.

The patients enrolled in the dapagliflozin programme were not excluded on the basis of previous history of UTIs.

Events of UTI were reported in a slightly higher proportion of patients treated with dapagliflozin than with control (Table 42 and Table 43). The great majority of events of UTI were non-serious, mild to moderate in intensity, and generally responded to conventional treatment. Few events of UTI resulted in discontinuation. Kidney infections or pyelonephritis were reported infrequently and were balanced among patients treated with dapagliflozin or control.

Table 42. Diagnoses of UTI (up to 24 weeks)

	Placebo	Dapagliflozin 10mg od
Overall number of patients - N	1393	1193
Patients with diagnosis of UTI, n (%)	52 (3.7)	51 (4.3)
Pyelonephritis, n (%)	1 (0.1)	0
Patients with a history of recurrent UTI, n	35/1393	34/1193
Patients with a prior history of recurrent UTI with clinical diagnosis of UTI, n (%)	6/35 (17.1)	6/34 (17.6)
Women - N	677	598
Women with diagnoses of UTI, n (%)	45 (6.6)	46 (7.7)

	Placebo	Dapagliflozin 10mg od
Men - N	716	595
Men with diagnoses of UTI, n (%)	7 (1.0)	5 (0.8)

Parikh et al 2011

Table 43. Diagnoses and treatment of UTI (up to 24 weeks)

	Placebo	Dapagliflozin 10mg od
Overall number of patients - N	1393	1193
Patients with diagnosis of UTI, n (%)	52	51
Patients experiencing 1 event only, n (%)	48 (92.3)	41 (80.4)
Episodes of diagnosed UTI, n	56	63
Diagnoses of UTI given antimicrobial treatment, n (%)	50 (89.3)	53 (84.1)
Patients with diagnoses of UTI resulting in discontinuation, n (%)	1 (0.1)	3 (0.3)

Renal Safety

In the short-term period, events of renal impairment or failure were reported for few patients (<1.5%) with no apparent difference between treatment groups. Most renal events consisted of small and reversible increases in serum creatinine, consistent with a diuretic effect seen with other agents. Most were non-serious, mild to moderate in intensity and resolved while continuing treatment, and did not lead to discontinuation of study drug.

Volume Depletion

Events of volume depletion (hypotension/hypovolaemia/dehydration) were considered events of special interest in the dapagliflozin development program due to dapagliflozin's mechanism of action. This results in an increased urinary volume and a modest but consistent blood pressure-lowering effect. The concern would be if patients experienced excessive diuresis (loss of fluid) resulting in hypotension (e.g. falls, dizziness).

Events of volume depletion were slightly more common in patients treated with dapagliflozin compared with placebo/control. These events were generally non serious, most were reported as hypotension, and few resulted in discontinuation. In dapagliflozin-treated patients who received concomitant treatment with anti-hypertensive drugs (e.g. angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), or thiazides) the risk of volume depletion was not increased.

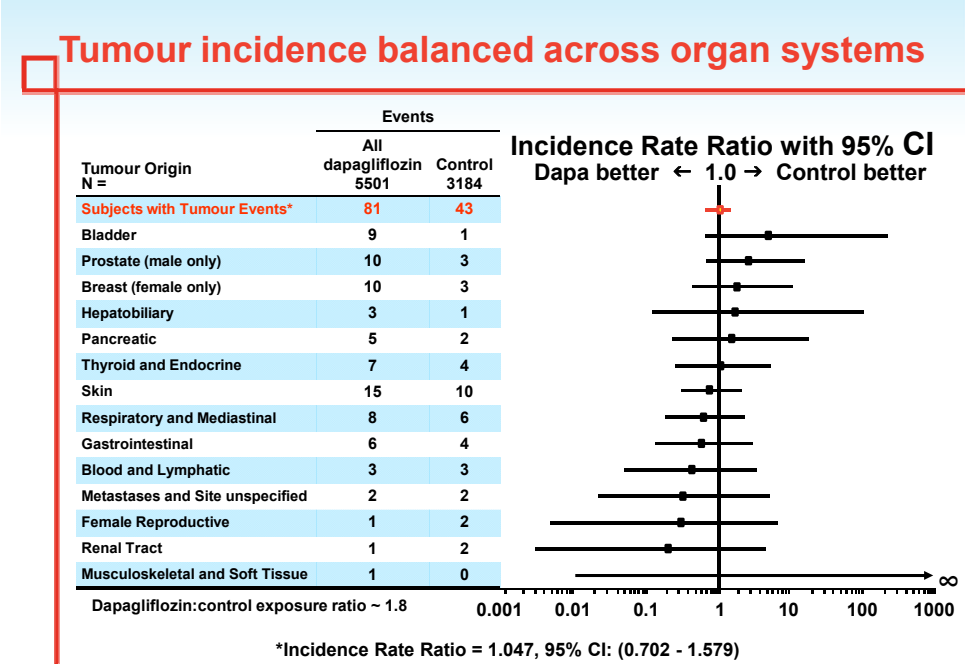
Dapagliflozin is not recommended for patients receiving loop diuretics or who are volume depleted.

Neoplasms (cancers)

During clinical trials, the overall proportion of patients with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.47%; 81/5,501) and placebo/comparator (1.35%; 43/3,184), and there was no carcinogenicity or mutagenicity signals in animal data.

The forest plot diagram (Figure 23) shows that in the dapagliflozin arm numerical reductions in respiratory and mediastinal (chest and lung), renal tract, skin and haematological (blood and lymphatic) neoplasms (cancers) were observed. However, numerical increases were observed for bladder and breast cancers in the dapagliflozin arm. However, the SGLT2 receptor is not expressed in human breast or bladder tissue.

Figure 23. Malignant and unspecified tumours by tumour origin



Wilding 2012b

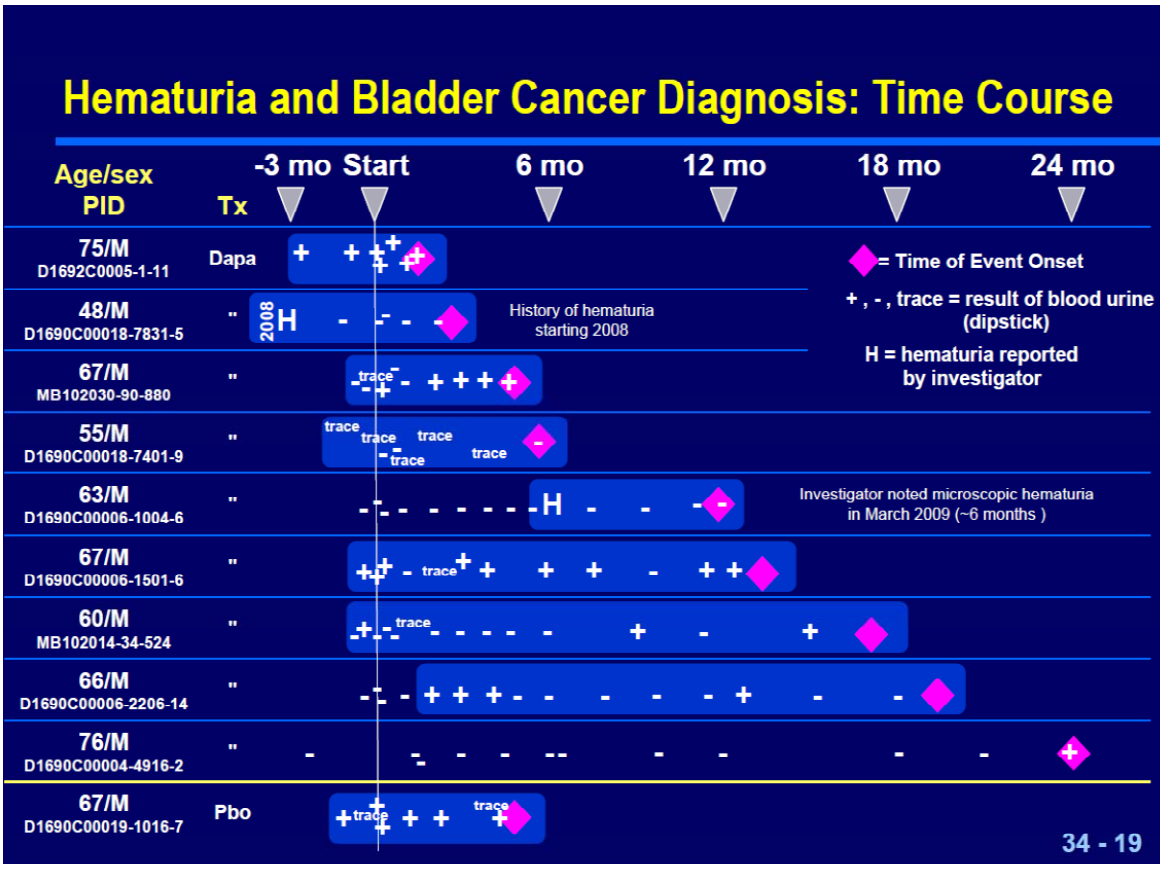
Bladder cancer

Newly diagnosed cases of bladder cancer were reported in 9/5,501 patients (0.16%) treated with dapagliflozin and 1/3,156 patients (0.03%) treated with placebo/comparator. After excluding patients in whom exposure to study medicinal product was less than one year at the time of diagnosis of bladder cancer, there were 4 cases with dapagliflozin and no cases with placebo/comparator.

Figure 24 shows that 5 out of the 9 dapagliflozin patients suspected of bladder cancer had trace, positive or frank haematuria at baseline before dapagliflozin was initiated. Four of these five patients were diagnosed within 6 months of drug initiation.

It needs to be noted that given the mechanism of action of dapagliflozin (leading to glucose in the urine) and the proactive soliciting of any symptoms relating to urinary infections, early detection of pre-existing disease and subsequent investigation was likely.

Figure 24: Haematuria and bladder cancer diagnosis: time course



BMS/AZ presentation to FDA (2011) (Slide 13)

Breast cancer

Breast cancer in female patients was reported in 10/2,531 females (0.40%) treated with dapagliflozin and 3/1,359 females (0.22%) treated with placebo/comparator, all were diagnosed within one year. This was an unexpected imbalance and it was difficult to consider if it was related to dapagliflozin treatment due to the following:

- the small number of breast cancer events and the fact that 2.2 times more patients were treated with dapagliflozin than with control;
- no detectable SGLT2 expression was found in breast tissue;
- no carcinogenicity or mutagenicity risk was shown in nonclinical studies with dapagliflozin;

- patients with breast cancer experienced a short (< 1 year) duration of exposure to dapagliflozin in studies;

- an overall frequency of breast cancer in the dapagliflozin groups that was comparable with incidence rates in patients with T2DM.

The numerical Increase in breast cancer rates may be due to detection bias. Patients who have lost weight may be more likely to detect breast lumps and present for investigation and diagnosis. For example, the weight loss drug orlistat showed a similar numerical imbalance in breast cancers between active and placebo arms in a 2 year study (Davidson et al 1999).

Prostate cancer

Prostate cancer was reported in 0.34% of male patients treated with dapagliflozin and 0.16% of male patients treated with placebo/comparator. After excluding patients in whom exposure to study medicinal product was less than one year at the time of diagnosis of prostate cancer, there was one case with dapagliflozin and one case with placebo/comparator.

The overall rates of all cancers in both placebo and dapagliflozin arms were balanced. From the mechanism of action and the pre-clinical studies of dapagliflozin, there are no obvious pathways which would cause an increase in cancer risk. In addition there were too few events of bladder, breast or prostate cancer to establish causality.

The following presents detailed tabular summaries describing the AEs reported in the RCTs involving the interventional agent of interest (dapagliflozin 10 mg).

Metformin add-on RCTs

Study 14

- The rate of reported hypoglycaemia was similar in both the placebo and dapagliflozin arms, with no major hypoglycaemic episodes reported, suggesting that dapagliflozin, on its own, has a low inherent risk for causing hypoglycaemia.
- There was a higher rate of signs, symptoms or reports suggestive of genital infections in the dapagliflozin arm. All events were of mild to moderate intensity, and either resolved with self-treatment or readily responded to conventional treatments. None led to discontinuation from the study.
- Signs, symptoms and other reports suggestive of urinary tract infections were reported in similar proportions in both placebo and dapagliflozin groups.

Symptoms of hypoglycaemia occurred in similar proportions of patients in the dapagliflozin (5.2%) and placebo groups (5.8%) (Table 44). Signs, symptoms, and other reports suggestive of GIs were more frequent in the dapagliflozin 10 mg group (17 [12.6%]) than in the placebo group (7 [5.1%]). 28 patients had SAEs (14 in each of the dapagliflozin 10 mg and placebo groups).

There were no deaths during the 24-week short-term study. During the extension period (up to week 102), one patient died in the placebo group (lung malignant neoplasm).

One patient receiving dapagliflozin 10 mg experienced breast cancer.

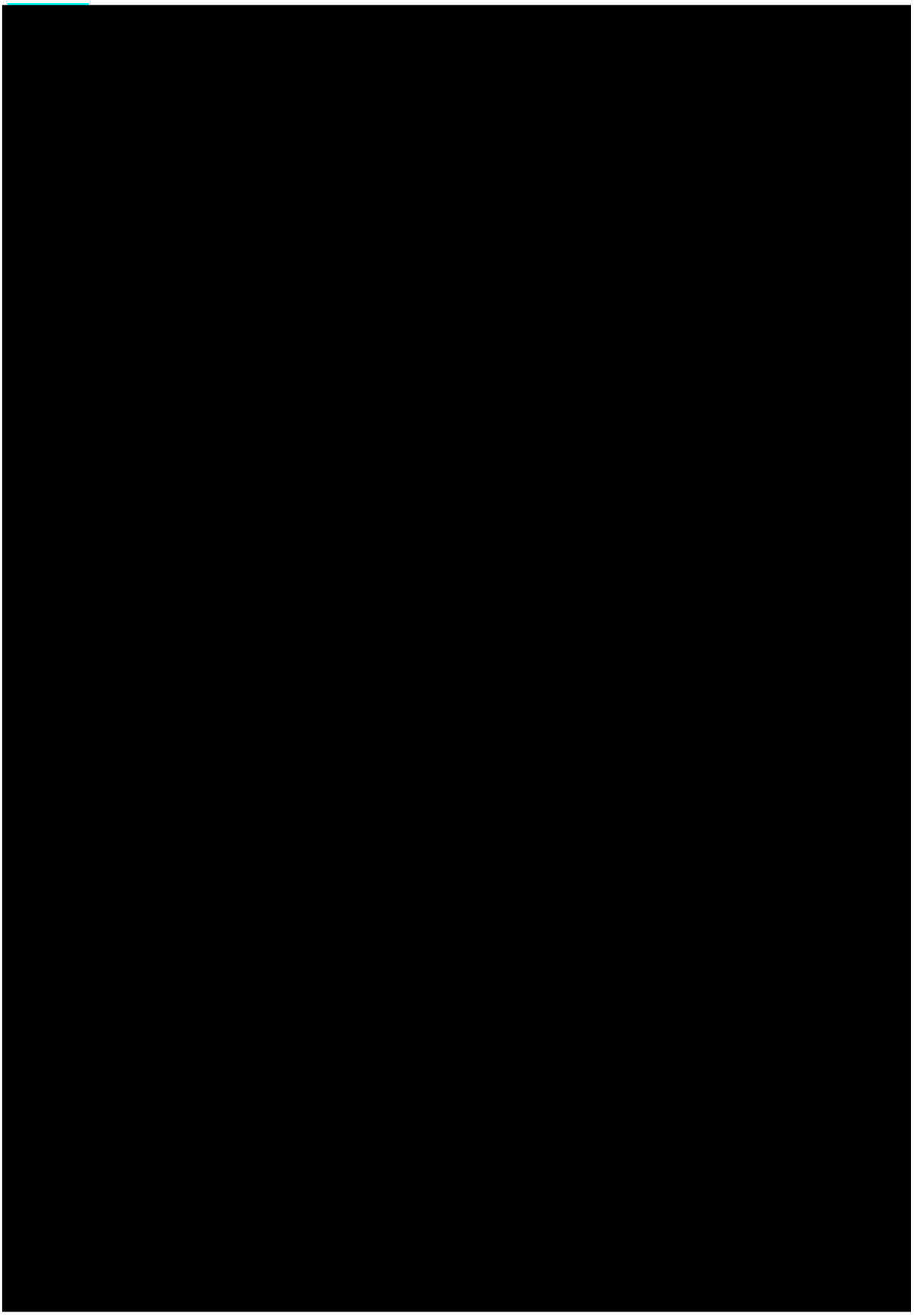
AEs leading to discontinuation were less frequent in the dapagliflozin 10 mg group (4.4%) than in the placebo group (6.6%) (Table 44). Symptoms of hypoglycaemia occurred infrequently, were mild, and occurred in similar proportions of patients in the placebo (5.8%) and dapagliflozin (5.2%) groups. There were no major events of hypoglycaemia (defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose concentration <3 mmol/L, and prompt recovery after glucose or glucagon administration). Signs, symptoms, and other reports suggestive of urinary tract infections were reported in more patients in the dapagliflozin 10 mg group (18 [13.3%]) than in the placebo group (11 [8.0%]). Signs, symptoms, and other reports suggestive of genital infections were also more frequent in the dapagliflozin 10 mg group (17 [12.6%]) than in the placebo group (7 [5.1%]), with the little difference between men and women. For most of these patients only a single event was reported. Three events were reported for a single patient. All events were of mild or moderate intensity, and either resolved with self-treatment or responded readily to conventional interventions. None led to discontinuation from the study.

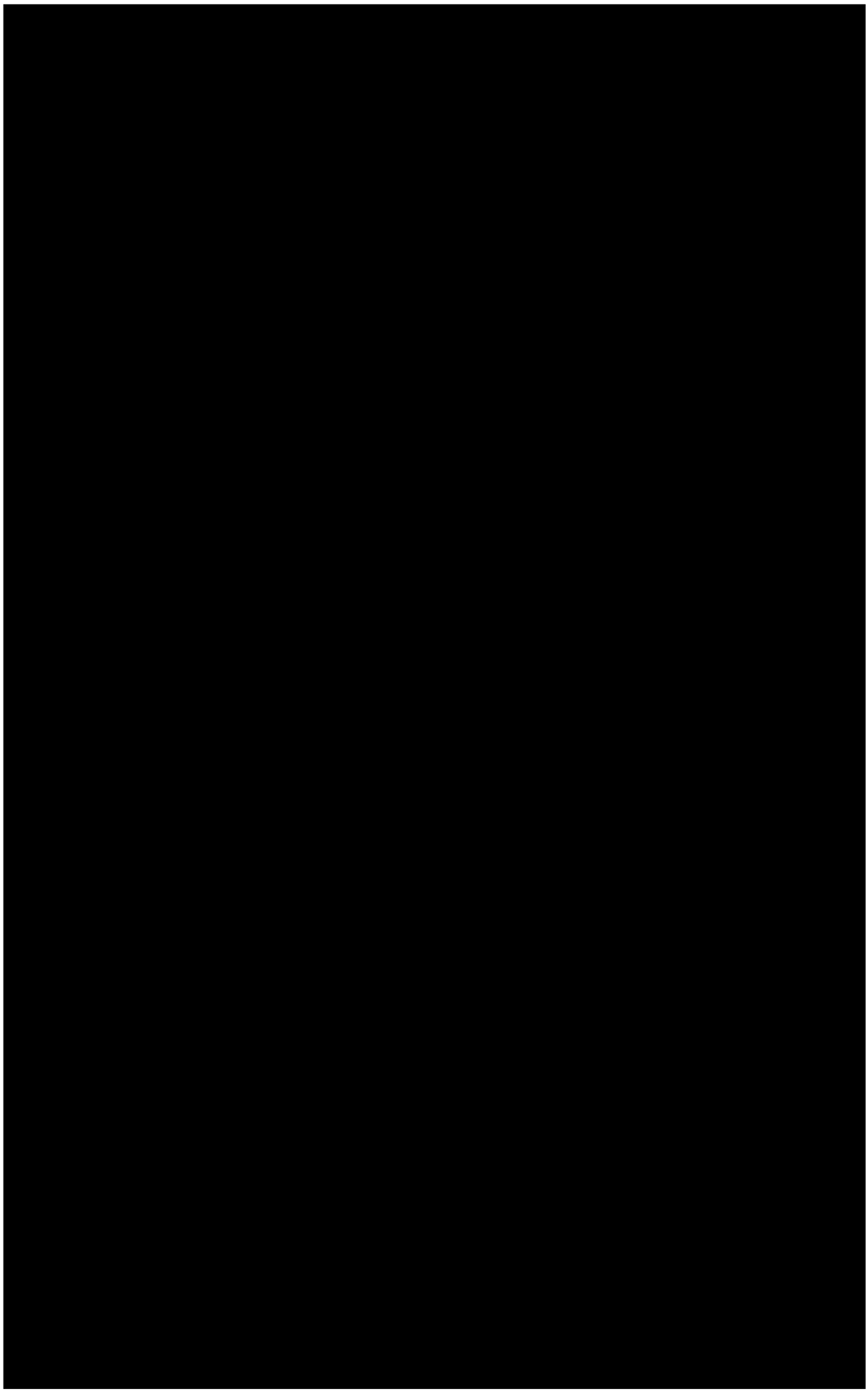
Table 44. Summary of adverse events in Study 14 (Week 102 results) ¶

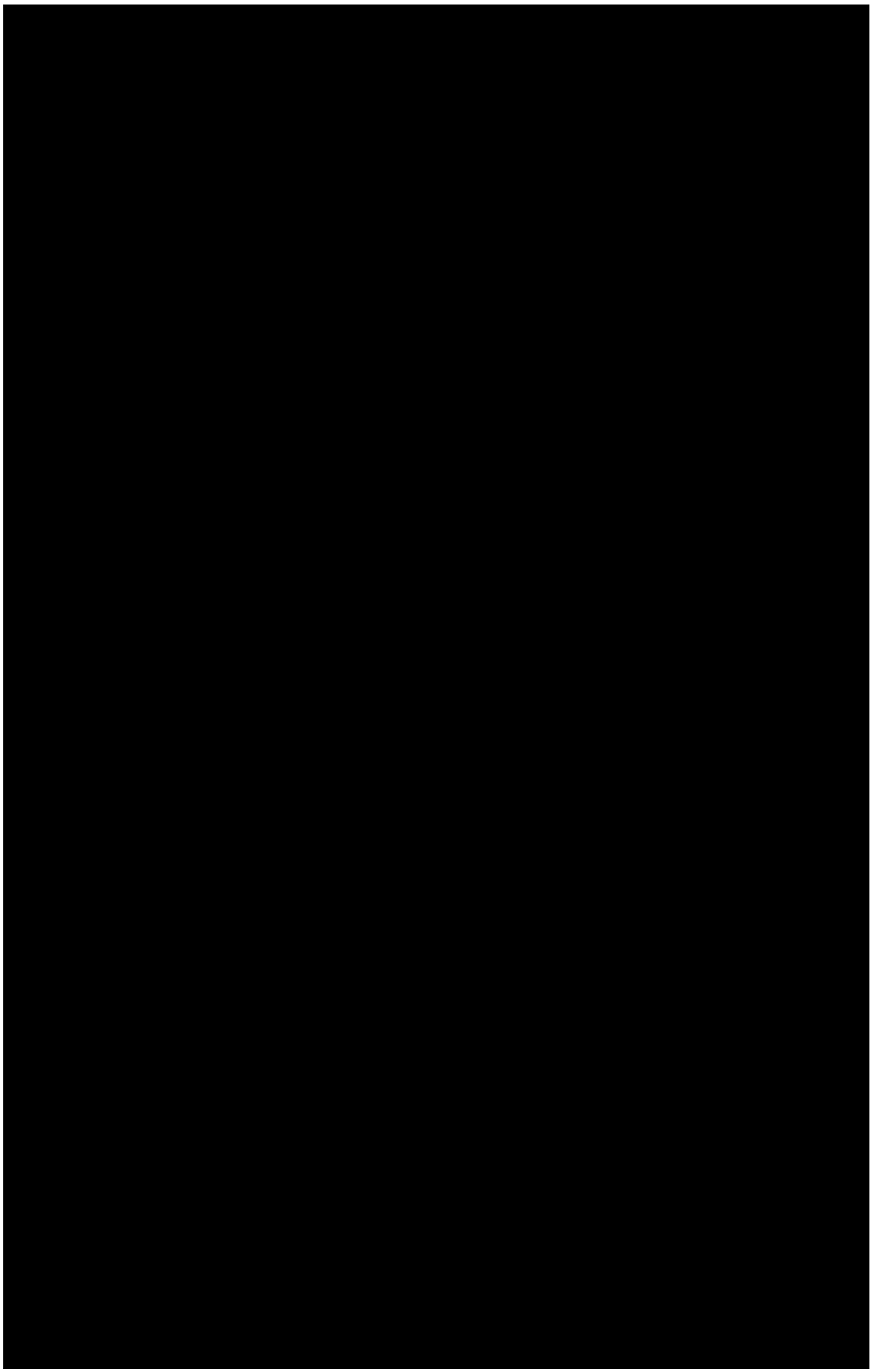
Adverse events (AE) **Number (%) patients**	**Dapagliflozin 10 mg** **n/N (%)**	**Placebo** **n/N (%)**
≥ 1 AE	111/135 (82.2)	111/137 (81.0)
≥ 1 treatment related AE	45/135 (33.3)	28/137 (20.4)
≥ 1 SAE	14/135 (10.4)	14/137 (10.2)
≥ 1 treatment related SAE	1/135 (0.7)	3/137 (2.2)
Deaths	0/135 (0)	1/137 (0.7)
AEs leading to discontinuation	6/135 (4.4)	9/137 (6.6)
AEs of special interest §		
Hypoglycaemia†	7/135 (5.2)	8/137 (5.8)
Events suggestive of UTI ‡	18/135 (13.3)	11/137 (8.0)
Events suggestive of genital infection ‡	17/135 (12.6)	7/137 (5.1)
Hypotension	0/135 (0)	0/137 (0)
Syncope	1/135 (0.7)	2/137 (1.5)

Abbreviations: AE, Adverse event; n. Number of patients with the event; N, Number of patients in the analysis; SAE, Serious adverse event; UTI, Urinary tract infection; †, Number of patients with at least one hypoglycaemia event; ‡, A pre-specified list of preferred terms (Medical Dictionary for Regulatory Activities

[MedDRA] terms) was used to identify signs, symptoms and other reports suggestive of UTI or genital infections; §, This is a pre-specified AE list selected based on mechanism of action following treatment with dapagliflozin; ¶, Treated patient dataset (consisting of all patients who took at least one dose of blinded study medication) including data after rescue







[redacted]

Study 12

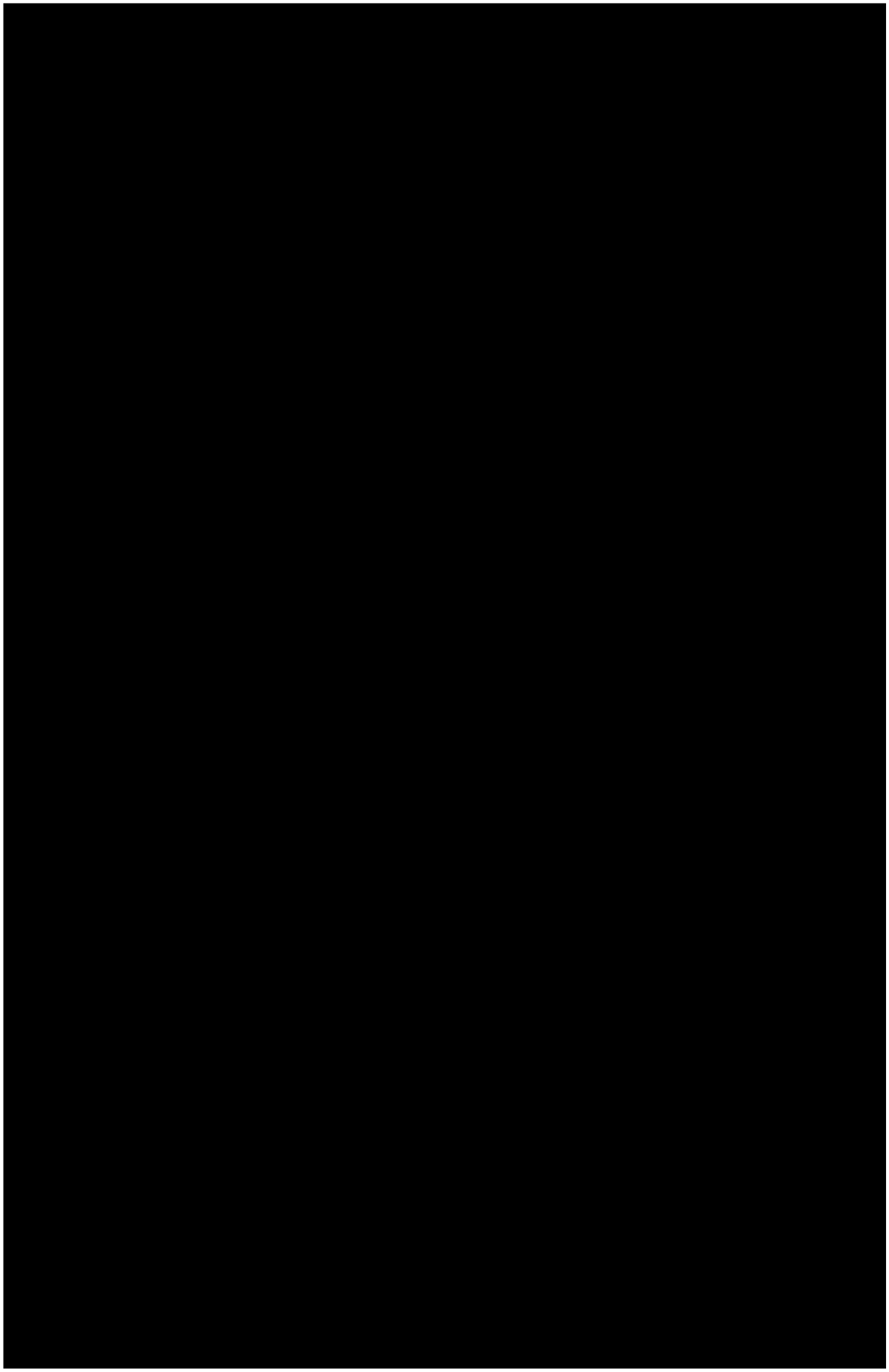
- There was no significant difference in rates of hypoglycaemia between the 2 arms, suggesting that dapagliflozin, on its own, has a low inherent risk for causing hypoglycaemia.
- There was a higher rate of signs, symptoms and other reports suggestive of genital infections in the dapagliflozin arm, most of which were mild to moderate in intensity, easily treated, with non leading to discontinuation of therapy.

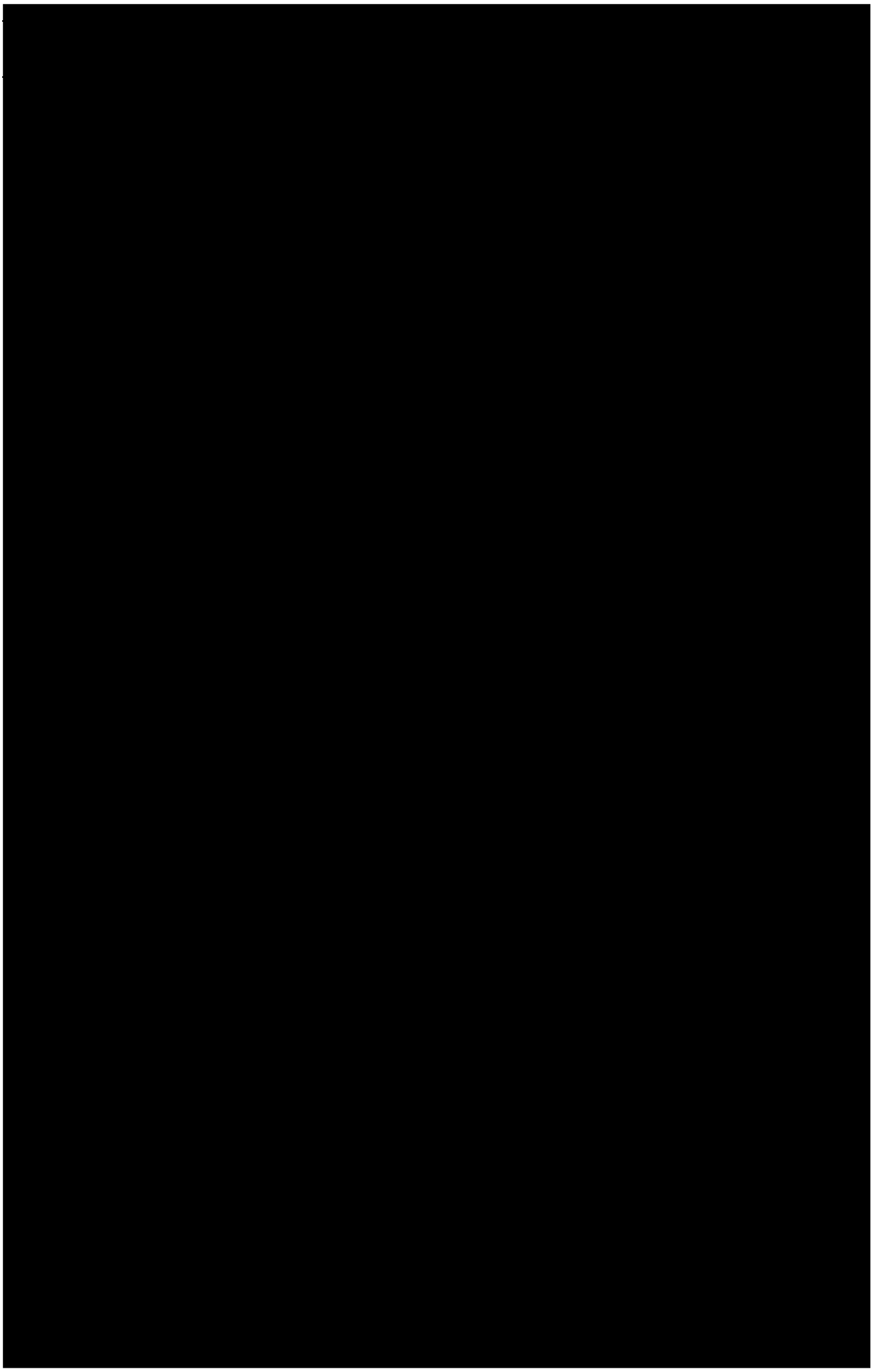
Proportions of patients with at least one AE were similar in the dapagliflozin 10 mg [redacted] and placebo group [redacted] A higher proportion of patients in the dapagliflozin 10 mg group experienced at least one SAE compared with placebo ([redacted] or were discontinued from study medication due to an AE ([redacted] None of the SAEs were assessed as related to the double-blind study medication. The proportion of patients with at least one AE assessed as related to the study medication was higher in the dapagliflozin 10 mg ([redacted] than in the placebo group ([redacted]

Events suggestive of vulvovaginitis, balanitis, and related GI and lower UTI were observed more frequently with dapagliflozin compared with placebo (Bolinder et al 2012). No kidney infections or AE suggestive of renal impairment, renal failure, or renal stones were reported.

[redacted] in the dapagliflozin 10 mg group and [redacted] in the placebo group experienced at least one hypoglycaemic event. No hypoglycaemic event was classified as major, and no patient was discontinued from the study or study medication due to a hypoglycaemic event.

During the 24 week short-term study one patient in the dapagliflozin 10 mg group died during hospitalization for pneumonia due to oesophageal variceal haemorrhage.





[redacted]

Study 4

- There was a more than ten-fold lower rate of patients reporting hypoglycaemia in the dapagliflozin arm compared with the SU arm, with no reported major hypoglycaemic episodes in the dapagliflozin arm. [redacted].
- There was a higher rate of signs, symptoms and other reports suggestive of GIs in the dapagliflozin arm, most of which were mild to moderate in intensity, easily treated, and rarely led to discontinuation of therapy.
- There was a higher rate of signs, symptoms and other reports suggestive of UTIs in the dapagliflozin arm, most of which were mild to moderate in intensity, easily treated, and rarely led to discontinuation of therapy. However, there were 2 episodes of upper UTIs in the SU arm (1 pyelocystitis and 1 pyelonephritis) and none in the dapagliflozin arm.

There was a significantly lower proportion of dapagliflozin patients experiencing hypoglycaemia (4.2%) versus glipizide (45.8%) at 2 years. No patients discontinued dapagliflozin treatment as a result of a hypoglycaemic event compared with six patients receiving glipizide. Three patients taking glipizide, but none taking dapagliflozin, reported major hypoglycaemic episodes (Nauck et al 2011a, 2011b).

Events suggestive of GIs and lower UTIs were reported more frequently with dapagliflozin 10 mg compared with glipizide (Table 48) but responded to standard treatment and rarely led to study discontinuation. One report of renal failure was considered related to dapagliflozin and resulted in treatment discontinuation. This AE

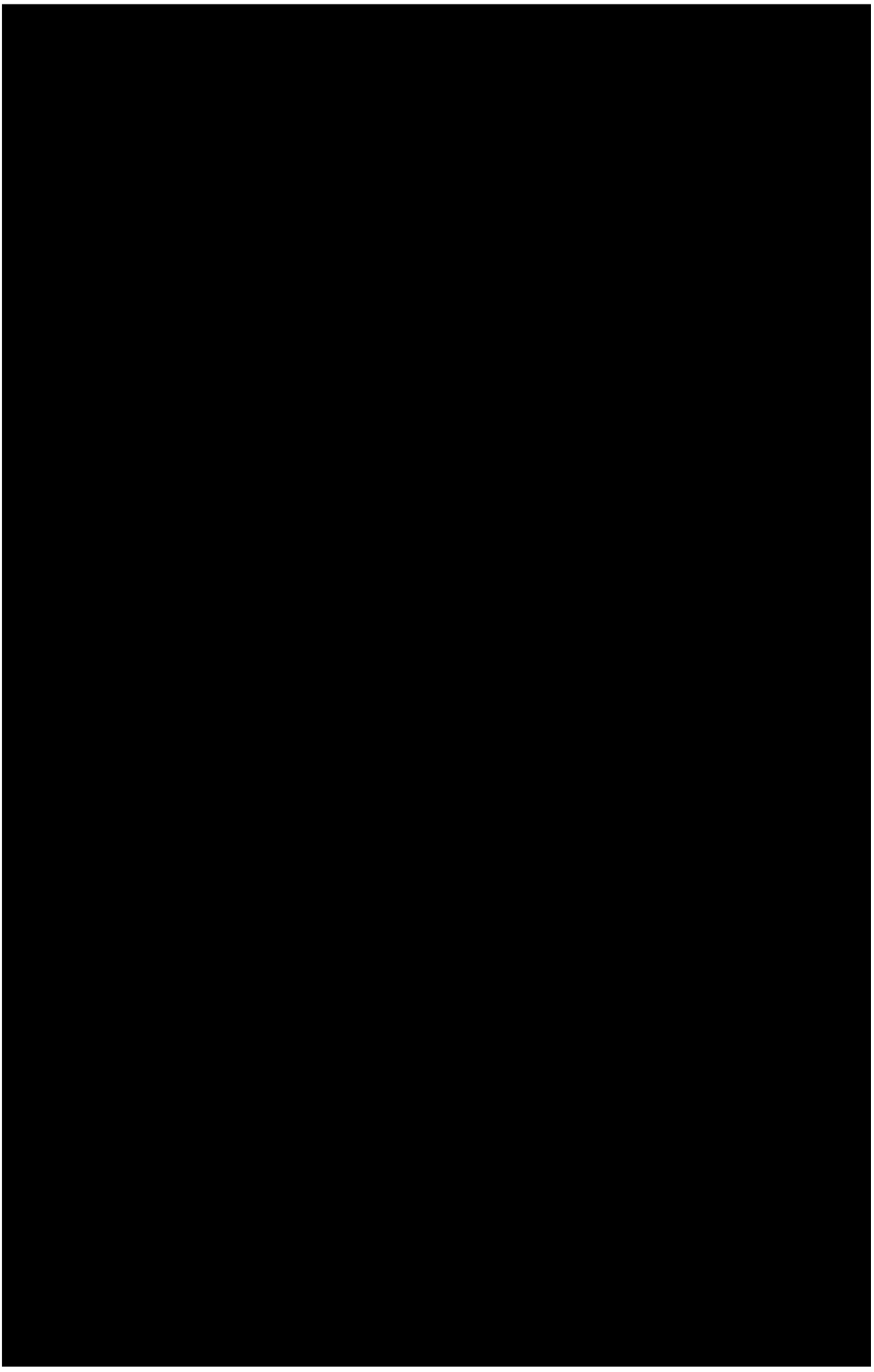
was assessed as mild in intensity and non serious by the investigators, and no treatment was administered. Overall AEs, and AEs and SAEs leading to study discontinuation, were balanced in the dapagliflozin 10 mg and glipizide groups. No deaths were reported in patients receiving dapagliflozin. No deaths were reported in the dapagliflozin group during the 104 week extension period; there were three deaths reported in the 52 week short-term period among patients in the glipizide group and an additional death in this group up to 104 weeks due to a road traffic accident.

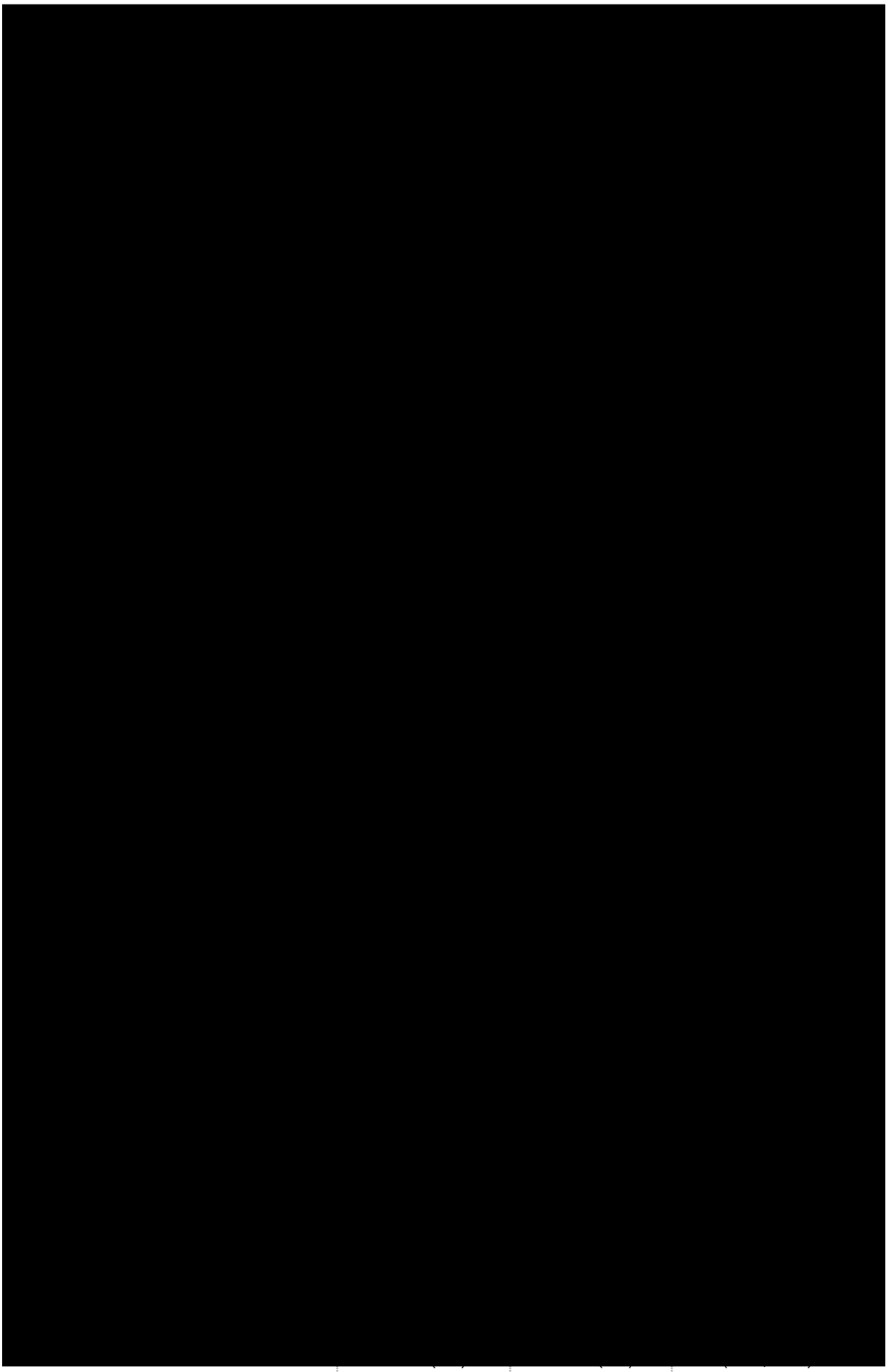
After the extension period (up to week 104), one patient in the dapagliflozin group died more than 30 days after the last dose of double-blind study medication, and one further patient in each treatment group died after the follow-up visit was performed. The deaths of these patients were not included in the analysis.

Table 48. Summary of adverse events in Study 4 (Week 104 results) †

Adverse events (AE) **Number (%) patients**	**Dapagliflozin 10 mg** **n/N (%)**	**Glipizide** **n/N (%)**
≥ 1 AE	337/406 (83.0)	338/408 (82.8)
≥ 1 treatment related AE	122/406 (30.0)	118/408 (28.9)
≥ 1 SAE	51/406 (12.6)	62/408 (15.2)
≥ 1 treatment related SAE	8/406 (2.0)	7/408 (1.7)
Deaths	0/406 (0)	4/408 (1.0)
AEs leading to discontinuation	40/406 (9.9)	31/408 (7.6)
AEs of special interest ¶		
Hypoglycaemia‡	17/406 (4.2)	187/408 (45.8)
Events suggestive of UTI §	55/406 (13.5)	37/408 (9.1)
Events suggestive of genital infection §	60/406 (14.8)	12/408 (2.9)
Hypotension	5/406 (1.2)	5/408 (1.2)
Syncope	1/406 (0.2)	1/408 (0.2)

Abbreviations: AE, Adverse event; n, Number of patients with the event; N, Number of patients in the analysis; SAE, Serious adverse event; UTI, Urinary tract infection; †, Safety analysis set, consisting of all patients who received at least one dose of study medication; ‡, Number of patients with at least one hypoglycaemia event; §, A pre-specified list of preferred terms (Medical Dictionary for Regulatory Activities [MedDRA] terms) was used to identify signs, symptoms and other reports suggestive of UTI or genital infections; ¶, This is a pre-specified AE list selected based on mechanism of action following treatment with dapagliflozin





[redacted]

Insulin add-on RCTs

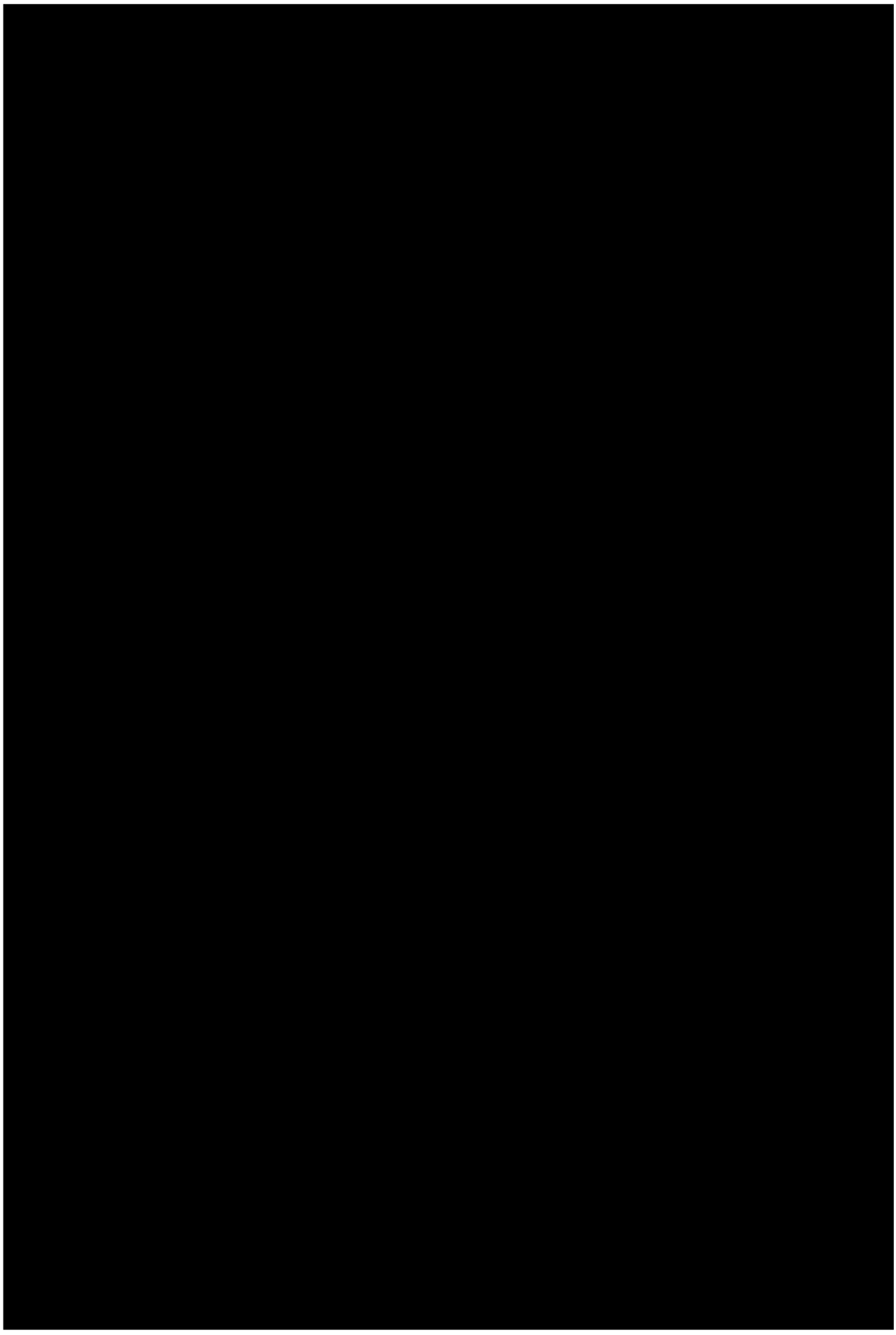
Study 6

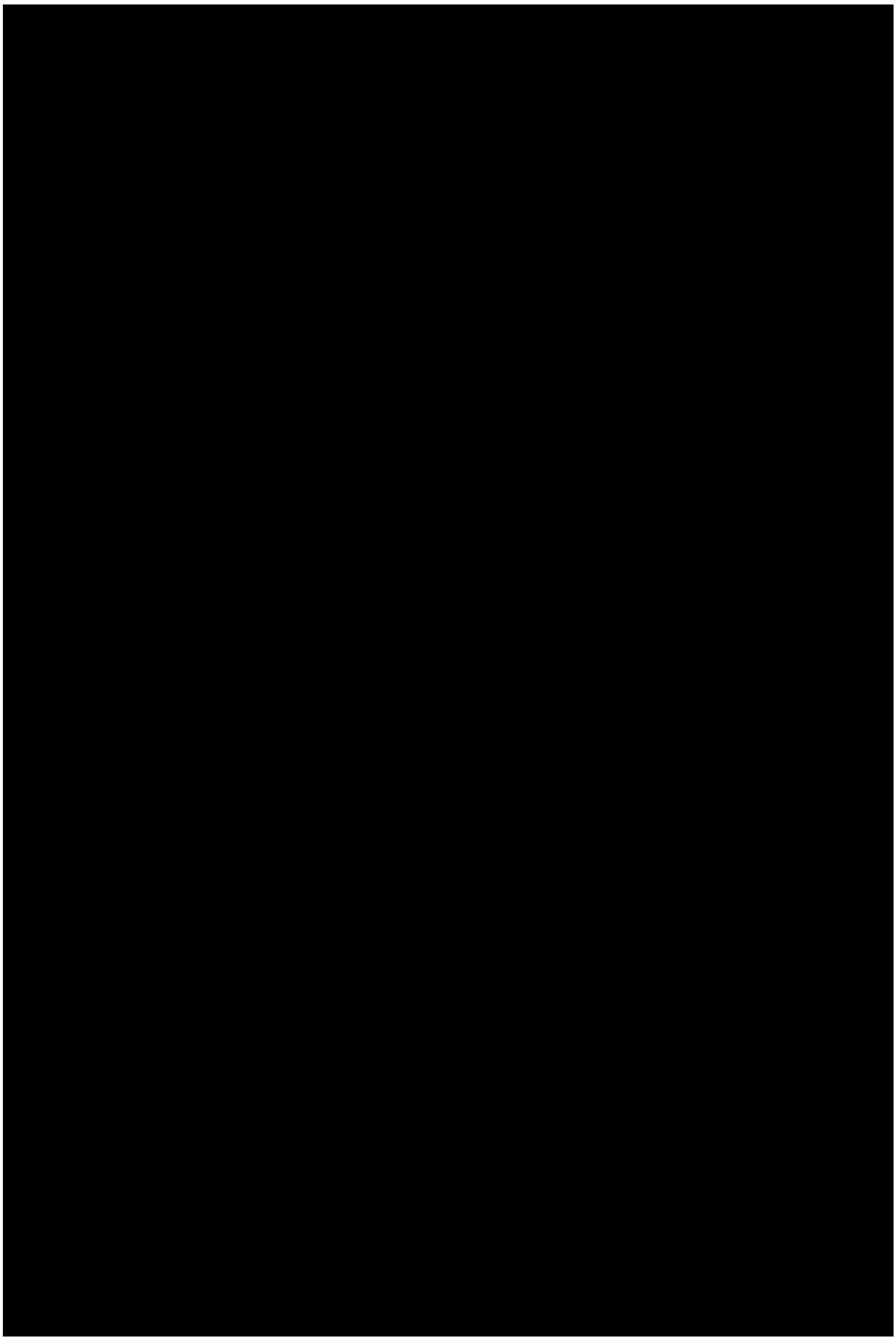
- There were slightly fewer episodes of hypoglycaemia in the dapagliflozin plus insulin patients than those on placebo plus insulin at 2 years. There was a similarly low number of major episodes of hypoglycaemia in both groups.
- There was a higher rate of signs, symptoms and other reports suggestive of UTIs or GIs in the dapagliflozin arm at 24 weeks. [redacted].
- Most UTIs and GIs were mild to moderate in intensity, easily treated, and rarely led to discontinuation of therapy.

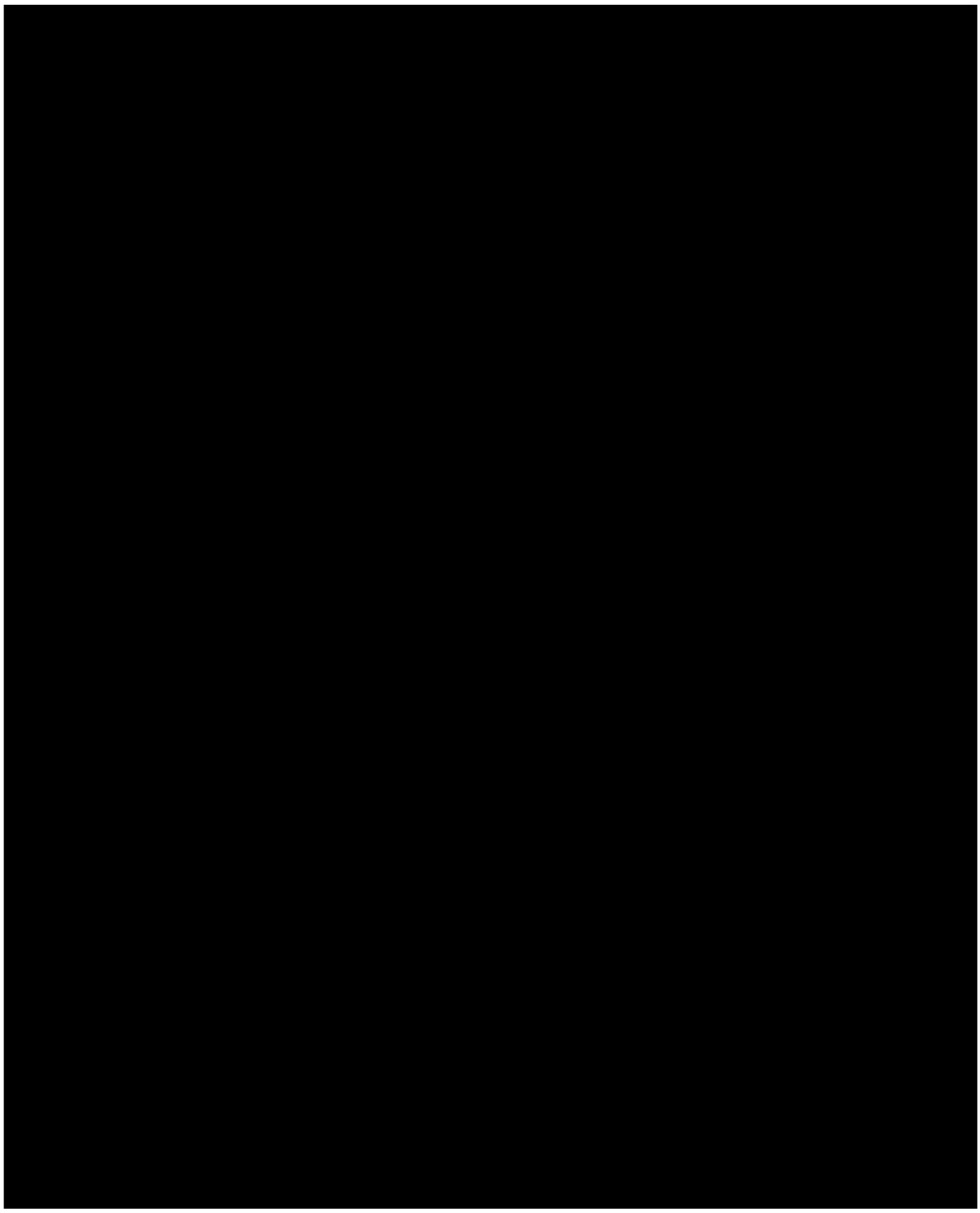
Signs and symptoms suggestive of GI and UTI were higher with dapagliflozin 10 mg after 48 weeks (Wilding et al 2010a) and [redacted] (Table 50). Most events occurred during

the first 24 weeks of treatment. Signs, symptoms and other reports suggestive of GI led to treatment discontinuation in 2 patients receiving dapagliflozin 10 mg during weeks 0 to 24.

Major episodes of hypoglycaemia were few and evenly distributed among treatment arms; there were no withdrawals due to hypoglycaemia.







Study 9

- In this pilot study more patients experienced hypoglycaemia in the dapagliflozin arm than in the placebo arm.

Treatment-related AEs were balanced across both dapagliflozin 10 mg and placebo groups (Table 52 and Table 53) (Wilding et al 2009). The majority of AEs reported during the treatment period were of mild or moderate intensity. One subject in each group discontinued study medication due to one or more AEs during treatment. Although the total number of hypoglycaemic events reported was greater with dapagliflozin (7 patients) than with placebo (3 patients), there were no major hypoglycaemia episodes with dapagliflozin and 1 major episode in the placebo group. No deaths were reported during this 12-week short-term study.

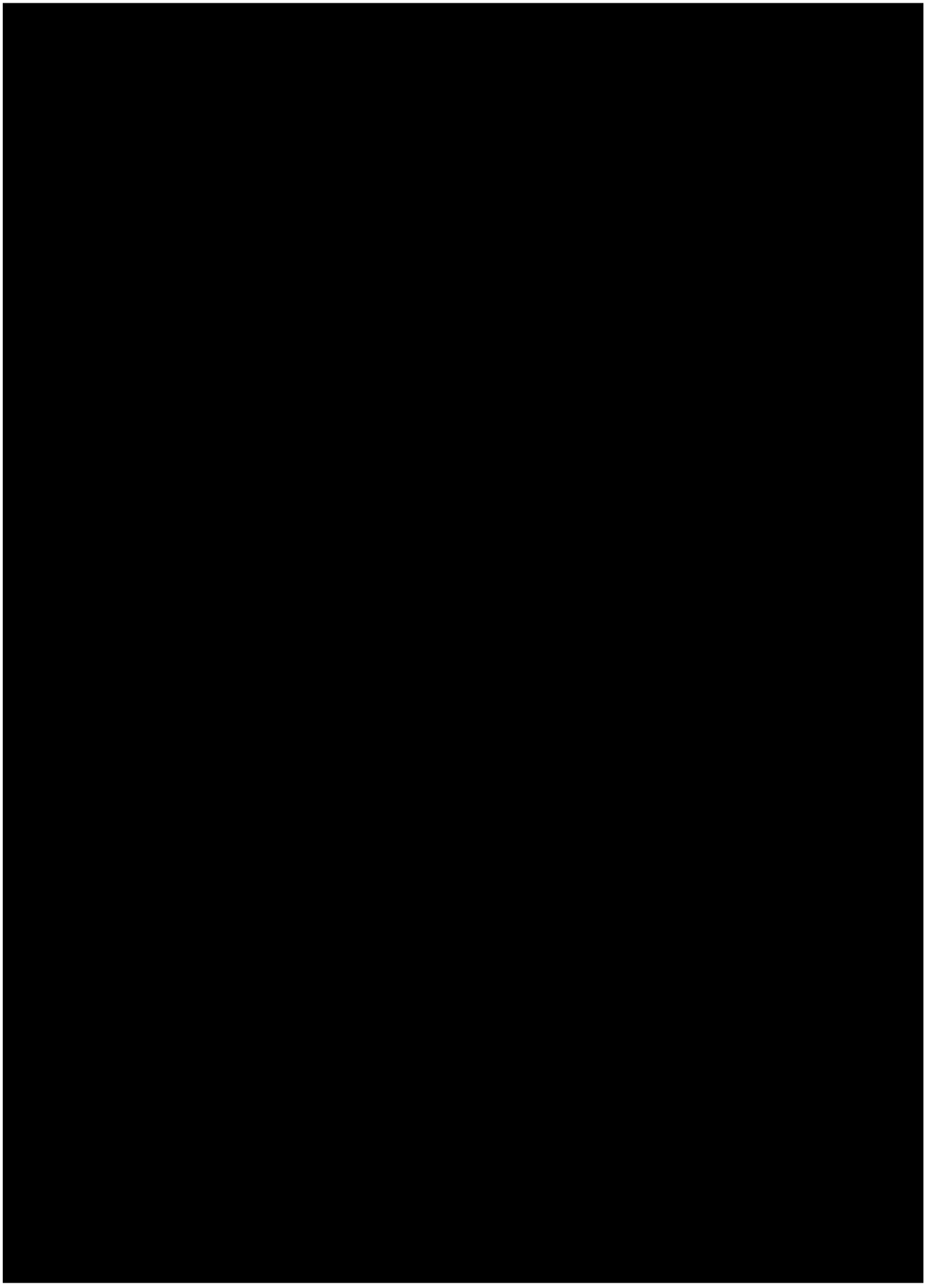
Events of pollakiuria were reported across all treatment groups, including the placebo group. One event of renal failure occurred during treatment with 10 mg dapagliflozin. The patient was being treated chronically with multiple antihypertensive agents.

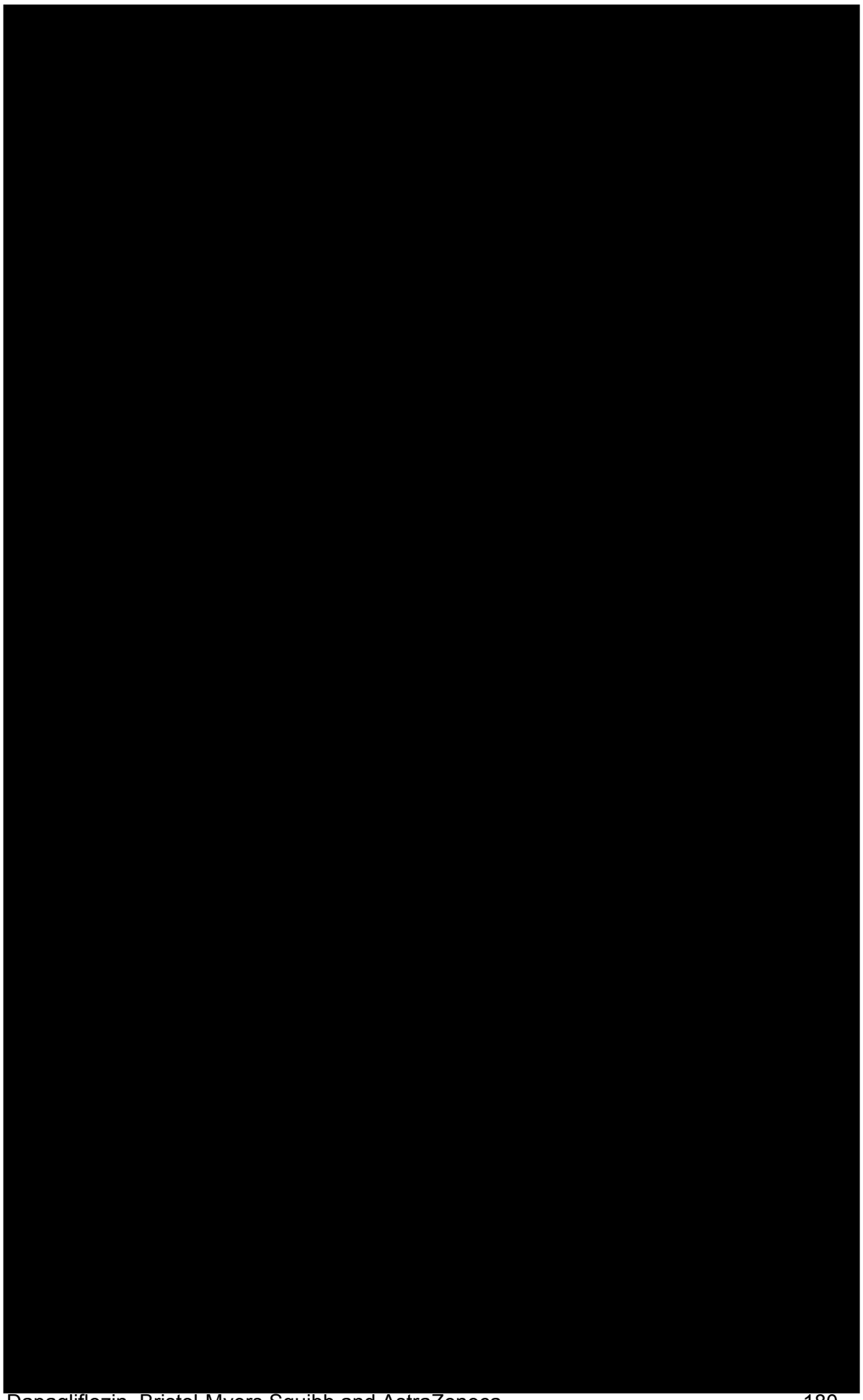
In general, dapagliflozin was well tolerated.

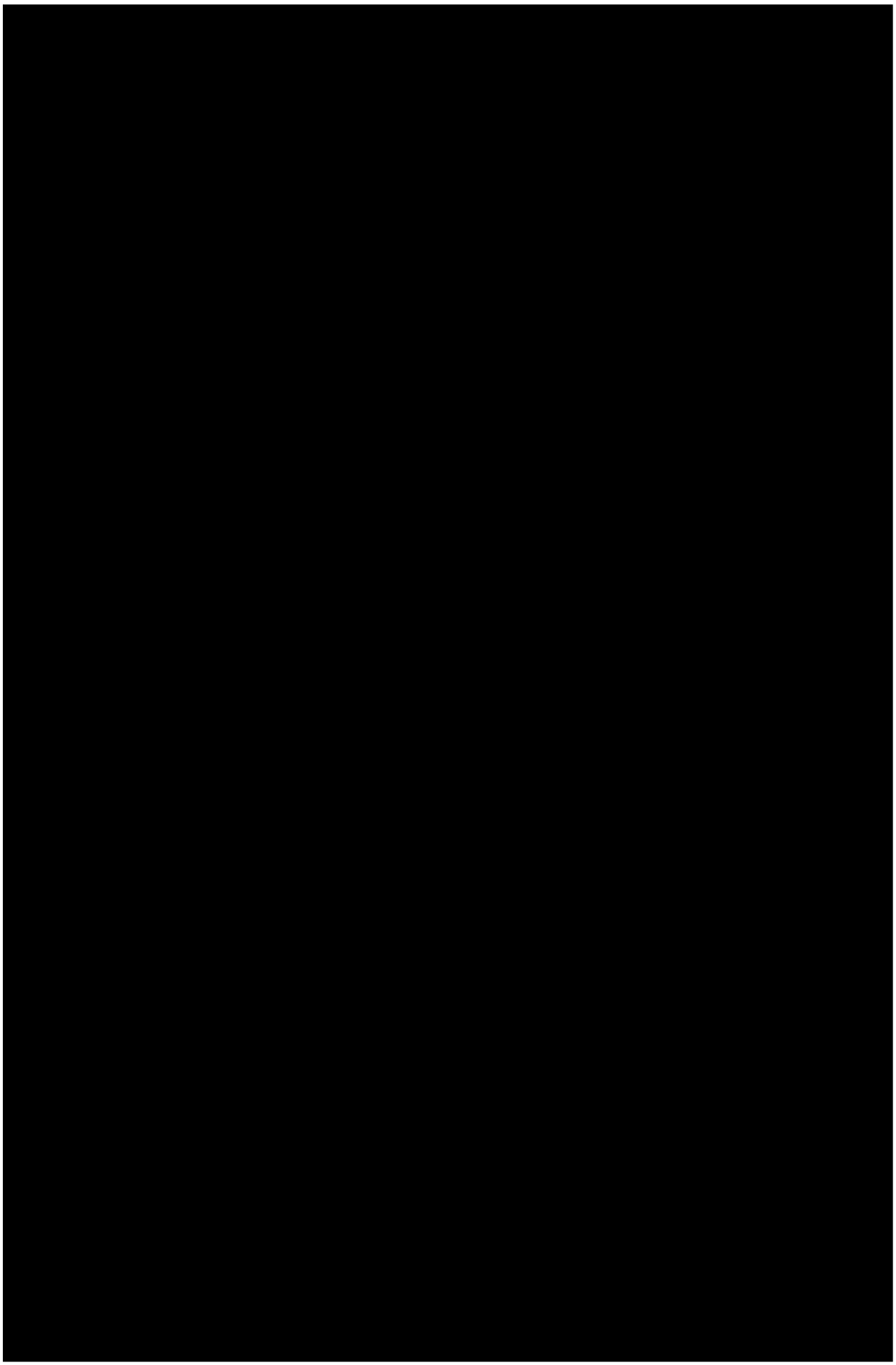
Table 52. Summary of adverse events in Study 9 (Week 12 results) §§§

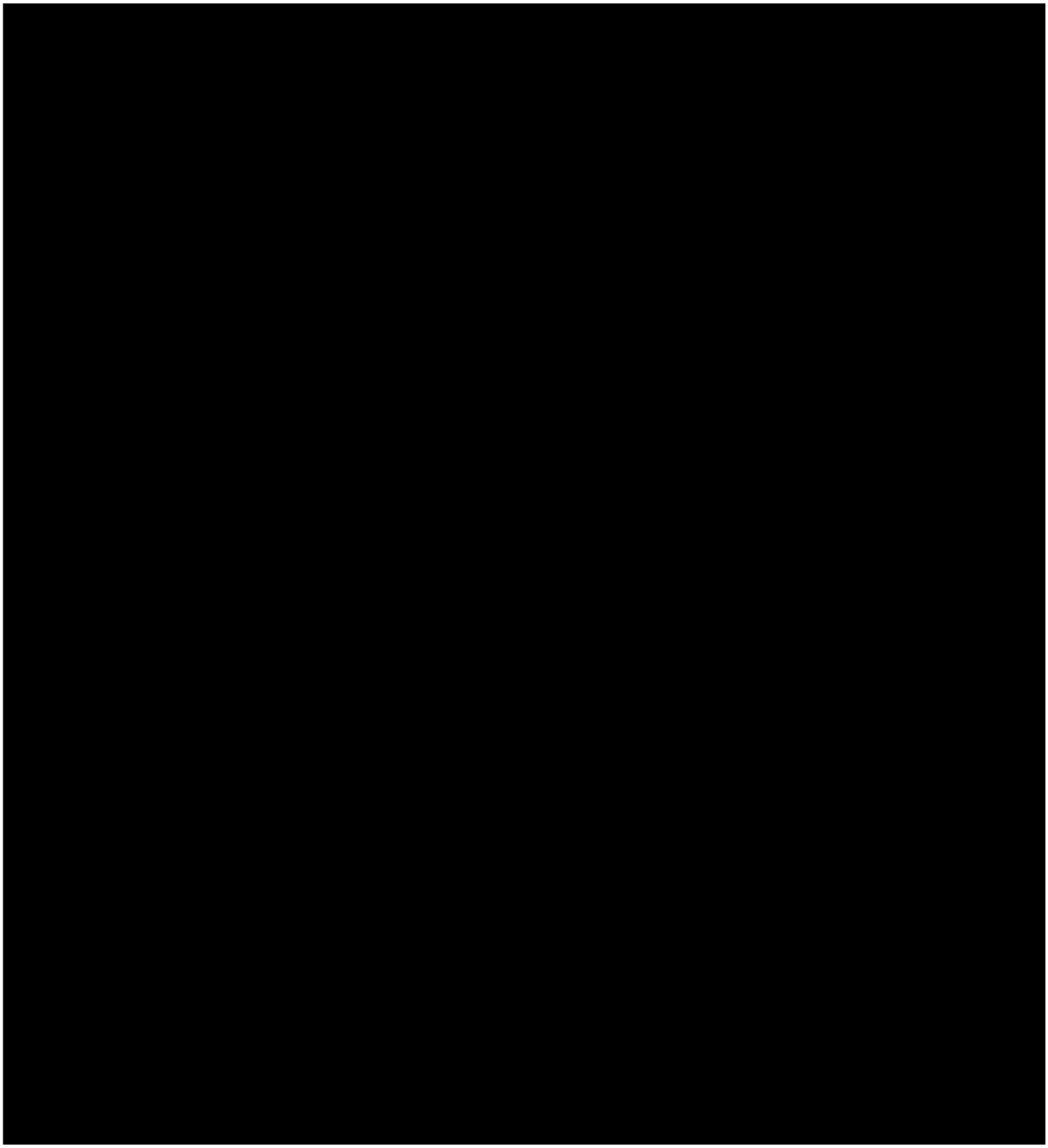
Adverse events (AE) **Number (%) patients**	**Dapagliflozin 10 mg** **n/N (%)**	**Placebo** **n/N (%)**
≥ 1 AE	18/24 (75.0)	15/23 (65.2)
≥ 1 treatment related AE	10/24 (41.7)	10/23 (43.5)
≥ 1 SAE	0	1/23 (4.3)
≥ 1 treatment related SAE	0	1/23 (4.3)
Deaths	0	0
AEs leading to discontinuation	1/24 (4.2)	1/23 (4.3)
AEs of special interest ‡‡‡		
Total patients with hypoglycaemia	7/24 (29.2)	3/23 (13.0)
Events suggestive of UTI	0	0
Events suggestive of genital infection	0	1/23 (4.4)

Abbreviations: AE, Adverse event; n. Number with the event; N, Number in the analysis; SAE, Serious adverse event; UTI, Urinary tract infection; ‡‡‡, AEs extracted from the CSRs correspond to those classified as AEs of special interest in the published Bailey et al 2010 study; §§§, Table captures only short-term period summaries; AEs occurring during study extension periods are not reported here









5.9.3 Safety results from other relevant studies

Not applicable.

5.9.4 Give a brief overview of the safety of the technology in relation to the decision problem

Please see end of Section 5.10.2.

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Please see Section 5.10.2.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Dapagliflozin is the first in class SGLT-2 inhibitor that works by inducing urinary excretion of excess glucose, with the associated calories, thereby reducing HbA1c, weight and blood pressure, without increasing incidences of hypoglycaemia.

Strengths and relevance of the evidence base

The dapagliflozin trial programme

The dapagliflozin trial programme is one of the largest diabetes programmes carried out to date, with 29 clinical studies completed or ongoing. The entire Phase 3 programme was conducted globally, with 42% of patients from European countries. In the Phase 2b and 3 clinical trial programme 4287 patients were exposed to dapagliflozin and 1941 to control, covering 4009 and 1682 patient-years, respectively.

The 3 main 'add-on to metformin' RCTs (Studies, 14, 12 and 4) presented in this submission were all Phase 3, multicentre, double-blind studies. The extension phases at 2 years continued with double-blind (patient-investigator) methodology, with all end-points calculated using ITT analyses which provided robust results for both efficacy and safety. Study 4 is currently collecting data for a total of 4 years. As well as placebo-controlled studies to identify true drug effect, a head-to-head study was conducted against SU, the most routinely used class of drug after metformin in clinical practice to manage T2D in the UK.

The robust study designs and long duration of blinded data collection included in this submission provide a strong evidence base to support the use of dapagliflozin.

Study patient population

The 3 'add-on to metformin' studies involved T2D patients who had inadequate glycaemic control on stable current therapy and are all relevant to the decision problem of this submission. Patients were eligible for study inclusion if they were on stable doses of metformin for at least 2 months prior to study enrolment. In the 'add-on to insulin' studies (Studies 6 and 9), patients were on a stable insulin dose for 6-8 weeks prior to

study initiation. This ensured the trial results reflected the true effect of the study intervention (dapagliflozin) and not that of the background metformin or insulin.

Diabetes is characterised by a steady decline in the function of insulin-secreting cells (β-cells). This means that patients have less and less body insulin over time. Patients in the studies had a history of diabetes for at least 6 years and up to 14 years. Dapagliflozin has an insulin-independent mechanism of action and does not rely on β-cell function for its activity; consistent results for HbA1c reduction were shown, regardless of duration of diabetes.

Study Endpoints

HbA1c is the 'gold standard' clinical measurement of glycaemic control. HbA1c was the primary endpoint of this study. HbA1c is also a surrogate marker for both micro and macrovascular complications. There is a wealth of evidence to support the fact that reduction in HbA1c improves both micro and macrovascular outcomes. There was a consistent reduction in HbA1c observed across the 5 studies presented in this submission.

Obesity is a significant problem in patients with T2D and weight gain is caused by many anti-diabetic medications. Study 12 was specifically designed to evaluate weight change in T2D patients and this was the primary endpoint. Dapagliflozin showed significant clinically relevant weight reduction versus placebo.

Hypoglycaemia is a major concern for patients with diabetes. Some antidiabetic medications (e.g. SUs/insulin) are associated with an increased risk of hypoglycaemic events. The dapagliflozin studies specifically monitored for incidences of hypoglycaemia. In the dapagliflozin 'add-on to metformin' studies, there was generally a low incidence of hypoglycaemia and no major events. This shows that dapagliflozin can improve glycaemic control in patients who have inadequate control with metformin alone without an increased risk of hypoglycaemia.

Approximately one third of T2D patients have raised blood pressure (Health Survey for England 2009), which has been shown to contribute to the mortality and morbidity of diabetes (UKPDS 1998). In the dapagliflozin trial programme SBP and DBP were measured, however investigators were allowed to treat patients with raised blood pressure by the usual standard of care with antihypertensive agents.

Limitations of clinical evidence base

Throughout the Phase 3 programme of studies the observed effect on blood pressure was noted; however, background anti-hypertensive medications were not controlled. Although this was not ideal, in reality this is closer to real-world use of dapagliflozin. Two studies which control for background medication with the specific aim of determining blood pressure reduction are underway.

Although a wide range of patients were included in the clinical trial programme, patients with severe renal impairment (eGFR < 30) were not studied. Dapagliflozin's mechanism

of action relies on kidney function and therefore it was not anticipated to be efficacious in these patients.

Study 9 was a 12-week Phase 2b study looking at the effect of dapagliflozin in patients on a high background of insulin therapy, small patient numbers were involved and therefore any conclusions are exploratory and were further investigated in the larger Phase 3, Study 6.

Clinical Benefits

Dapagliflozin offers a number of advantages which address current unmet medical needs:

Glycaemic control

- From the landmark UK Prospective Diabetes Study (UKPDS 35, 2000), a 1% reduction in HbA1c was associated with a reduction of 14% in myocardial infarction, 37% in microvascular complications and 21% in diabetes-related deaths at 10 years.

- Dapagliflozin results in improved glycaemic control compared to baseline [-0.84% (Study 14), -0.52% (Study 4), -0.90% (Study 6)].

    - This benefit was maintained [redacted] -0.71% (Study 6)]. The 4 year results for Study 4 are not yet available.

    - In patients at high initial HbA1c (≥ 9%), larger reductions from baseline were found in dapagliflozin patients [-1.32% (Study 14), -1.28% (Study 4), -1.41% (Study 6)].

A flexible addition to the treatment pathway

- Dapagliflozin can be added to metformin as an alternative treatment option to SU, in patients whom SU is not appropriate because of the risk of hypoglycaemia, or in whom weight loss is a treatment goal. Dapagliflozin may also delay progression to the addition of a third oral agent, GLP-1 analogue or insulin.

- Dapagliflozin can also be added to insulin with or without metformin as an insulin-sparing agent. The body would not need as much insulin to control blood sugar and the daily insulin dose could be reduced; this would minimise additional weight gain caused by insulin.

- Its insulin-independent mechanism of action allows dapagliflozin to be used as an appropriate choice at any stage of the treatment pathway.

Hypoglycaemia

- Hypoglycaemia can have detrimental effects on patients' quality of life, especially those who drive, work at heights, or operate heavy machinery or have erratic lifestyles. The effect of hypoglycaemia episodes (severe or non severe) has a

measurable negative effect on patients, as measured by the Audit of Diabetes-Dependent Quality of Life (ADDQoL) average weighted impact scores, Diabetes Treatment Satisfaction Questionnaire (DTSQ) score and Hypoglycaemic Fear Survey (HFS-II) score (Bradley et al 2010).

- Dapagliflozin has a low propensity to cause hypoglycaemia. This means that patients on metformin, who are also receiving dapagliflozin, do not require regular blood sugar monitoring. This may be of particular benefit to this large group of patients.

Weight loss

- It has been suggested that even modest reductions in weight may be associated with health benefits, with reductions in blood pressure, cholesterol, and triglycerides achievable with just a 5-10% reduction in initial body weight (Goldstein 1992).

- Patients with diabetes have a tendency to be overweight. Weight loss that can be achieved is both beneficial to management of their disease and quality of life.

- Dapagliflozin has the additional benefit of weight loss. Study 4 and Study 6 results are particularly relevant because weight gain is an issue for patients on SU and insulin.

    - Compared to SU patients, dapagliflozin patients initially lost 4.66kg at 1 year and [redacted] at 2 years.

    - In Study 6 the addition of dapagliflozin to insulin results in weight loss, compared to patients on insulin alone (1.69kg at 24 weeks and 2.88kg at 2 years, compared to placebo).

Blood pressure reduction

- A 10/5 mmHg (SBP/DBP) drop in blood pressure in patients with T2D achieved a significant reduction in risk of 32% for death related to diabetes, 44% for stroke, 37% for microvascular disease and 56% in heart failure (UKPDS 38, 1998).Even an isolated SBP reduction of 12 mmHg was found to reduce the risk of stroke by 36%, MI or CV death by 17% (SHEP 1991).

- Dapagliflozin has the additional benefit of reducing blood pressure.

    - In Study 14, 38% of dapagliflozin patients who were initially hypertensive achieved a target blood pressure of 130/80 mmHg compared to 9% of placebo patients.

    - In Study 4, SBP decreased in the dapagliflozin arm compared to a small increase in the SU arm (-4.3 mmHg vs. +0.8 mmHg). A similar change was seen in DBP (-1.6 mmHg vs. -0.4 mmHg).

- In patients who were initially hypertensive (SBP >140 mmHg) greater reductions were found with dapagliflozin compared to SU (-13 mmHg vs. -8mmHg).

Patient convenience and quality of life

- Dapagliflozin can be taken once daily at any time of day with or without food.
- Dapagliflozin was associated with numerically higher patient satisfaction ratings (DTSQs* and DTSQc†) than patients taking SU (Medin et al 2011).
- In study 12, dapagliflozin treated patients maintained high QoL scores from baseline to week 24 as measured by EQ-5D and VAS (Grandy et al 2012)

*DTSQs Diabetes Treatment Satisfaction Score (status version)

†DTSQc Diabetes Treatment Satisfaction Score (change version)

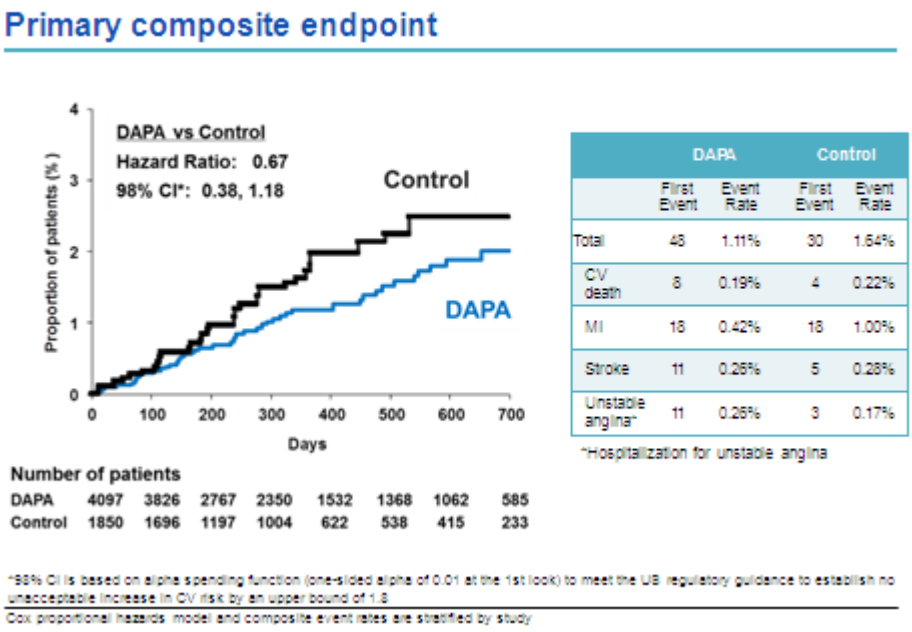
Clinical Safety

Cardiovascular safety

As part of the FDA submission process the cardiovascular safety of dapagliflozin was assessed using a pre-specified meta-analysis of all clinical studies. Fourteen studies were pooled with an average patient exposure of 1 year. Cardiovascular events were systematically identified and underwent blind independent adjudication. The primary endpoint was the composite of CV death, myocardial infarction, stroke and hospitalisation for unstable angina.

The baseline characteristics of the population were similar in the dapagliflozin and control groups with two-thirds of patients having at least two CV risk factors in addition to diabetes. The estimated hazard ratio for the primary endpoint was 0.67, suggesting there is no increase in CV risk with dapagliflozin treatment in patients with T2DM (Figure 25).

Figure 25. Kaplan-Meier curve showing probability of CV death, MIs, stroke and hospitalisation for unstable angina



	DAPA		Control	
	First Event	Event Rate	First Event	Event Rate
Total	48	1.11%	30	1.64%
CV death	8	0.19%	4	0.22%
MI	18	0.42%	18	1.00%
Stroke	11	0.26%	5	0.28%
Unstable angina*	11	0.26%	3	0.17%

*Hospitalization for unstable angina

Langkilde et al 2011

Hypoglycaemia

Dapagliflozin has a low propensity to cause hypoglycaemia. Incidences of major hypoglycaemic events were rare. Dapagliflozin has no or negligible influence on the ability to drive and use machines. No studies on the effects on the ability to drive and use machines have been performed. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

Blood pressure

Dapagliflozin is associated with blood pressure reductions. Cases of hypotension or syncope were rare and were similarly reported in dapagliflozin and comparator arms.

Urinary Tract Infections (UTIs)

The dapagliflozin mechanism of action involves urinary excretion of glucose and as such would be expected to increase the rate of UTIs. It should be noted that the patients enrolled in the dapagliflozin programme were NOT excluded on the basis of previous history of UTIs. Patients were actively monitored throughout the trials for clinical signs and symptoms suggestive of UTIs. In addition to spontaneous reports, patients were actively questioned for signs or symptoms. Reports were based on 20 definitions for upper UTI and 44 definitions for lower UTIs. This approach was comprehensive, but may encourage more reports than would be expected in normal clinical practice. However, in reality most of the events were of mild or moderate intensity, responded to routine

treatment and rarely led to treatment discontinuation. There was no clear trend in the dapagliflozin patients showing increased incidences of UTI with some trials showing similar rates to placebo.

Genital Infections (GIs)

Patients were actively monitored throughout the trials for clinical signs and symptoms suggestive of GIs. In addition to spontaneous reports, patients were actively questioned for signs or symptoms. Reports were based on 49 definitions for GI. Again, this approach was comprehensive and may also encourage more reports than would be expected in normal clinical practice. There were more reports of GIs in the dapagliflozin arms, however, most events were of mild or moderate intensity, responded to routine treatment and rarely led to treatment discontinuation.

Neoplasms

During clinical trials, the overall proportion of patients with malignant or unspecified tumors was similar between those treated with dapagliflozin (1.47%; 81/5,501) and placebo/comparator (1.35%; 43/3,184), and there was no carcinogenicity or mutagenicity signal in animal data. In addition, the SGLT2 receptor is not expressed in human breast or bladder tissue. However, imbalances were observed for breast, bladder and prostate cancers. Newly diagnosed cases of bladder cancer were reported in 9/5,501 patients (0.16%) treated with dapagliflozin and 1/3,156 patients (0.03%) treated with placebo/comparator. After excluding patients in whom exposure to study medicinal product was less than one year at the time of diagnosis of bladder cancer, there were 4 cases with dapagliflozin and no cases with placebo/comparator. Breast cancer in female patients was reported in 10/2,531 females (0.40%) treated with dapagliflozin and 3/1,359 females (0.22%) treated with placebo/comparator, all were diagnosed within one year. Prostate cancer was reported in 0.34% male patients treated with dapagliflozin and 0.16% male patients treated with placebo/comparator. After excluding patients in whom exposure to study medicinal product was less than one year at the time of diagnosis of prostate cancer, there was one case with dapagliflozin and one case with placebo/comparator. There are too few events of bladder, breast and prostate cancer to establish causality.

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The 5 main studies presented in this submission involved T2DM patients who had inadequate glycaemic control on their current stable therapy and therefore the evidence base is relevant to the decision problem of this submission, the outcomes described above are relevant to clinical practice and of benefit to patients.

The primary or key outcomes of the studies presented were:

HbA1c reduction (i.e. glycaemic control)

HbA1c is the standard measure of glycaemic control and is indicative of the short term glucose levels. Reductions in HbA1c have been shown to be associated with a lower rate of diabetic complications and cardiovascular events (UKPDS 35, 2000). Indeed, a 1% reduction in HbA1c at 10 years was associated with a:

- 21% decrease in diabetes related death
- 14% decrease in all-cause mortality
- 14% decrease in fatal and non-fatal MI
- 12% decrease in fatal and non-fatal stroke
- 37% decrease in microvascular endpoints (e.g. fatal or non-fatal renal failure)
- 43% decrease in amputation or death from peripheral vascular disease

Rates of hypoglycaemia

Severe hypoglycaemia has important clinical consequences, especially in the elderly. Up to 25% of hospital admissions associated with diabetes were due to severe hypoglycaemia (Greco & Angileri 2004). Severe hypoglycaemia is also associated with increased mortality, for example SU-induced hypoglycaemia has an estimated mortality rate of 9% (Campbell 1985). A retrospective cohort study looking at 1986-2008 showed that there was a U-shaped association with all-cause mortality and HbA1c with the lowest hazard ratio approximately at an HbA1c of 7.5% in patients who had their therapy intensified from monotherapy. It should be noted that during this period the most likely agent used for intensifying therapy would have been SUs and the authors considered that hypoglycaemia could have been a contributing factor in the increased mortality when the HbA1c of patients dropped below 7.5% (Currie et al 2010). The ACCORD study which investigated the effect of intensive glucose control to a target HbA1c of 6% was prematurely terminated because of excessive mortality, especially in patients who had experienced severe hypoglycaemia (Gerstein et al 2008).

In the UK there are 5 fatal road accidents each year and 45 serious road accidents each month as a result of hypoglycaemia (Hitchen 2006). This has recently prompted the Driver and Vehicle Licensing Agency (DVLA) to extend the rules that apply to the eligibility of patients with diabetes to drive from not only those receiving insulin but also subjects managed by SUs and glinides (DVLA Drivers Medical Group 2011). For Group 2 drivers (e.g. lorry and taxi), regular blood glucose monitoring is required at least twice a day and at times relevant to driving.

In addition, hypoglycaemia can be a significant burden on ambulance services. For example, in the East of England ambulance service's audit report, in the space of one month 365 cases of hypoglycaemia were attended to with 3 out of 4 events being dealt with on site and only 1 in 4 emergency callouts resulting in the patient being admitted to hospital. However, on average around 30 minutes more was spent dealing with patients

at the scene. The audit concludes that if all patients were taken to hospital 600 hours a year would be saved (Oosterom 2007).

Although mild symptomatic hypoglycaemia episodes are not reported to have serious clinical effects they can still have detrimental consequences such as fear of hypoglycaemia, which may in turn inhibit concordance with therapy (Amiel et al 2008).

Hypoglycaemia has been shown to have significant detrimental impact on quality of life measures, such as health-related quality of life (HRQoL), health related utility (HRU) as measured by EQ-5D (Lundkvist et al 2005). In a recent cross-sectional survey of 9 European countries, including the UK, it was found that even 2 or more non-severe episodes of hypoglycaemia had a significant detrimental effect on quality of life (as measured by ADDQoL, DTSQ and the Hypoglycaemia Fear Survey [HFS]-II) (Bradley et al 2010).

Weight loss

Patients with diabetes have a tendency to be overweight so achieving any loss in weight is beneficial to both the management of their disease and their quality of life. It has been suggested that even modest reductions in weight may be associated with health benefits, with reductions in blood pressure, cholesterol, and triglycerides achievable with just a 5-10% reduction in initial body weight (Goldstein 1992).

With regards to the NHS, it has been shown that drug prescription costs increase from a minimum in patients with a BMI of 20kg/m^2 from a mean £50-60 per annum, rising sharply to £160-200 per annum in patients above a BMI of 40kg/m^2 (Counterweight project team 2008).

Unfortunately weight gain can be a consequence of diabetes treatments *per se*. In this regard SUs have a particular propensity to cause hypoglycaemia, prompting defensive snacking to alleviate symptoms and thus causing further weight gain. A similar issue occurs with insulin and TZDs, which are associated with hypoglycaemia, decreased glucosuria, decreased basal metabolic rate, expansion of adipose tissue and fluid retention. It is estimated that, whilst on these agents, for every 1% decrease in HbA1c there would be a 2kg gain in weight (Sesti 2011).

Thus any therapies that alleviate weight gain and minimise potential progression to more expensive therapies (e.g. GLP-1 analogues, weight-loss clinic, bariatric surgery) can only benefit the patient and the NHS.

Blood pressure

Blood pressure control is a cornerstone of cardiovascular risk management. A 10/5 mmHg (SBP/DBP) drop in blood pressure in patients with T2DM achieved a significant reduction in risk of 32% for death related to diabetes, 44% for stroke, 37% for microvascular disease and 56% in heart failure (UKPDS 38, 1998).Even an isolated systolic blood pressure reduction of 12 mmHg was found to reduce the risk of stroke by 36%, MI or CV death by 17% (SHEP 1991).

Reduction in insulin requirements

Nearly one in four patients with T2DM will require insulin treatment. Patients inadequately controlled despite substantial doses of insulin are particularly challenging to treat due to the increasing risk of weight gain, hypoglycaemia, fluid retention and congestive heart failure (Wilding et al 2012). In addition, patients at this disease stage are likely to have little residual β-cell function, limiting therapeutic options.

The treatment aims in these patients involve not only glycaemic control but also balancing reduction in hypoglycaemia and weight. Introducing an agent that acts in an insulin-independent way would help to improve all of these parameters, mainly through an insulin sparing effect (i.e. reduction in daily insulin requirements).

All of the clinical evidence presented in this submission supports the licensed, recommended dose for dapagliflozin of 10 mg once a day. The 5 mg dose was also investigated in the clinical studies.

5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Renal impairment

The efficacy of dapagliflozin is dependent on renal function. Dapagliflozin is not recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m2). No dosage adjustment is indicated in patients with mild renal impairment.

Patients at risk of volume depletion and/or electrolyte imbalances

Dapagliflozin is not recommended for patients receiving loop diuretics. Dapagliflozin is also not recommended for initiation of therapy in patients who are volume depleted

Hepatic impairment

No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg.

Urinary tract infections

Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis.

Elderly (≥ 65 years)

In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account. Due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended.

All of the clinical evidence presented in this submission supports the licensed, recommended dose for dapagliflozin of 10 mg once a day. The 5 mg dose was also investigated in the clinical studies

6 Cost-effectiveness

Summary

Key findings from the dapagliflozin economic analysis:

- Dapagliflozin is the first of a new class of oral antidiabetic drug (SGLT2) that has the added benefit over other OADs used in clinical practice of reducing T2DM patient body weight. There is clinical evidence supporting maintained weight control over a 2 year follow-up period although it is plausible to expect that weight control will be sustained beyond the period of data collection (see section 5).
- For patients whose T2DM is not well controlled with metformin alone, or with insulin (with or without OADs), dapagliflozin in combination with metformin and insulin was shown to be cost-effective compared to current therapies.
    - In dual therapy, as an add-on to metformin therapy dapagliflozin is cost-effective compared to SU with an incremental cost per QALY gained of £2.7K, and 'dominates' the DPP-4 and TZD classes.
    - In the dual therapy setting, probabilistic sensitivity analysis indicates a 100% probability of dapagliflozin being considered cost-effective compared to SU and versus TZD, and 66% probability versus DPP-4 at a willingness to pay of £20,000/QALY.
    - As an add-on to insulin, dapagliflozin is associated with an incremental cost per QALY gained of £4.4K vs. DPP-4 class, and a probability of cost-effectiveness at a willingness to pay of £20,000/QALY of 99.6%.
- The key driver of these cost-effectiveness results is the relative QALY gain vs the comparators associated with superior weight control of dapagliflozin and the benefit that has on patient quality of life as well as well as reducing risks of long term CV complications.
- In addition, there are modest cost-offsets and utility gains associated with a marginally favourable overall reduction in T2DM complications over a 40 year model time horizon.
- The results are based on clinical trial data (direct and indirect) that can be considered generalisable to England and Wales.

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

A systematic search and review covering economic evaluations of relevance to a UK context for drug interventions for T2DM (including dapagliflozin and comparator drugs) was performed. The search was driven by the decision problem set out in the draft NICE scope for the appraisal of dapagliflozin that was available at the time of the search (October 2011). This provided the context for the systematic search by specifying the patient populations covered, comparators to dapagliflozin, outcomes of interest, economic outcomes and other considerations.

To avoid running three separate searches, a single comprehensive search strategy was developed to cover the identification of relevant cost-effectiveness studies (this section), as well as health measurement/valuation (i.e. utility) studies (Section 6.4.5 and Section 6.4.6), and resource utilisation studies (Section 6.5.3).

The search for economic evaluations was based on addressing the following review question:

"What evidence exists for the cost-effectiveness of dapagliflozin, or relevant comparators for specific T2DM patient populations from a UK healthcare perspective?"

The key inclusion criteria for the search covered:

- Any full economic evaluation: cost-utility, cost-effectiveness, cost-benefit, cost-minimisation conducted in a UK specific setting.
- In order to match the patient populations covered by the dapagliflozin economic model presented in this submission, the search included the following indications within the dapagliflozin licence:
    - **Dual therapy, with any of the following used as an add-on to metformin** (or background therapy): dapagliflozin, SUs, Pioglitazone (a TZD), DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin), GLP-1 (liraglutide, exenatide), insulin and insulin analogues, in adults with T2DM.
    - **Add-on therapy to insulin** with one of: dapagliflozin, pioglitazone, a DPP-4 inhibitor or a GLP-1 analogue.

Further details of the single comprehensive search strategy (databases searched -, electronic and non-electronic, search strategies, additional exclusion criteria, data extraction strategy) are provided in Section 9.10.

6.1.2 Description of identified studies

There were no published economic evaluations identified from the search covering dapagliflozin in T2DM (either for the UK or any other country context). In total 4 economic evaluations that reported cost per QALY outcomes in a UK context for therapy as an add-on to metformin (i.e. dual therapy) were identified, and no relevant UK economic evaluations for add-on to insulin therapy were identified. A brief overview of the methods and results of the four selected dual therapy evaluations are presented in Table 54. An economic analysis using the UKPDS health outcomes model performed by Waugh et al (2010) to support the development of the NICE clinical guideline on new drugs for T2DM (NICE Clinical Guideline 87, 2009) performed assessments of the GLP-1 analogues exenatide vs. insulin (glargine), and the DPP-4 inhibitors sitagliptin and vildagliptin vs. TZDs, but in the context of third line therapy when patients had failed on metformin and an SU (Waugh et al 2010). Hence, this analysis was not included in the review of cost-effectiveness evaluations. The manufacturer of liraglutide (a GLP-1 analogue) performed an economic evaluation of the liraglutide as part of dual therapy for their STA submission to NICE, which was reviewed by the NICE ERG (Cummins et al 2009). However, as the review did not cover unpublished economic analyses from manufacturer submissions we have not included this in the studies in Table 54.

The key findings from the four dual therapy evaluations included in the review were:

- All the studies adopted a lifetime horizon and used the UKPDS risk equations to estimate long run outcomes associated with the incidence of complications.

- Two of the studies used the CORE model, and one the JADE model that had been previously published.

- Two of the studies found pioglitazone to be cost-effective (based on UK thresholds of cost-effectiveness) compared to placebo, or an alternative TZD rosiglitazone (although this TZD no longer has marketing authorisation) (Valentine et al 2007, Tilden et al 2007).

- One study found sitagliptin (a DPP-4 inhibitor) to be cost-effective compared to rosiglitazone or SU (Schwarz et al 2008), and the other found liraglutide (a GLP-1 analogue) to be cost-effective vs. SU or sitagliptin (Davies et al 2011).

- All studies appear to be manufacturer-sponsored.

As no relevant economic evaluations for dapagliflozin were identified a de novo economic evaluation was performed using a different model than used previously in economic evaluations of dual therapy as presented in Table 54. However, the model used is based on a validated (Mount Hood 4 Modelling Group, 2007) and previously published model (Woehl et al 2008, McEwan et al 2010), which like all the other studies reviewed also uses the UKPDS outcomes data as the basis for estimating long term complications associated with T2DM (Clarke et al 2004, Palmer et al 2004, Chen et al 2008, Schwarz et al 2008). The details of the dapagliflozin model are presented in Section 6.2 onwards.

Table 54: Summary list of cost-effectiveness evaluations identified for dual therapy, and add-on to insulin therapy

Study and year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
DUAL THERAPY (add on to metformin)					
Valentine 2007	Existing Markov based simulation model –the CORE diabetes model – used to compare: **Pioglitazone (TZD) as an add-on to current background therapy vs. p**lacebo (current therapy alone). **Time horizon**: 36 months trial with simulation to lifetime (35 years) **Perspective:** healthcare **Time horizon**: 40 years **Discount rate:** 3.5%	PROactive study: 5,238 patients with Type 2 diabetes with an established history of macrovascular disease, and inadequate glycaemic control on met alone Mean age: 61.8 yrs	**Mean QALY per patient:** Pioglitazone: 8.54 Placebo: 8.38	**Mean costs per patient** (drugs, complications, AEs)**:** Pioglitazone: £67,863 Placebo: £67,244 **Price year**: 2005	ICER for pioglitazone vs placebo= £4,060 **PSA** demonstrated a 79.5% probability of cost-effectiveness at a threshold of £20K/QALY
Tilden, 2007	A new Markov based simulation model utilising UKPDS data was developed to compare: **Pioglitazone (TZD) as an add-on to metformin vs**, rosiglitazone (TZD) as an add-on to metformin **Perspective:** healthcare **Time horizon**: Lifetime (max 100years age) **Discount rate:** 3.5%	Simulated cohort of T2DM patients from an RCT (n=802) with inadequate glycaemic control on metformin. 10,000 simulations run for Caucasian males aged 56	**Mean QALY s per patient:** Pioglitazone: 8.833 Rosiglitazone: 8.793	**Mean costs per patient** (drugs, complications)**:** Pioglitazone: £9,585 Rosiglitazone: £10,299 **Price year**: 2004/05	**ICERs:** Pioglitazone+met 'dominates' rosiglitazone+met **PSA** not performed (only one way sensitivity analysis).

Study and year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Schwarz et al, 2008	A discrete event simulation model- the Januvia Diabetes Economic (JADE) model, was used to compare: **Sitagliptin (DPP-4) (as add on to Metformin)** vs. A. Rosiglitazone (TZD) (as add-on to Metformin) B. SU (as add on to Metformin) In a and b after failing / intolerance on sitagliptin or SU, basal insulin is co-administered with Metformin. C. As b), but rosiglitazone is co-administered with metformin after sitagliptin or SU failure/intolerance. **Perspective:** healthcare **Time-horizon**: Lifetime **Discount rate:** 3.5%	Simulated cohort of 50,000 patients with T2DM, utilising the UKPDS Outcomes Model risk equations for diabetes-related complications Publication covered 6 European countries, including UK (Scotland) – results here reported for UK only. Mean age: 64.9 years	**Mean incremental QALYs per patient reported** **Comparisons:** A) 0.016 QALYs **B)** 0.095 QALYs **C)** 0.103 QALYs	**Mean incremental costs per patient in Euros** (drugs, complications, AEs) **Comparisons:** **A)** €36 **B)** **€**1,097 **C)** **€**1,109 **Price year**: 2007	**ICERs:** **A)** €2,250 **B)** €11,547 **C)** €10,767 **PSA** not performed (only one way sensitivity analysis)
Davies 2011	An existing Markov based simulation model (CORE Diabetes Model) used to compare: **Comparison A:** Liraglutide (1.2 or 1.8 mg) (GLP-1) as an add-on to metformin vs. Glimepiride (SU) as an add-on to metformin. **Comparison B:** Liraglutide (1.2 or 1.8 mg) (GLP-1) as an add-on to metformin vs. Sitagliptin (DPP-4) as an add-on to metformin. **Perspective:** healthcare **Time horizon**: Lifetime **Discount rate:** 3.5%	Simulated cohort of 1,000 T2DM patients with inadequate glycaemic control on met alone **A**: Liraglutide vs. Glimepiride mean age: 55.8yrs **B**:Liraglutide vs. sitagliptin mean age: 55.3yrs	**Mean QALY s per patient:** **A**: Liraglutide 1.2 mg; 7.76 Liraglutide 1.8 mg: 7.73 Glimepiride: 7.44 **B:** Liraglutide 1.2 mg: 7.52 Liraglutide 1.8 mg: 7.64 sitagliptin: 7.34	**Mean costs per patient** (drugs, complications, AEs)**:** **A:** Liraglutide 1.2mg: £22,122 Liraglutide 1.8 mg: £23,807 Glimepiride: £19,119 **B:** Liraglutide 1.2 mg: £21,793 Liraglutide 1.8 mg: £23,175 Sitagliptin: £19,951 **Price year**: 2008	**ICERs:** **A:** Liraglutide 1.2mg =£9,449 Liraglutide 1.8 mg=£16,501 **PSA=**88% and 65% probability of Lira cost-effective at £20K/QALY for the 1.2mg and 1.8mg doses respectively. **B:** Liraglutide 1.2mg = £9,851 Liraglutide 1.8 mg =£10,465 **PSA=**77% and 85% probability of Lira cost-effective at £20K/QALY for the 1.2mg and 1.8mg doses respectively.

Abbreviations: ICER, Incremental cost-effectiveness ratio, QALY(s), Quality-adjusted life year(s).

6.1.3 Quality assessment

Although there are no published economic evaluations for dapagliflozin, a quality assessment of the four UK dual therapy economic evaluations in T2DM identified from the search are presented in Appendix 11 (Section 9.11) using the suggested format. This shows that the evaluations are generally of a reasonable standard in terms of model structure and methodology. However, there are some limitations across studies in terms of transparency, for example none of the studies presented disaggregated outcomes (Q32 in Table 110) or separated resource use and unit costs (except Valentine et al 2007, Q16 in Table 110). This may have been related to constraints on manuscript length imposed by the journal.

6.2 De novo analysis

6.2.1 Patients

In line with the licensed indication, the economic evaluation consists of analyses of the cost-effectiveness of dapagliflozin in adults aged 18 years and older with T2DM. Dapagliflozin has a licence in mono- and combination therapy (see Section 1.5). However, this economic evaluation is to support the use of dapagliflozin in clinical practice in England and Wales as follows:

1. Use in dual therapy as an add-on to metformin, compared to the current treatment option of a) SU ,or b) DPP-4s or TZD (pioglitazone), in T2DM patients for whom metformin alone (with diet and exercise) does not provide adequate glycaemic control.

2. Use as add-on to insulin (with or without other OADs), compared to DPP-4s when the underlying treatment regimen including insulin does not provide adequate glycaemic control.

The populations considered represent the most likely use in clinical practice for dapagliflozin. Hence the use of dapagliflozin in the monotherapy setting is not considered, given clinical guidelines (CG87) recommend first line use of metformin in addition to diet and exercise. Of particular concern with SUs are the risk of hypoglycaemia, and potential weight gain. Dapagliflozin is the first drug of a new class of OAD (SGLT-2 inhibitor) that is associated with a low risk of hypoglycaemia and has weight loss properties, hence represents an alternative option to SU on this basis. Dapagliflozin has also been compared to DPP-4 and TZDs which are used in practice as dual therapy with metformin, often if SUs are contraindicated. As add-on to insulin therapy the predominant type of therapy used in clinical practice is a DPP-4 inhibitor.

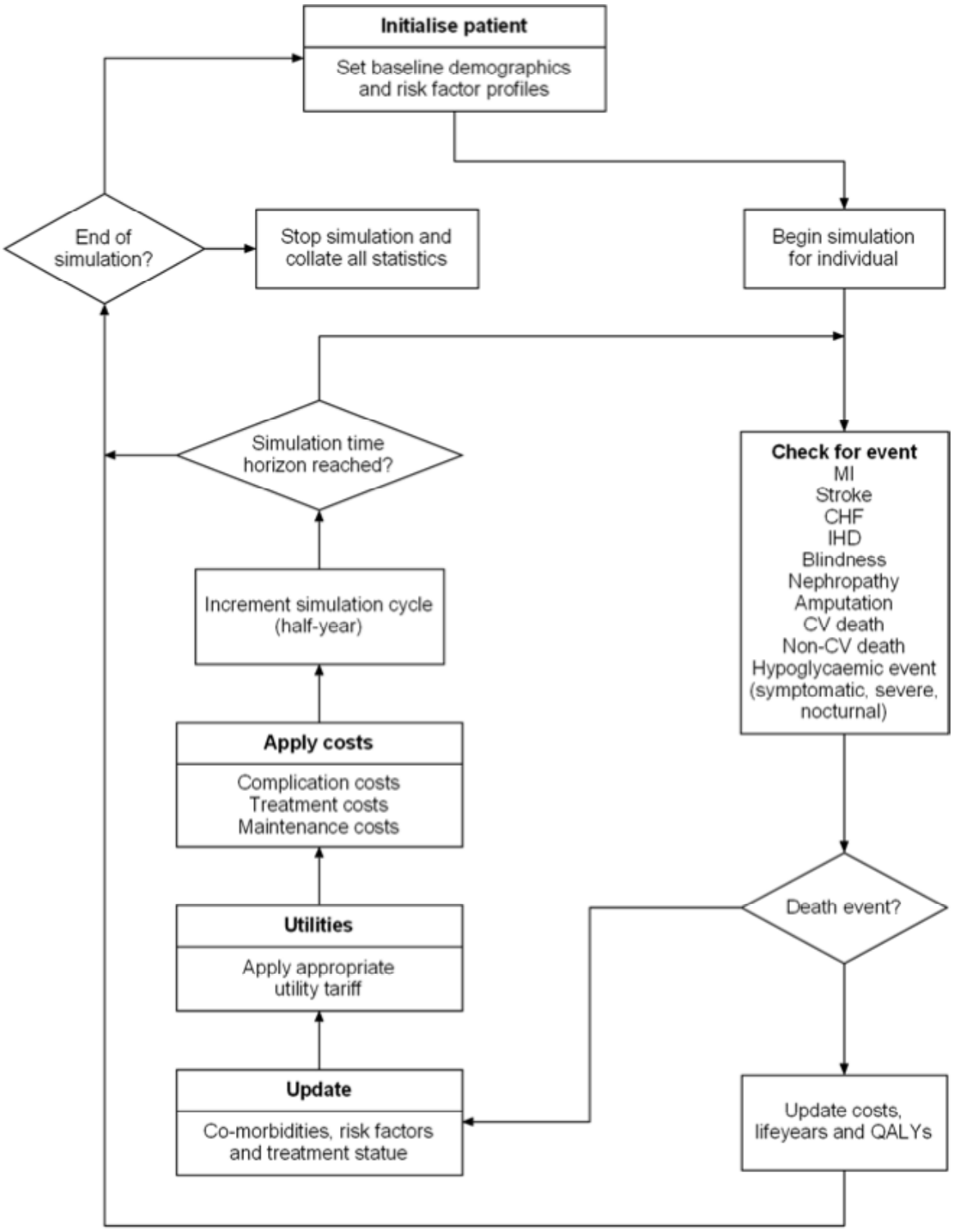
Phase 3 randomised controlled studies have been performed for dapagliflozin in the situations considered here (including a comparative non-inferiority study vs. SU in dual therapy).

Model structure

6.2.2 Model schematic

A flow diagram of the dapagliflozin cost-effectiveness model is presented in Figure 26.

Figure 26. Flow diagram of the dapagliflozin cost-effectiveness model



Abbreviations: CHF, congestive heart failure; CV, cardiovascular; IHD, ischaemic heart disease; MI, myocardial infarction; QALYs ,quality-adjusted life years.

6.2.3 Justification of model structure

T2DM is a condition characterised by excess micro- and macro-vascular morbidity and mortality and blood glucose control forms a central feature of risk factor management in patients with T2DM. Current evidence and guidelines advocate the attainment of sustained near normal glycaemia levels (Nathan et al 2009). Based on the UKPDS, metformin is widely accepted as the treatment of choice for the initiation of pharmacotherapy in T2DM; however, secondary failure of oral monotherapy with metformin occurs in 60% of patients [Monami et al 2009], resulting in the need for multiple pharmacotherapy and eventually insulin initiation. In recent years, a variety of anti-diabetes agents (TZDs, DPP-4 inhibitors, GLP-1 analogues) have been introduced into clinical practice. The current T2DM clinical guideline issued by NICE advocates a stepwise failure-driven therapy algorithm for blood-glucose lowering that leads to the sequential addition of therapies (NICE clinical guideline 87). Initial lifestyle modification is followed by initiation of oral monotherapy and subsequent dual combination therapy if adequate glycaemic control is not achieved. The various therapies do not only have a therapeutic effect on HbA1c, and on other modifiable risk factors such as blood pressure and lipids, but they also have adverse effects, such as weight gain and hypoglycaemia.

The economic evaluation utilises a discrete event simulation (DES) model run within an Excel front-end (McEwan et al 2010). The simulation uses C++ programming compiled into dll format. The model is similar to other established diabetes models used in the UK previously with NICE and/or published (e.g. the UKPDS Health Outcomes model (Clarke 2004), the CORE model (Palmer 2004), and the JADE model (Chen 2008, Schwartz 2008), in that it utilises UKPDS 68 derived risk equations to estimate long run micro- and macro-vascular complications, diabetes and non-diabetes mortality, and time paths for risk factors such as HbA1c and systolic blood pressure (Clarke 2004). The model has the advantage of reflecting clinical reality to a greater extent than the UKPDS outcomes model as it allows diabetes treatment sequences to be modelled.

The patient cohort enters the model with a set of baseline characteristics and modifiable risk factors for long run micro and macrovascular complications. The modifiable risk factors in the model are as follows: HbA1c, total body weight, total cholesterol (TC), high density lipoprotein (HDL) cholesterol (total:HDL cholesterol) and SBP. The value of these variables will change as the model simulation progresses, through treatment effects and through natural progression, based on using UKPDS risk equations.

The model predicts the incidence of specific macro and micro-vascular complications utilising the UKPDS health outcomes risk equations. In total, seven diabetes complications are included in the model, and non-CV death.

Macro-vascular events predicted in the model are:

- ischaemic heart disease (IHD);
- myocardial infarction (MI);
- congestive heart failure (CHF);
- stroke.

Micro-vascular events predicted in the model are:

- amputation;
- nephropathy;
- blindness

The risks associated with patient clinical history can be considered in the model by defining the proportion of patients who have previously experienced each of the complications.

The model also captures the probability of drug related hypoglycaemic events, and other specified AEs. Treatment effect estimates for dapagliflozin and comparators for HbA1c, SBP and lipids are applied for the first year after treatment initiation. Patients in the intervention and comparator groups are simulated through the model in 6 month cycles. The model simulates a cohort of patients with T2DM over the 40-year time horizon. For the dapagliflozin economic analysis the cohort size was 30,000 patients to ensure stability in the simulation results. At the end of the first six month cycle, the UKPDS risk equations determine the occurrence of the fatal and non-fatal complications, with the order in which these events occur generated randomly within the model. In addition, non-cardiovascular (all-cause) and direct diabetes deaths are estimated also based on risk equations from UKPDS 68 (Clarke 2004). If the patient survives beyond the first cycle they transition to the next cycle whereby they remain at risk of treatment related AEs and long run complications. Once a fatal event or death from other causes occurs, life years and QALYs are updated and the simulation ends for that patient. Although the model has the capacity to include secondary events, due to a lack of data and to reduce complexity, only the absolute risk of the first event is estimated (in line with other diabetes economic evaluations, e.g. Schwarz et al 2008).

6.2.4 Definition of health states

The following health states outcomes are included in the model are intended in order to capture the micro- and macro-vascular morbidity and mortality associated with the disease progression of T2DM:

- T2DM without complications
- T2DM with one or more of the following diabetes-related complications:
    - IHD (non-fatal)
    - MI (fatal or non-fatal)
    - CHF (fatal or non-fatal)
    - stroke (fatal or non-fatal)
    - amputation (fatal or non-fatal)
    - blindness (non-fatal)
    - end stage renal disease (non-fatal)
- Death (non-specific, i.e. not caused by diabetes-related complications)

Treatment-related AEs are included in the model to capture the costs and reduced quality of life due to side effects. All the antidiabetic drugs considered have an impact on patient body weight whilst on treatment. Change in total body weight and its impact on BMI is incorporated in the model in terms of risk of CV complications, but also has a direct HRQoL impact based on data showing an association between BMI and utilities in patients with T2DM (Section 6.4). In addition, the impact on HRQoL of treatment-related hypoglycaemic events associated with fear of hypoglycaemia, and specific AEs of urinary tract infection and genital infection related to the dapagliflozin mechanism of action, are included in the model.

6.2.5 Context

An overview of T2DM and the course of the disease is presented in Section 2.1. T2DM is a progressive metabolic disorder characterised by an impaired response to insulin and a progressive deterioration in the capacity to secrete endogenous insulin resulting in chronic hyperglycaemia. As a consequence of elevated levels of glucose in the blood, diabetes-related complications including cardiovascular disease, renal disease and retinopathy develop at later stages of disease progression. The symptoms of T2DM typically become manifest during middle age and are often associated with excess body weight that further worsens patient prognosis. Lower blood glucose levels, as reflected by HbA1c, were associated with reduced incidence of diabetes-related complications. Based on the strength of this evidence, achieving good glycaemic control has become a cornerstone of risk factor management in patients with T2DM.

The model captures the progressive nature of T2DM by an underlying progressive deterioration in the capacity to secrete endogenous insulin which is reflected in a gradual increase in HbA1c over time. In addition to HbA1c, the model incorporates other factors associated with T2DM that impact upon the risk of occurrence of micro- and macro-vascular events, namely, TC:HDL-C ratio and SBP. The value of these variables will change as the model simulation progresses, through treatment effects and through natural progression. The risk of events will change likewise reflecting the changes in these variables.

The economic model is able to accommodate up to two additional therapy lines after dapagliflozin and the comparator for the add-on to metformin and add-on to insulin analyses. The simulation consists of a cohort of patients who receive dapagliflozin (the ‘treatment’ cohort), and a cohort with the same baseline characteristics who receive comparator treatments (the ‘comparator’ cohort). Simulated patients in each cohort will receive a particular therapy until their HbA1c increases to cross a specified threshold which represents inadequate glycaemic control, at which point they cease receiving that therapy and move on to the next therapy (Section 6.2.8).

6.2.6 Key features of the economic evaluation

The key features of the economic evaluation are presented in **Table 55**.

Table 55. Key features of analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (maximum of 40 years)	T2DM is a chronic, progressive disease. Treatments have impacts on costs and outcomes over a patient's lifetime.
Cycle length	0.5 year	Standard duration of trial follow-up and treatment decisions.
Half-cycle correction	The model does not use half-cycle correction	The cycle length (6 monthly) is sufficiently small
Were health effects measured in QALYs; if not, what was used?	Yes	As in the NICE Guide to the methods of Technology Appraisal (2008)
Discount of 3.5% for utilities and costs	Yes	As in the NICE Guide to the methods of Technology Appraisal (2008)
Perspective (NHS/PSS)	NHS/PSS	As in the NICE Guide to the methods of Technology Appraisal (2008)

Abbreviations: NHS, National Health Service; PSS, Personal Social Services; QALYs, Quality-adjusted life years.

Technology

6.2.7 Intervention and comparator

The intervention and comparator(s) are implemented in the model as per their marketing authorisations/CE marking and doses as stated in Section 1.3 and Section 1.5.

6.2.8 Treatment continuation rule

For the T2DM patient population for whom metformin provides inadequate glycaemic control, the first modelled therapy line is dapagliflozin 10mg daily + metformin in the treatment cohort or a comparator OAD (SU, DPP-4 or TZD) plus metformin in the comparator cohort. Second line therapy is the same for both treatment arms and is assumed to consist of metformin plus insulin, and third line treatment is assumed to be intensified insulin (assumed to be a 50% increase in dose over the initial dose used when starting insulin treatment). Patients then remain on this therapy for the remainder of the simulation.

For the T2DM patient population for whom insulin provides inadequate glycaemic control, two therapy lines are modelled: dapagliflozin as an add-on to insulin in the treatment cohort, or insulin plus a DPP-4 inhibitor in the comparator cohort as the first modelled line, followed by intensified insulin in both treatment arms for the remainder of the simulation.

The decision to switch treatment regimens is based on patients reaching a defined HbA1c threshold, representing the point at which the current treatment is assumed to be no longer providing sufficient glycaemic control. The base case values used in the dapagliflozin analyses were the average HbA1c value at baseline from the phase 3 trials and NMAs of dapagliflozin versus comparators in the add-on to metformin and add-on to insulin positions. A list of baseline patient characteristics and risk factors used in add-on to metformin and add-on to insulin analyses is provided in Table 56. Age, duration of diabetes and modifiable risk factor parameters change as the simulation progresses due either to treatment effects or natural progression (Table 56).

Although in clinical practice it may not be expected that treatment switching thresholds will necessarily vary according to the drug concerned, we have used the trial/NMA based values in order to be consistent with the source used for treatment efficacy in the model. The impact of alternative higher and lower single level thresholds have been explored in sensitivity analysis. NICE clinical guidelines specify a relatively low threshold of 7.5% for switching treatment (NICE Clinical Guideline 87) – hence, this value has also been included as part of sensitivity analysis on the threshold values for the add-on to metformin analysis.

Table 56. Base case HbA1c thresholds for switching to the next line of therapy

Comparison	HbA1c threshold (%)	Source
Add-on to MET		
Comparison with SU		
vs SU	7.72	Nauck, 2011
Comparison with DPP-4, TZD		
vs DPP-4	8.17	NMA add-on to MET (see Section 5.7) †
vs TZD	8.17	NMA add-on to MET (see Section 5.7) †
Add-on to INS		
vs DPP-4	8.90	NMA add-on to INS (see Section 5.7) ‡

Abbreviations: DPP-4, dipeptidyl peptidase 4 inhibitor; INS, insulin; MET, metformin; NMA, network meta-analysis; SU, sulphonylurea; TZD, thiazolidinedione.
† Excel file BMS Dapagliflozin Model Inputs (April 18) KB
‡ Excel file BMS Dapagliflozin Model Inputs (April 13) insulin

6.3 Clinical parameters and variables

6.3.1 How were clinical data implemented in the model?

Clinical data from appropriate dapagliflozin RCTs and NMAs informed the following parameters in the model:

- baseline demographics and risk factors;
- treatment effects: change in HbA1c from baseline, change in weight from baseline, change in SBP, TC, and HDL-C from baseline;
- hypoglycaemia: probability of a severe event, number of symptomatic events;
- other adverse event rates: UTI, GI
- treatment discontinuation rates.

The clinical input data in the comparison of MET+dapagliflozin versus MET+SU were sourced from the head-to-head RCT of dapagliflozin vs glipizide (Study Code D1690C00004; Nauck et al 2011a, 2011b; see Section 5.5). Values applied in the comparisons with MET+DPP-4 and MET+TZD were taken from a NMA of RCTs of anti-diabetic agents added-on to metformin (see Section 5.7). Two separate analyses were performed within the NMA: one including 24-week RCT data, and one including 52-week RCT data. The 24-week NMA data were chosen as the base case, as this was regarded as the more complete and more robust. The 52 week NMA data were used in a scenario analysis. The clinical input data for the add-on to INS analysis were sourced from a NMA that included 24-week data from RCTs of dapagliflozin and DPP-4, as add-on to INS therapies (see Section 5.7).

Mean baseline demographics and risk factors from the clinical sources were used to generate a demographic and risk factor profile for the patient cohort of interest entering the model simulation. Risk factor profiles were adjusted at initiation of a particular therapy to reflect treatment effects that were determined in the relevant clinical source. In addition, the probability or rate of experiencing a hypoglycaemic or other AE associated with a particular therapy were applied to patients receiving that therapy in the model.

6.3.2 Transition probabilities

As the model is a discrete event simulation model, transition probabilities as applied in conventional Markov models were not calculated. Instead, the occurrence of the seven diabetes-related complications and death is estimated using the risk equations of the UKPDS 68 Outcomes Model (Clarke, 2004). The UKPDS health outcomes risk equations were derived using Weibull proportional hazards models utilising data for a cohort of 5,102 diabetic patients, aged 25 – 65 years in the UK (UKPDS 1998). From this, equations for the ten year risk of ischemic heart disease, coronary heart failure, stroke and MI were developed.

6.3.3 Variation of transition probabilities over time

In the simulation model the risk of occurrence of micro- or macro-vascular events in the model varies over time, dependent on levels of HbA1c, SBP, TC:HDL-C, and body weight and a set of baseline characteristics (see Section 6.3.6).

6.3.4 Linking intermediate outcome measures to final outcomes

Intermediate outcome measures (i.e. the modifiable risk factors) were linked to final clinical outcomes (i.e. micro- and macro-vascular fatal and non-fatal events) based on the UKPDS 68 risk equations (Clarke, 2004). This is standard in most of the validated economic models in diabetes (see also Section 6.1.2).

6.3.5 Clinical experts

Clinical experts were not directly used to supply or verify values for parameters used in the economic model. However, a number of advisory boards were held with clinical and health economic experts at which the model and the input parameters were discussed in order to strengthen the model and analyses. The experts were asked to consider the clinical information included in the model (comparators, outcomes, treatment pathway), the economic data included in the model (data sources, model approach, health states) and the comparability of the results of the model (clinical outcomes) with those from other economic models.

Summary of selected values

6.3.6 Summary list of variables used

A list of baseline patient characteristics and risk factors used in add-on to metformin and add-on to insulin analyses is provided in Table 57. Age, duration of diabetes and modifiable risk factor parameters change as the simulation progresses due either to treatment effects or natural progression

Table 57. Summary of variables applied in the economic model

Input parameter	Add-on to MET			Add-on to INS
	vs SU †	vs DPP-4 ‡	vs TZD ‡	vs DPP-4 §
Baseline demographics				
Current Age (yrs)	58.4	55.16	55.16	57.8
Proportion female	0.449	0.442	0.442	0.53
Duration diabetes (yrs)	6.32	5.03	5.03	12.8
Height (m)	1.67	1.70	1.70	1.675
Proportion AC	0.062	0.062	0.062	0.062
Proportion smokers	0.176	0.55	0.55	0.176
Modifiable risk factors				
HbA1c (%)	7.72	8.17	8.17	8.9
Total-Cholesterol (mg/dL)	182.54	185	185	195.04
HDL Cholesterol (mg/dL)	45.87	45.53	45.53	45.07
SBP (mmHg)	133.3	133.83	133.83	134.5
Weight (kg)	88.02	90.14	90.14	91.4
Reference to section in the submission	Study 4 Section 5.3.4	NMA add-on to MET, Section 5.7		NMA add-on to INS, Section 5.7

Abbreviations: AC, Afro-Caribbean; DPP-4, dipeptidyl peptidase 4 inhibitor; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; INS, insulin; MET, metformin; n/a, not available; NMA, network meta-analysis; SBP, systolic blood pressure; SU, sulphonylurea; TZD, thiazolidinedione.
† Values were sourced from Nauck, 2011, except for proportion of smokers which was taken from the Clinical Study Report of Study 4.
‡ Values were based on a NMA that included 24-week data of randomised controlled trials of anti-diabetic agents as add-on to MET, except for proportion AC which was not available. For this, the value from Nauck, 2011, was taken.
§ Values were based on a NMA that included 24-week data of randomised controlled trials of anti-diabetic agents as add-on to INS, except for proportion AC and proportion smokers which was not available. For these parameters, the same values as in the comparison vs SU add-on to MET were taken.

In scenario analysis, the impact on the cost-effectiveness results of using alternative baseline characteristics derived from a published UK observational study in T2DM was explored (Alvarez-Guisasola et al 2008) (see Section 6.6.2).

As no data were available for prior macro or micro vascular complications from the RCTs or NMA these values were set to zero in the base case. To explore the potential impact of assuming a prior history of such complications in a proportion of patients a scenario analysis was performed in which prevalence estimates where available for clinical history parameters derived from a UK general practice database were used (see Section 6.6.2).

A summary of treatment effect and AE parameters applied for each treatment in the model are listed in Table 58, followed by a description of the data inputs used.

Table 58. Treatment effects and AE parameters applied in the economic model

Variable	Source	Change from baseline *					Prob. Discontinuation #	No. of hypo (sympt)^	Prob. Hypo (severe) ^	Prob.UTI ^	Prob.GI ^
		HbA1c (%)	Weight (kg)	TC (mg/dL)	HDL-C (mg/dL)	SBP (mmHg)					
First therapy line											
Add-on to MET											
SU	Nauck, 2011	-0.52	+1.44	-0.028	-0.002	+0.8	0.059	0.408	0.00735	0.064	0.027
Dapagliflozin	Nauck, 2011	-0.52	-3.22	+0.071	+0.07	-4.3	0.091	0.035	0.000	0.108	0.123
DPP-4	NMA add-on to MET, Section 5.7 †	-0.74	-0.51	0**	0**	-1.37	0.031	0.049	0.00005	0.052	0.005
TZD		-0.90	+1.72	0**	0**	-2.87	0.060	0.023	0.000024	0**	0**
Dapagliflozin		-0.58	-2.79	0**	0**	-4.5	0.022	0.075	0.000077	0.067	0.089
Add-on to INS											
DPP-4	NMA add-on to INS, Section 5.7 ‡	-0.69	+0.19	0**	0**	0**	0**	1.44	0.007	0.063	0.003
Dapagliflozin		-0.82	-1.63	0**	0**	0**	0**	1.4	0.0068	0.056	0.092
Parameters used for 2nd or 3rd therapy lines for each comparison											
MET+INS	Monami, 2008	-1.1	+1.084	0**	0**	0**	0**	0.0108	0.037	0**	0**
Intensified INS	NICE HTA report Ch.4 (Waugh, 2010)	-1.11	+1.9^^	0**	0**	0**	0**	0.616	0.022	0**	0**

Abbreviations: DPP-4, dipeptidyl peptidase 4 inhibitor; GI, genital infection; HbA1c, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; hypo, hypoglycaemia; MET, metformin; NMA, network meta-analysis; SBP, systolic blood pressure; SGLT2, sodium-glucose co-transporter 2 inhibitor (dapagliflozin); SU, sulphonylurea; sympt, symptomatic; TC, total cholesterol; TZD, thiazolidinedione; UTI, urinary tract infection.

* Effects apply to the first year after treatment initiation. Absolute change from baseline values were applied in the model.

** No estimate available and/or zero value assumed.

Probability of treatment discontinuation due to adverse events was applied during the first model cycle (= first 6 months).

^ Probabilities of adverse events were applied during every model cycle; ^^ Weight change from Montanana, 2008, chosen as most recent study reporting weight effect included in the NICE HTA report

† Excel file BMS Dapagliflozin Model Inputs (April 18) KB; ‡ Excel file BMS Dapagliflozin Model Inputs (April 13) insulin

The modifiable risk factors

The treatment effects of dapagliflozin and SU (glipizide) as an add-on to metformin are derived from the comparative 52 week non-inferiority study comparing dapagliflozin and SU (Nauck et al 2011a, 2011b). The absolute treatment effects for dapagliflozin, DPP-4 and TZD in the add-on to metformin assessment, and for dapagliflozin and DPP-4 in the add-on to insulin assessment, have been derived from indirect comparisons performed using Bayesian NMA. Separate NMAs were performed for dapagliflozin vs. these comparators for add-on to metformin, and for add-on to insulin analyses

To increase the amount of data available for the NMAs, comparator drugs were considered as drug classes for the purposes of treatment effect assessment. In the base case the best fitting random effects models were used for the comparisons. As a default, treatment effect data from the NMAs for 24 weeks' follow-up was used as data was available for all outcomes of interest for the comparisons with DPP-4 and TZD as add-on to metformin, and for the comparison with DPP-4 as add-on to insulin. Hence, this was considered to represent the most complete and relatively robust evidence base for the NMA. The outcomes were applied to the first year of treatment (i.e. first two cycles) in the model. The NMAs were also performed using 52-week follow-up data although 52-week data were not available for all outcomes of interest (Section 9.14). Where data were available for each outcome, the results from the 52-week NMAs were used in scenario analysis.

The methods and results from the NMA are presented in detail in Section 9.14. The absolute treatment effect parameters for the modifiable risk factors applied in the model from the comparative study vs. SU, and from the NMAs are presented in Table 58. The comparative study with SU and the NMA for the add-on to metformin analysis shows similar change from baseline in HbA1c results for dapagliflozin and each of the comparator drugs. There are significant differences associated with change in weight from baseline with a reduction of -3.22kg for dapagliflozin in the comparative study vs. SU, whereas the SU and TZD classes are associated with weight gain, and DPP-4s show only a small weight loss effect (Table 58). There is also evidence that dapagliflozin improves SBP outcomes relative to each of the comparators, and especially vs. SU (Table 58).

For the comparison with SU, the non-inferiority trial was used as it represents a direct comparative study. In addition, a further advantage of using this source in the base case was that the clinical parameters for change from baseline in total cholesterol and HDL-C were available from this study, whilst this data was not possible to obtain from the NMA. Hence, these values have been set to zero for each treatment in the comparisons using the NMA.

Hypoglycaemia and other adverse events

The economic analysis included assessment of hypoglycaemic episodes associated with dapagliflozin and the comparator therapies. The types of hypoglycaemic episode considered in the economic model were symptomatic, severe and nocturnal episodes as these have been shown to be associated with a treatment cost and/or a utility decrement. In addition, those adverse events that may be associated with the

dapagliflozin mechanism of action as an SGLT-2 inhibitor and so have a higher incidence than for the comparator treatments were included; UTIs and GIs (see Section 4). For the add-on to metformin analysis data on the number of symptomatic hypoglycaemic episodes, and the probability that the episode was severe, and the percentage of patients experiencing a UTI or GI adverse event was derived from the comparative study of dapagliflozin vs. SU (Nauck et al 2011a, 2011b) and using data available from the add-on to metformin NMA for the comparisons with DPP-4 and TZD. For the add-on to insulin analysis, the data for hypoglycaemic episodes and UTIs/GIs were derived from the add-on to insulin NMA.

For the add-on to metformin analysis, a lower frequency of symptomatic hypoglycaemic episodes and a lower proportion of severe episodes were found for dapagliflozin vs. SU (Table 60). There was a slightly higher frequency of episodes for dapagliflozin compared to DPP-4 and TZD, although this was low in absolute terms (Table 60). The probabilities of UTI/GIs for dapagliflozin were higher than the comparators in the add-on to metformin analysis (Table 58) and similar for hypoglycaemic episodes and UTIs, and higher for GIs, vs. DPP-4 in the add-on to insulin analysis (Table 58).

Discontinuations due to AEs

Table 58 also contains the data applied in the model for the probability of treatment discontinuation due to AEs for dapagliflozin and SU that was available from the comparative Study (Nauck et al 2011a, 2011b), and the NMA. These data were not possible to derive from the NMA for the add-on to insulin analysis, hence the probability of discontinuation due to AEs was set at zero for both dapagliflozin and the comparator DPP-4 (Table 58).

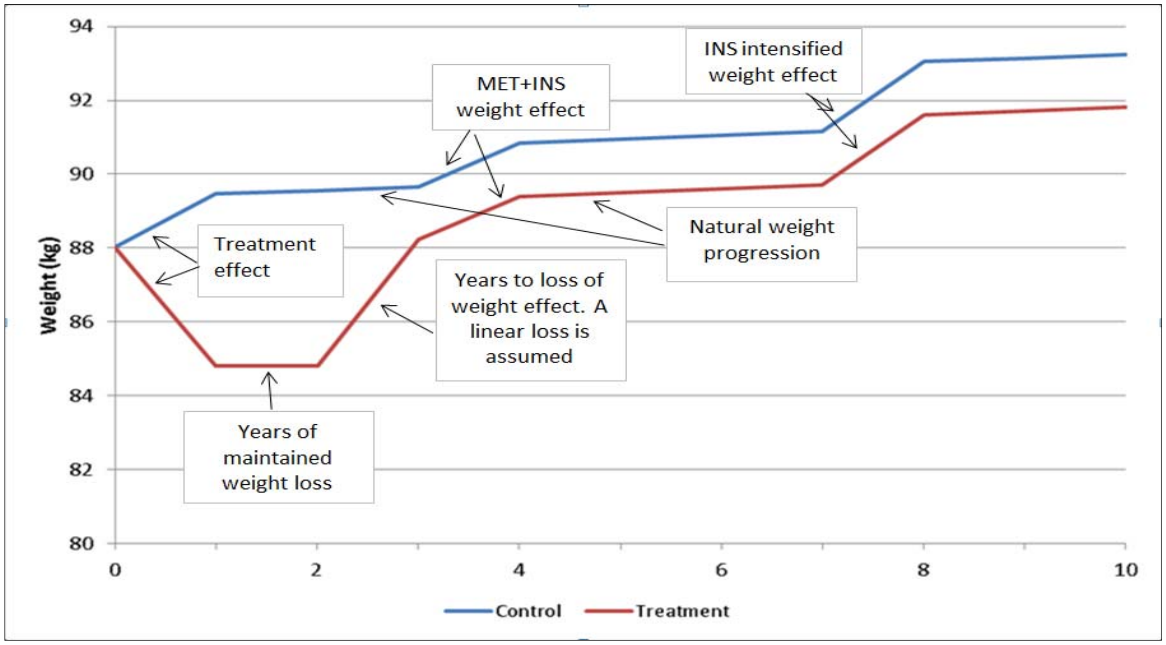
6.3.7 Extrapolation of trial outcomes

The trial outcomes HbA1c, SBP, cholesterol ratio, and body weight are extrapolated beyond the trial periods.

The introduction of a new treatment results in a reduction in HbA1c according to the efficacy of the drugs from clinical trial evidence, applied for one year. However, after this initial one year reduction in HbA1c natural progression consists of a gradual rise in HbA1c associated with a natural decline in the capacity to secrete endogenous insulin whilst patients continue on drug therapy (Clarke et al 2004). Regression analysis of the UKPDS dataset estimated a non-linear slope coefficient of 0.759 for the time varying annual risk of this HbA1c % ‘creep’, lagged one year. The slope of the curve is non-linear as HbA1c rises at a quicker rate immediately following the reduction (this is in line with the time paths reported in the UKPDS 68 study) (Clarke et al 2004). It is assumed that a full 12 months of treatment effect (i.e. 2 model cycles) is obtained after initiating dapagliflozin or comparator treatment based on the evidence from the NMAs performed. The analysis then assumes there is a 12-month stable period before the natural HbA1c creep commences, hence this is applied from the start of the year 3 of the model. When the natural increase in HbA1c reaches the target threshold specified a treatment change is triggered. The simulation then continues until the end of the time horizon or until the subject dies.

Weight change is included in the model as a further modifiable risk factor and is associated with CV risk and a HRQoL impact whilst on treatment. The implementation in the model of treatment effects on body weight and progression in weight over time are illustrated in Figure 27. UKPDS derived CV risk equations based on BMI are included in the model, hence changes in patient weight over time are converted to a BMI value based on baseline weight and height characteristics (see Table 57). Progression of weight in kg over time is based on the initial impact of each treatment on weight over a 12-month period. Dapagliflozin has been shown in the phase 3 clinical trials to be associated with significant weight loss, in particular from the add-on to metformin study where the primary endpoint consisted of change in patient body weight (Bolinder et al 2012), but also from the other phase 3 studies reported in Section 5 and from the NMAs (Section 9.14). In the dapagliflozin arm, weight reduction is assumed to be maintained in year 2 based on 2-year extension data from the phase 3 study vs. SU (glipizide) (Del Prato et al 2011). An assumption of stable weight is also assumed in year 2 for the comparator arm. After year 2, weight is assumed to be fully regained by next treatment switch in a linear manner for patients on dapagliflozin to a level at which it corresponds to the patients' natural weight progression (i.e. the weight had no weight reduction effect occurred). A natural progression in weight as the patient ages is included in the model, at a rate of 0.1kg per year. The approach described here for weight control effects of dapagliflozin should be considered conservative as they reflect the availability of clinical trial data alone whereas the anticipated effects are likely to continue beyond the period of data collection. In a real world setting an effect on weight control is likely to continue beyond 2 years, i.e. the years of weight control for dapagliflozin is likely to extend further than that depicted by the years of maintained weight loss for dapagliflozin in Figure 27.

Figure 27. Illustration of dynamic body weight profile implemented in the model



x axis = years

6.3.8 Summary of assumptions used

1. There is no long term data available on the effect of dapagliflozin and its comparator treatments on the development of diabetes related micro-vascular and macro-vascular complications. Instead, it is assumed that valid lifetime predictions of events can be made by using the UKPDS 68 risk equations (Clarke et al 2004). The UKPDS is widely considered to be the gold standard in long-term diabetes trials and contains the most relevant risk data to use to date.

2. Several assumptions were made regarding extrapolation of treatment effects on body weight. For the dapagliflozin treatment arm, the weight lowering effect is applied in the first year of treatment and it is maintained for the second year of treatment. This period of maintained effect on body weight can be substantiated by 2-year data from the long term extension of the dapagliflozin vs glipizide as add-on to MET trial (Del Prato et al 2011), and on long term data of the placebo-controlled dapagliflozin add-on to INS trial (Study Code D1690C00006). After that, it is assumed that the patient will have regained the treatment-induced weight loss within the next years. Dapagliflozin study data show that the effect on weight is maintained at 2 years, so it is conservative to assume that the weight effect is lost abruptly (see Figure 27). Since no data were available for DPP-4, the same assumptions regarding maintenance and loss of weight effect as for dapagliflozin were applied.

3. Treatment effects on SBP were applied during the first year. After Year 1, the model assumes that patient's progress according to the UKPDS 68 panel regression throughout the rest of the modelled time horizon. This means that the SBP difference established at commencement of therapy is maintained over time. This could be to the benefit of dapagliflozin, which has a more favourable effect on SBP following treatment start than SU, DPP-4 and TZD therapy. The comparative long term effects of these treatments on SBP are yet to be established. In the comparison of dapagliflozin with DPP-4 add-on to INS, treatment effects on SBP were assumed to be zero in both arms as the NMA did not produce a result for this parameter (see Section 5.7.6.6).

4. All-cause mortality events were estimated using gender specific life tables for the UK. These life tables show the annual probability of death at each age in male and female patients. Since mortality events relating to CV events and diabetes have already been accounted for in the UKPDS risk equations, all-cause mortality does not include deaths from these variables (i.e. CV and diabetes-related deaths were subtracted from all-cause mortality).

5. As data on some modifiable risk factors (i.e. lipids) was not available from the NMA, these were set as equal between the treatments in the model.

6.4 Measurement and valuation of health effects

Patient experience

6.4.1 Effects of the condition on patients' quality of life

The factors which impact the quality of life of patients with T2DM, as they relate to this economic assessment, are outlined below.

Disease progression and its consequences i.e. complications: As T2DM progresses, patients are exposed to an ever greater risk of complications, including CV disease, renal disease, amputation and retinopathy. As patients experience an event the impact on their quality of life is determined by the nature of the event and the consequences unique to that event. The occurrence of diabetes-related complications results in significant reductions in quality of life (Clarke et al 2002).

Body weight change. A number of antidiabetic drugs are associated with weight gain, in particular the SUs and TZDs which, as well as increasing risk of complications in patients with an already high body weight, is associated with a reduction in HRQoL. Conversely, any reductions in patient body weight, such as is apparent with dapagliflozin, can have a positive impact on HRQoL.

Attributes of the individual treatments: the route and frequency of administration of different treatment s affects patients' HRQoL. Complex treatment regimens and the frequency of injections may adversely affect some individual's quality of life. Fear of experiencing hypoglycaemia associated with T2DM pharmacological treatments also affects patients' quality of life.

6.4.2 Change in HRQoL over time

T2DM is a progressive disorder. The risk of developing diabetes-related complications increases over time. Consequently, patients' HRQoL is likely to decrease over time.

In addition, HRQoL related to patients' body mass index changes over time, either through treatment effects on body weight or through natural weight progression. As time and T2DM progress, and patients move on to T2DM therapies associated with weight gain (e.g. insulin), patients' HRQoL decreases.

HRQoL data derived from clinical trials

6.4.3 Description of trial based HRQoL data

Patient reported outcome (PRO) measures were used in Study 04 and Study 05 (Nauck et al 2010; Strojek et al 2010).

The DTSQ data show a high level of treatment satisfaction was maintained by patients in both studies with up to 48 weeks of treatment with dapagliflozin. Measures of both satisfaction status (DTSQs) and changes in satisfaction (DTSQc) were numerically higher with dapagliflozin (up to 10 mg) than control in both studies. Perception of hyperglycaemia in patients receiving dapagliflozin was similar to that seen with glipizide over 52 weeks and showed a numerical improvement compared with placebo over 48 weeks (Medin et al 2011).

Data from the EQ-5D questionnaire was collected at baseline and at week 24. EQ-5D index baseline means (SD) were 0.85 (0.16) and 0.82 (0.15) for dapagliflozin and placebo, respectively. Corresponding 24-week values were 0.88 (0.17) and 0.87 (0.16), respectively. The ANCOVA model indicated no difference (-0.01; CI [-0.05, 0.03]; p-value 0.49). EQ-5D visual analogue scale (VAS) baseline means (SD) were 72.8 (19.39) and 73.7 (15.49) for dapagliflozin and placebo, respectively. Corresponding 24-week values were 77.4 (15.21) and 78.3 (10.65), respectively. The ANCOVA model indicated no difference (-0.6; CI [-3.9, 2.8]; p-value 0.74). Overall the results indicated that patients maintained high QOL scores from baseline to week 24 in both treatment groups as measured by EQ-5D index and VAS. Given the questionnaire was included in the study to assess changes in QOL from baseline to 24 weeks and was collected at only 2 time points, these data were not considered appropriate for inclusion within the economic model and consequently, the utility values used in the model for the different health states and complications of diabetes have been sourced from a bespoke utility study and from existing publications (Grandy et al 2012).

Mapping clinical trial HRQoL data

6.4.4 Description of mapping exercise

Not applicable.

HRQoL studies

6.4.5 Literature search to identify HRQoL studies

A systematic search was performed which covered utility studies for HRQoL outcomes and the impact of drug related adverse events in T2DM from any country using a recognised direct or indirect measurement technique as follows:

- Direct measurement using time trade-off, standard gamble, rating scale or other recognised direct technique.
- Indirect methods using a generic instrument such as EQ-5D, Health utilities Index, SF-6D.
- Mapping methods involving cross-walking from a disease specific instrument to a generic utility instrument.
- Preference based disease specific measures.

This was part of a single comprehensive systematic review that also covered the identification of economic evaluations and resource utilisation studies for the selected drug interventions and specific T2DM patient populations that match those included in the dapagliflozin economic model in this submission i.e. dual therapy (add-on to metformin) and add-on to insulin therapy (Section 6.1).

Further details of the single comprehensive search strategy (databases searched, search strategies for each database, additional exclusion criteria, data extraction strategy) are provided in Section 9.10.

6.4.6 HRQoL studies identified

From the searches, 14 utility studies considered of direct relevance for this submission and were selected for review. A summary of the objectives, methods and results from these studies are presented in Table 59.

Table 59. Utility studies reviewed from the HRQoL search

Study, year and country	Primary objective of evaluation	Details of methods	Key utility results
UKPDS Group, Diabetes Care, 1999 UK	Assessment of HRQoL outcomes in T2DM using UKPDS data	**Source of utilities:** Two cross-sectional studies of 3,667 T2DM patients (the UKPDS). **Utilities of relevance cover:** Instruments: EQ 5D tariff (UK) and VAS. • Utilities for overall macro and microvascular complications • Prior hypoglycaemic episodes (on insulin)	Median (inter-quartile range) EQ 5D utility score (tariff based) for: **Complications:** Macrovasular = 0.73 (0.62-0.85) [n=61] Microvascular = 0.76 (0.62-1.0) [n=52] None = 0.80 (0.69-1.0) [n=3052] **Hypoglycaemic episodes (number):** No episodes = 0.8 (0.69-1.0) [n=559] One episode = 0.8 (0.66-1.0) [n=285] Two+ episodes = 0.8 (0.69-1.0) [n=277]
Clarke 2002 UK	Assessment of HRQoL of major complications in T2DM using UKPDS data	**Source of utilities:** Observational data for 3,667 T2DM patients (the UKPDS). **Utilities of relevance cover:** Instrument: EQ 5D tariff (UK) and VAS. • Utilities for specific macro and microvascular complications (using regression methods)	Mean EQ5D tariff utility was 0.77, mean VAS was 0.77. Regression analyses demonstrated the marginal impact of complications on utilities (e.g. TOBIT model results – tariff values, 95%CI's): MI -0.055 (-0.067, -0.042); IHD -0.090 (-0.126, -0.054); Stroke -0.164 (-0.222, -0.105); CHF -0.108 (-0.169, -0.048); Amputation -0.280 (-0.389, -0.170); Blindness in one eye -0.074 (-0.252, -0.124) Regression results using a CLAD model yielded lower dis-utilities.
Hakim 2002 USA	Association of BMI on HRQoL	**Source of utilities:** 402 patients with obesity, unknown how many (if any) have T2DM. **Utilities of relevance cover:**	One unit decrease in BMI over a 1-year period = 0.020 utility gain (with VAS), & 0.017 utility gain (with TTO)

Study, year and country	Primary objective of evaluation	Details of methods	Key utility results
		Instrument: VAS, converted to TTO (using formula) Regression model to model influence of severity of obesity, age and gender on TTO utilities.	
Coffey 2002. USA	Assessment of the HR QoL impact associated with diabetes, -treatment, -complication and comorbidities	**Source of utilities:** 2,041 patients with type 1 (n=784) and type 2 (1,257) diabetes recruited from treatment clinics. **Utilities of relevance cover:** Instruments: • Diabetes Staging Questionnaire (DSQ) • QWB-SA utility instrument Regression models for type 1 and T2DM to calculate utility based on patient characteristics including gender, BMI, diabetes treatment (oral drugs or insulin), specific complications	Utility of nonobese, diet-controlled men and women with T2DM and no complications was 0.69 and 0.65, respectively. Utility decrement due to obesity= -0.021 (SE: 0.007) Utility decrement due to other complications (SE): Blind in one eye: -0.043 (0.011), Blind in two eyes: -0.170 (0.011), Kidney disease: -0.011 (0.009), Dialysis: -0.078 (0.026), Tingling and burning: -0.060 (0.010), neuropathy: -0.065 (0.008), sores: -0.099 (0.013), Amputation: -0.105 (0.020), TIA/stroke: -0.044 (0.012), Stroke with residual: -0.072 (0.016), CHF: -0.052 (0.011), High blood pressure (with meds): -0.011 (0.007)
Lee 2005. UK	Association of BMI and HRQoL	**Source of utilities:** Postal questionnaire among 1,863 patients with T2DM from the HODaR study. **Utilities of relevance cover:** Instrument: EQ 5D tariff (UK) and VAS Regression model to calculate utility based on patient characteristics, age and BMI.	Increasing BMI reduced utility predicted to be by 0.01 (SE 0.001) per unit increase in BMI

Study, year and country	Primary objective of evaluation	Details of methods	Key utility results
Bagust 2005; Belgium, Spain, Italy, Netherlands, Sweden	Assessment of HRQoL (utility) impact of BMI and other complications in T2DM	**Source of utilities:** Observational data for 4,641 T2DM patients from Belgium, Italy, Netherlands, Spain, Sweden (the CODE-2 study). **Utilities of relevance cover:** Instrument: EQ 5D tariff (UK) and VAS OLS regression model to calculate complications dis- utility based on patient characteristics including gender, age, duration of diabetes, diabetic treatment, specific complications	Regression model. TTO results (SE): CHD: -0.028 (0.010), Stroke : -0.115 (0.017), proteinuria: -0.048 (0.022), ESRD: -0.175 (0.028), Neuropathy: -0.084 (0.014), PVD: -0.061 (0.015), Neuropathy and PVD: -0.085 (0.018), Foot ulcers -0.170 (0.019), amputation: -0.272 (0.029), blindness: -0.057 (0.022), depression: -0.202 (0.014). All results were statistically significant at p<0.01 except blindness (p=0.057), and proteinuria (p=0.03) TTO utility decrement due to obesity (per 1 unit BMI > 25) = -0.0061 (SE 0.001, p<0.001), with VAS was 0.29 (SE 0.64, p<0.001)
Davis 2005 UK/Wales	Assessment of the impact of hypoglycaemia on HRQoL in diabetes (type 1 and type 2)	**Source of utilities:** UK/Wales Postal survey sent to 3200 people with diabetes with 590 respondents with T2DM. **Utilities of relevance cover:** Instrument: EQ 5D tariff (UK).	EQ 5D utility associated with each level of hypoglycaemia severity: Severe: 0.53 (SD:0.38) Mild/moderate: 0.65 (SD: 0.33) Nocturnal: 0.77 (SD: 0.17)
McEwan 2006. UK	Assessment of costs and HRQoL of modifiable risk factors in Type 2 diabetes	**Source of utilities:** Health Outcomes Data Repository (HODaR). **Utilities of relevance cover:** Instrument: EQ 5D tariff (UK).	Average utility without complications 0.710. Mean utility associated with primary T2DM complications: MI:0.661, stroke: 0.478, PVD without amputation: 0.455, PVD with amputation:0.488, ESRD: 0.496, Retinopathy: 0.536, Severe Visual loss: 0.267 Mean utilities were also estimated for secondary complications
Currie 2006.	Assessment of HRQoL of	**Source of utilities:** Postal survey in 768 T2DM patients from UK.	Effect of worst hypoglycaemic event in the past 3 months: No event: 0.71 (SD: 0..281), Mild: 0.656 (SD:0.309), Moderate:

Study, year and country	Primary objective of evaluation	Details of methods	Key utility results
UK	hypoglycaemic events and other complications in diabetes	**Utilities of relevance cover:** Instrument: EQ 5D tariff (UK) related to Hypoglycaemia Fear Survey (worry sub-scale) (HFS) scores using regression analysis. Regression analysis performed for other predictors of EQ 5D utility decrements.	0.490 (SD:0.353), Severe: 0.467 (SD: 0.326) Impact of each hypoglycaemic event on utility through increased fear of further events: Symptomatic episode: -0.0142 Severe episode: -0.047 Nocturnal episode: -0.0084 Other factors/complications with estimated utility decrement in model excluding nocturnal hypoglycaemia (SE): Per unit increase in BMI = -0.014 (0.002), CHD: -0.090 (0.024), CVD: -0.160 (0.042), diabetic foot: -0.144 (0.038), ESRD: -0.105 (0.001). (all statistically significant at p<0.05).
Clarke 2006 UK	Association of QoL and visual acuity in T2DM	**Source of utilities:** 4,051 patients with T2DM from Lipids in Diabetes Study. **Utilities of relevance cover:** Instruments: SF-36 converted to SF-6D utilities Regression analysis was used to model association between utility and visual acuity.	Worse visual acuity (VA) was associated with lower SF 6D utility scores: Legal blind VA disutility of -0.054 (SE:0.010) vs normal VA In addition, regression estimated: Per 1 unit increase in BMI: -0.002 (SE:0.00) disutility Being a current smoker: -0.016 (SE:0.005) disutility vs ex-smoker History of complications: -0.065 (SE:0.014) disutility vs. none
Wexler 2006. USA	Assessment of the impact of comorbidities, complications and treatment intensity on HRQOL in T2DM	**Source of utilities:** Survey (mail and phone) of 909 patients with T2DM in primary care clinics. **Utilities of relevance cover:** Instrument: HUI-3. Regression model to calculate utility based on	Median health utility was 0.70. Regression model results show HUI dis-utilities estimated for the following complications (SE): Microvascular: -0.12 (0.02), Heart Failure: -0.24 (0.03), Depression: -0.42 (0.02), CHD: -0.11 (0.02), Stroke: -0.07 (0.03), COPD: -011 (0.03).

Study, year and country	Primary objective of evaluation	Details of methods	Key utility results
		patient characteristics including:: age, gender, education, co-morbidities, microvascular complications, treatment intensity	Depression had the largest impact on utility. All utility decrements were statistically significant at p<0.0001, except Stroke with p=0.01
Boye 2007 Spain	Assessment of HRQoL and complications in T2DM	**Source of utilities:** 339 T2DM patients seen by participating physicians. **Utilities of relevance cover:** Instrument: EQ5D tariff (Spain) and VAS Regression model to calculate utility based on patient characteristics including gender, age, education, duration of diabetes, diabetic treatment, microvascular/macrovascular complications	Mean EQ-5D VAS utility was 65. (SE: 20.3). Mean EQ-5D index utility was 0.70 (SE:0.3) The presence of microvascular/microvascular complications produced an estimated EQ-5D utility decrement of -0.142 (SE:0.0029, p <0.0001)
Matza 2007. UK	Assessment of PROs in T2DM patients with and without obesity.	**Source of utilities:** 129 patients, 74 of whom obese, with T2DM. **Utilities of relevance cover:** Instruments: • EQ5D tariff (UK) and VAS Utilities were assessed for those with and without obesity.	Average EQ-5D index utility for obese patients: 0.72 (SE:0.03) Average EQ-5D index utility for non obese patients: 0.80 (SE:0.04). Average EQ-5D VAS utility for obese patients: 64 (SE:2.0) Average EQ-5D VAS utility for non obese patients: 75.2 (SE:2.5)
Alvarez-Guisasola 2010 Finland,	Assessment of QoL of hypoglycaemic symptoms in T2DM	**Source of utilities:** European multicenter study of 1,709 patients of whom 342 from UK (the RECAP-DM study). **Utilities of relevance cover:**	Average utility of all UK patients: 68.77 (SD:17.87) **By presence of hypoglycaemic symptoms (UK patients):** With hypoglycaemic symptoms: 65.35 (SD:18.28) [n=185] Without hypoglycaemic symptoms: 72.50 (SD:16.73) [n=157] **By hypoglycaemic symptom severity (UK patients):**

Study, year and country	Primary objective of evaluation	Details of methods	Key utility results
France, Germany, UK, Netherlands, Norway, Poland, Spain		Instrument: EQ 5D VAS • Utilities for patients with and without self-reported and self-graded hypoglycaemic symptoms (based on questionnaire).	Without symptoms: 72.50 (SD:16.73) [n=157] Mild symptoms: 67.69 (SD:17.75) [n=99] Moderate symptoms: 64.65 (SD:17.42) [n=69] Severe symptoms: 51.54 (SD:21.51) [n=17] The results for all patients were similar.

Abbreviations: MI=myocardial infarction, IHD=ischaemic heart disease, CHF=congestive heart failure, PVD=peripheral vascular disease, QWB-SA = Quality of Well Being Self Administered, HUI= Health Utilities Index; HODaR= Health Outcomes Data Repository; OLS=ordinary least squares TTO=time trade-off

Key findings from the utility/HRQoL studies reviewed in Table 59 were as follows:

- The HRQoL studies identified have reported utilities or disutilities for complications of T2DM, the relationship between BMI/weight and utility in T2DM, and disutilities associated with hypoglycaemia and the fear of further hypoglycaemic episodes.

- Many of the utility studies performed in T2DM have used the EQ 5D (tariff and VAS), which is consistent with the NICE reference case.

- A key study used in many of the economic models of T2DM interventions is that of Clarke et al (2002), which uses regression methods to estimate EQ 5D based disutilities for microvascular and microvascular complications (UKPDS sub-study 62). These are the values used in the dapagliflozin economic model for most of the complications considered, with the exception of end-stage renal disease (ESRD) and BMI.

- There have been several studies that have investigated the relationship between BMI and utility, demonstrating a significant correlation between increased BMI or obesity and disutility using EQ-5D and other recognised methods (Hakim et al 2002, Coffey et al 2002, Lee et al 2005, Bagust et al 2005, Currie et al 2006, Matza et al 2007).

- There appears to be a significant impact of renal failure/ESRD on utilities in T2DM (McEwan et al 2006, Currie et al 2006).

- There is limited evidence of the impact of depression on utilities, but two studies reported this to have a significant impact on utility decrements, one using the HUI-3 generic utility measure (-0.42) (Wexler et al 2006), the other EQ 5D (Bagust et al 2005).

- The fear of hypoglycaemia following related to symptomatic and severe episodes have an impact on HRQoL/utility, especially as shown in the study by Currie et al (2006). The independent impact of nocturnal hypoglycaemia is less clear (Currie et al 2006, Davis et al 2005).

A key advantage of dapagliflozin over comparator drugs used as add-on to metformin, or add-on to insulin, is the weight loss potential achieved with the drug. Therefore, the relationship between change in weight associated with T2DM drugs and change in utility is an important component of the economic assessment of dapagliflozin. It is possible to use values from the literature to model the impact of a per unit increase in BMI on T2DM patient disutility. However, none of the studies reviewed above have specifically assessed the relationship between reduction in BMI and change in utility in T2DM patients. Hence, for the base case of the dapagliflozin economic evaluation a bespoke utility analysis was conducted which obtained specific T2DM patient utilities associated with both increasing and decreasing BMI (Lane et al 2012) (see Section 6.4.8).

6.4.7 Comparison of HRQoL data

Only one of the clinical studies for dapagliflozin included utility instruments but was not considered suitably detailed to use to derive utilities for health outcomes included in the economic model (see Section 6.4.3).

Adverse events

6.4.8 The impact of adverse events on HRQoL

Weight gain

Certain T2DM treatments, such as insulin and TZD, are associated with weight gain which can be considered as an adverse effect of pharmacological treatment. Dapagliflozin on the other hand reduces body weight. The effect of changes in BMI (as a measure of body weight) on quality of life has been included in the model. An increase in BMI has a larger (negative) effect on quality of life than the (positive) effect of a decrease in BMI. The utilities were estimated in a bespoke study on patient utilities for T2DM health states, using a time trade-off utility valuation method (Lane et al 2012).

The patient sample consisted of 100 patients completing time trade-off (TTO) interviews, and was performed in Canada, with the TTO results based on 96 useable responses. The mean age of respondents was 55.2 years and 51.0% were male. Just under half of the respondents were Caucasian (45.0%), married (49.0%), and employed full time (44.0%). The mean weight of respondents was 89.9 kg and the mean height was 167.2 cm, which translated to a mean BMI of 32.2 kg/m2. Most of the respondents (84.0%) reported a desire to lose weight, while 15.0% wanted to maintain their weight and only 1% wanted to gain weight.

Health states were developed based on literature review and expert opinion, and consisted of a base case with T2DM, then separate health states with a 3%, 5% and 7% increase and a 3%, 5% and 7% decrease in weight relative to the base case health state. These weight gains/losses were chosen as the lower value represents the threshold for clinically meaningful weight loss (Stevens et al 2006), whilst 7% weight loss was chosen as the upper level of weight loss seen in dapagliflozin clinical studies. These same proportional changes in weight were used for weight gain, to capture the typical range of weight change amongst individuals with T2DM on OADs (Matza et al 2007). The health states were anchored by Perfect Health, and Dead states. An interviewer led TTO exercise was then performed.

Regression modelling was performed to estimate the association between respondents' BMI and the elicited utility for the base case health state (current weight without adding any weight change to the health state). This found no association between the health state utility score and respondents BMI (coefficient of -0.0021 with increasing BMI, 95% CI of -0.0061, 0.000). To estimate the utility increment or decrement associated with each unit change in BMI, percentage change in weight was converted to an actual change in BMI, based on each individual's weight and height. Individuals' elicited health states (at each successive weight-related health state) were modelled as repeated measures, using generalized linear mixed models (Shaw et al 2009) and including random effects on the intercept and the BMI coefficient. The effect of including other coefficients, including age (continuous and categorical), sex, and weight preference

(gain, lose, or maintain) were investigated, as well as the effect of including interaction terms with these covariates and BMI. The effect of increasing BMI from baseline and decreasing BMI from baseline were modelled separately to achieve parsimonious models of the differential effect of weight gain and of weight loss on the utility results.

The result from this regression was that a 1 unit increase in BMI in the economic model was significantly associated with a -0.0472 reduction in utility (95%CI: -0.0375, -0.0569) and each 1 unit decrease in BMI was significantly associated with a 0.0171 increase in utility (95%CI: 0.010, 0.0238) both associations being statistically significant. These values were applied in the economic model base case (see Table 60), and the upper and lower limits applied in univariate sensitivity analysis.

The findings from this study performed in T2DM patients are supported by evidence in the literature (Table 59). Hakim et al (2002) using a TTO valuation approach and multiple regression analysis also found a 0.017 utility gain associated with each unit BMI decrease in mixed patients including T2DM from a clinical study. In scenario analysis the results from the study by Bagust et al (2005) are applied as this was carried out in a European population of T2DM patients which included the UK, and used the EQ 5D instrument. The value derived from this study was a -0.0061 disutility per 1 unit increase in BMI for patients with T2DM with a BMI >25. The values from this study show a relatively lower impact on HRQoL/utility associated with BMI change than in the TTO study; hence provided a more conservative scenario than the model base case values. The TTO study utilities were used in the base case as the study enabled separate and different utility values for both weight gain and weight loss to be estimated, which is relevant to the decision problem for dapagliflozin as whilst some drugs such as SUs and TZDs lead to weight gain, dapagliflozin is associated with weight loss. In addition, the TTO study was performed in actual patients with T2DM who were selected to provide a range of weight/BMI characteristics and who were likely to have experienced weight change on T2DM medications (Lane et al 2012). Other studies have used the EQ 5D instrument to develop a relationship between BMI and utility using general datasets in T2DM patients. However, the use of direct TTO methodology in the Lane study enabled specific weight gain/loss health state descriptions to be valued by patients likely to be experiencing some of these health states and so enables a more precise valuation of the impact of loss/gain scenarios.

We recognise that the TTO values from this study divert somewhat from the NICE preferred reference case. However, we feel they are justified to use due to the specific attention given to a utility increase associated with BMI decrease, whereas previous studies, including Bagust et al that has been used in previous HTAs, have focussed on disutilities associated with BMI increase. There is a need for further research and ideally analysis of the relationship between BMI decrease and utility using an instrument such as the EQ 5D. However, we use the TTO results in the base case due to the plausibility of a utility increase associated with drugs that are associated with weight loss (and in scenario analysis we explore the impact of assuming the Bagust EQ 5D utility change associated with weight gain also applies in a linear fashion to weight reduction).

Hypoglycaemia

Utility decrements associated with hypoglycaemic events were based on a study by Currie et al., who developed a statistical model that relates the fear of hypoglycaemia to changes in utility measured with the EQ-5D in a UK population of 1,305 patients with diabetes, conditioned upon the severity and frequency of hypoglycaemic events (Currie et al 2006). The published equations characterising this relationship were included in the cost-effectiveness model. For each cycle in the model, the number and the severity of hypoglycaemic events in the patients' history is determined. Each event experienced causes a loss of utility through increased fear of hypoglycaemia. The resultant disutility is calculated as follows:

*Severe event (binary variable: if ≥1 event then [1], else [0]) * 0.047 + number of symptomatic events * 0.0142 + number of nocturnal events * 0.0084*

In the economic analyses performed for dapagliflozin vs the comparators disutilities associated with symptomatic (-0.042), severe (-0.047) and nocturnal (-0.0084) hypoglycaemia were applied.

Other adverse events

The model also allows for utility decrements to be applied to the occurrence of AEs other than hypoglycaemia. The most common adverse events occurring in the dapagliflozin clinical trials have been highlighted in Section 5.9. Events suggestive of urinary tract infection (UTI) and genital infection (GI) were reported more frequently with dapagliflozin than with control treatment (glipizide or placebo). Therefore these two AEs were included in the model and were assumed to incur a quality of life decrement, estimated to be 0.00283 per event derived from a published economic evaluation of care interventions for UTIs in women; this represented the highest utility decrement in the published study (Barry et al 1997). The utility reported in the study by Barry et al. was presented as quality adjusted life months and was converted to QALYs. The decrements were applied only in the year in which the event occurred.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Summary of HRQoL values used

The values in Table 60 were used to calculate utilities for patients in the cost-effectiveness analysis.

Table 60. Summary of quality of life values for cost-effectiveness analysis

State	Utility value or decrement	Reference to section in submission	Justification
Diabetes-related complications			
IHD	-0.090	Study identified in HRQoL search, section 6.4.6	Most appropriate study on HRQoL related to T2DM complications (UKPDS 62)
MI	-0.055	Same as for IHD	
CHF	-0.108	Same as for IHD	
Stroke	-0.164	Same as for IHD	
Amputation	-0.280	Same as for IHD	
Blindness	-0.074	Same as for IHD	
ESRD	-0.263	Database identified in HRQoL search, Section 6.4.6	Most appropriate value based on analysis of a UK database (Health Outcomes Data Repository, Currie, 2005).
Hypoglycaemia			
Symptomatic	-0.042	Study identified in HRQoL search, Section 6.4.6	Most appropriate study on HRQoL related to hypoglycaemia (Currie et al 2006)
Nocturnal	-0.0084		
Severe	-0.047		
Adverse events			
Urinary tract infection	-0.00283	As not in T2DM study was identified in supplementary to the HRQoL search, Section 6.4.6	Most appropriate value identified in the literature (Barry et al 1997)
GI	-0.00283		No utility value related to GI was identified in the supplementary search. The same value as for UTI was assumed.
BMI changes			
per unit increase	–0.0472	Results for this	Unlike published

State	Utility value or decrement	Reference to section in submission	Justification
per unit decrease	+0.0171	study have recently been reported in an ISPOR poster (Lane et al 2012)	estimates this study uses direct T2DM patient experience to provide separate and more precise utility association with both decreasing and increasing BMI, and is more recent than published estimates.

Abbreviations: BMI, body mass index; CHF, congestive heart failure; ESRD, end stage renal disease; GI, genital infection; HRQoL, health-related quality of life; IHD, ischaemic heart disease; MI, myocardial infarction; UTI, urinary tract infection.

Utility values for the 7 diabetes-related complications in the model were drawn from the UKPDS 62 sub-study (Clarke, 2002). In the UKPDS 62 the EQ-5D instrument was administered to 3,667 UKPDS patients with T2DM in 1996 to estimate the impact of diabetes-related complications on utility-based measures of quality of life. The utility decrement for ESRD was sourced from the Health Outcomes Data Repository (HODaR), a database of patients treated at Cardiff and Vale National Health Service Hospitals Trust (Currie, 2005). The utility values for complications in Table 60 were previously used in other published cost-effectiveness studies (Woehl, 2008; Schwartz, 2008; Granström et al 2012). In addition, the values have been used by the NICE Clinical Guideline Group within the UKPDS Health Outcomes model for health technology assessment of newer agents for blood glucose control within the scope of a clinical guidance update (Waugh et al 2010).

6.4.10 Input from clinical experts

As noted in Section 6.3.5, clinical experts were not directly used to supply or verify values for parameters used in the economic model. However, there were a number of advisory boards held with clinical and health economic experts where the model and the input parameters were discussed in order to strengthen the model and analyses.

6.4.11 HRQoL experienced in each health state

If a patient experiences a diabetes-related complication a decrement is subtracted from the age specific baseline utility for a patient without any complications (see Section 6.4.13) in the year in which the complication occurs, and in all subsequent years. The model assumes that for patients experiencing more than one complication the disutilities are additive (i.e. if stroke and MI are experienced the disutility is the sum of both subtracted from the age dependent baseline utility). The assumptions of additive properties and lifetime disutility are justified by the methods used to generate the utilities within the UKPDS sub-study 62 (Clarke 2002).

6.4.12 Health effects excluded from the analysis

The literature review identified studies that included an assessment of disutilities associated with T2DM macro and micro-vascular complications, the relationship between BMI/weight and obesity and utility outcomes in T2DM patients, utilities associated with

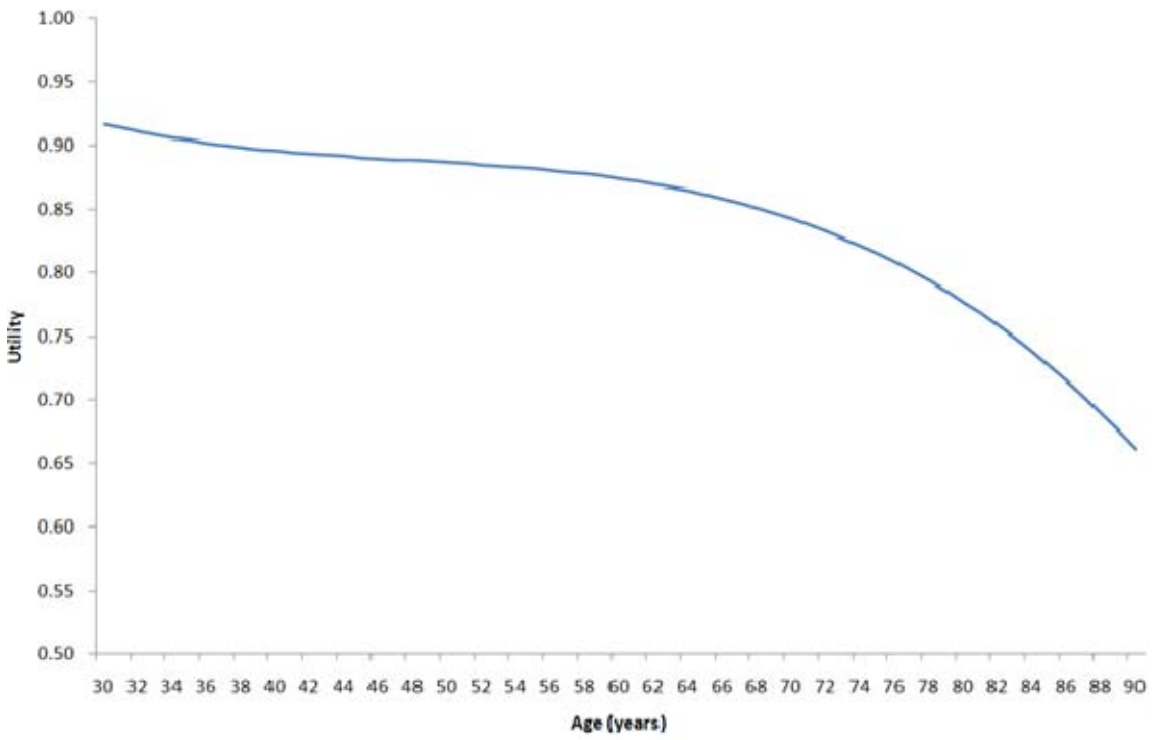
the fear of hypoglycaemia and hypoglycaemic episodes and baseline utilities associated with patients not achieving glycaemic control on metformin alone. In the dapagliflozin economic analyses account has been taken of disutilities from macro/micro-vascular complications associated with lack of glycaemic control and other risk factors of T2DM, BMI/weight, hypoglycaemia, and also other adverse effects identified in the dapagliflozin clinical trials for add-on to metformin, and add-on to insulin (specifically, UTIs and GIs). Hence, none of the main health effects identified in the literature or clinical trials have been excluded from the dapagliflozin economic evaluation.

6.4.13 Baseline HRQoL

An age-dependent utility value corresponding with age at baseline was assumed as baseline quality of life in the analyses. Quality-of-life events were taken from this baseline.

Age-dependent utility values were derived from an inverse relationship between age and utility that was modelled using mean EQ-5D by age group in subjects with no major complications, obtained from the DoH Health Survey for England (2003). The resulting polynomial is shown Figure 28.

Figure 28. Age-dependent baseline utility function



6.4.14 Changes in HRQoL over time

HRQoL changes over time due to the incidence of complications, hypoglycaemia and other adverse events are modelled (see Section 6.4.7). In addition, HRQoL associated

with changes in body weight/BMI related to each drug and due to natural weight progression is also modelled (see Section 6.3.7 and Section 6.4.8).

6.4.15 Have the values in Sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

6.5 Resource identification, measurement and valuation

NHS costs

6.5.1 How is the clinical management of the condition currently costed in the NHS?

HRGs and NHS reference costs covering elective and non-elective inpatient and day case management of diabetes are available. The codes in the 2010-11 NHS reference costs cover diabetes with:

- hypoglycaemic disorders by age/with or without complications,
- lower limb complications
- ketoacidosis or coma
- foot procedures

However, NHS reference costs or PbR tariffs have not been used in the economic evaluation of dapagliflozin (see Section 6.5.2).

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

The available NHS reference costs and PbR tariffs are not appropriate for use in the dapagliflozin economic model as they represent average costs for all diabetes patients and not those with T2DM. Instead, resource use data and costs derived from published studies have been used. In particular, a key source for estimates of the costs of complications associated with T2DM is the published UKPDS estimates (Clarke et al 2003). This is consistent with previous NICE HTAs in T2DM, including recent STAs (TA203, liraglutide; TA248 exenatide) and NICE clinical guideline 87 (NICE Clinical Guideline 87).

Resource identification, measurement and valuation studies

6.5.3 Literature search to identify resource data

A systematic search was performed which covered resource utilisation studies for selected treatments/patient populations in T2DM performed in a UK setting. Studies that reported resource use quantities or costs associated with health outcomes or drug related adverse events in T2DM for the selected treatments/patient populations were included.

This was part of a single comprehensive systematic review that also covered the identification of economic evaluations and utility studies (see Section 6.1).

Further details of the single comprehensive search strategy (databases searched, search strategies for each database, additional exclusion criteria, data extraction strategy) are provided in Section 9.10.

From the searches, 8 UK resource use/cost studies in T2DM considered of most relevance for this submission were selected for review. A summary of the coverage, methods and results from these studies are presented in Table 61.

Table 61. Resource use/cost studies identified from the systematic review

Study and year	Resources/Costs covered, region	Valuation methods	Key results
Donnan, 2000	Hospital in-patient use for patients with T2DM (also assessed for type 1 diabetes and no diabetes). Region: Data collected from the Tayside region of Scotland	The study population was a cohort of 6,871 patients with T2DM from the DARTS database (1995). Hospital in-patient resource use was derived from hospital records from the DARTS database, used to estimate number of finished consultant episodes (FCE) by type of diabetes complication. No costs evaluated	1,859 T2DM patients had a hospitalization in the study year. Median hospital days per patient: 7% of patients who had ever had an in patient FCE by type of complication: MI: 5.1%, Stroke: 4.3%, PVD: 2.2%, amputation: 1.1%, renal failure: 1.8%, cataract: 7.1%
Evans 2000	Drug costs for patients with T2DM (also assessed for type 1 diabetes). Region: Data collected from the Tayside region of Scotland	The study population was a cohort of 6,869 patients with T2DM from the DARTS/MEMO database. Drug resource use: MEMO prescription database from community pharmacies was used to gather resource use.	After adjusting for age patients with T2DM were 1.7 times (95% CI 1.69–1.71) more likely to be dispensed a drug item (excluding anti-diabetic drug items) than non-diabetic patients.
Clarke 2003	Costs from major complications, both in-patient and out-patient, in T2DM. Region: UK	5,102 patients from the UKPDS database for inpatient resource use; 3,488 patients from the UKPDS for non-inpatient resource use (UKPDS study 65). Hospital in-patient resource use: clinical records were used to gather resource use. Non-inpatient (e.g. GP) resource use: Patient survey used to gather resource use. Regression models to estimate probability to incur costs, and amount of these costs. Patient	Results are given for hospital in-patient costs and non-inpatient costs (original price year, 95%CI). Cost for first year, followed by cost for subsequent years if non-fatal: <u>Inpatient costs:</u> No complications: £157 (145,70) Fatal MI: £1152 (941,1396) Non-fatal MI: £4070 (3580, 4722) ; £464 (377,578) Fatal stroke: £3383 (1935,5431) Non-fatal stroke: £2367 (1599, 3274); £249 (166, 357)

Study and year	Resources/Costs covered, region	Valuation methods	Key results
		characteristic in the regression model are age, gender, current complications and history of complications. Also described are average probability to incur costs and average costs per complication, both for the year of the complication and the subsequent year. Costs based on 1997/98 NHS Trust Financial Returns (TFR2) data.	IHD: £1959 (1476, 2541); £493 (392, 606) Heart failure: £2221 (1690,2896); £631 (403, 896) Blindness 1 eye: £872 (526,1299); £281 (189,401) Amputation: £8459 (5295,13200); £300 (154,531) Cataract: £1553 (1320,1855); £105 (80,142) <u>Non-inpatient costs</u> No complications: £159 (149, 173) Macrovascular: £315 (247,394); £258 (228, 297) Microvascular: £273 (215, 343); £204 (181, 255)
Leese 2003	Assessment of the incidence and costs of emergency treatment of hypoglycaemic events in type 1 and T2DM. Region: Data collected from the Tayside region of Scotland	7,678 patients with T2DM from the DARTS/MEMO database (type 1 diabetes analyses separately). Hospital records were used to gather resource use, linked to the Scottish Morbidity Registry. Costs were based on the Information Statistics Division (ISD) cost book (year unclear).	Incidence of patients with emergency treatment of hypoglycaemia is 0.9 for those treated with sulphonylurea tablets and 0.05 for those treated with metformin or diet. Costs per day of emergency treatment of hypoglycaemia were: Ambulance: £127, A&E: £89, Inpatient ward: £218
Gulliford 2005	Assessment of resource use in primary care patients *before* diagnosis of T2DM (case) and subjects without diabetes (controls). Region UK	5,158 patients from the GPRD database (over 1992-2000). Consultations with GPs and drug prescriptions were derived from the GPRD database.	Patients with T2DM incur additional healthcare resource use before diagnosis relative to controls. From 5 years before diagnosis of diabetes, case subjects had rates of consultation that were 25% higher than control subjects. The RRs remained approximately constant And one year before diagnosis was 50% higher. From 5 years before diagnosis onwards, the number of pharmaceutical items prescribed per year was between 40 and 60% higher for case compared with control subjects.

Study and year	Resources/Costs covered, region	Valuation methods	Key results
Hammer 2009	Assessment of the costs of hypoglycaemic events in type 1 and T2DM. Region: UK (Germany and Spain are assessed separately)	Questionnaire survey among patients with type 2 (n=100) diabetes (type 1 diabetes was also assessed). Costs for severe hypoglycaemic episodes covered direct costs within hospital, out of hospital, follow-up treatment, indirect costs (productivity losses). Costs were based on local health service tariffs (not specified in publication). 2007 values presented.	UK costs for severe hypoglycaemic episodes in T2DM were: Direct treatment cost = €537 per episode (based on 65% hospital based treatment vs 35% non-hospital). Range of €410 – 640 depending on proportion of patients treated in hospital (40% to 90%)
Currie 2010	Costs of primary care treatment for type 1 and T2DM. Region: UK	114,752 patients with T2DM (type 1 diabetes analysed separately) participating in The Health Improvement Network (THIN) study. This is a database comparable to the GPRD. Resource use including prescriptions and consultations were gathered from this database. Prescription costs based on BNF. Primary care consultation costs derived from Unit Costs of Health & Social Care source.	Costs are given for all years from 1997 to 2007. In the latest year of study (2007): Mean diabetes prescription costs: £209 Mean overall prescription costs: £740, Mean total treatment costs: £1080 11.5 primary care consultations per patient
Govan 2011	Hospital in-patient costs for patients with T2DM. Region: Scotland	195,433 patients with T2DM gathered from the SCI-DC registry. Resource use: data were gathered using the Scottish Care Information – Diabetes Collaboration (SCI-DC), linked to Scottish Morbidity Records. Costs were derived from the Scottish National Tariff 2007-2008.	Reason for admission and estimated mean cost per admission (SD) for patients with T2DM as follows: All admissions: £3,034 (2298) Diabetes: 49% of admissions, £3,232 (2409) Hypoglycaemia: 1.1% of admissions, £2,582 (1608) Hyperglycaemia: 0.3% of admissions, £2,583 (1880) Vascular: 4% of admissions, £4,658 (2487) Cancer: 14.6% of admissions, £3,324 (2,363)

Key findings from the resource use/cost studies reviewed in Table 61:

- The studies identified covered resource use/cost of hospital care, T2DM complications, and hypoglycaemic episodes.
- The studies demonstrate the impact of T2DM on hospital costs, and on primary care costs after and prior to diagnosis (Currie et al 2010, Gulliford et al 2005)
- A number of the studies have used large resource utilisation databases from the UK such as the GPRD in England (Gulliford et al 2005), or DARTS/MEMO in Scotland (Donnan et al 2000, Evans et al 2000) in order to estimate the impact of T2DM on drug prescription and within and out of hospital resource use/costs.
- A key study used in many of the economic models of T2DM interventions is that of Clarke et al (2003), which uses regression methods to estimate costs associated with microvascular and microvascular complications (UKPDS sub-study 65). These are the values used in the dapagliflozin economic model updated to current prices.
- There is also some cost data from two studies for the treatment of hypoglycaemic events (Hammer et al 2009, Leese et al 2003). UK values from the Hammer study (2009) have been used in the dapagliflozin economic model as they are the most recent and are more comprehensive than those available from Leese et al (2003).
- None of the included studies in T2DM directly reported the costs associated with change in weight/BMI, ESRD, or specific AEs such as UTIs or GIs that are included in the dapagliflozin economic model. For these values data from studies not in T2DM have been used (see Sections 6.5.6, 6.5.7 and 6.6.2).

6.5.4 Input from clinical experts

Not applicable.

6.5.5 Intervention and comparators' costs

Drug acquisition costs

The drug acquisition costs used to represent specific drugs and classes of drugs in the model are presented in Table 62. Comparator drug acquisition costs are based on England and Wales Drug tariff costs http://www.ppa.org.uk/edt/February_2012/mindex.htm. These were used instead of BNF costs as they represent the drug cost actually paid by the NHS.

For dapagliflozin, the price per pack is £36.59 for 28 x 10mg tablets, representing a daily cost of £1.31 for the 10mg once daily dose. In the base case the daily cost of the most frequently prescribed generic SU (gliclazide 80mg tablet, representing 89% of the SU market in the UK based on IMS Disease Analyzer, Nov 2011, and IMS BPI/HPAI combined data, Dec 2011) and the most frequently prescribed DPP-4 (sitagliptin 500mg tablet, representing 80% of the DPP-4 market in the UK, based on IMS BPI/HPAI

combined data, Dec 2011) were applied to representative of these classes of drug. The only TZD available currently in the UK is pioglitazone. The weighted average of the daily costs of generic pioglitazone 15mg, 30mg and 45mg doses were applied, based on an estimated 34%, 40% and 26% use of each dose in clinical practice respectively (PACT data, January-Sept 2011). The lowest generic cost for metformin was used, and also the lowest cost available human NPH insulin regimen was applied (Insuman Basal). The cost of insulin in the model was applied as a cost per kg body weight per day, and hence changes with changes in patient body weight during the model simulation. The costs of insulin as the subsequent therapy options in the add-on to metformin indication are based on applying WHO defined daily doses (DDD) and dividing this by the mean body weight at baseline from the dapagliflozin Study 4 (88kg across all treatment arms) (Table 58). In the add-on to insulin analysis the insulin dose at initiation was calculated by dividing the mean insulin dose at baseline in dapagliflozin Study 6 (77.16 International Units) by the mean patient weight at baseline in this study (93.81kg for all patients in the study).

Intensified insulin used as second or third line treatment in the model (with or without OAD), and can consist of several frequently patient-tailored regimens of daily insulin injections. It was assumed that this consisted of a 50% increase in dose over the initial starting dose in the add-on to metformin analysis, and a 25% increase in the add-on to insulin analysis. Hence an annual drug cost 1.5 and 1.25 times that of insulin has been assumed for intensified insulin in each of the add-on to metformin and add-on to insulin analyses respectively (Table 58).

Table 62. Drug acquisition costs applied in the model for the add-on to metformin and add-on to insulin analyses

Therapy	Price per tablet Φ	Dose per tablet	Daily dose	Annual cost (£)
Dapagliflozin	£1.31	10mg	10mg	£476.92
SU (Gliclazide)	£0.04	80mg	160mg	£27.90
DPP-4 (sitagliptin)	£1.19	100mg	100mg	£433.57
TZD (non-proprietary pioglitazone)	£1.13	28.8mg*	28.8mg	£414.07
Metformin	£0.02	500mg	2000mg	£23.46
Insulin† (Insuman basal) – add-on to metformin	£0.0053 per kg/day			
Intensified insulin – add-on to metformin	£0.0080 per kg/day			
Insulin† (Insuman basal) – add-on to insulin	£0.0096 per kg/day**			
Intensified insulin – add-on to insulin	£0.0120 per kg/day**			

Φ The daily costs are based on pack costs and have been rounded. The source of the unit costs are England and Wales Drug Tariff costs, February 2012. These costs are in general consistent with BNF63 drug prices, although the estimates for pioglitazone are slightly lower than the BNF prices. In addition, BNF prices for metformin are about 1.5 times the cost in Table 23. However, as metformin is very low cost and is represented in both dapagliflozin and comparator arms this does not impact on the economic evaluation results.

*Weighted average of 15mg, 30mg and 45mg doses

**In addition to insulin, 50% of patients were assumed to be taking metformin, based on baseline data from study D1690C00006

†The cost of insulin in the add-on to metformin analysis was based on a patient baseline weight of 88kg, which if it remained stable would equate to an annual cost of £170.23 (and £256.96 for intensified insulin). The cost of insulin in the add-on to insulin analysis was based on patient baseline weight of 93.81kg, which if remained stable would equate to an annual cost of £328.71 (and £410.89 for intensified insulin). However, in the model weight changed over time, hence the actual annual cost of insulin (with dosage according to weight) in the economic analysis varies according to the simulated change in weight.

Drug administration and monitoring costs

As dapagliflozin and the primary comparators are oral antidiabetic drugs, no administration costs have been assumed. In addition, insulin is assumed to be self-administered.

As the efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients with moderate impairment and absent in patients with severe impairment it is not recommended for use in patients with moderate to severe renal impairment (Dapagliflozin SPC). Patient monitoring, including renal monitoring, is part of the routine clinical management of T2DM. However, we have included in the economic analysis the incremental cost associated with introducing renal monitoring on initiation of dapagliflozin treatment. This is estimated to include one GP visit (unit cost of £36, from Curtis 2011), and a 24 hour urine creatinine clearance test (unit cost of £2.67, NHS Kidney Care 2010).

6.5.6 Health-state costs

Complications costs

The annual costs of complications used in the economic model are presented in Table 63. The costs for fatal and non-fatal macrovascular (IHD, MI, CHF, and stroke) and microvascular events (blindness, ESRD and amputation) were primarily derived from the UKPDS sub-study (UKPDS 65) of the healthcare resource use during 1996-97 of 3,488 T2DM patients (inpatient and non-inpatient costs) (Clarke et al 2003). The original cost estimates are for the 1998/99 financial year but have been uprated to 2010-11 values using the Community Health Services inflator (Curtis 2011). The UKPDS 65 study estimated the first year event cost and the subsequent annual maintenance costs for patients who survived until the end of the simulation. Although dated, these estimates have been used as the basis for the cost of complications in all of the main validated T2DM models, including the UKPDS health outcomes model.

A cost for ESRD/renal failure was not covered by UKPDS 65; hence estimates for the costs of dialysis from a study in the UK setting by Baboolal et al (2008) was used instead, uprated to 2011 levels. The annual cost of £34,806 represents the average cost for automated peritoneal dialysis, continuous ambulatory peritoneal dialysis (PD), hospital haemodialysis (HD) and satellite unit based haemodialysis, weighted by an estimated proportion of use of each approach in the UK (i.e. 20% PD, 80% HD). A cost estimate for ESRD beyond year 1 was not directly available, so it was assumed that a constant annual cost of £34,806 associated with ongoing dialysis would be incurred. The

cost of blindness can only be incurred once as patients were assumed to incur severe vision loss/blindness in both eyes simultaneously.

Table 63. Annual direct medical complication costs included in the model (for both add-on to metformin, and insulin analyses*)

Event	Fatal	Non-fatal	Maintenance	Reference
Ischaemic heart disease	-	£ 3,479	£ 1,149	Clarke, 2003
Myocardial infarction	£ 2,244	£ 6,709	£ 1,105	Clarke, 2003
Congestive heart failure	£ 3,880	£ 3,880	£ 1,360	Clarke, 2003
Stroke	£ 5,658	£ 4,103	£ 776	Clarke, 2003
Amputation	£ 13,359	£ 13,359	£ 771	Clarke, 2003
Blindness	-	£ 1,752	£ 742	Clarke 2003
End stage renal disease	-	£ 34,806	£ 34,806	Baboolal et al., 2008

* Prices were indexed to 2011 using the Hospital and Community Health Services Pay & Prices index reported in the PSSRU Unit Costs of Health and Social Care reports of 2007 and 2011, available at http://www.pssru.ac.uk/project-pages/unit-costs/2011/index.php.

6.5.7 Adverse-event costs

Hypoglycaemia

The costs associated with hypoglycaemic events are shown in Table 64.

Table 64. Cost of hypoglycaemic events

Hypoglycaemic event	Event cost †	Reference
Symptomatic	£ 0	Assumption
Nocturnal	£ 0	Assumption
Severe	£ 390	Hammer et al., 2009

† 2007 costs were inflated to 2011 costs using the Hospital and Community Health Services Pay & Prices index reported in the PSSRU Unit Costs of Health and Social Care 2011 available at http://www.pssru.ac.uk/project-pages/unit-costs/2011/index.php (index 2006/7: 249.8; 2010/11: 276).

Costs were included in the model for severe hypoglycaemic events only, based on evidence from a published study by Hammer et al (2009) of health service resource use covering 320 T2DM patients in Germany, Spain and the UK (approximately one third of the patients), who had experienced ≥1 hypoglycaemic event in the previous year (Hammer et al 2009). From data on direct healthcare costs in this study an estimated cost of £390 per severe episode was applied in the dapagliflozin economic model (Table 64). This cost has been converted back to GBP from Euros presented in the publication

and uprated from the original 2007 cost year to 2010-11 values using the hospital and community health services (HCHS) inflator (Curtis 2011). It was assumed no costs were associated with non-severe symptomatic and nocturnal hypoglycaemic events, in line with most other economic evaluations of T2DM treatments.

The Hammer et al study was used as it represents the most recent assessment of health care costs associated with hypoglycaemia. It covers a wide range of direct health care costs including primary care visits, hospital costs, and out of hospital health care professional contacts, ambulance services and drug treatment. An earlier UK relevant study on the inpatient, ambulance and A & E costs of severe hypoglycaemia has been performed, with original cost year estimates of £218, £127 and £89 for each type of resource respectively (Leese et al 2003). However, this study was not used as separate cost estimates were not available for type 1 and T2DM, and the cost year was 1997/98 hence dated compared to the Hammer et al study which had a 2007 cost year.

Other adverse events

A cost was included in the model for the management of UTI and GI AEs, assumed to consist of the cost of a GP visit at £36, derived from Curtis (2011). This does not include the costs of antibiotics, urine analysis or other drugs/tests. However, the main cost is likely to be the GP consultation. A UK study on the cost-effectiveness of management strategies for UTIs included these additional costs and reported a cost ranging from £31-£37 per UTI mainly driven by the initial GP consultation (Turner et al 2010), hence supportive of the value assumed in the model.

Table 65. Cost of treatment-related adverse events

Event	Event cost*	Assumption (source)
Urinary tract infection	£ 36	1 GP surgery consultation
Genital infection	£ 36	

Source : Curtis 2011

6.5.8 Miscellaneous costs

Treatment discontinuation was assumed to incur the cost of a visit to the GP (£36; Curtis 2011).

6.6 Sensitivity analysis

6.6.1 Uncertainty around structural assumptions

The structure of the model was similar to a previously developed and validated cost-effectiveness model (AZ Diabetes model; McEwan et al 2010). This model has been previously tested and internally validated against the UKPDS 68, upon which it was based (Clarke et al 2004). In addition, the model was also externally validated as part of the Mount Hood Challenges and has endured the scrutiny associated with peer-review publications and health technology assessments (in support of submissions of saxagliptin). In this light, structural assumptions of the model concerning long term

predictions of complications based on the UKPDS 68 were assumed to be valid and were not investigated in scenario or sensitivity analyses. Additional model validation is also presented in Section 9.19, Appendix 19.

Scenario analyses relating to structural assumptions consisted of investigating the following (see also Section 6.6.2, Table 67):

- Alternative HbA1c treatment switching thresholds.
- Alternative scenarios regarding the prediction of body weight/BMI over time.
- Alternative time horizons.

6.6.2 Deterministic sensitivity analysis

Univariate sensitivity analysis was performed, varying treatment effect and BMI utility parameters around the 95% confidence/credible intervals available, varying disutilities for T2DM complications by ±10%, and total non-drug costs by ±25% (Table 66).

Table 66. Parameters varied in univariate sensitivity analyses

Parameter	Mean	Lower limit (CI or CrI)*	Upper limit (CI or CrI)*
Specific for MET + SU comparison			
ΔHbA1c dapagliflozin	-0.52	-0.60	-0.44
ΔHbA1c SU	-0.52	-0.60	-0.44
ΔWeight dapagliflozin	-3.22	-3.56	-2.88
ΔWeight SU	1.44	1.10	1.78
ΔSBP dapagliflozin	-4.30	-5.45	-3.15
ΔSBP SU	0.80	-0.35	1.95
Specific for MET + DPP-4 comparison			
ΔHbA1c dapagliflozin	-0.58	-0.90	-0.26
ΔHbA1c DPP-4	-0.74	-0.88	-0.60
ΔWeight dapagliflozin	-2.79	-3.69	-1.89
ΔWeight DPP-4	-0.51	-1.05	0.03
ΔSBP dapagliflozin	-4.50	-7.20	-1.80
ΔSBP DPP-4	-1.37	-4.36	1.62
Specific for MET + TZD comparison			
ΔHbA1c dapagliflozin	-0.58	-0.90	-0.26
ΔHbA1c TZD	-0.90	-1.14	-0.66
ΔWeight dapagliflozin	-2.79	-3.69	-1.89
ΔWeight TZD	1.72	0.79	2.65
ΔSBP dapagliflozin	-4.50	-7.20	-1.80
ΔSBP TZD	-2.87	-7.27	1.53
Specific for INS + DPP-4 comparison			
ΔHbA1c dapagliflozin	-0.82	-0.96	-0.68
ΔHbA1c DPP-4	-0.69	-0.85	-0.53
ΔWeight dapagliflozin	-1.63	-2.13	-1.13
ΔWeight DPP-4	0.19	-0.18	0.56
Generic (univariate sensitivity analyses conducted for all comparisons)			
Utility BMI increase	0.0472	0.038	0.057
Utility BMI decrease	0.0171	0.011	0.024
Utilities complications	n/a	-10%	+10%
All costs except drug costs	n/a	-25%	+25%

*Confidence Interval (CI) for efficacy variables if from clinical trial, or Credible interval (CrI) if from NMA

An overview of scenario analyses that were conducted for each of the comparator treatments is shown in Table 67.

Table 67. Overview of scenario analyses conducted for each comparison

		Dapa as add-on to metformin		Dapa as add-on to INS	
		Comparator treatment			
No	Scenario	MET+SU	MET+DPP-4	MET+TZD	INS+DPP-4
1	HbA1c threshold 7.5% - add-on to met	x	x	x	
2	HbA1c threshold 8.5% - add on to met	x	x	x	x
3	HbA1c threshold 8.0% - add on to INS	x	x	x	x
4	HbA1c threshold 9.0%- add on to INS				x
5	HbA1c threshold 9.5%- add on to INS				x
6	Use utility values by Bagust et al (±0.0061)	x	x	x	x
7	Adjusted Bagust (±0.0038)	x	x	x	x
8	Zero disutilities for hypoglycaemia	x	x	x	x
9	Extrapolation weight: set years until loss of weight effect to 1	x	x	x	x
10	Extrapolation weight: convergence of weight curves after second switch			x	x
11	Use of 52-week NMA data	x	x	x	
12	Same discontinuation rate for all drugs (set to zero)	x	x	x	x
13	Baseline characteristics of UK population with clinical history parameters	x	x	x	x
14	Include BMI costs	x	x	x	x
15	Leese 2003 costs for hypoglycaemic events	x	x	x	x
16	50% lower year 2 onwards ESRD costs	x	x	x	x
17	Discount rates cost/effects 0%	x	x	x	x
18	Discount rates costs/effect 6%	x	x	x	x
19	Time horizon of 20 years	x	x	x	x
20	Multivariate scenarios	x	x	x	x

The main rationale for each of the scenario analyses conducted is as follows:

HbA1c treatment switch thresholds (Scenarios 1-5):

In the base case threshold HbA1c values from the dapagliflozin clinical trials and NMAs were used to determine treatment switch decisions in the model. These were applied in

the base case as they relate to the treatment efficacy estimates used for the add-on to metformin and add-on to insulin analyses. However, this meant that the thresholds varied for each dapagliflozin comparison according to the specific data source used which may not reflect clinical practice. Hence, a number of scenario analyses were conducted using a constant HbA1c thresholds for switching to the next line of treatment for each comparison. For the add-on to metformin analyses, single values of 7.5% and 8.5% were used (scenarios 1-2). For the add-on to insulin analyses, single HbA1c thresholds ranging between 8%, 9% and 9.5% were tested (scenarios 3- 5).

BMI-related utilities (Scenarios 6-7)

As body weight and quality of life effects related to BMI are important parameters in these analyses, scenario analyses were conducted whereby alternative published utilities assigned to a unit change in BMI was used i.e. in scenario 6 a value of -0.0061 per unit increase in BMI which was based on Bagust et al (2005). Although not directly assessed in Bagust et al, as this value was derived from a linear regression modelling exercise we also applied a +0.0061 value to each unit decrease in BMI to reflect a gain in HRQoL from a reduction in patient body weight associated with treatment. The TTO study that was used to provide the base case values for BMI related utilities specifically assessed the value associated with weight loss and found a HRQoL benefit from weight loss as well as a HRQoL loss from weight gain. Hence, given the plausibility of this outcome (and conversely the implausibility that there would be no HRQoL benefit from weight loss) we also apply the Bagust estimate as both a utility loss and utility gain. This represents a relatively pessimistic scenario relative to the base case (scenario 6). In the ERG report for the HTA performed for exanetide (Waugh et al 2011) an adjusted Bagust disutility value of utility of -0.0038 was applied (page 45 of the ERG report). In this analysis the ERG found that the EQ-5D TTO tariff based values used to estimate the value of 0.0061 were constrained to fall within the interval of -0.6 to 1.0, whereas the VAS EQ 5D values fell between 0-1. Therefore adjusting the TTO values resulted in the value of 0.0038. We feel this is an arbitrary and unduly pessimistic adjustment as it is based on a VAS adjustment, and the EQ-5D TTO tariff, the relatively robust valuation method, is not typically constrained by a zero to one value in usual applications of the EQ-5D. Hence, we feel it is plausible for there to be negative EQ-5D values for weight increase. Nonetheless, in a highly pessimistic scenario we apply this as a disutility to BMI increase, and a utility gain for BMI decrease in scenario 7.

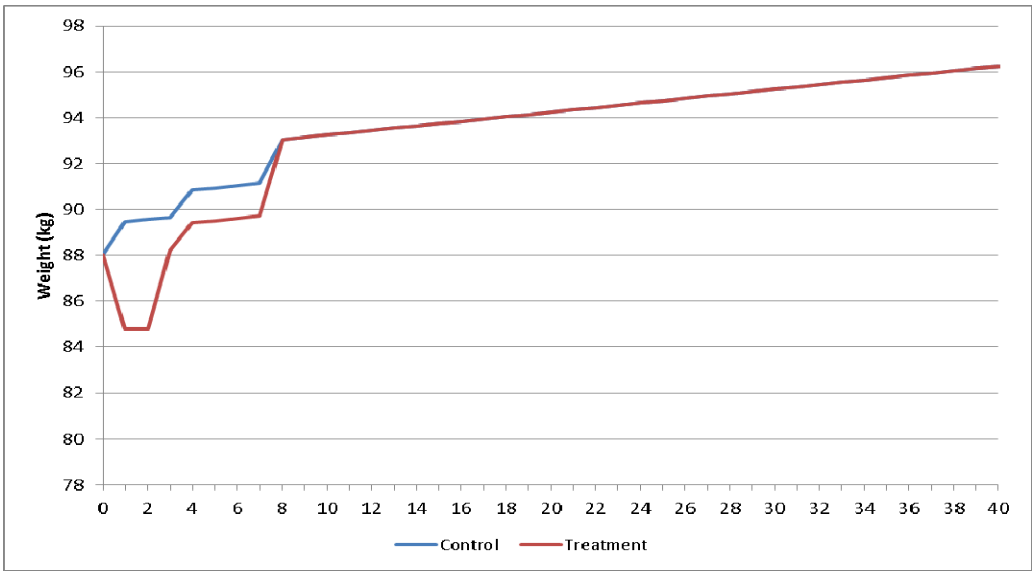
Hypoglycaemia related disutilities (scenario 8)

A scenario in which no disutility is applied to fear of hypoglycaemic episodes was also examined. This is a relatively extreme scenario but reflects some uncertainty in the values derived for this from the Currie et al (2006) study. This is applied as scenario 8.

Body weight change (scenarios 9-10)

Assumptions regarding extrapolation of weight were varied (scenarios 9-10). In scenario 9, it has been assumed that patients will have regained the weight lost within one year following the 2-year period of sustained weight loss. In scenario 10 it has been assumed that the weight curves of dapagliflozin and its comparator arm converge after the second treatment switch, as illustrated in Figure 29.

Figure 29. Illustration of converging body weight profiles (Scenario analysis No. 11)



52 week NMA data, and discontinuations due to AEs (scenario 11)

In the base case 24 week NMA data was used for comparisons with DPP-4 and TZD, as well as the comparative trial vs. SU (add-on to met). However, NMA was also performed using 52 week data. The 24-week NMA data were chosen as the base case, as this was regarded as the more complete and more robust dataset in terms of range of endpoints and amount of evidence informing the NMA. However, scenario analysis 9 uses the 52 week NMA in place of the comparative data vs SU, and the 24 week NMA data. The baseline characteristics as per the 52 week NMA are also applied (Table 68).

Table 68. Baseline, efficacy and tolerability inputs for add-on to MET comparisons based on 52-week NMA data (Scenario analysis 9)

Variable	Value			
Baseline characteristics †				
Age (yrs)	57.51			
% female	0.47			
Duration diabetes (yrs)	5.17			
Height (m)	1.69			
%AC	0.062 ‡			
% smokers	0.369			
HbA1c (%)	8.05			
TC (mg/dL)	199.57			
HDL-C (mg/dL)	44.09			
SBP (mmHg)	133.3			
Weight (kg)	87.84			
Treatment effects of efficacy and tolerability	**MET+SGLT2**	**MET+SU**	**MET+DPP-4**	**MET+TZD**
ΔHbA1c (%)	-0.92	-0.916	-0.84	-0.9
ΔWeight (kg)	-2.86	1.81	-0.11	0**
ΔSBP, ΔTC, ΔHDL-C	0**	0**	0**	0**
%Hypo (sympt)	0.031	0.394	0.046	0.061
%Hypo (severe)	0.00036	0.00453	0.00053	0.0007
%UTI	0.074 * 0.108 ^	0.064	0.054	0**
%GI	0.123	0.027	0**	0**
%Disc. due to AE	0.081	0.047	0.043	0.041

Abbreviations: AC, Afro-Caribbean; AE, adverse event; Disc. Discontinuation; DPP-4, dipeptidyl peptidase 4 inhibitor; GI, genital infection; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hypo, hypoglycaemia; MET, metformin; n/a. not available; NMA, network meta-analysis; SBP, systolic blood pressure; SGLT2, sodium-glucose co-transporter 2 inhibitor (dapagliflozin); SU, sulphonylurea; sympt, symptomatic; TC, total cholesterol; TZD, thiazolidinedione; UTI, urinary tract infection.
† Baseline data are the same for all comparisons.
‡ There was no estimate available from the 24-week NMA for %AC; instead the value of Nauck, 2011, was taken.
* This rate was used for the comparison versus MET+DPP-4
^ This rate was used for the comparison versus MET+SU
** No estimate available; assumed zero value.

In a further scenario analysis the discontinuation rates associated with AEs were set to the same for both dapagliflozin and the comparator treatments (scenario 12).

Baseline characteristics and clinical history parameters (scenario 13)

In scenario analysis 13 baseline characteristics of a UK diabetic population have been applied sourced from an observational study including England, in patients who have failed on MET monotherapy (Alvarez Guisasola et al 2008) (Table 69).

Table 69. Alternative baseline patient characteristics (Scenario analysis 13)

Variable	UK (Alvarez Guisasola et al., 2008)
Baseline characteristics	
Age	60.2
Gender (%male)	57.9%
Duration of diabetes (yrs)	5.1
Height (m)	1.67 **
HbA1c (%)	8.6
Total cholesterol (mg/dL)	189.5
HDL cholesterol (mg/dL)	50.3
SBP (mmHg)	139.3
Weight (kg)	88.02 **
Smokers (%)	15.5%

**These data were not available from Alvarez Guisasola et al hence the Values for weight and height from the comparative trial vs SU (Nauck 2011) have been used instead (see Table 57).

As part of scenario 13, the prevalence estimates for clinical history parameters as presented in Table 70 were applied at model baseline. These are the values that were used in the UKPDS Health Outcomes model by the NICE Clinical Guidelines Group within the scope of assessing newer T2DM drugs (Waugh et al 2010). The positive prevalence values are derived from a study using data from a large UK general practice database (Rubino et al 2007). Direct estimates for amputations, blindness in one eye and ESRD were not available from this study.

Table 70. Clinical history parameters (Scenario analysis 13)

Prior complication	Prevalence
MI	8.2%
Stroke	4.9%
CHF	3.7%
Blindness	0%
Amputation	0%
End stage renal disease	0%

Inclusion of BMI related costs, and alternative costs for hypoglycaemia and ESRD (scenario 14-16)

A number of scenario analyses were conducted relating to costs. The base case assumes no costs related to change in weight/BMI outcomes for each of the drugs considered. In scenario 14 an annual cost related to the patient's BMI, stratified by gender was applied as shown in Table 71. The costs were derived from a published study into the influence of BMI on prescribing costs in a UK healthcare setting (Counterweight Project Team, 2008). In this study, annual mean total costs of drug prescriptions for men and women by BMI level were estimated following review of medical records of 3400 randomly selected adult patients from 23 UK primary care practices (period 2000-2002). The study showed a clear trend of increase in prescription costs with increasing BMI. Thus, weight reduction could potentially lead to cost savings. However, from the published source it is not known to what extent the additional prescribing costs associated with BMI are related to the use of anti-diabetic therapies. The costs of drug therapy has already been accounted for in the model, hence inclusion

of the costs in Table 71 related to weight change outcomes associated with each OAD considered may risk an element of double counting. As there is uncertainty over the additional costs associated with weight management in T2DM patients the BMI related costs are only applied in scenario analysis.

Table 71. Annual cost of drug prescriptions by BMI level (Scenario analysis 14)

Body mass index	Annual cost (£ 2011)		Reference
	Men	Women	
18.5-20	£71	£88	Counterweight Project Team, 2008. 2001 costs were using the Hospital and Community Health Services Pay & Prices index (Curtis 2011)
21	£78	£93	
22	£84	£99	
23	£92	£105	
24	£100	£111	
25	£108	£117	
26	£111	£114	
27	£114	£111	
28	£116	£107	
29	£119	£104	
30	£163	£156	
31	£172	£162	
32	£182	£168	
33	£192	£175	
34	£203	£181	
35	£214	£188	
36	£226	£195	
37	£238	£202	
38	£251	£210	
39	£265	£218	
≥40	£279	£226	

A further scenario analysis (scenario 15) was performed using the costs of hypoglycaemia reported in a published study by Leese et al (2003), which has been used in several previous HTAs. The base case used more recent and comprehensive cost estimates from Hammer et al (2009). In addition, as there is uncertainty concerning year 2 and subsequent year costs for ESRD a reduction in cost of 50% in year 2 onwards has been applied (scenario 16).

Discount rates and time horizon (scenarios 17-19)

Two scenario analyses were conducted to investigate the impact on the CE results of 0% discount rates (Scenario 17), and a 6% discount rate (Scenario 18) for costs and effects. The impact of assuming a shorter time horizon (20 years) than in the base case was also explored (scenario 19).

Multivariate scenario (scenario 20)

In this scenario a combination of the above scenarios above were combined. This consisted of using a single HbA1c treatment switch threshold of 8% for add-on to MET, and 8.5% for the add-on to insulin analyses, the use of the Bagust utility values (±0.0061), the characteristics of the UK baseline population only, non-zero clinical history

parameters, and use of the 52 week NMA results (for the add-on to MET analysis). This has been designed to represent a pessimistic multivariate scenario to show the impact on the ICER range for each comparison.

6.6.3 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted by simulating 1,000 cohorts of 30,000 patients in which values of key parameters were drawn randomly and independently from the parameter distributions. If standard errors (SE) were available, then these were used for the parameter distribution. If an SE was not available then it was assumed to be 20% of the mean. For probabilities, missing SEs were calculated assuming that the probability estimate had been determined based on 100 subjects. In general, beta distributions were used for utilities and probability estimates, gamma distributions were used for costs, and normal distributions were used for the other parameters. Details on the parameters, standard errors and assumptions are provided in Table 72.

Table 72. Model parameters and parameter distributions varied in the PSA

Parameter	Mean	SE	Parameter 1	Parameter 2	Distribution
Specific for MET + SU comparison					
ΔHbA1c dapagliflozin	-0.52	0.04	-0.52	0.04	Normal
ΔHbA1c SU	-0.52	0.04	-0.52	0.04	Normal
ΔWeight dapagliflozin	-3.22	0.18	-3.22	0.18	Normal
ΔWeight SU	1.44	0.18	1.44	0.18	Normal
ΔSBP dapagliflozin	-4.30	0.59	-4.30	0.59	Normal
ΔSBP SU	0.80	0.59	0.80	0.59	Normal
ΔTC dapagliflozin	0.071	0.0142	0.071	0.0142	Normal
ΔTC SU	-0.028	0.0056	-0.028	0.0056	Normal
ΔHDL dapagliflozin	0.070	0.0140	0.070	0.0140	Normal
ΔHDL SU	-0.0019	0.0004	-0.0019	0.0004	Normal
No. hypo sympt– dapagliflozin	0.035	0.0092	0.035	0.0092	Normal
No. hypo sympt– SU	0.408	0.0240	0.408	0.0240	Normal
% hypo severe – SU	0.0074	0.0085	0.0074	0.0085	Normal
% UTI – dapagliflozin	0.108	0.0310	0.108	0.0310	Normal
%UTI – SU	0.064	0.0245	0.064	0.0245	Normal
% GI – dapagliflozin	0.123	0.0328	0.123	0.0328	Normal
% GI – SU	0.027	0.0162	0.027	0.0162	Normal
Specific for MET + DPP-4 comparison					
ΔHbA1c dapagliflozin	-0.58	0.16	-0.58	0.16	Normal
ΔHbA1c DPP-4	-0.74	0.07	-0.74	0.07	Normal
ΔWeight dapagliflozin	-2.79	0.46	-2.79	0.46	Normal
ΔWeight DPP-4	-0.51	0.28	-0.51	0.28	Normal
ΔSBP dapagliflozin	-4.5	1.38	-4.50	1.38	Normal
ΔSBP DPP-4	-1.37	1.53	-1.37	1.53	Normal
No. hypo sympt– dapagliflozin	0.075	0.0150	0.075	0.0150	Normal
No. hypo sympt– DPP-4	0.049	0.0098	0.049	0.0098	Normal
% hypo severe – dapagliflozin	0.000077	0.0009	0.0001	0.0009	Normal
% hypo severe – DPP-4	0.00005	0.0007	0.0001	0.0007	Normal
% UTI – dapagliflozin	0.067	0.0250	0.0670	0.0250	Normal
%UTI – DPP-4	0.052	0.0222	0.0520	0.0222	Normal
% GI – dapagliflozin	0.089	0.0285	0.0890	0.0285	Normal
% GI – Dpp4	0.005	0.0071	0.0050	0.0071	Normal
Specific for MET + TZD comparison					
ΔHbA1c dapagliflozin	-0.58	0.16	-0.58	0.16	Normal
ΔHbA1c TZD	-0.90	0.12	-0.90	0.12	Normal
ΔWeight dapagliflozin	-2.79	0.46	-2.79	0.46	Normal
ΔWeight TZD	1.72	0.47	1.72	0.47	Normal
ΔSBP dapagliflozin	-4.50	1.38	-4.50	1.38	Normal
ΔSBP TZD	-2.87	2.24	-2.87	2.24	Normal
% hypo sympt – dapagliflozin	0.075	0.015	0.075	0.015	Normal
% hypo sympt – TZD	0.023	0.0046	0.023	0.0046	Normal
% hypo severe – dapagliflozin	0.000077	0.0009	0.000077	0.0009	Normal
% hypo severe – TZD	0.000024	0.0005	0.0000	0.0005	Normal
% UTI – dapagliflozin	0.081	0.0273	0.081	0.0273	Normal
%UTI – TZD	n/a	n/a	n/a	n/a	n/a
% GI – dapagliflozin	0.089	0.0285	0.089	0.0285	Normal
% GI – TZD	n/a	n/a	n/a	n/a	n/a
Specific for INS + DPP-4 comparison					
ΔHbA1c dapagliflozin	-0.82	0.07	-0.82	0.07	Normal
ΔHbA1c DPP-4	-0.69	0.08	-0.69	0.08	Normal
ΔWeight dapagliflozin	-1.63	0.26	-1.63	0.26	Normal
ΔWeight DPP-4	0.19	0.19	0.19	0.19	Normal
ΔSBP dapagliflozin	n/a	n/a	n/a	n/a	n/a
ΔSBP DPP-4	n/a	n/a	n/a	n/a	n/a
No. hypo sympt– dapagliflozin	1.4	0.042	1.4	0.042	Normal
No. hypo sympt – DPP-4	1.44	0.037	1.44	0.037	Normal
% hypo severe – dapagliflozin	0.0068	0.008	0.0068	0.008	Normal
% hypo severe – DPP-4	0.007	0.008	0.007	0.008	Normal
% UTI – dapagliflozin	0.056	0.023	0.056	0.023	Normal
%UTI – DPP-4	0.063	0.024	0.063	0.024	Normal
% GI – dapagliflozin	0.092	0.029	0.092	0.029	Normal

Parameter	Mean	SE	Parameter 1	Parameter 2	Distribution
% GI – DPP-4	0.003	0.005	0.003	0.005	Normal
Generic parameters utilities					
BMI (unit decrease)	0.0171	0.0035	23.8661	1371.8137	Beta
BMI (unit increase)	0.0472	0.0049	86.6192	1748.5337	Beta
Baseline Age-dependent (study 4)	0.877	0.1754	2.1980	0.3083	Beta
Baseline Age-dependent (24 week NMA)	0.882	0.1764	2.0680	0.2767	Beta
Baseline Age-dependent (24 week NMA)	0.878	0.1756	2.1720	0.3018	Beta
IHD	0.090	0.0180	22.6600	229.1178	Beta
MI	0.055	0.0110	23.5700	404.9755	Beta
CHF	0.108	0.0216	22.1920	183.2895	Beta
Stroke	0.164	0.0328	20.7360	105.7030	Beta
Amputation	0.280	0.0560	17.7200	45.5657	Beta
Blindness	0.074	0.0148	23.0760	288.7618	Beta
ESRD	0.263	0.0526	18.1620	50.8950	Beta
Generic parameters Costs					
Severe hypoglycaemia	£390	78	15.6	25.00	Gamma
IHD – Non fatal	£3,479	695.8	139.16	25.00	Gamma
IHD – Maintenance	£1,149	229.8	45.96	25.00	Gamma
MI - Fatal	£2,244	448.8	89.76	25.00	Gamma
MI - Non fatal	£6,709	1341.8	268.36	25.00	Gamma
MI – Maintenance	£1,105	221	44.2	25.00	Gamma
Stroke – Fatal	£5,658	1131.6	226.32	25.00	Gamma
Stroke - Non fatal	£4,103	820.6	164.12	25.00	Gamma
Stroke – Maintenance	£776	155.2	31.04	25.00	Gamma
CHF – Fatal	£3,880	776	155.2	25.00	Gamma
CHF - Non fatal	£3,880	776	155.2	25.00	Gamma
CHF – Maintenance	£1,360	272	54.4	25.00	Gamma
Amputation - Fatal	£13,359	2671.8	534.36	25.00	Gamma
Amputation - Non fatal	£13,359	2671.8	534.36	25.00	Gamma
Amputation – Maintenance	£771	154.2	30.84	25.00	Gamma
Blindness - Non fatal	£1,752	350.4	70.08	25.00	Gamma
Blindness – Maintenance	£742	148.4	29.68	25.00	Gamma
ESRD - Non fatal	£34,806	6961.2	1392.24	25.00	Gamma
ESRD – Maintenance	£34,806	6961.2	1392.24	25.00	Gamma

*Bounded between 0 and 1

Abbreviations: BMI, body mass index; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase 4 inhibitor; ESRD, end stage renal disease; GI, genital infection; HbA1c, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; hypo, hypoglycaemia; IHD, ischaemic heart disease; MET, metformin; MI, myocardial infarction; n/a, not available; NMA, network meta-analysis; SBP, systolic blood pressure; SU, sulphonylurea; sympt, symptomatic; TC, total cholesterol; TZD, thiazolidinedione; UTI, urinary tract infection.

6.7 Results

Clinical outcomes from the model

6.7.1 Summary of clinical outcomes from the model

Comparative data for dapagliflozin and SU were available for the comparison with SU as an add-on to metformin, and 24-Week/52-week clinical trial data were used within a NMA to provide the main efficacy and tolerability estimates in the model for the other comparisons. Therefore clinical outcomes in the model at Year 1 are as presented in the table of clinical data inputs in Section 6.3.6. Two-year efficacy and safety data were available for dapagliflozin but not in sufficient detail for comparator drugs. No longer-term data of outcomes were available from the clinical trials and cannot therefore be compared to outcomes from the model.

The disaggregated lifetime predicted complication events, hypoglycaemia, UTI and GI, from the model are presented below for each comparison.

Add-on to metformin: dapagliflozin versus SU

Table 73 shows the model predicted lifetime (40 year) cumulated number of diabetes related complications per patient for both treatment arms, as well as the predicted number of treatment related AEs.

Table 73. Lifetime predicted cumulative number of events per patient; MET+dapagliflozin vs MET+SU

	MET+dapagliflozin		MET+SU		Incremental	
Variable	Non-Fatal	Fatal	Non-Fatal	Fatal	ΔNon-fatal	ΔFatal
Macrovascular events						
IHD	0.129	0.000	0.132	0.000	*-0.003*	*0.000*
MI	0.202	0.116	0.205	0.121	*-0.003*	*-0.005*
Stroke	0.087	0.015	0.092	0.017	*-0.004*	*-0.002*
CHF	0.058	0.039	0.059	0.017	*-0.001*	*0.023*
Microvascular events						
Blindness	0.078	0.000	0.078	0.000	*0.000*	*0.000*
Nephropathy	0.014	0.015	0.015	0.016	*-0.001*	*-0.001*
Amputation	0.026	0.026	0.027	0.028	*-0.001*	*-0.001*
Adverse events						
UTI	0.386		0.237		*0.149*	
GI	0.440		0.100		*0.340*	
Hypoglycaemia (sympt)	8.803		10.058		*-1.254*	
Hypoglycaemia (severe)	0.448		0.469		*-0.022*	

Abbreviations: CHF, congestive heart failure; GI, genital infection; IHD, ischaemic heart disease; MET, metformin; MI, myocardial infarction; SU, sulphonylurea; sympt, symptomatic; UTI, urinary tract infection.

Table 74 presents the average duration on each treatment line simulated in the model with a lifetime horizon for the MET+dapagliflozin strategy and the MET+SU strategy.

Table 74. Duration in years on each treatment line;MET+dapagliflozin vs MET+SU

	Dapagliflozin	SU
Duration Met+dapa vs Met+SU (yrs)	3.59	3.71
Duration 2nd therapy –insulin (yrs)	3.78	3.77
Duration 3rd therapy – intensified insulin (yrs)	14.24	14.03
Total	***21.61***	***21.51***

Add-on to metformin: dapagliflozin versus DPP-4

Table 75 shows the model predicted lifetime cumulated number of diabetes related events per patient for both treatment arms, and the estimated number of treatment related AEs.

Table 75. Lifetime predicted cumulative number of events per patient; MET+dapagliflozin vs MET+DPP-4

	MET+dapagliflozin		MET+DPP-4		Incremental	
Variable	Non-Fatal	Fatal	Non-Fatal	Fatal	ΔNon-fatal	ΔFatal
Macrovascular events						
IHD	0.139	0.000	0.140	0.000	*-0.001*	*0.000*
MI	0.238	0.129	0.240	0.130	*-0.002*	*-0.002*
Stroke	0.098	0.017	0.101	0.018	*-0.002*	*-0.001*
CHF	0.056	0.036	0.057	0.018	*-0.001*	*0.018*
Microvascular events						
Blindness	0.080	0.000	0.079	0.000	*0.001*	*0.000*
Nephropathy	0.016	0.017	0.017	0.018	*-0.001*	*-0.001*
Amputation	0.033	0.032	0.033	0.032	*-0.001*	*0.000*
Adverse events						
UTI	0.322		0.295		*0.027*	
GI	0.428		0.028		*0.399*	
Hypoglycaemia (sympt)	8.462		7.862		*0.599*	
Hypoglycaemia (severe)	0.493		0.470		*0.023*	

Abbreviations: CHF, congestive heart failure; DPP-4, dipeptidyl peptidase 4 inhibitor; GI, genital infection; IHD, ischaemic heart disease; MET, metformin; MI, myocardial infarction; sympt, symptomatic; UTI, urinary tract infection.

The estimated average duration on each treatment line is presented for the MET+dapagliflozin strategy and the MET+DPP-4 strategy in Table 76.

Table 76. Duration in years on each treatment line;MET+dapagliflozin vs MET+DPP-4

	Dapagliflozin	DPP-4
Duration Met+dapa vs Met+DPP-4 (yrs)	4.82	5.70
Duration 2nd therapy –insulin (yrs)	5.55	5.46
Duration 3rd therapy – intensified insulin (yrs)	13.26	12.41
Total	***23.63***	***23.58***

Add-on to metformin: dapagliflozin versus TZD

Table 77 shows the model predicted lifetime cumulated number of diabetes related events per patient are presented for MET+dapagliflozin and MET+TZD, and the estimated number of treatment related AEs.

Table 77. Lifetime predicted cumulative number of events per patient; MET+dapagliflozin vs MET+TZD

	MET+dapagliflozin		MET+TZD		Incremental	
Variable	Non-Fatal	Fatal	Non-Fatal	Fatal	ΔNon-fatal	ΔFatal
Macrovascular events						
IHD	0.139	0.000	0.139	0.000	*-0.001*	*0.000*
MI	0.238	0.129	0.240	0.128	*-0.001*	*0.000*
Stroke	0.098	0.017	0.099	0.017	*-0.001*	*-0.001*
CHF	0.056	0.036	0.056	0.017	*0.000*	*0.018*
Microvascular events						
Blindness	0.080	0.000	0.079	0.000	*0.000*	*0.000*
Nephropathy	0.016	0.017	0.017	0.017	*-0.001*	*0.000*
Amputation	0.033	0.032	0.033	0.031	*0.000*	*0.001*
Adverse events						
UTI	0.389		0.000		*0.389*	
GI	0.428		0.000		*0.428*	
Hypoglycaemia (sympt)	8.462		7.373		*1.088*	
Hypoglycaemia (severe)	0.493		0.455		*0.038*	

Abbreviations: CHF, congestive heart failure; GI, genital infection; IHD, ischaemic heart disease; MET, metformin; MI, myocardial infarction; sympt, symptomatic; TZD, thiazolidinedione; UTI, urinary tract infection.

In Table 78 the duration on each treatment line simulated in the model is presented for the MET+dapagliflozin strategy and the MET+TZD strategy.

Table 78. Duration in years on each treatment line;MET+dapagliflozin vs MET+TZD

	Dapagliflozin	TZD
Duration Met+dapa vs Met+TZD (yrs)	4.82	6.42
Duration 2nd therapy –insulin (yrs)	5.55	5.39
Duration 3rd therapy – intensified insulin (yrs)	13.26	11.83
Total	***23.63***	***23.64***

Add-on to insulin: dapagliflozin versus DPP-4

Table 79 shows the model predicted lifetime cumulated number of diabetes related events per patient for INS+dapagliflozin and INS+DPP-4, and the estimated number of treatment related AEs.

Table 79. Lifetime predicted cumulative number of events per patient; INS+dapagliflozin vs INS+DPP-4

	INS+dapagliflozin		INS+DPP-4		Incremental	
Variable	**Non-Fatal**	**Fatal**	**Non-Fatal**	**Fatal**	**ΔNon-fatal**	**ΔFatal**
Macrovascular events						
IHD	0.123	0.000	0.123	0.000	*-0.0003*	*0.0000*
MI	0.165	0.080	0.165	0.081	*0.0001*	*-0.0006*
Stroke	0.058	0.010	0.058	0.011	*-0.0003*	*0.0000*
CHF	0.049	0.021	0.049	0.011	*-0.0003*	*0.0102*
Microvascular events						
Blindness	0.058	0.000	0.058	0.000	*0.0000*	*0.0000*
Nephropathy	0.019	0.012	0.019	0.012	*0.0000*	*0.0000*
Amputation	0.043	0.024	0.044	0.025	*-0.0007*	*-0.0003*
Adverse events						
UTI	0.419		0.420		*-0.0009*	
GI	0.689		0.020		*0.6688*	
Hypoglycaemia (sympt)	19.87		19.49		*0.3862*	
Hypoglycaemia (severe)	0.386		0.400		*-0.0143*	

Abbreviations: CHF, congestive heart failure; DPP-4, dipeptidyl peptidase 4 inhibitors; GI, genital infection; IHD, ischaemic heart disease; INS, insulin; MI, myocardial infarction; sympt, symptomatic; UTI, urinary tract infection.

In Table 80, the average duration on each treatment line simulated in the model is presented for the INS+dapagliflozin strategy and the INS+DP-P4 strategy.

Table 80. Duration in years on each treatment line; INS+dapagliflozin vs INS+DPP-4

	Dapagliflozin	DPP-4
Duration INS+dapa vs INS+DPP-4 (yrs)	7.51	6.68
Duration 2nd therapy – intensified insulin (yrs)	15.48	16.29
Total	***22.98***	***22.97***

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Not applicable.

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

For each simulated patient within a cohort, after every cycle, the model verifies whether micro-vascular or macro-vascular events, hypoglycaemic events or other AEs have occurred, and notes whether BMI changed over the cycle period. The appropriate utility decrements are then applied. The simulation continues until the end of the time horizon or until the subject dies. Once all individuals have been simulated summary statistics of QALYs over time are calculated for that particular cohort.

6.7.4 Life years and QALYs accrued for each clinical outcome

The model is not set up to report life years and QALYs accrued for individual clinical outcomes, therefore they are not presented here.

6.7.5 Disaggregated incremental QALYs and costs

The model is not set up to report disaggregated incremental QALYs by health state; therefore they are not presented here.

The costs by category per patient for the dapagliflozin strategy and the comparator strategies are presented below.

Add-on to metformin: dapagliflozin versus SU

Table 81: Lifetime discounted costs per patient: MET+dapagliflozin vs MET+SU

Variable	Dapagliflozin	SU	Difference
Treatment related			
Drug treatment (total)	£ 4,502	£ 2,977	*£ 1,525*
Severe hypoglycaemia	£ 115	£ 123	*– £ 8*
Other AE & renal monitoring	£ 67	£ 14	*£ 53*
Event related			
IHD	£ 1,168	£ 1,194	*– £ 26*
MI	£ 2,311	£ 2,355	*– £ 43*
Stroke	£ 583	£ 616	*– £ 33*
CHF	£ 582	£ 590	*– £ 8*
Blindness	£ 399	£ 396	*£ 3*
Nephropathy	£ 2,682	£ 2,878	*– £ 196*
Amputation	£ 497	£ 516	*– £ 19*
Total	**£ 12,904**	**£ 11,658**	***£ 1,246***

Abbreviations: AE. Adverse event; CHF, congestive heart failure; IHD, ischaemic heart disease; MET, metformin; MI, myocardial infarction; SU, sulphonylurea.

Add-on to metformin: dapagliflozin versus DPP-4

Table 82**. Lifetime discounted costs per patient; MET+dapagliflozin vs MET+DPP-4**

Variable	Dapagliflozin	DPP-4	Difference
Treatment related			
Drug treatment (total)	£4,984	£4,932	*£52*
Severe hypoglycaemia	£120	£112	*£8*
Other AE & renal monitoring	£64	£12	*£52*
Event related			
IHD	£1,287	£1,297	*-£10*
MI	£2,771	£2,783	*-£13*
Stroke	£662	£680	*-£18*
CHF	£566	£573	*-£7*
Blindness	£414	£411	*£3*
Nephropathy	£3,263	£3,469	*-£207*
Amputation	£602	£612	*-£9*
Total	**£14,733**	**£14,882**	***-£149***

Abbreviations: AE, adverse event; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase 4 inhibitor; IHD, ischaemic heart disease; MET, metformin; MI, myocardial infarction.

Add-on to metformin: dapagliflozin versus TZD

Table 83: Lifetime discounted costs per patient; MET+dapagliflozin vs MET+TZD

Variable	Dapagliflozin	TZD	Difference
Treatment related			
Drug treatment (total)	£ 4,984	£ 4,985	*– £ 1*
Severe hypoglycaemia	£ 120	£ 107	*£ 13*
Other AE & renal monitoring	£ 66	£ 2	*£ 64*
Event related			
IHD	£ 1,287	£ 1,289	*– £ 1*
MI	£ 2,771	£ 2,771	*£ 0*
Stroke	£ 662	£ 669	*– £ 7*
CHF	£ 566	£ 570	*– £ 4*
Blindness	£ 414	£ 412	*£ 3*
Nephropathy	£ 3,263	£ 3,394	*– £ 132*
Amputation	£ 602	£ 594	*£ 8*
Total	**£ 14,735**	**£ 14,793**	***– £ 58***

Abbreviations: AE, adverse event; CHF, congestive heart failure; IHD, ischaemic heart disease; MET, metformin; MI, myocardial infarction; TZD, thiazolidinedione.

Add-on to insulin: dapagliflozin versus DPP-4

Table 84. Lifetime discounted costs per patient: INS+dapagliflozin vs INS+DPP-4

Variable	Dapagliflozin	DPP-4	Difference
Treatment related			
Drug treatment (total)	£ 8,881	£ 8,402	*£ 479*
Severe hypoglycaemia	£ 92	£ 96	*-£ 4*
Other AE & renal monitoring	£ 74	£ 15	*£ 59*
Event related			
IHD	£ 1,164	£ 1,169	*-£ 5*
MI	£ 1,838	£ 1,842	*-£ 4*
Stroke	£ 394	£ 396	*-£ 1*
CHF	£ 484	£ 488	*-£ 4*
Blindness	£ 314	£ 314	*£ 0*
Nephropathy	£ 3,875	£ 3,867	*£ 7*
Amputation	£ 699	£ 709	*-£ 10*
Total	**£ 17,815**	**£ 17,298**	***£ 517***

Abbreviations: AE, adverse event; CHF, congestive heart failure; DPP-4, dipeptidyl peptidase 4 inhibitor; INS, insulin; IHD, ischaemic heart disease; MI, myocardial infarction.

Base-case analysis

6.7.6 Summary of results

The base case results for the model are presented in Table 85 as incremental comparisons for each of the main comparisons vs SU as add-on to metformin, vs DPP-4 or TZD as add-on to metformin, or DPP-4 as add-on to insulin.

Table 85. Base-case results

Technologies	Total			Incremental			ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	Incremental cost per QALY gained
Add-on to metformin							
Dapagliflozin vs SU							
SU	£ 11,658	14.71	11.28	-	-	-	-
Dapagliflozin	£ 12,904	14.76	11.74	+£ 1,246	+0.050	+0.467	£ 2,671
Dapagliflozin vs DPP-4, TZD							
Dapagliflozin	£ 14,733	15.67	12.62				Dominant
TZD	£ 14,793	15.67	12.20	+£60	-0	-0.42	Dominated by dapa
DPP-4	£ 14,882	15.64	12.60	+£149	-0.03	-0.02	Dominated by dapa
Add-on to insulin							
Dapagliflozin vs DPP-4							
DPP-4	£ 17,298	15.41	12.21	-	-	-	
Dapagliflozin	£ 17,815	15.41	12.33	+£ 517	0.007	0.119	£ 4,358

Abbreviations: DPP-4, dipeptidyl peptidase 4 inhibitor; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; QALYs, Quality-adjusted life years; SU, sulphonylurea; TZD, thiazolidinedione.

Sensitivity analyses

6.7.7 Deterministic sensitivity analysis

Add-on to metformin: dapagliflozin versus SU

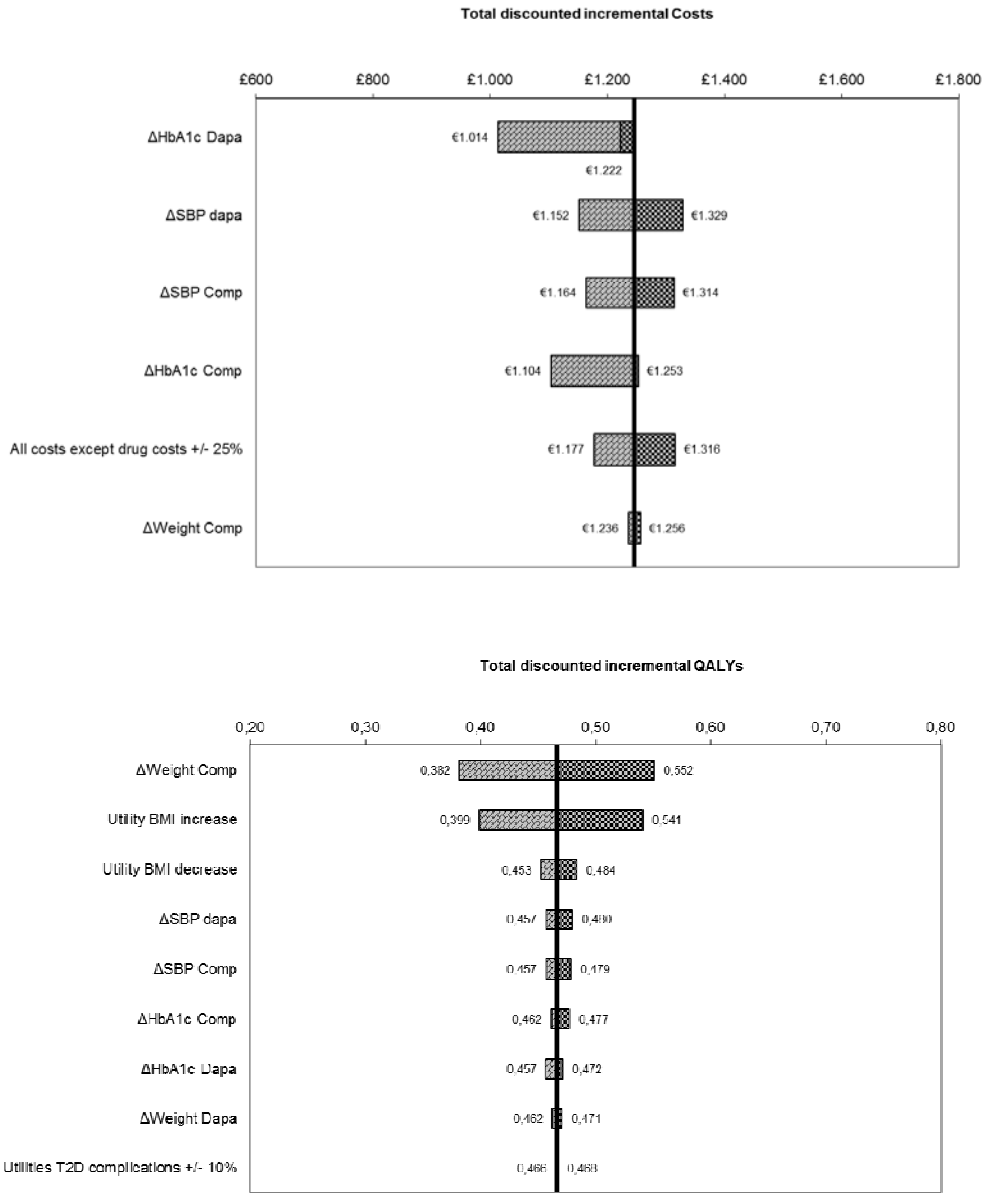
The results of the univariate sensitivity analysis are shown in Table 86, and displayed graphically by Tornado graphs in Figure 30.

Table 86. Summary of univariate sensitivity analyses: MET+dapagliflozin vs MET+SU

Parameter	Distribution	Value	ΔCosts	ΔQALYs	ICER
Base Case			***£1,246***	***0.467***	***£2,671***
HbA1c dapagliflozin LL	Normal	-0.60	£1,222	0.472	£2,589
HbA1c dapagliflozin UL	Normal	-0.44	£1,014	0.457	£2,218
HbA1c comparator LL	Normal	-0.60	£1,253	0.462	£2,714
HbA1c comparator UL	Normal	-0.44	£1,104	0.477	£2,312
Weight dapagliflozin LL	Normal	-3.56	£1,246	0.471	£2,647
Weight dapagliflozin UL	Normal	-2.88	£1,246	0.462	£2,695
Weight comparator LL	Normal	1.10	£1,256	0.382	£3,290
Weight comparator UL	Normal	1.78	£1,236	0.552	£2,241
SBP dapagliflozin LL	Normal	-5.45	£1,152	0.480	£2,400
SBP dapagliflozin UL	Normal	-3.15	£1,329	0.457	£2,907
SBP comparator LL	Normal	-0.35	£1,314	0.457	£2,875
SBP comparator UL	Normal	1.95	£1,164	0.479	£2,433
Utility BMI increase LL	Beta	0.038	£1,246	0.399	£3,122
Utility BMI increase UL	Beta	0.057	£1,246	0.541	£2,303
Utility BMI decrease LL	Beta	0.011	£1,246	0.453	£2,753
Utility BMI decrease UL	Beta	0.025	£1,246	0.484	£2,577
Utilities complications +10%			£1,246	0.468	£2,666
Utilities complications −10%			£1,246	0.466	£2,676
All costs except drug +25%			£1,177	0.467	£2,521
All costs except drug −25%			£1,316	0.467	£2,820

Abbreviations: BMI, body mass index; CI, confidence interval; HbA1c, glycosylated hemoglobin; LL, lower limit; MET, metformin; QALY, quality adjusted life year; SBP, systolic blood pressure; SU, sulphonylurea; UL, upper limit.

Figure 30. Univariate sensitivity analyses: Tornado graphs of incremental costs (top) and incremental effects (bottom); MET+dapagliflozin vs MET+SU



It can be observed from the tornado graph for incremental costs that varying the effect of dapagliflozin on HbA1c around the base case always leads to a reduction in incremental costs. This is because in the case of a lower HbA1c reduction patients will switch sooner to the next treatment line, leading to lower drug costs. Varying the other parameter values had a limited impact on the point estimate of incremental costs. This is in line with the finding that the incremental costs can mainly be attributed to higher total drug costs in the treatment arm than in the comparator arm, and drug costs were not varied in the sensitivity analysis.

Regarding QALYs, the uncertainty around the point estimate was largest when the treatment effect on body weight of the comparator was varied between the outer limits of the 95% CI, causing the incremental QALY to range from 0.382 to 0.552. Varying the utility decrement per unit increase in BMI had a similar effect on the incremental QALY, ranging from 0.399 to 0.541. Varying the other parameter values had a limited impact on the incremental QALY estimate.

Add-on to metformin: dapagliflozin versus DPP-4

The results of the univariate sensitivity analysis are presented in Table 87, and displayed graphically by Tornado graphs in Figure 31.

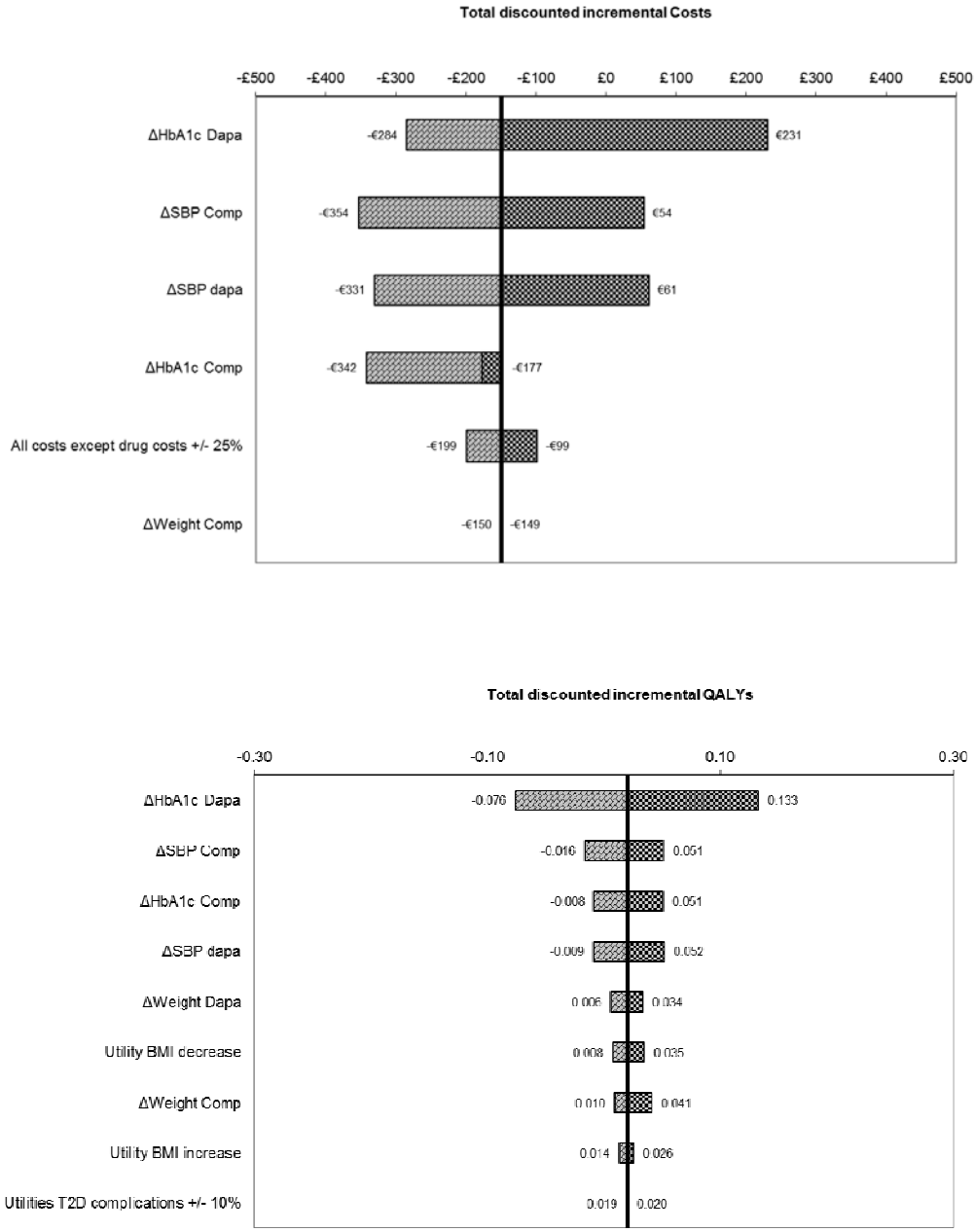
Table 87. Summary of univariate sensitivity analyses; MET+dapagliflozin vs MET+DPP-4

Parameter	Distribution	Value	ΔCosts	ΔQALYs	ICER
Base Case			***-£149***	***0.020***	***Dominant***
HbA1c dapagliflozin LL	Normal	-0.90	£231	0.133	£1,739
HbA1c dapagliflozin UL	Normal	-0.26	-£284	-0.076	£3,764
HbA1c comparator LL	Normal	-0.88	-£342	-0.008	£40,354*
HbA1c comparator UL	Normal	-0.60	-£177	0.051	Dominant
Weight dapagliflozin LL	Normal	-3.69	-£149	0.034	Dominant
Weight dapagliflozin UL	Normal	-1.89	-£149	0.006	Dominant
Weight comparator LL	Normal	-1.05	-£149	0.010	Dominant
Weight comparator UL	Normal	0.03	-£150	0.041	Dominant
SBP dapagliflozin LL	Normal	-7.20	-£331	0.052	Dominant
SBP dapagliflozin UL	Normal	-1.80	£61	-0.009	Dominated
SBP comparator LL	Normal	-4.36	£54	-0.016	Dominated
SBP comparator UL	Normal	1.62	-£354	0.051	Dominant
Utility BMI increase LL	Beta	0.038	-£149	0.026	Dominant
Utility BMI increase UL	Beta	0.057	-£149	0.014	Dominant
Utility BMI decrease LL	Beta	0.011	-£149	0.008	Dominant
Utility BMI decrease UL	Beta	0.025	-£149	0.035	Dominant
Utilities complications +10%			-£149	0.020	Dominant
Utilities complications -10%			-£149	0.019	Dominant
All costs except drug +25%			-£199	0.020	Dominant
All costs except drug -25%			-£99	0.020	Dominant

Abbreviations: BMI, body mass index; CI, confidence interval; DPP-4, dipeptidyl peptidase 4 inhibitor; HbA1c, glycosylated hemoglobin; LL, lower limit; MET, metformin; QALY, quality adjusted life year; SBP, systolic blood pressure; UL, upper limit.

* this represents the ICER for the comparator vs. dapagliflozin

Figure 31. Univariate sensitivity analyses: Tornado graphs of incremental costs (top) and incremental effects (bottom); MET+dapagliflozin vs MET+DPP-4.



The incremental cost estimate ranged at most between –£284 and +£231, when the dapagliflozin treatment effect on HbA1c was varied between the outer limits of the 95% CI.

Regarding QALYs, the uncertainty around the point estimate was largest when the dapagliflozin treatment effect on HbA1c was varied between the outer limits of the 95% CI, causing the incremental QALY to range from –0.076 to +0.133. Varying the other parameter values only had a limited impact on the incremental QALY estimate.

Add-on to metformin: dapagliflozin versus TZD

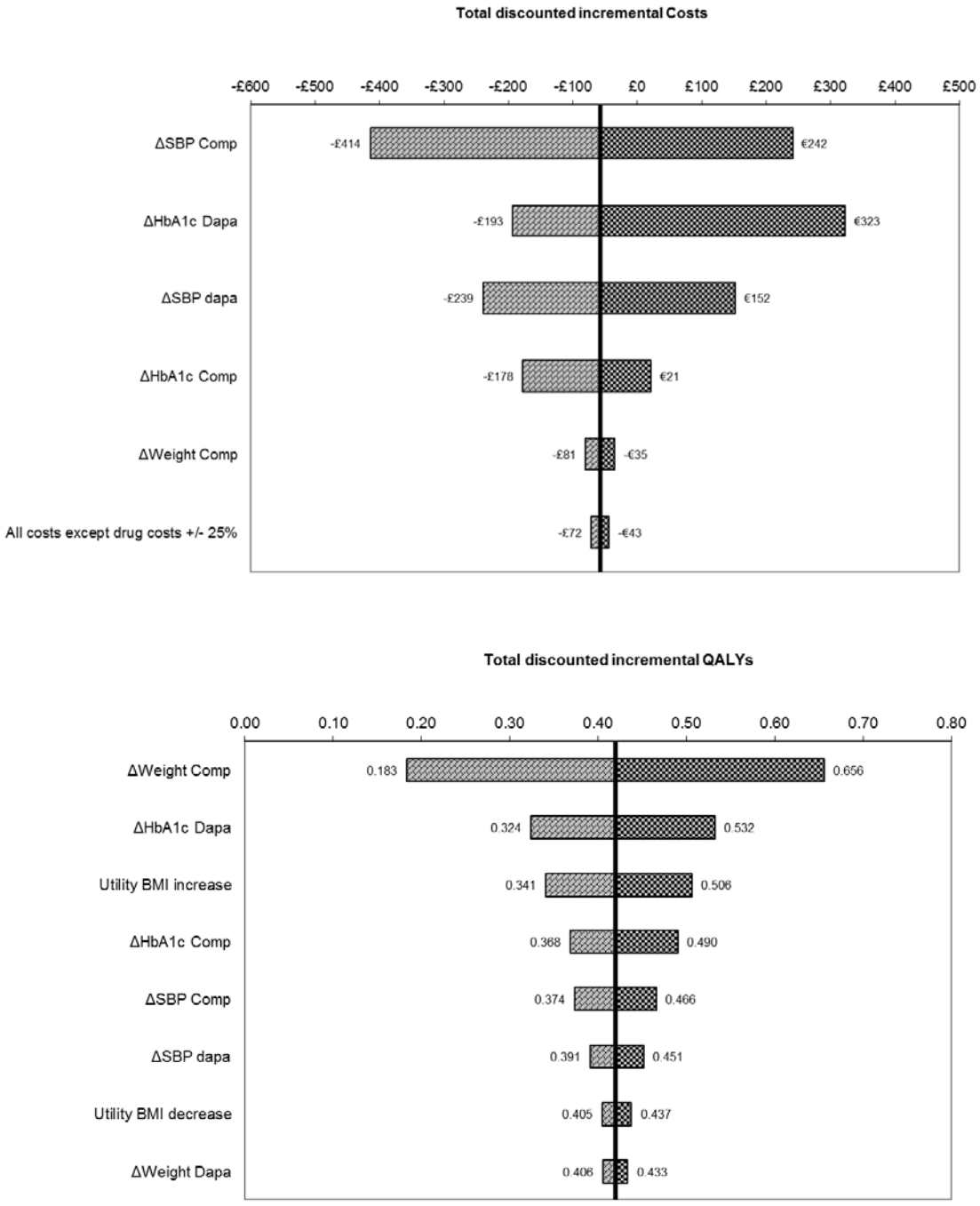
The results of the univariate sensitivity analyses are presented in Table 88, and displayed graphically by Tornado graphs in Figure 32.

Table 88. Summary of univariate sensitivity analyses: MET+dapagliflozin vs MET+TZD

Parameter	Distribution	Value	ΔCosts	ΔQALYs	ICER
Base Case					***Dominant***
			-£ 58	***0.419***	
HbA1c dapagliflozin LL	Normal	-0.90	£323	0.532	£ 607
HbA1c dapagliflozin UL	Normal	-0.26	-£193	0.324	Dominant
HbA1c comparator LL	Normal	-1.14	-£178	0.368	Dominant
HbA1c comparator UL	Normal	-0.66	£21	0.490	£ 43
Weight dapagliflozin LL	Normal	-3.69	-£58	0.433	Dominant
Weight dapagliflozin UL	Normal	-1.89	-£58	0.406	Dominant
Weight comparator LL	Normal	0.79	-£35	0.183	Dominant
Weight comparator UL	Normal	2.65	-£81	0.656	Dominant
SBP dapagliflozin LL	Normal	-7.20	-£239	0.451	Dominant
SBP dapagliflozin UL	Normal	-1.80	£152	0.391	£ 390
SBP comparator LL	Normal	-7.27	£242	0.374	£ 647
SBP comparator UL	Normal	1.53	-£414	0.466	Dominant
Utility BMI increase LL	Beta	0.038	-£58	0.341	Dominant
Utility BMI increase UL	Beta	0.057	-£58	0.506	Dominant
Utility BMI decrease LL	Beta	0.011	-£58	0.405	Dominant
Utility BMI decrease UL	Beta	0.025	-£58	0.437	Dominant
Utilities complications +10%			-£58	0.420	Dominant
Utilities complications -10%			-£58	0.419	Dominant
All costs except drug +25%			-£72	0.419	Dominant
All costs except drug -25%			-£43	0.419	Dominant

Abbreviations: BMI, body mass index; CI, confidence interval; HbA1c, glycosylated hemoglobin; LL, lower limit; MET, metformin; QALY, quality adjusted life year; SBP, systolic blood pressure; TZD, thiazolidinedione; UL, upper limit.

Figure 32. Univariate sensitivity analyses: Tornado graphs of incremental costs (top) and incremental effects (bottom); MET+dapagliflozin vs MET+TZD



It can be observed from the tornado graph for incremental costs that varying the treatment effect of TZD on SBP had the highest impact on incremental costs. The estimate ranged from –£414 to £242 when this parameter was varied between the outer limits of the 95% CI.

Regarding QALYs, the uncertainty around the point estimate was largest when the treatment effect on body weight of the comparator was varied between the outer limits of the 95% CI, causing the incremental QALY to range from 0.183 to 0.656.

Add-on to insulin: dapagliflozin versus DPP-4

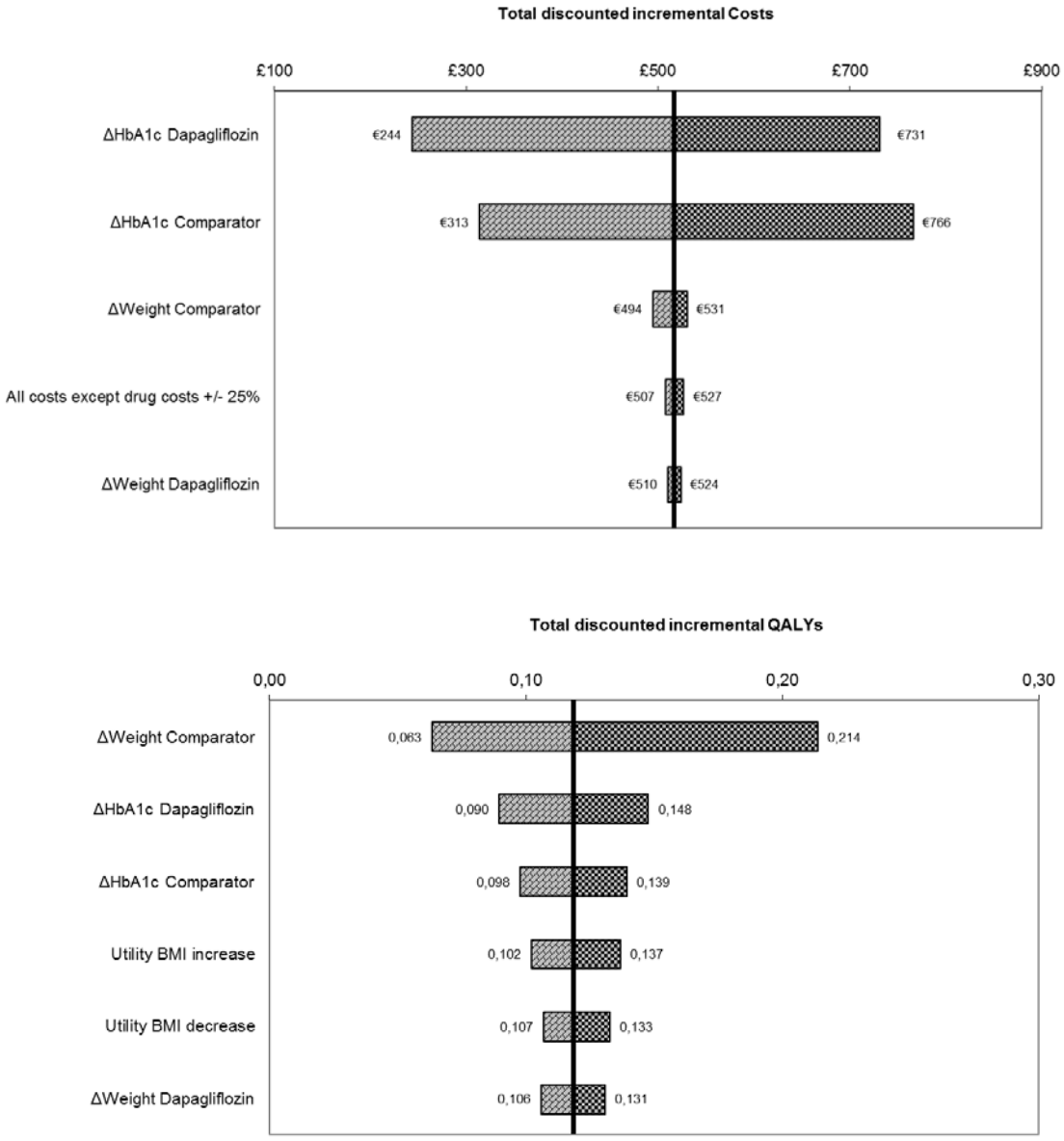
The results of the univariate sensitivity analyses are presented in Table 89, and displayed graphically by Tornado graphs in Figure 33.

Table 89. Summary of univariate sensitivity analyses; INS+dapagliflozin vs INS+DPP-4

Parameter	Distribution	Value	ΔCosts	ΔQALYs	ICER
Base Case			***£517***	***0.119***	***£ 4,358***
HbA1c dapagliflozin LL	Normal	-0.96	£731	0.148	£4,948
HbA1c dapagliflozin UL	Normal	-0.68	£244	0.090	£2,716
HbA1c comparator LL	Normal	-0.85	£313	0.098	£3,206
HbA1c comparator UL	Normal	-0.53	£766	0.139	£5,499
Weight dapagliflozin LL	Normal	-2.13	£510	0.131	£3,901
Weight dapagliflozin UL	Normal	-1.13	£524	0.106	£4,936
Weight comparator LL	Normal	-0.18	£531	0.063	£8,370
Weight comparator UL	Normal	0.56	£494	0.214	£2,312
SBP dapagliflozin LL	Normal	0	-	-	-
SBP dapagliflozin UL	Normal	0	-	-	-
SBP comparator LL	Normal	0	-	-	-
SBP comparator UL	Normal	0	-	-	-
Utility BMI increase LL	Beta	0.0380	£517	0.102	£5,060
Utility BMI increase UL	Beta	0.0574	£517	0.137	£3,780
Utility BMI decrease LL	Beta	0.0110	£517	0.107	£4,831
Utility BMI decrease UL	Beta	0.0245	£517	0.133	£3,895
Utilities complications +10%			£517	0.119	£4,352
Utilities complications −10%			£517	0.118	£4,365
All costs except drug +25%			£527	0.119	£4,439
All costs except drug −25%			£507	0.119	£4,277

Abbreviations: BMI, body mass index; CI, confidence interval; DPP-4, dipeptidyl peptidase 4 inhibitor; HbA1c, glycosylated hemoglobin; INS, insulin; LL, lower limit; QALY, quality adjusted life year; SBP, systolic blood pressure; UL, upper limit.

Figure 33. Univariate sensitivity analyses: Tornado graphs of incremental costs (top) and incremental effects (bottom); INS+dapagliflozin vs INS+DPP-4



It can be observed from the tornado graph for incremental costs, that varying the HbA1c effect of INS+dapagliflozin and INS+DPP-4 has the highest impact on incremental costs. The estimate ranged from £244 to £731 and from £313 to £766 respectively, when these parameters were varied between the outer limits of the 95% CI.

Regarding QALYs, the uncertainty around the point estimate was largest when the treatment effect of INS+DPP-4 on body weight was varied between the outer limits of the

95% CI, causing the incremental QALY to range from 0.063 to 0.214. Varying the other parameters only had a limited impact on the incremental QALY estimate

6.7.8 Probabilistic sensitivity analysis

Add-on to metformin: dapagliflozin versus SU

Figure 34 presents the scatterplot of the ICER estimates of the PSA. The 95% confidence intervals around the point estimates for incremental QALYs and costs were estimated accordingly (Table 90).

The distribution of the ICER estimates of the PSA over the quadrants of the PSA scatterplot is summarised in Table 91. All estimates are in the upper-right quadrant, indicating that dapagliflozin has a 100% probability of being more effective and more costly than SU.

The acceptability curve for dapagliflozin add-on to MET versus SU add-on to MET is presented in Figure 35. At a willingness-to-pay (WTP) threshold of £20,000 per QALY gained, dapagliflozin is estimated to have a 100% probability of being cost-effective compared to SU.

Figure 34. Scatterplot of the ICER estimates of the PSA; MET+dapagliflozin vs MET+SU

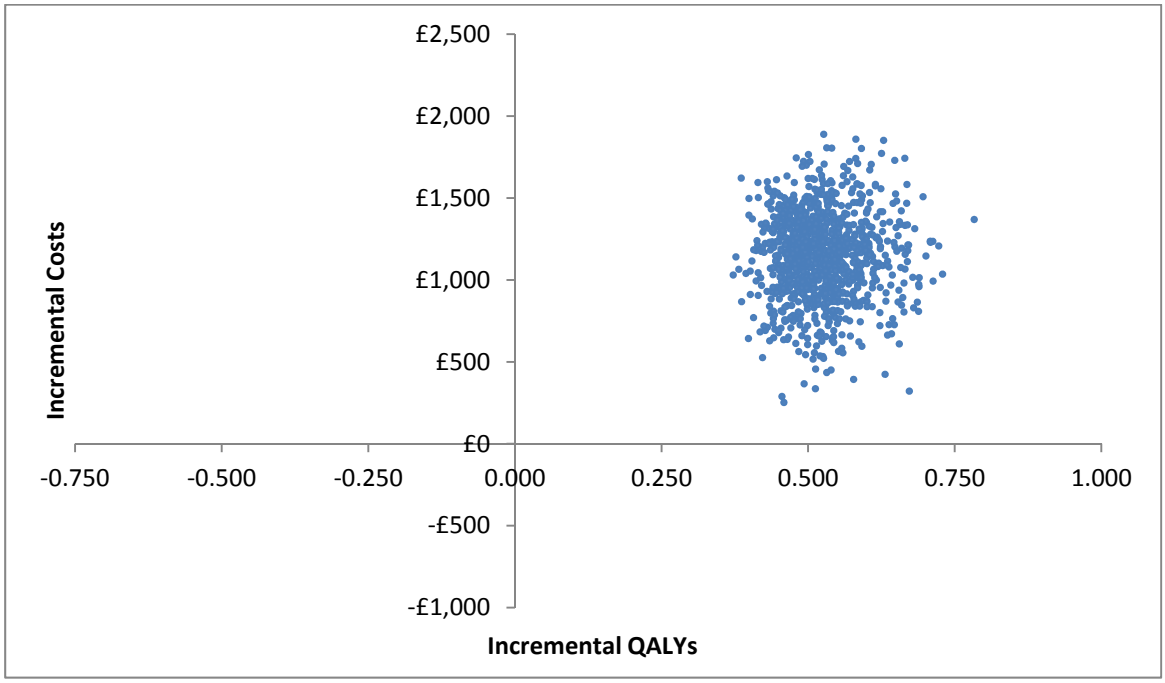


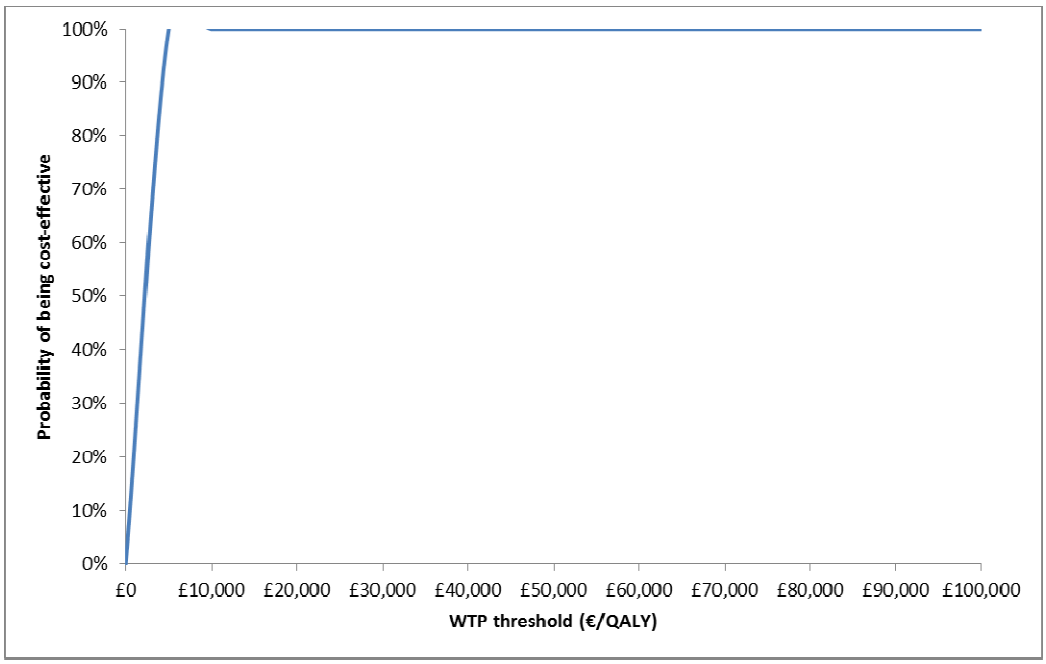
Table 90. Results of the PSA: 95% CI around incremental QALYs and costs; MET+dapagliflozin vs MET+SU

Outcome	Point estimate	LL 95%CI	UL 95%CI
ΔQALYs	0.467	0.420	0.665
ΔCosts	£ 1,246	£ 613	£ 1,637

Table 91. Distribution of ICER estimates of the PSA; MET+dapagliflozin vs MET+SU

Quadrant		% of estimates
Upper-left	Less effective, more costly	0%
Upper-right	More effective, more costly	100%
Lower-right	More effective, less costly	0%
Lower-left	Less effective, less costly	0%

Figure 35. Cost-effectiveness acceptability curve; MET+dapagliflozin vs MET+SU



Add-on to metformin: dapagliflozin versus DPP-4

Figure 36 presents the scatterplot of the ICER estimates of the PSA. The 95% confidence intervals around the point estimates for incremental QALYs and costs were estimated accordingly (Table 92).

Figure 36. Scatterplot of the ICER estimates of the PSA; MET+dapagliflozin vs MET+DPP-4

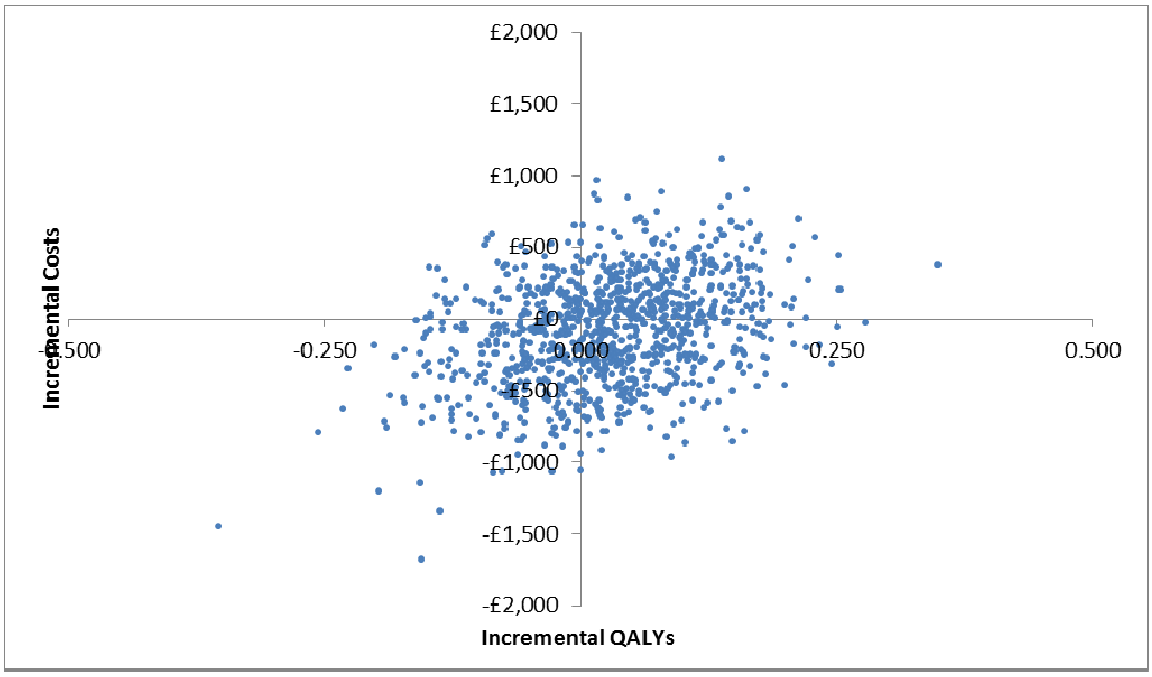


Table 92. Results of the PSA: 95% CI around incremental QALYs and costs; MET+dapagliflozin vs MET+DPP-4

Outcome	Point estimate	LL 95%CI	UL 95%CI
ΔQALYs	0.020	-0.147	0.181
ΔCosts	-£149	-£805	£604

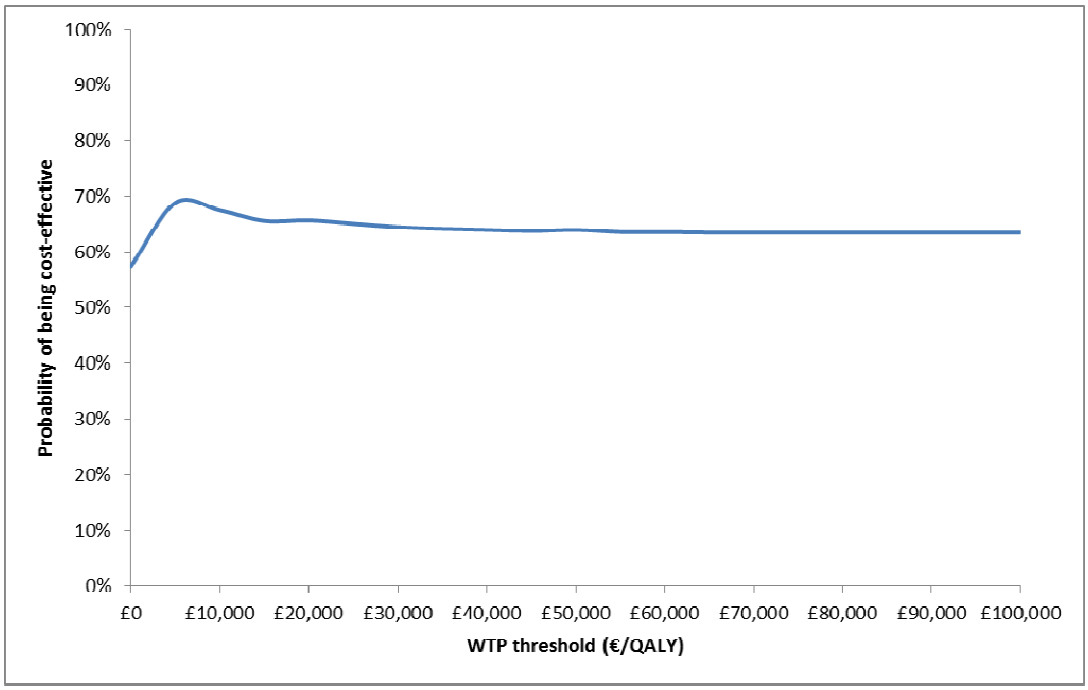
The distribution of the ICER estimates of the PSA over the quadrants of the PSA scatterplot is summarised in Table 93. The PSA resulted in a considerable spread of ICER estimates distributed across all four quadrants of the scatterplot, and consequently a wide 95% CI around the point estimates of incremental costs and QALYs.

The acceptability curve for dapagliflozin add-on to MET versus DPP-4 add-on to MET is presented in Figure 37. At a WTP threshold of £20,000 per QALY gained dapagliflozin is estimated to have a 66% probability of being cost-effective compared to DPP-4.

Table 93. Distribution of ICER estimates of the PSA; MET+dapagliflozin vs MET+DPP-4

Quadrant		% of estimates
Upper-left	Less effective, more costly	10.7%
Upper-right	More effective, more costly	31.9%
Lower-right	More effective, less costly	30.8%
Lower-left	Less effective, less costly	26.6%

Figure 37. Cost-effectiveness acceptability curve; MET+dapagliflozin vs MET+DPP-4



Add-on to metformin: dapagliflozin versus TZD

Figure 38 presents the scatterplot of the ICER estimates of the PSA. The 95% CI around the point estimates for incremental QALYs and costs were estimated accordingly (Table 94).

Figure 38. Scatterplot of the ICER estimates of the PSA; MET+dapagliflozin vs MET+TZD

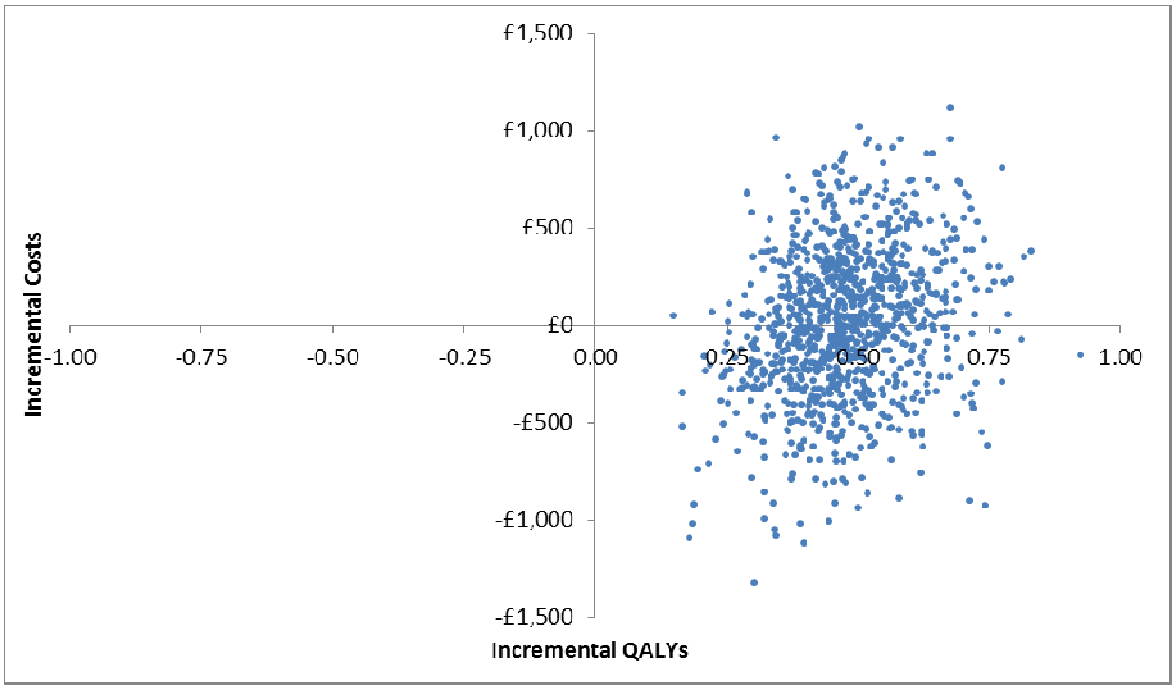


Table 94. Results of the PSA: 95% CI around incremental QALYs and costs; MET+dapagliflozin vs MET+TZD

Outcome	Point estimate	LL 95%CI	UL 95%CI
ΔQALYs	0.419	0.259	0.719
ΔCosts	–£ 58	–£ 783	£ 743

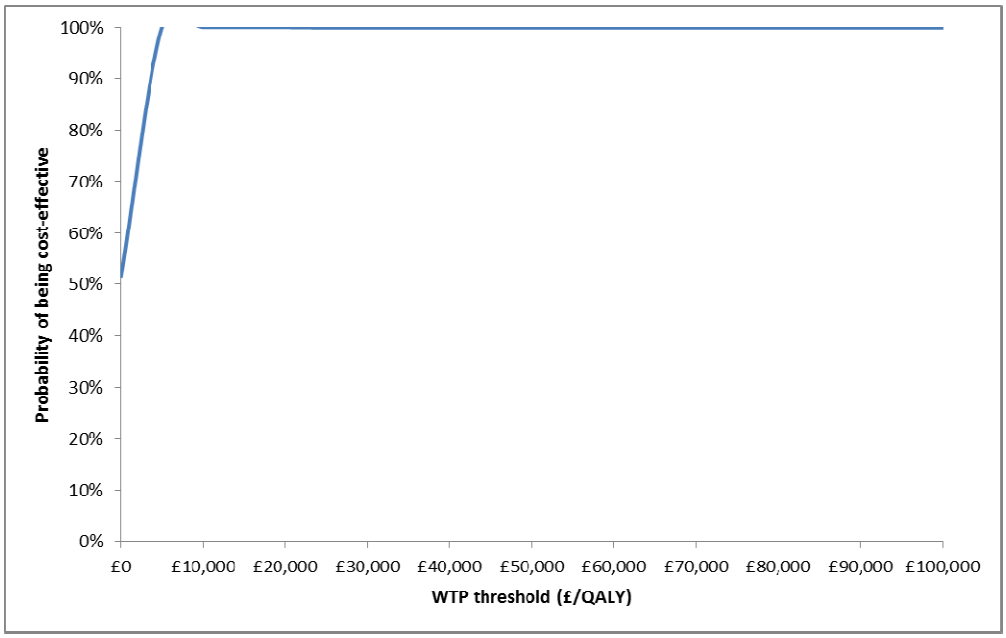
The distribution of the ICER estimates of the PSA over the quadrants of the PSA scatterplot is summarised in Table 95. About half of the estimates were in the lower-right quadrant, indicating that dapagliflozin has a 49% probability of being dominant compared to TZD. The other half of the estimates was in the upper-right quadrant, indicating that dapagliflozin is more effective at additional cost.

The acceptability curve for dapagliflozin add-on to MET versus TZD add-on to MET is presented in Figure 39. At a WTP threshold of £20,000 per QALY gained dapagliflozin is estimated to have a 100% probability of being cost-effective compared to TZD.

Table 95. Distribution of ICER estimates of the PSA; MET+dapagliflozin vs MET+TZD

Quadrant		% of estimates
Upper-left	Less effective, more costly	0.0%
Upper-right	More effective, more costly	50.8%
Lower-right	More effective, less costly	49.2%
Lower-left	Less effective, less costly	0.0%

Figure 39. Cost-effectiveness acceptability curve; MET+dapagliflozin vs MET+TZD



Add-on to insulin: dapagliflozin versus DPP-4

Figure 40 presents the scatterplot of the ICER estimates of the PSA. The 95% CI around the point estimates for incremental QALYs and costs was estimated accordingly (Table 96).

Figure 40. Scatterplot of ICER estimates of the PSA; INS+dapagliflozin versus INS+DPP-4

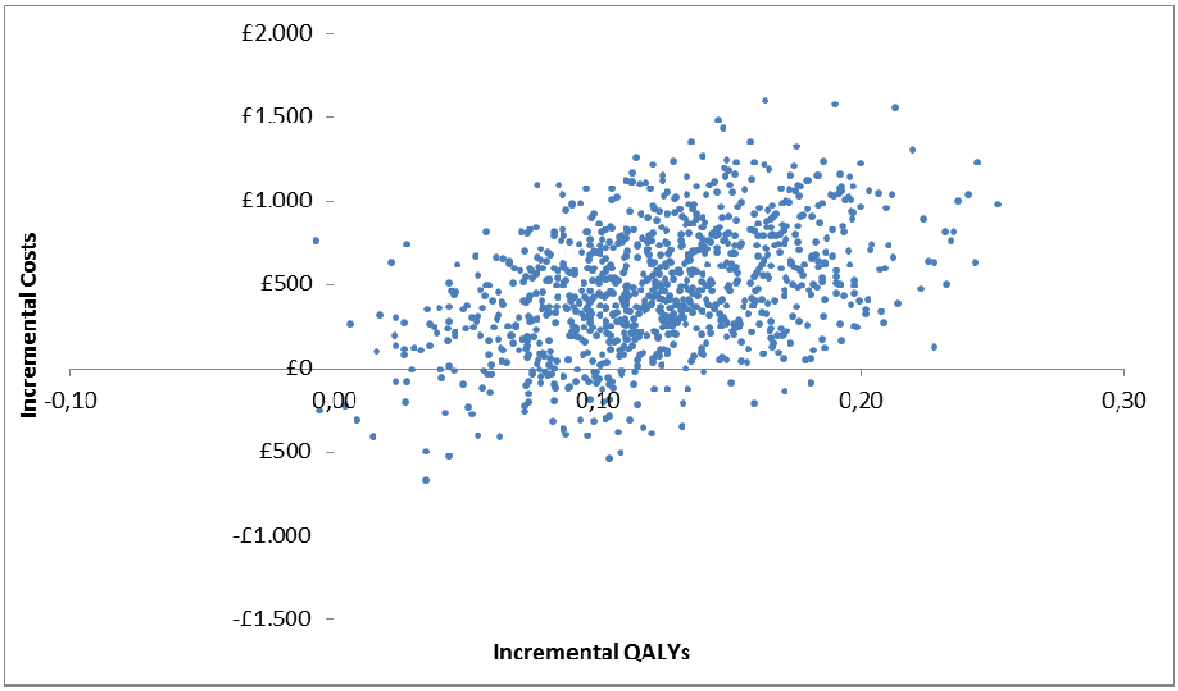


Table 96. Results of the PSA: 95% CI around incremental QALYs and costs; INS+dapagliflozin vs INS+DPP-4

Outcome	Point estimate	LL 95%CI	UL 95%CI
ΔQALYs	0.119	0.036	0.207
ΔCosts	£ 517	–£ 253	£ 1,157

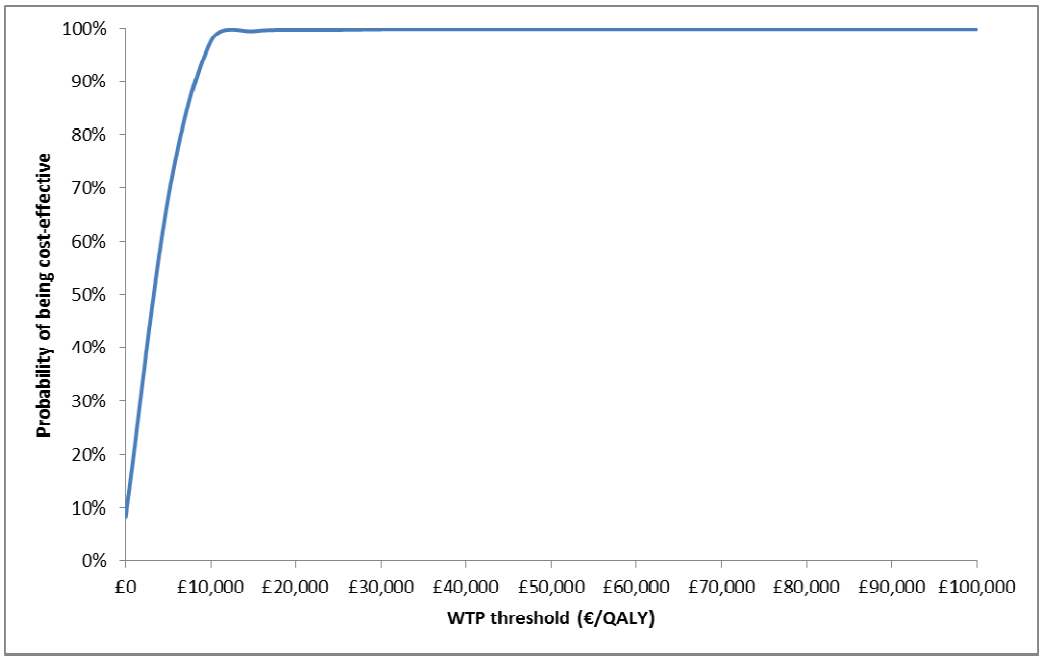
The distribution of the ICER estimates of the PSA over the quadrants of the PSA scatterplot is summarised in Table 97. The majority of the estimates are in the upper-right quadrant, indicating that the dapagliflozin strategy has a 90.6% probability of being more effective and more costly than the DPP-4 strategy.

The acceptability curve for INS+dapagliflozin versus INS+DPP-4 is presented in Figure 41. At a WTP threshold of £20,000 per QALY gained dapagliflozin is estimated to have a 99.6% probability of being cost-effective compared to DPP-4.

Table 97. Distribution of ICER estimates of the PSA; INS+dapagliflozin vs INS+DPP-4

Quadrant		% of estimates
Upper-left	Less effective, more costly	0.1%
Upper-right	More effective, more costly	90.6%
Lower-right	More effective, less costly	9.2%
Lower-left	Less effective, less costly	0.1%

Figure 41. Cost-effectiveness acceptability curve; INS+dapagliflozin vs INS+DPP-4



6.7.9 Scenario analysis

The results of the scenario analyses are summarised in Table 98, Table 99, Table 100, and Table 101 for the 4 comparisons respectively.

Add-on to metformin: dapagliflozin versus SU

Table 98. Summary of results of the scenario analyses; MET+dapagliflozin vs MET+SU

No.	Scenario	ΔCosts	ΔQALYs	ICER (£/QALY)
	Base case	***£1,246***	***0.467***	***£2,671***
1	HbA1c threshold 7.5%	£863	0.471	£1,830
2	HbA1c threshold 8.0%	£1,575	0.485	£3,246
3	HbA1c threshold 8.5%	£3,282	0.583	£5,633
6	Use utility BMI from Bagust et al (±0.0061).	£1,246	0.141	£,8,863
7	Adjusted Bagust (±0.0038)	£1,246	0.119	£10,514
8	Zero disutilities for hypoglycaemia	£1,246	0.436	£2,859
9	Extrapolation of weight dapagliflozin: convergence of weight curves after switch to second Insulin regimen	£1,469	0.270	£5,441
11	Use efficacy/tolerability data for dapagliflozin and SU based on 52-week NMA data	£2,589	0.540	£4,793
12	Discontinuation rates set to 0	£1,371	0.487	£2,814
13	Use baseline characteristics UK diabetes population	£2,309	0.497	£4,646
14	Include BMI costs	£1,182	0.467	£2,534
15	Costs for hypoglycaemia from Leese 2003	£1,252	0.467	£2,682
16	Costs or ESRD -50% from year 2	£1,334	0.467	£2,858
17	Discount rate costs/effects 0%	£1,062	0.676	£1,572
18	Discount rate costs/effects 6%	£1,296	0.380	£3,412
19	Time horizon 20 years	£1,321	0.400	£3,301
20	Multivariate scenario	£1,506	0.134	£11,269

The most important observation from the scenario analyses in Table 98 is that in using the Bagust et al utilities the ICER increases to £8,863 per QALY gained or to £10,514 using the adjusted Bagust utilities. The multivariate scenario is unsurprisingly the highest at £11,269. The impact of the other scenarios on the ICER vs SU is relatively modest.

Add-on to metformin: dapagliflozin versus DPP-4

Table 99. Summary of results of scenario analyses; MET+dapagliflozin vs MET+DPP-4

No.	Scenario	ΔCosts	ΔQALYs	ICER (£/QALY)
	Base case	***-£ 149***	***0.020***	***Dominant***
1	HbA1c threshold 7.5%	-£ 399	0.464	Dominant
2	HbA1c threshold 8.0%	-£ 190	0.012	Dominant
3	HbA1c threshold 8.5%	£ 27	0.049	£ 558
6	Use utility BMI from Bagust et al (±0.0061).	-£ 149	0.024	Dominant
7	Adjusted Bagust (±0.0038)	-£149	0.021	Dominant
8	Zero disutilities for hypoglycaemia	-£149	0.031	Dominant
9	Extrapolation of weight dapagliflozin: put years until loss of weight effect to 1	-£ 149	0.017	Dominant
11	Use efficacy/tolerability data for dapagliflozin and DPP-4 based on 52-week NMA data	£ 412	0.076	£ 5,455
12	Discontinuation rates set to zero	-£ 143	0.018	Dominant
13	Use baseline characteristics UK diabetes population clinical practice	£ 148	0.054	£ 2,758
14	Include BMI costs	-£ 162	0.020	Dominant
15	Costs for hypoglycaemia from Leese 2003			
16	Costs or ESRD -50% from year 2	-£55	0.020	Dominant
17	Discount rate costs/effects 0%	-£ 398	0.034	Dominant
18	Discount rate costs/effects 6%	-£ 59	0.017	Dominant
19	Time horizon 20 years	-£ 26	0.011	Dominant
20	Multivariate scenario	£295	0.056	£5,307

The results of the scenario analyses in Table 99 indicate that in all scenarios tested, dapagliflozin was either dominant or cost-effective compared to DPP-4. Using the clinical input data from the 52-week NMA instead of those from the 24-week NMA had the most effect on the ICER resulting in an estimate of £5,455 per QALY gained.

Scenarios in which the assumptions regarding the extrapolation of weight were varied or in which Bagust utilities associated with BMI were used did not have a large influence in the comparison of dapagliflozin and DPP-4 add-on to MET. This can be explained by the fact that both treatments were associated with an initial weight reduction (albeit larger for dapagliflozin than for DPP-4) which was assumed to be maintained throughout the second year of treatment. After the first 3-4 years, the body weight profiles over time, of patients in the dapagliflozin strategy and in the DPP-4 strategy, are similar.

Add-on to metformin: dapagliflozin versus TZD

Table 100. Summary of results of scenario analyses; MET+dapagliflozin vs MET+TZD

No.	Scenario	ΔCosts	ΔQALYs	ICER (£/QALY)
	Base case	***-£58***	***0.419***	***Dominant***
1	HbA1c threshold 7.5%	-£554	0.982	Dominant
2	HbA1c threshold 8.0%	-£136	0.404	Dominant
3	HbA1c threshold 8.5%	£320	0.458	£698
6	Use utility BMI from Bagust et al (±0.0061).	-£60	0.043	Dominant
7	Adjusted Bagust (±0.0038)	-£60	0.018	Dominant
8	Zero disutilities for hypoglycaemia	-£60	0.444	Dominant
9	Extrapolation of weight dapagliflozin: put years until loss of weight effect to 1	-£58	0.410	Dominant
10	Extrapolation of weight dapagliflozin: convergence of weight curves after switch to second Insulin regimen	£135	0.230	£586
11	Use efficacy/tolerability data for dapagliflozin and TZD based on 52w MTC data	£531	0.075	£7,071
12	Discontinuation rates set to zero	-£80	0.401	Dominant
13	Use baseline characteristics UK diabetes population clinical practice	£370-	0.427	£865
14	Include BMI costs	-£145	0.419	Dominant
15	Costs for hypoglycaemia from Leese 2003	-£66	0.419	Dominant
16	Costs or ESRD -50% from year 2	£2	0.419	£6
17	Discount rate costs/effects 0%	-£269	0.616	Dominant
18	Discount rate costs/effects 6%	£19	0.340	£55
19	Time horizon 20 years	£53	0.350	£150
20	Multivariate scenario	£344	0.056	£6,187

The results of the scenario analyses in Table 100 indicate that in all scenarios tested, dapagliflozin was either dominant or cost-effective compared to TZD. Using the clinical input data from the 52-week NMA instead of those from the 24-week NMA had the largest effect on the ICER resulting in an estimate of £7,071 per QALY gained.

Add-on to insulin: dapagliflozin versus DPP-4

Table 101. Summary of results of scenario analyses; INS+dapagliflozin vs INS+DPP-4

No.	Scenario	ΔCosts	ΔQALYs	ICER (£/QALY)
	Base case	***£ 517***	***0.119***	***£ 4,358***
2	HbA1c threshold 8.5%	£445	0.098	£4,539
3	HbA1c threshold 9.0%	£545	0.125	£4,360
4	HbA1c threshold 8.0%	-£64	0.461	Dominant
5	HbA1c threshold 9.5%	£631	0.237	£2,667
6	Use utility BMI from Bagust et al (±0.0061).	£517	0.024	£21,171
7	Adjusted Bagust (±0.0038)	£517	0.016	£32,409
8	Zero disutilities for hypoglycaemia	£517	0.123	£4,216
9	Extrapolation of weight dapagliflozin: put years until loss of weight effect to 1	£527	0.090	£5,849
10	Extrapolation of weight dapagliflozin: convergence of weight curves after switch to second Insulin regimen	£625	0.091	£6,864
12	Discontinuation rates set to zero	£538	0.126	£4,268
13	Use baseline characteristics UK diabetes population clinical practice	£336	0.114	£2,947
14	Include BMI costs	£495	0.119	£4,171
15	Costs for hypoglycaemia from Leese 2003	£520	0.119	£4,381
16	Costs or ESRD -50% from year 2	£513	0.119	£4,324
17	Discount rate costs/effects 0%	£593	0.154	£3,838
18	Discount rate costs/effects 6%	£468	0.102	£4,573
19	Time horizon 20 years	£521	0.091	£5,753
20	Multivariate scenario	£533	0.026	£20,579

In these scenario analyses changes in body weight again have the greatest impact on the ICER. Using the adjusted Bagust et al utilities resulted in the largest increase in the ICER vs DPP-4 to £32,409 per QALY gained. However, as before, this should be seen as an extreme scenario and the ICER remains at acceptable levels of cost effectiveness even in the multivariate scenario at £20,579.

6.7.10 Summary of main findings from sensitivity analysis

Add-on to Metformin

The CEA showed that over lifetime, treatment with dapagliflozin as an add-on to MET would improve QALYs and reduce the incidence of micro- and macro-vascular complications compared to treatment with SU as add-on to MET. The model estimated that MET+ dapagliflozin was associated with an incremental benefit of 0.467 (95 % CI: 0.420 to 0.665) at an additional cost of £1,246 (95% CI: £ 613 to £ 1,637), resulting in an ICER point estimate of £2,671 per QALY gained versus MET+SU. Sensitivity analyses showed that these results were robust to changes in input parameters, including clinical efficacy, costs and utilities for diabetes-related complications, changes in body weight and adverse events. At a WTP threshold of £20,000 per QALY gained, the dapagliflozin strategy is estimated to have a 100% probability of being cost-effective compared to SU.

Compared to DPP-4, dapagliflozin was estimated to be cost saving (incremental cost: – £149; 95% CI: –£805 to £ 604) with an incremental benefit of 0.020 (95% CI: –0.147 to 0.181), indicating that dapagliflozin is the dominant strategy in the base case scenario. Also, in all other scenarios tested, dapagliflozin was either dominant or cost-effective compared to DPP-4. However, the PSA resulted in a considerable spread of ICER estimates distributed across all four quadrants of the scatterplot, and consequently a wide 95% CI around the point estimates of incremental costs and QALYs. At a WTP threshold of £20,000 per QALY gained, dapagliflozin is estimated to have a 66% probability to be the cost-effective strategy compared to DPP-4.

Compared to TZD, dapagliflozin was estimated to be cost saving (incremental cost: –£ 58; 95%CI: –£ 783 to £ 743) with an incremental benefit of 0.419 (95%CI: 0.259 to 0.719), resulting in dapagliflozin being dominant over TZD. Based on the PSA, it was estimated that dapagliflozin has a 50/50 percent probability of being either dominant or more effective at additional cost compared to TZD. At a WTP threshold of £20,000 per QALY gained dapagliflozin is estimated to have a 100% probability of being the cost-effective strategy compared to TZD.

Multivariate analysis using Bagust et al utilities, a single switch threshold for HbA1c of 8%, UK baseline characteristics and including patients' clinical history, and using 52-week NMA outcomes resulted in the following ICERs: £11,269/QALY vs. SU, £5,307 vs DPP-4, and £6,187 vs. TZD.

Add-on to Insulin

The CEA showed that over a lifetime, treatment with dapagliflozin add-on to INS would improve QALYs and reduce the incidence of micro- and macro-vascular complications compared to DPP-4 add-on to INS. The model estimated that INS+dapagliflozin was associated with an incremental benefit of 0.119 (95% CI: 0.036 to 0.207) at an additional cost of £517 (95% CI: –£253 to £1,157), resulting in an ICER of £4,358 per QALY gained. Sensitivity analyses showed that, on the whole, these results were robust to changes in input parameters, including clinical efficacy, costs and utilities for diabetes-related complications, changes in body weight and adverse events. The most influential parameters in the comparison were the treatment effect on body weight in the control

arm, and utility values related to changes in BMI. Using Bagust et al utilities resulted in a higher ICER of over £11,000 per QALY gained at a WTP threshold of £20,000 per QALY gained, the dapagliflozin add-on to INS strategy has a 99.6% probability of being cost-effective compared to the DPP-4 add-on to INS strategy.

Multivariate analysis using Bagust et al utilities, a single switch threshold for HbA1c of 8%, UK baseline characteristics and including patients' clinical history resulted in the following ICER: £20,579 vs. DPP-4.

6.7.11 Key drivers of the cost-effectiveness results

The key driver of the cost-effectiveness results is the relative QALY gain vs the comparators associated with the superior weight control advantages of dapagliflozin, in particular against SU and TZDs, but also over DPP-4.

In addition, there are modest cost-offsets and utility gains associated with a marginally favourable overall reduction in T2DM complications over a 40 year model time horizon.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Two validation exercises have been performed and are detailed in Section 9.19. The first of these validation exercises used three approaches:

1. Validation of the model's ability to reproduce the observed vascular complications from the UKPDS 68 study (the data source used to construct the disease progression algorithm used by the model).

2. Validation of the model's ability to reproduce the outcomes of a broad range of major outcomes trials in type 2 diabetes (including UKPDS 80).

3. Validation to the IMS CORE Diabetes Model.

The second validation exercise assesses the cost-effectiveness of dapagliflozin using the CORE diabetes model.

6.9 Subgroup analysis

6.9.1 Rationale for subgroup analysis

As reported in Section 5.3.7 the clinical benefits of dapagliflozin were consistent across the study programme in terms of both pre-planned and post-hoc sub-group analyses. Given a lack of differential clinical effectiveness in all sub-groups, no further exploration of sub-groups is considered in the cost effectiveness assessment.

6.9.2 Subgroup patient characteristics

Not applicable.

6.9.3 Please describe how the statistical analysis was undertaken.

Not applicable.

6.9.4 Results of subgroup analyses

Not applicable.

6.9.5 Relevant subgroups not considered

Not applicable.

6.10 Interpretation of economic evidence

6.10.1 Comparison with published economic literature

The systematic review conducted for this submission identified no published studies of the cost-effectiveness of dapagliflozin. Hence, a *de novo* economic analysis was performed to evaluate the cost-effectiveness of dapagliflozin and the relevant comparators for the add-on to metformin and add-on to insulin assessments. No published economic evaluations of add-on to insulin therapies for the UK were identified in the systematic review conducted (see Section 6.1.2) A number of economic evaluations of dual therapy with metformin were identified, covering the assessment of pioglitazone, sitagliptin or liraglutide as add-on therapy to metformin (Table 54). All these evaluations used a now-standard approach to economic modelling of T2DM drug interventions, involving the use of Markov based simulation models to extrapolate the short term outcomes to predict long run outcomes over a lifetime horizon (typically 40 years), using UKPDS risk equation, cost and utility data. The dapagliflozin model does not deviate from the relatively standardised approach to diabetes modelling using a similar structure as other models, and makes similar use of the UKPDS dataset. The dapagliflozin model is a modified version of a validated economic model that has been used in previous economic evaluations of drug interventions for T2DM (see Sections 6.2.3 and 6.8). As in other dual therapy economic analyses, important drivers of outcome in the dapagliflozin analysis are the improvement in HbA1c and other modifiable risk factors such as systolic blood pressure, and adverse events such as hypoglycaemia are taken into account. Diabetes models tend also to take account of the impact of weight change on HRQoL outcomes. This is of particular importance in the dapagliflozin model as a driver of cost-effectiveness due to the significant weight loss benefits associated with the drug relative to SUs in particular, but also relative to TZD and DPP-4 inhibitors.

6.10.2 Relevance of the economic evaluation to all patient groups

The dapagliflozin economic analysis can be considered relevant for all T2DM patients who have failed to achieve adequate glycaemic control on metformin, or who have failed to achieve adequate glycaemic control on insulin therapy.

In particular, the findings from the economic evaluation are supportive of dapagliflozin in dual therapy being a valuable alternative option to SU in patients who are at risk of hypoglycaemia, or in whom weight loss is a treatment goal. As an add-onto insulin agent, the economic evaluation has demonstrated cost-effectiveness relative to DPP-4, but also has the advantage of achieving glycaemic control without the need for up-titration of insulin (as demonstrated by the evidence from clinical study 06, see Section 5.5.3.4) with the consequent weight gain or hypoglycaemia risks associated with higher insulin doses.

6.10.3 Strengths and weaknesses of the evaluation

Strengths

- The dapagliflozin economic analyses use a validated and previously published economic modelling structure, with long run outcomes driven by well accepted UKPDS risk equations.

- Most of the data inputs are standard to other validated diabetes models used and accepted in previous NICE HTA (including recent single technology assessments for exenatide [TA248, 2012], liraglutide [TA203, 2011], and Clinical Guideline 87, [2009]).

- As well as PSA and univariate sensitivity analysis, attention has been given to exploring the impact on the cost-effectiveness results of a wide range of scenarios, including several relating to weight change impact – a key driver of the cost-effectiveness of dapagliflozin.

- The economic analysis vs. SU as dual therapy with metformin was informed by a comparative 52 week clinical study (with 104 week total extension, study 04) showing non-inferiority in HbA1c but better outcomes for dapagliflozin in terms of weight/BMI, SBP and hypoglycaemic episodes.

- The base case utility study used (Lane et al 2012) has enabled an assessment of the specific relationship between both increases and decreases in BMI on utility outcomes, whereas previous published analyses have focussed on the linear impact of a unit increase in BMI on disutility. The utilities are also based on direct patient experience, with valuation of specific weight gain/loss vignettes. Therefore, the new data is relevant for dapagliflozin which demonstrates weight loss and hence BMI improvements, relative to other OADs that demonstrate weight gain (SU, TZDs).

These strengths mean that we believe the model is producing valid and robust results with the main uncertainties in key data inputs such as the relationship between BMI and utility addressed in probabilistic and scenario analysis.

Weaknesses

- As there were no comparative data against comparators other than SU, an indirect comparison was necessary. To be as robust as possible this was performed as a Bayesian NMA.

- There is some uncertainty over the precise relationship between change in BMI and disutilities in T2DM. The bespoke study that has been performed provides a useful new estimate of the impact of increasing/decreasing BMI on utilities in T2DM. However, there are some limitations with this data in that it is not based on the NICE reference case EQ-5D, but rather TTO derived utilities from patients. As the values for the relationship between BMI and utilities varies in the literature it was important to test this variation in sensitivity and scenario analysis.

As with all economic evaluations in T2DM, there are some limitations in the data inputs which lead to uncertainty which has been addressed by comprehensive sensitivity/scenario analysis.

6.10.4 Further analyses

Further new analyses of the relationship between increasing/decreasing BMI and EQ 5D derived utilities could be useful to verify the results found from the TTO study.

In addition, it would be useful for a new resource use/costs of complications study using observational data for the UK to be performed to inform future diabetes economic models, as the UKPDS data are becoming somewhat dated.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

We expect the total pool of patients eligible for dapagliflozin to be approximately 2 million in 2013, rising to 2.45 million in 2017. These figures are estimates of the total T2DM population who may receive oral antidiabetic medication. The figures have been derived from the UK population growth, estimates of the prevalence of diabetes (Diabetes UK), and the proportion of patients receiving oral anti-diabetic therapy.

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

The net resource implications for England and Wales will differ depending upon the comparator chosen. In the case of dapagliflozin this is complicated by the range of existing therapies which dapagliflozin may replace.

Estimates of the uptake of dapagliflozin are included in the following table. Dapagliflozin's displacement of existing therapies was derived from consultations with clinicians in both England and Wales and for simplicity we assume constant annual proportions of patient switching from the SU, TZD and DPP-4 classes (25%, 10% and 65% respectively).

	2013	2014	2015	2016	2017
Diabetes population in England & Wales	2,874,995	3,003,574	3,132,154	3,260,733	3,389,313
T2DM population in England & Wales	2,587,495	2,703,217	2,818,938	2,934,660	3,050,382
T2DM population receiving OAD	2,080,346	2,173,386	2,266,427	2,359,467	2,452,507
Uptake of dapagliflozin	0.30%	0.90%	2.20%	3.25%	4.30%
Potential number of dapagliflozin patients	6,241	19,560	49,861	76,683	105,458

7.3 What assumption(s) were made about market share (when relevant)?

As above, dapagliflozin is expected to have a total market share (oral OAD) of approximately 0.3% in the first full year following approval, rising to 4.3% by year 5 following approval. As dapagliflozin will be the first SGLT-2 inhibitor to market we have estimated market share based on existing technologies in this therapeutic area, in particular we have reviewed the uptake of DPP-4 inhibitor therapies and GLP-1 analogues within the NHS.

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

There are no other significant costs associated with treatment with dapagliflozin in the treatment of T2DM.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The unit costs applied in the budget impact analysis are the same as those used in the cost utility model regarding drug costs. Details of these costs can be found in Section 6.5.5.

7.6 Were there any estimates of resource savings? If so, what were they?

There are no additional resource savings expected from using dapagliflozin in the treatment of T2DM.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated net annual budget impact for the NHS in England and Wales following the introduction of dapagliflozin is estimated to be £530,100 in the first full year following introduction, rising to £10.8m in year 5.

Budget Impact (£)	**2013**	**2014**	**2015**	**2016**	**2017**
T2DM population receiving OAD	2,080,346	2,173,386	2,266,427	2,359,467	2,452,507
Uptake of dapagliflozin	0.30%	0.90%	2.20%	3.25%	4.30%
Potential number of dapa patients	6,241	19,560	49,861	76,683	105,458
New dapa patients per year*	5,247	14,313	35,548	41,134	64,323
Existing dapa patients per year	994	5,247	14,313	35,548	41,134
Cost of dapagliflozin	**£1,725,390**	**£5,916,387**	**£15,304,867**	**£26,765,781**	**£34,960,530**
Less cost of displaced medicines	£1,194,448	£4,095,779	£10,595,207	£18,529,333	£24,202,369
Net cost of dapagliflozin	**£530,942**	**£1,820,609**	**£4,709,660**	**£8,236,448**	**£10,758,161**

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

All the opportunities for resource savings have been identified.

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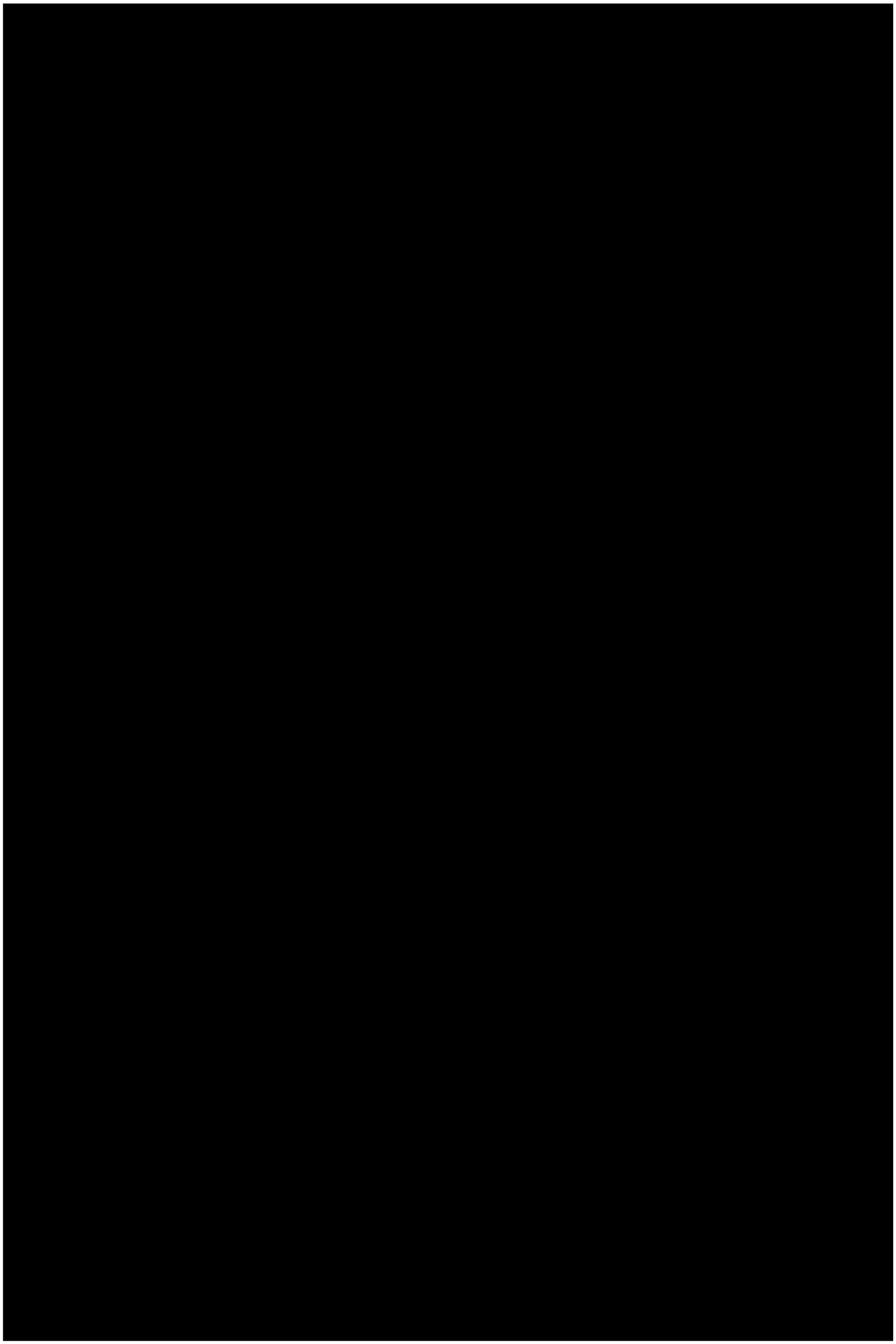
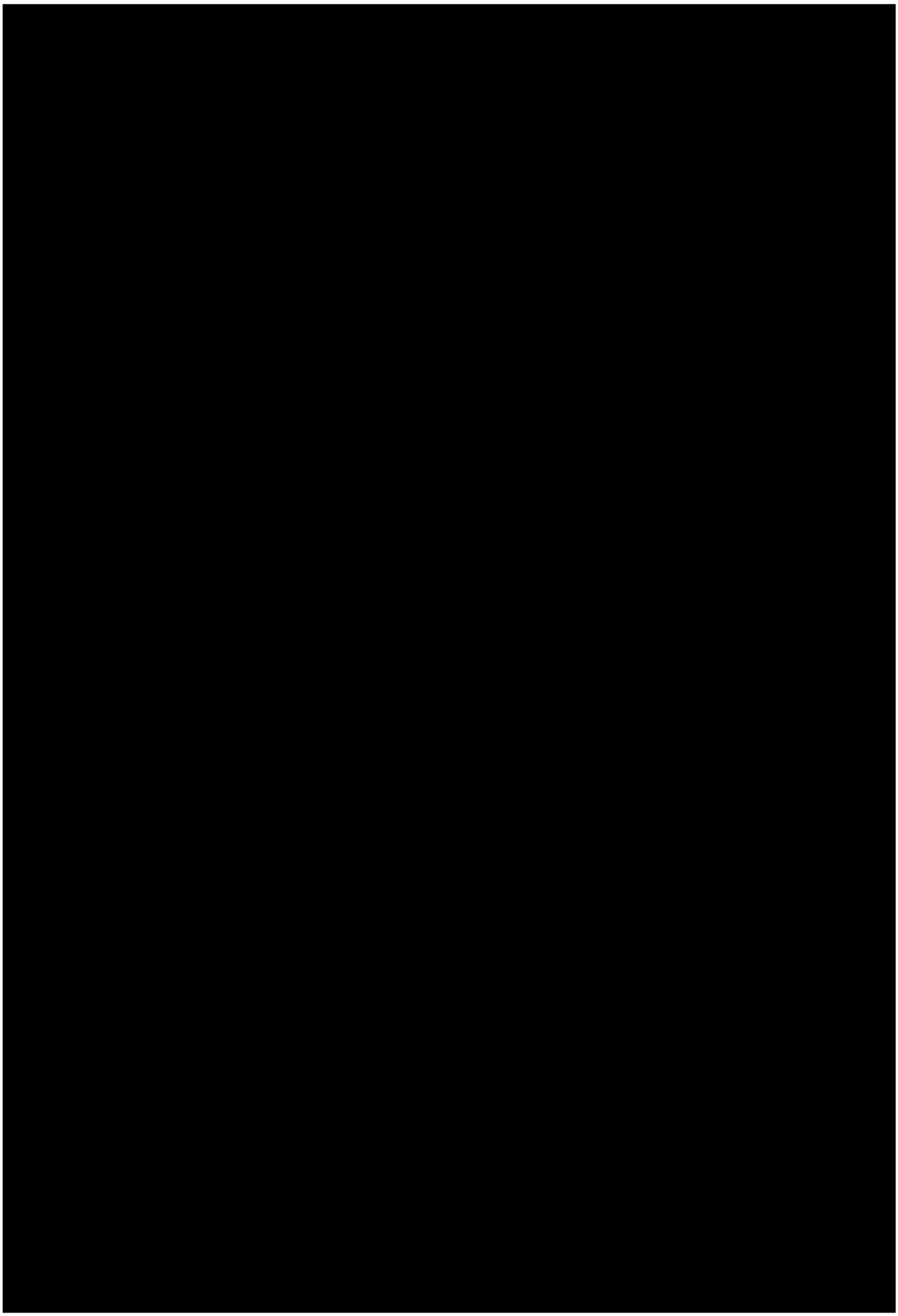
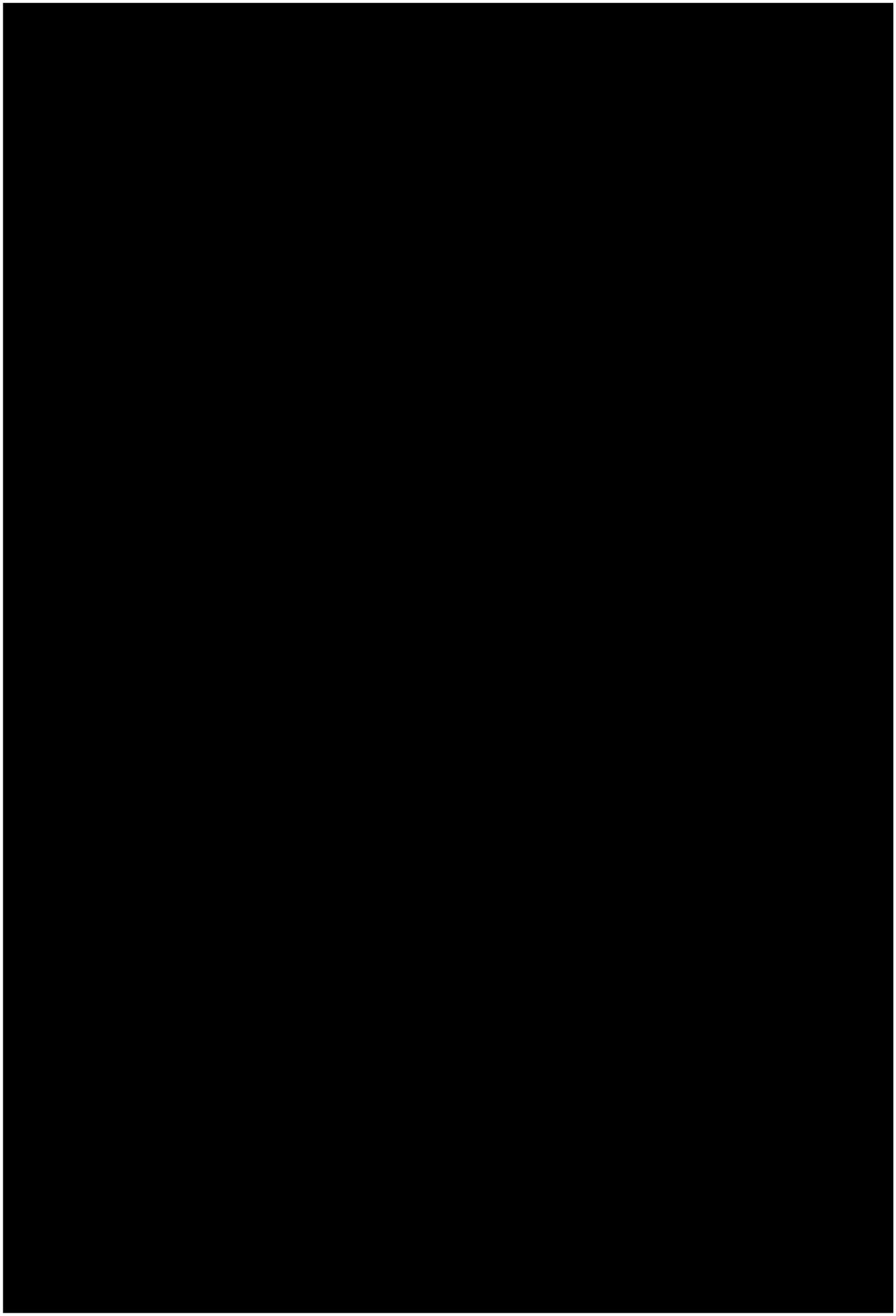
9 Appendices

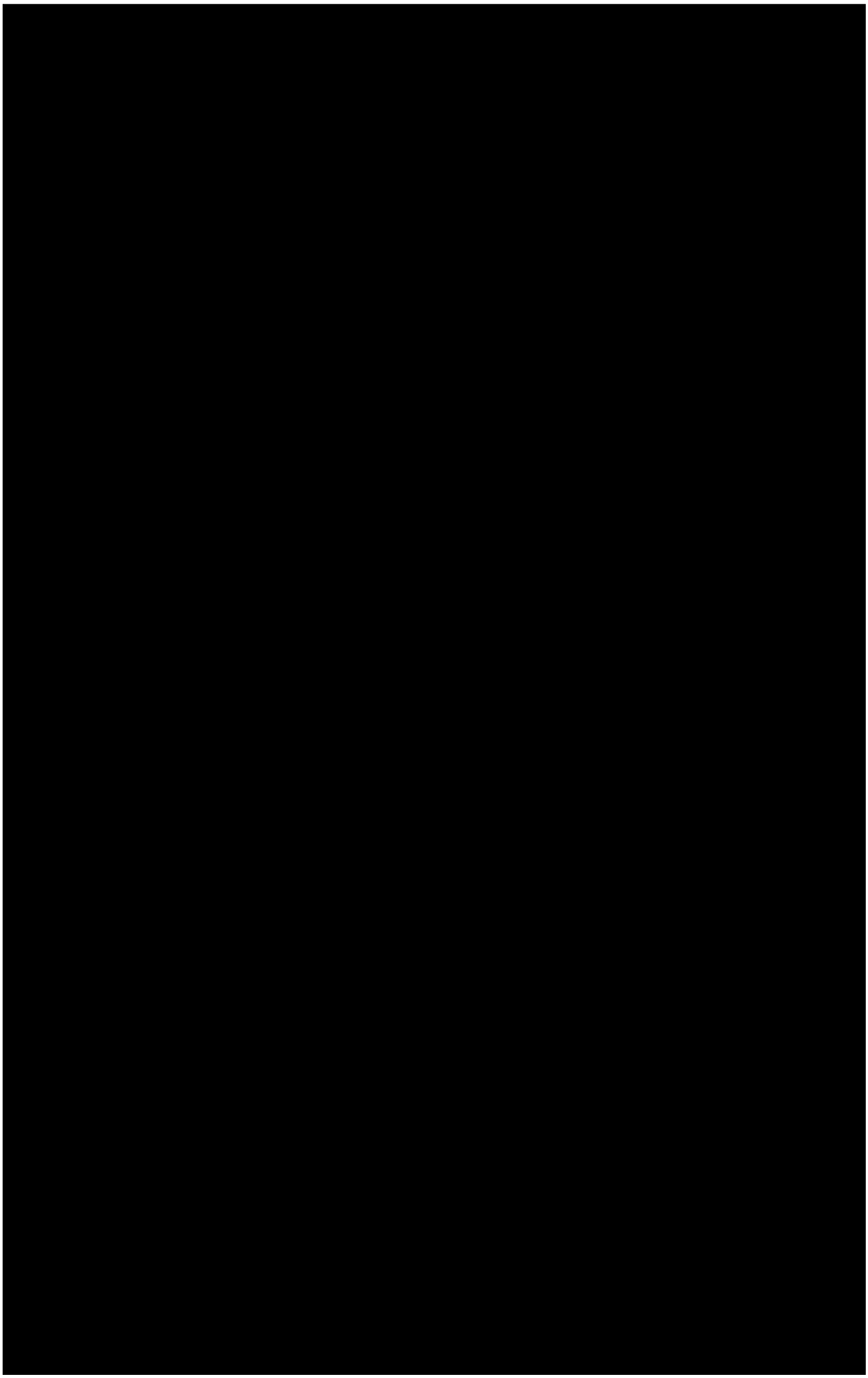
9.1 Appendix 1

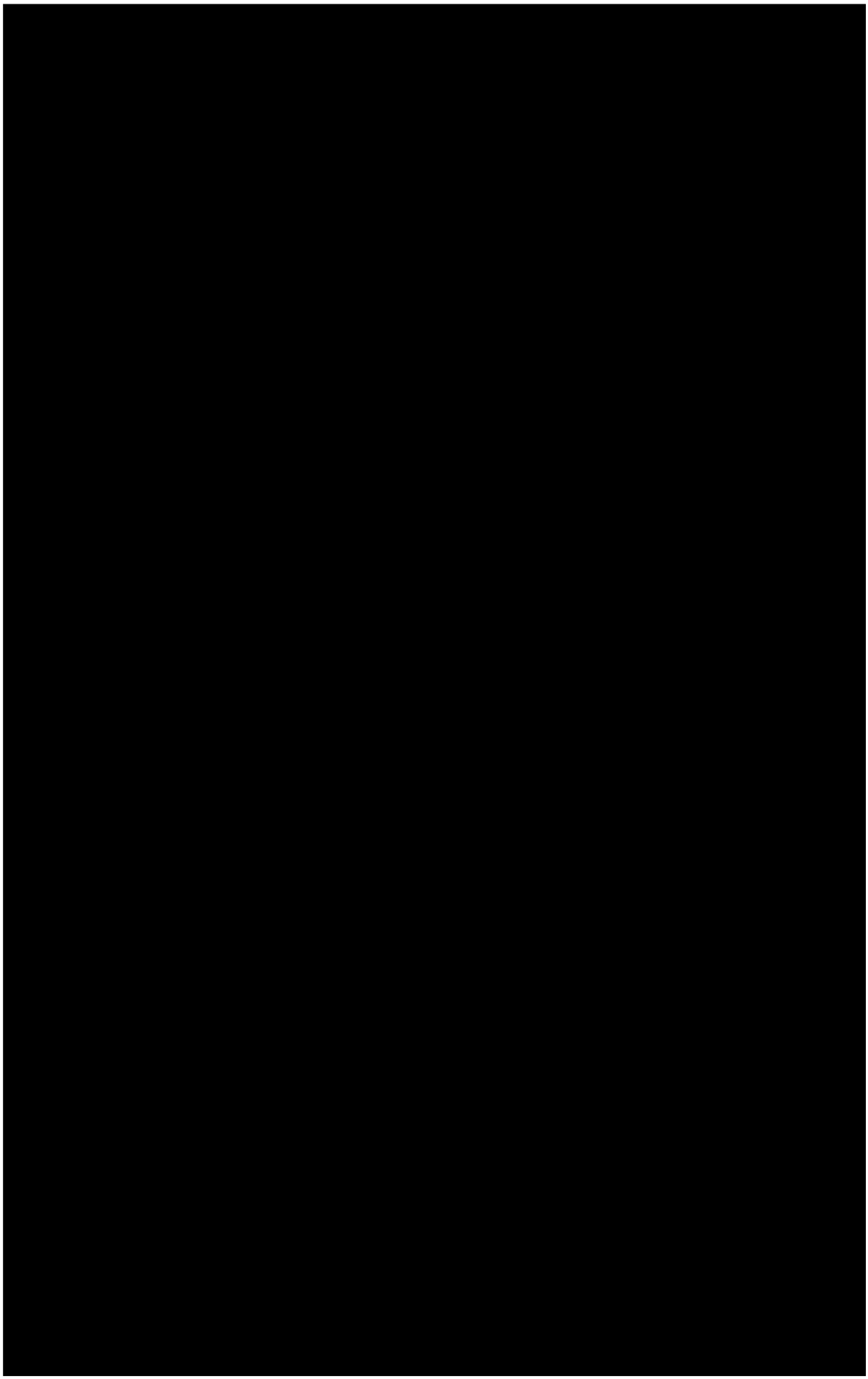
9.1.1 SPCs for Forxiga 5 mg / 10 mg – [redacted].

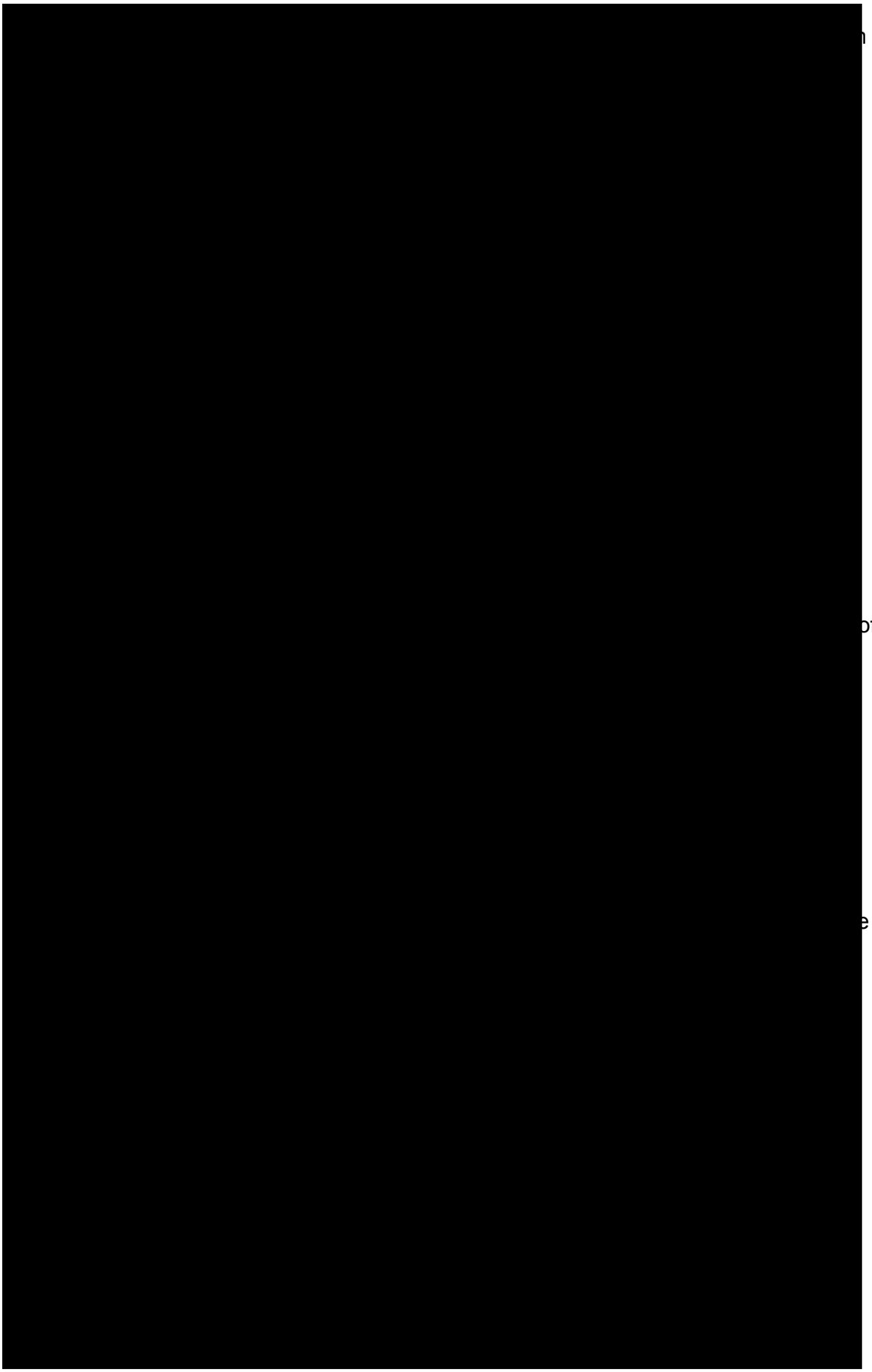


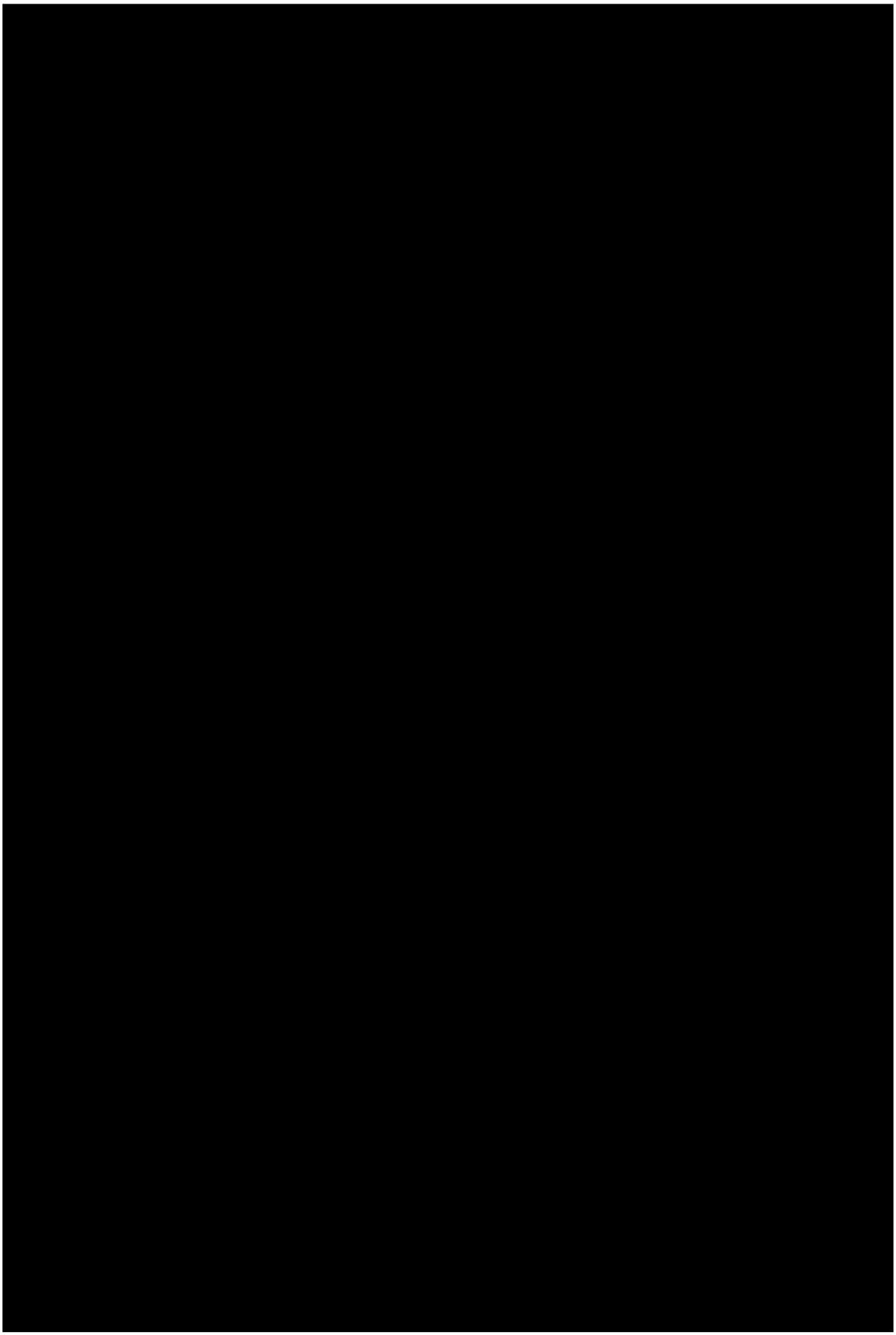












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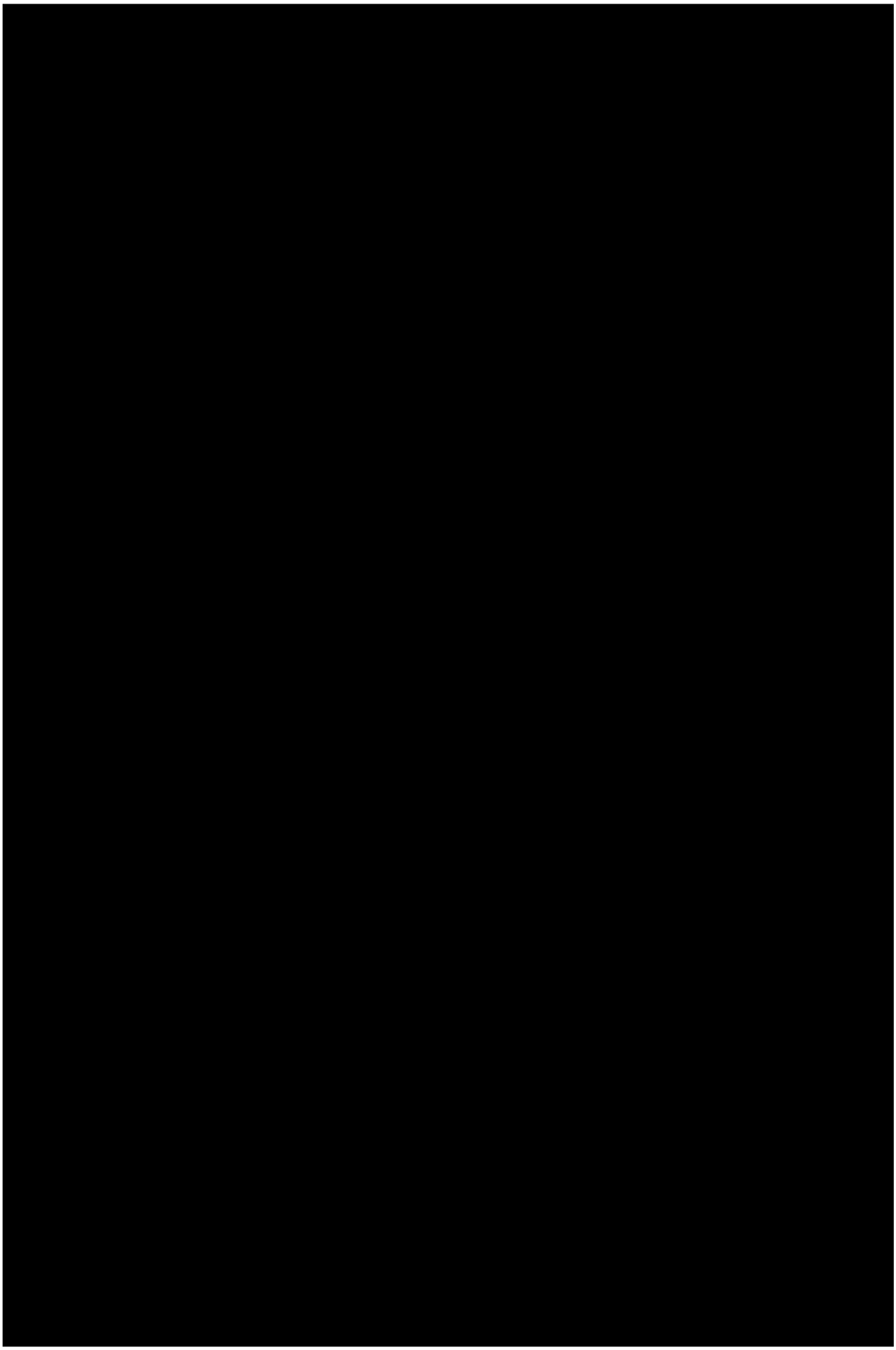

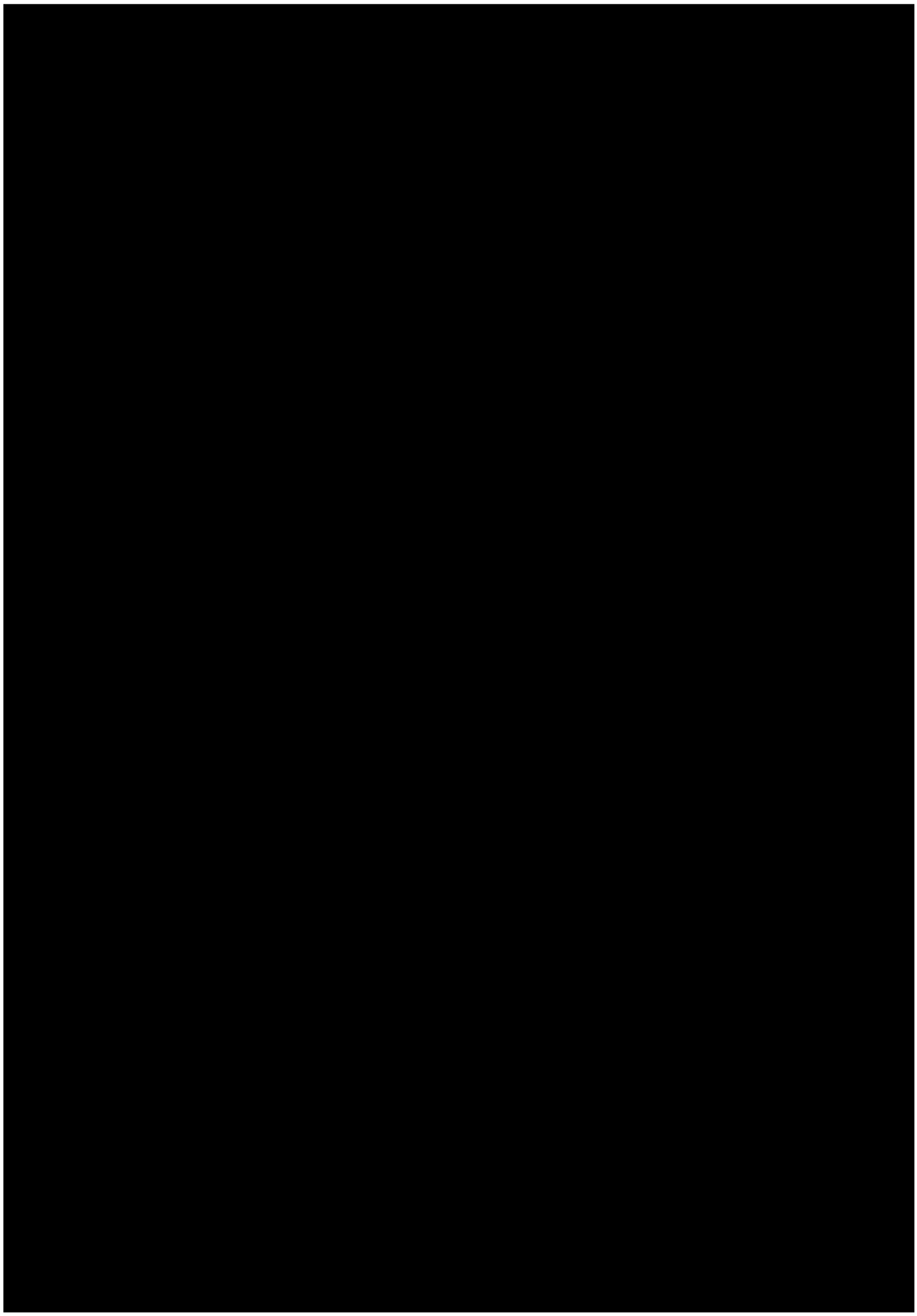

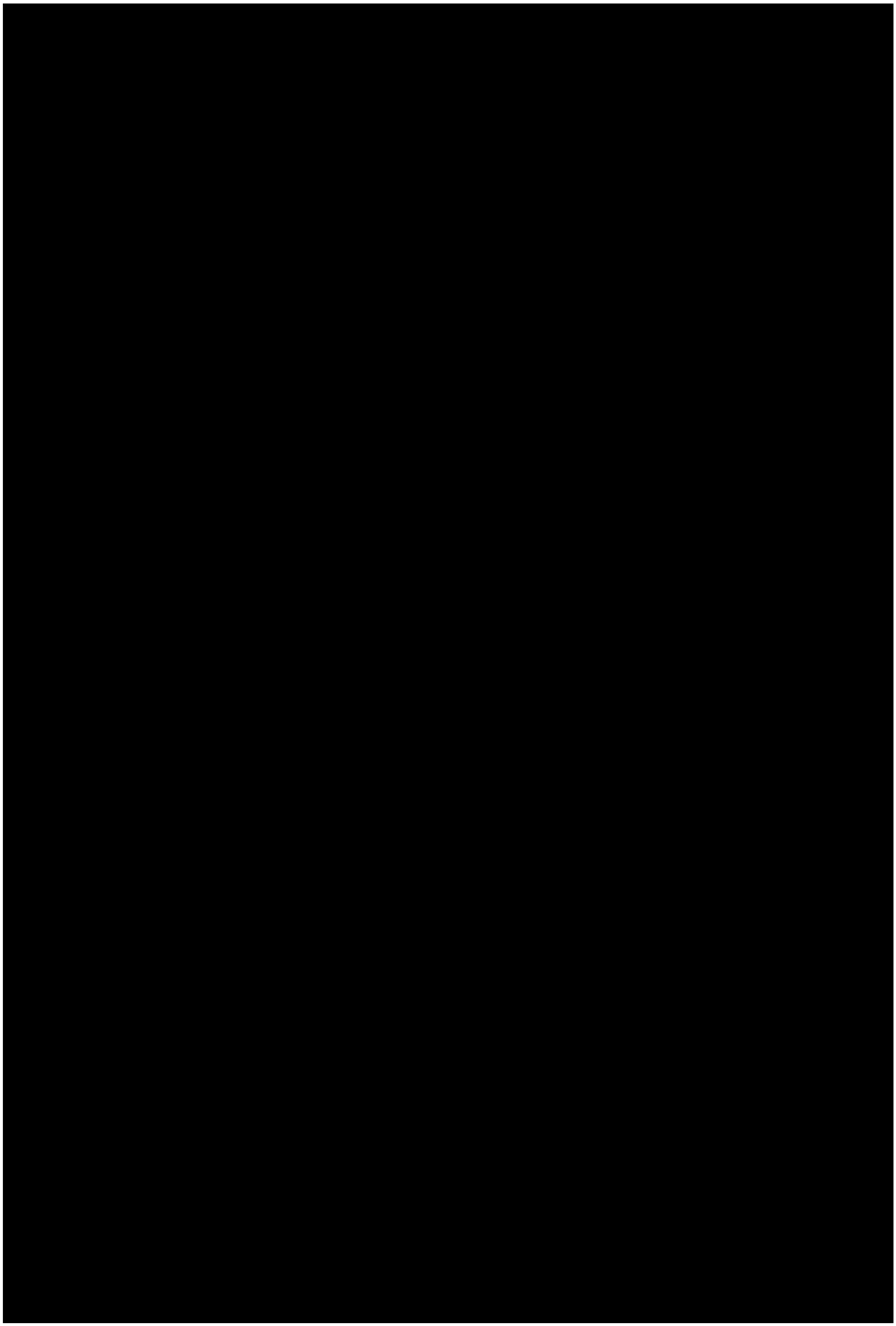

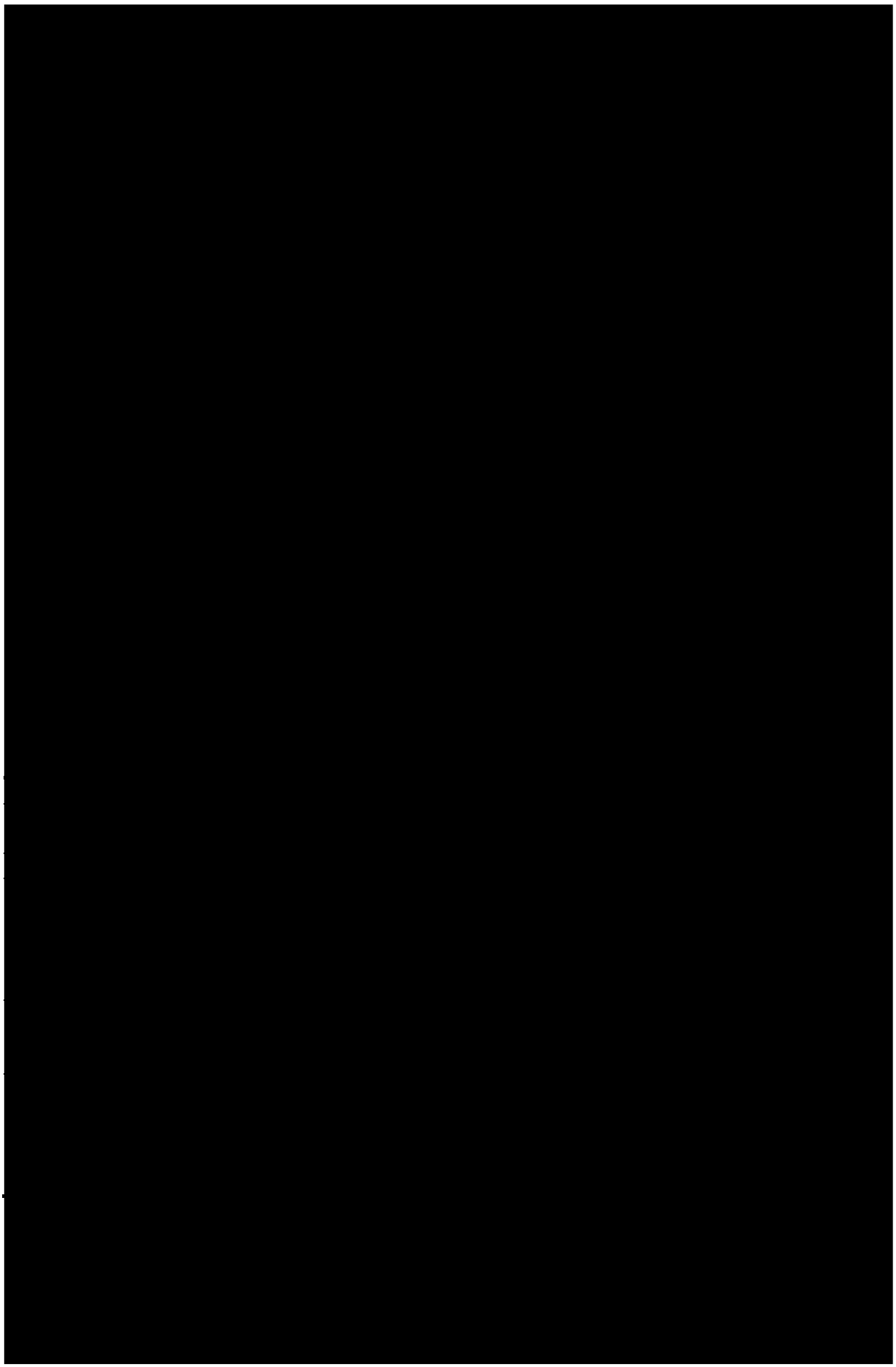

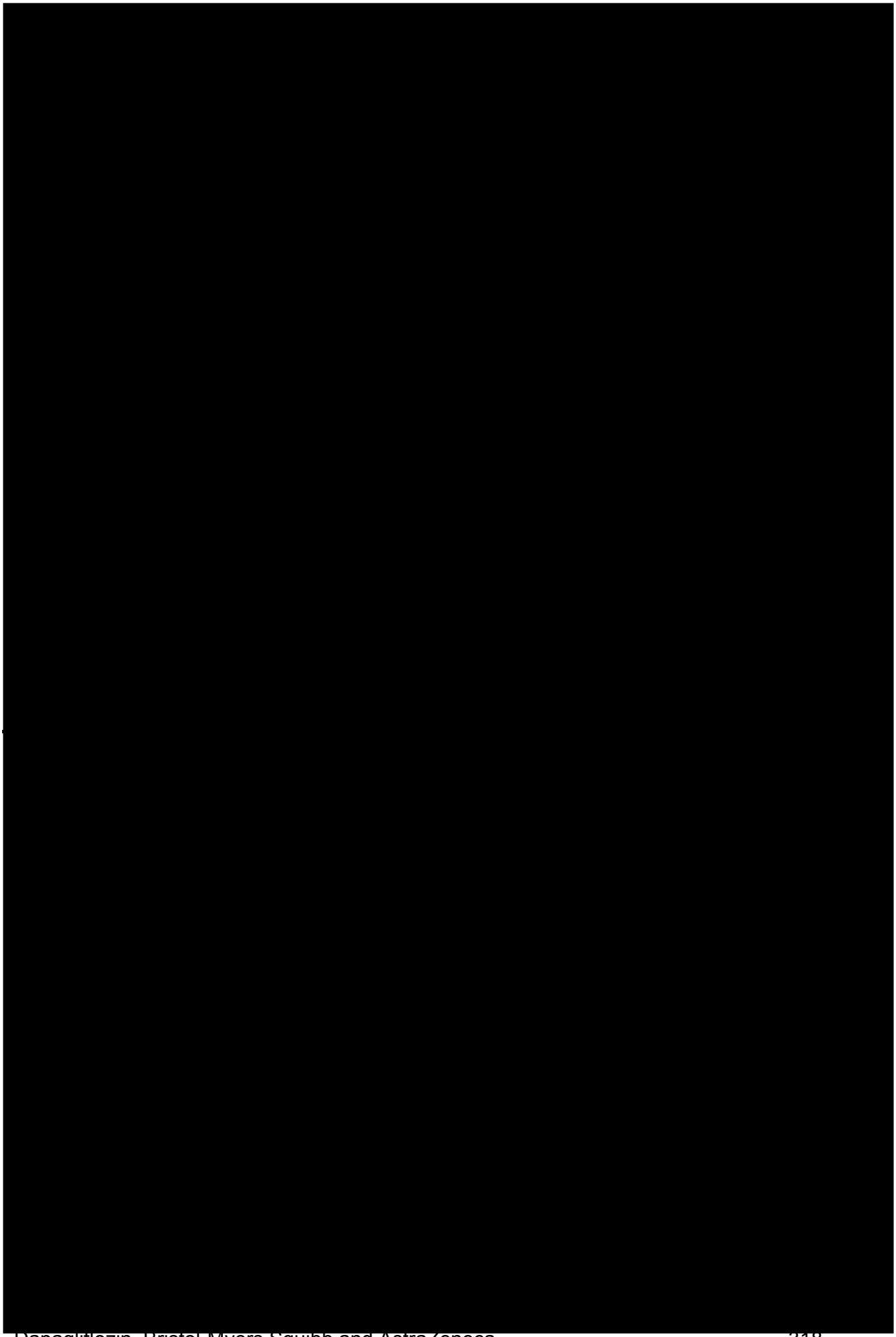

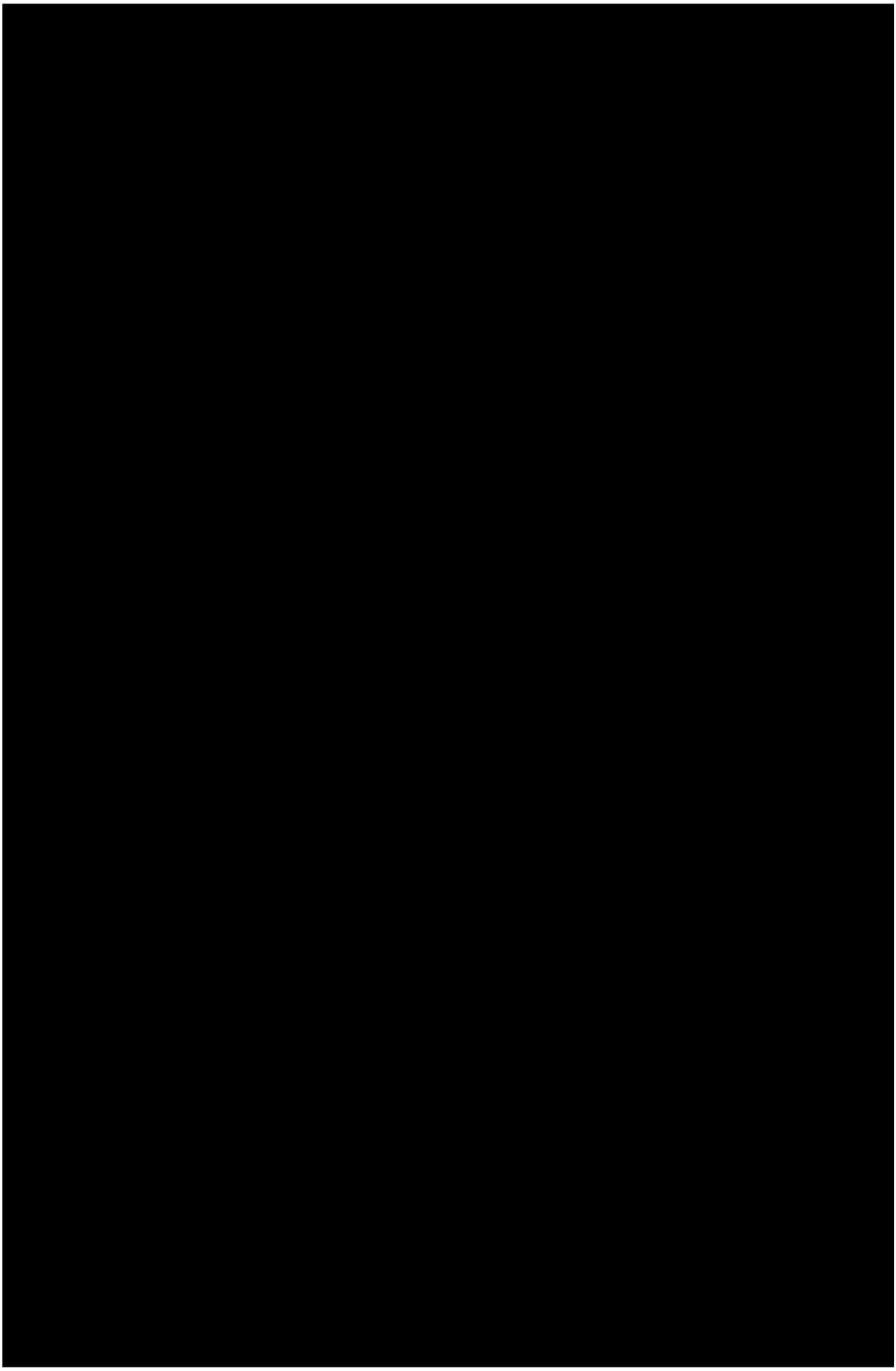

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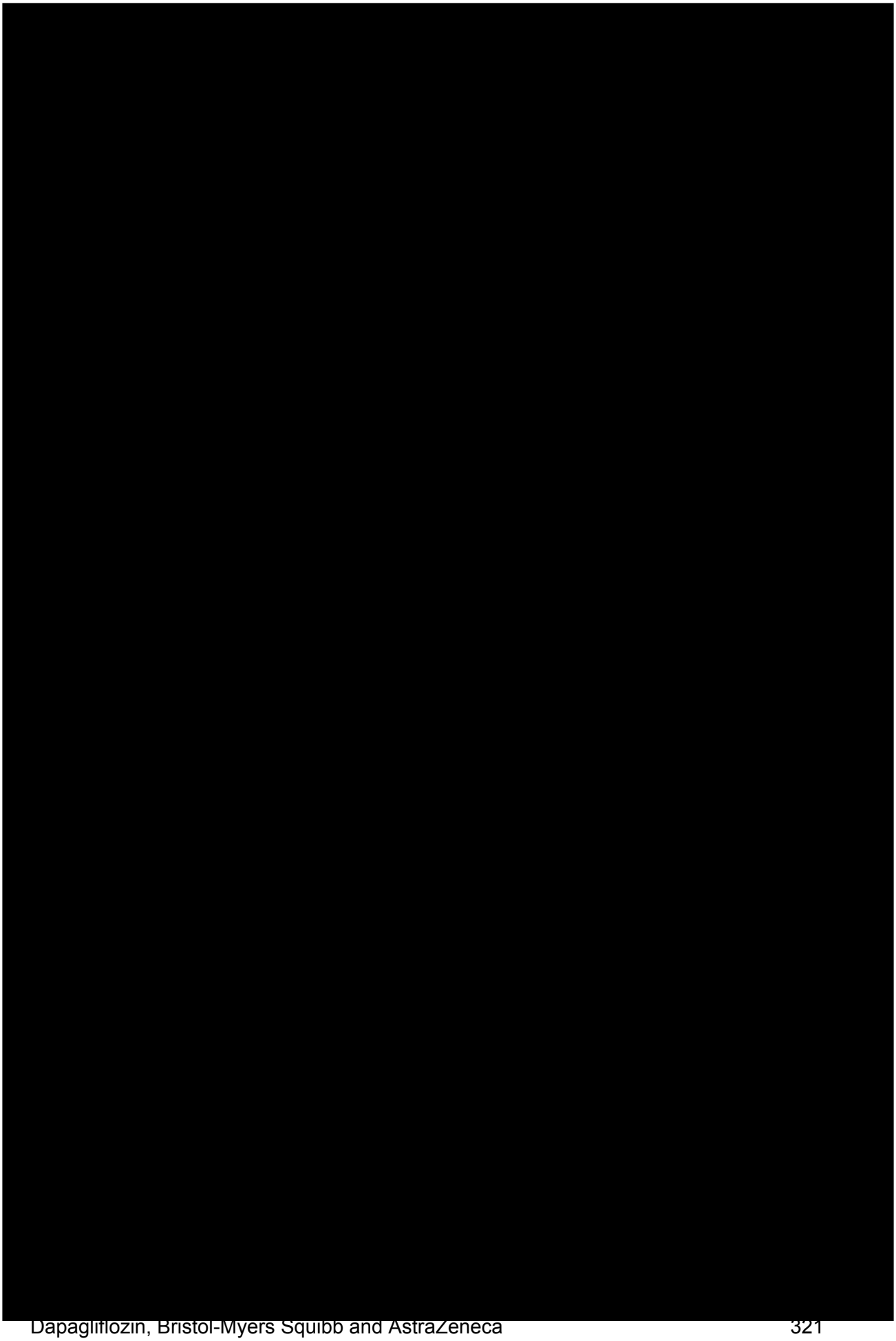

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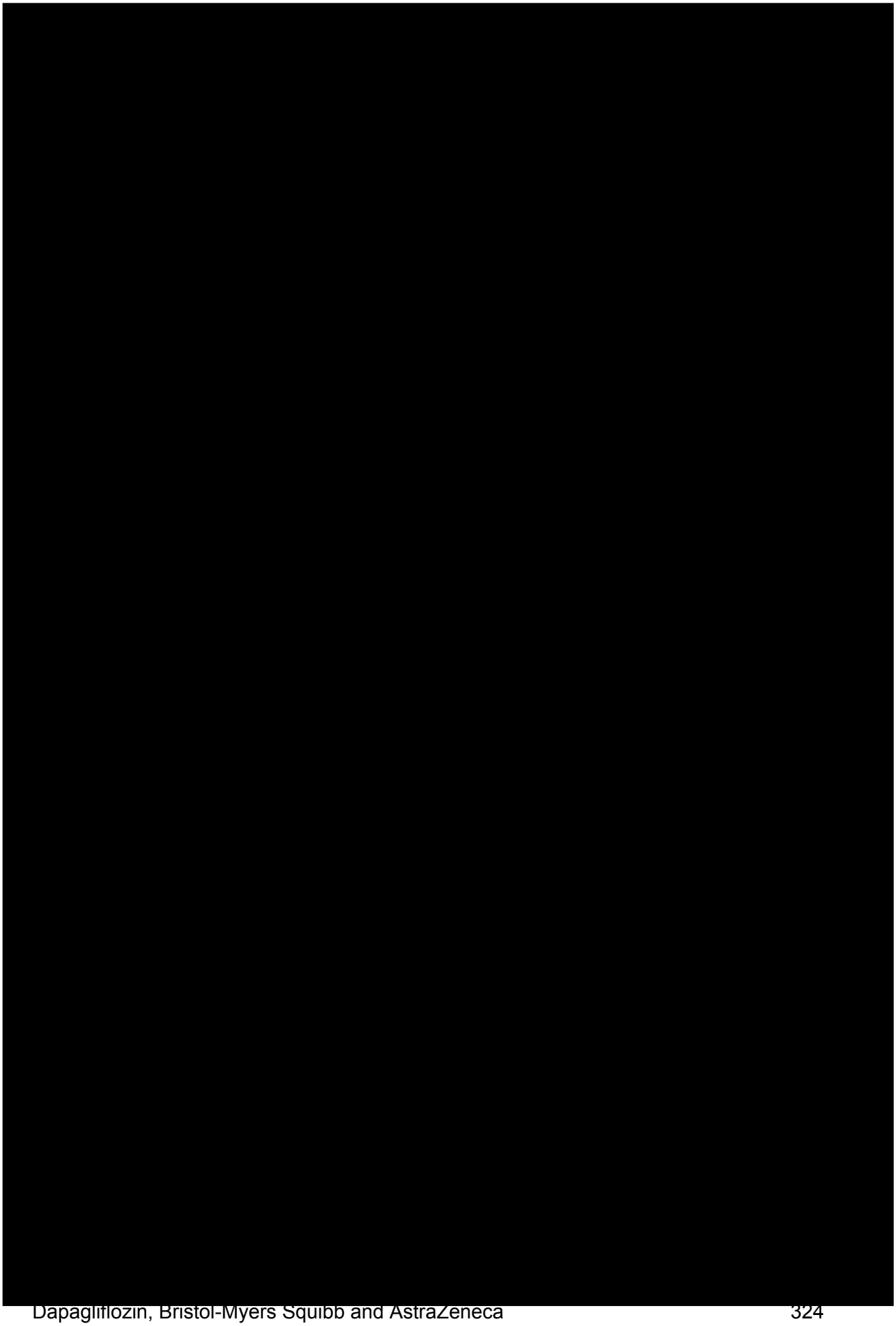

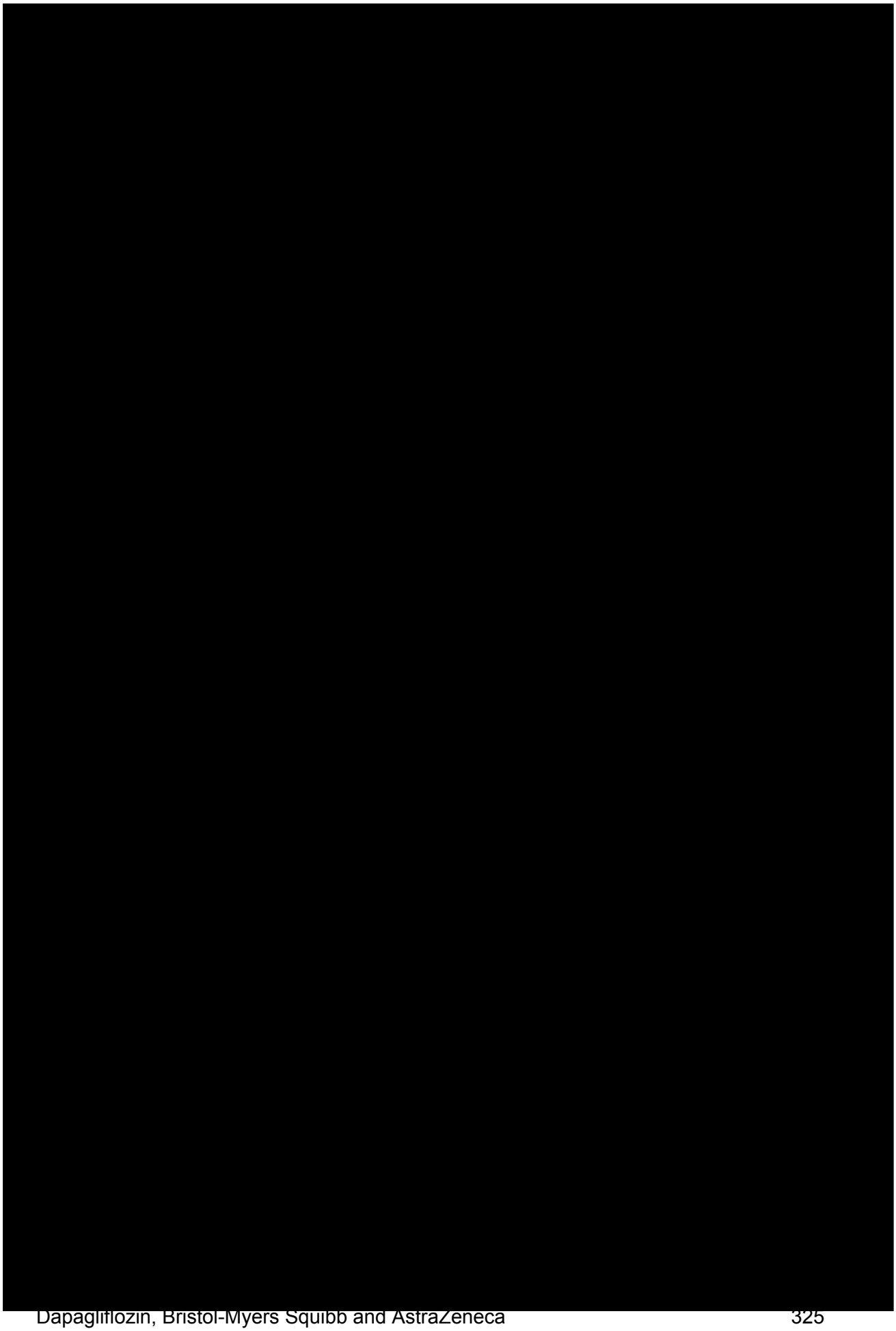

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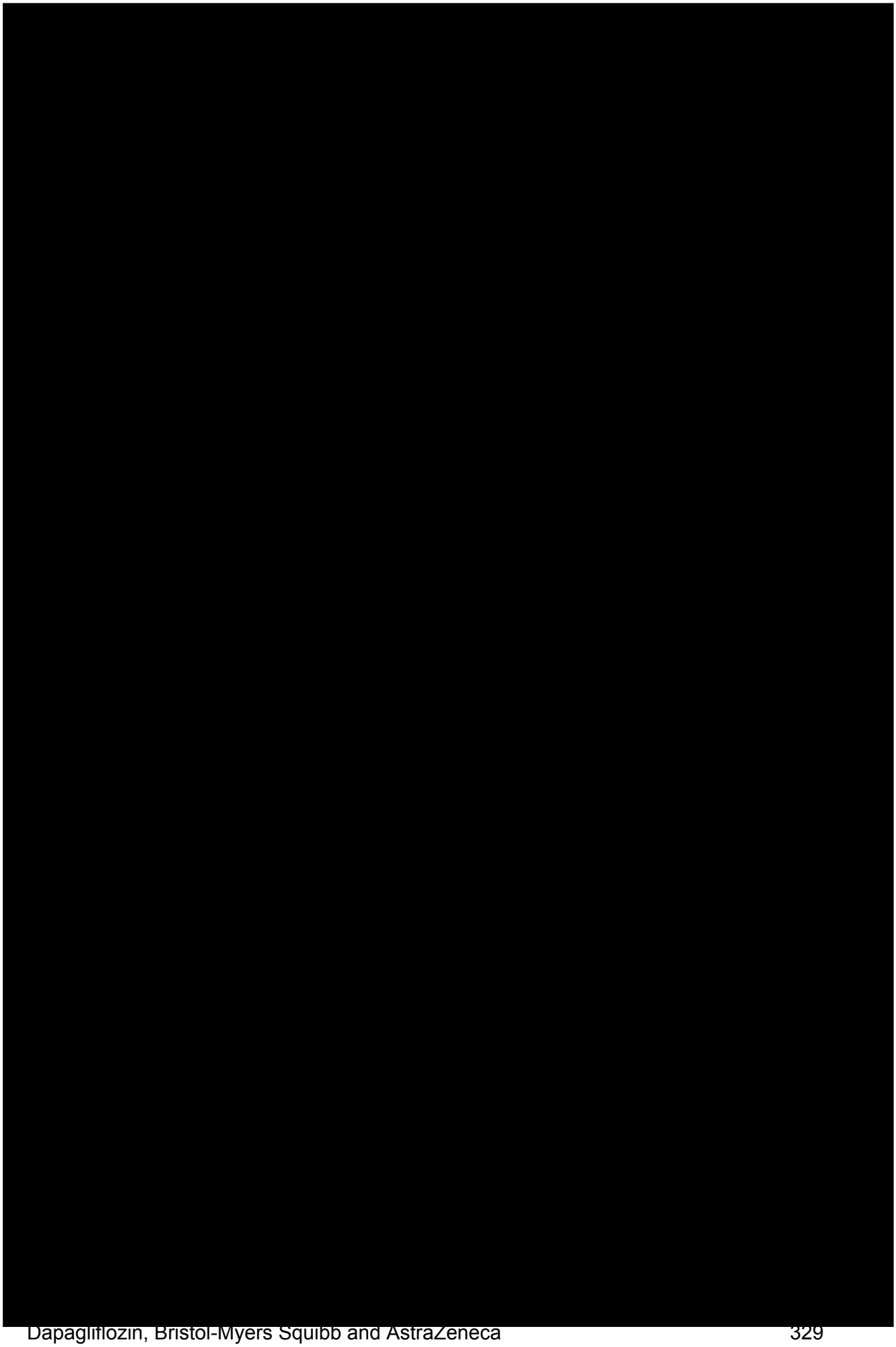

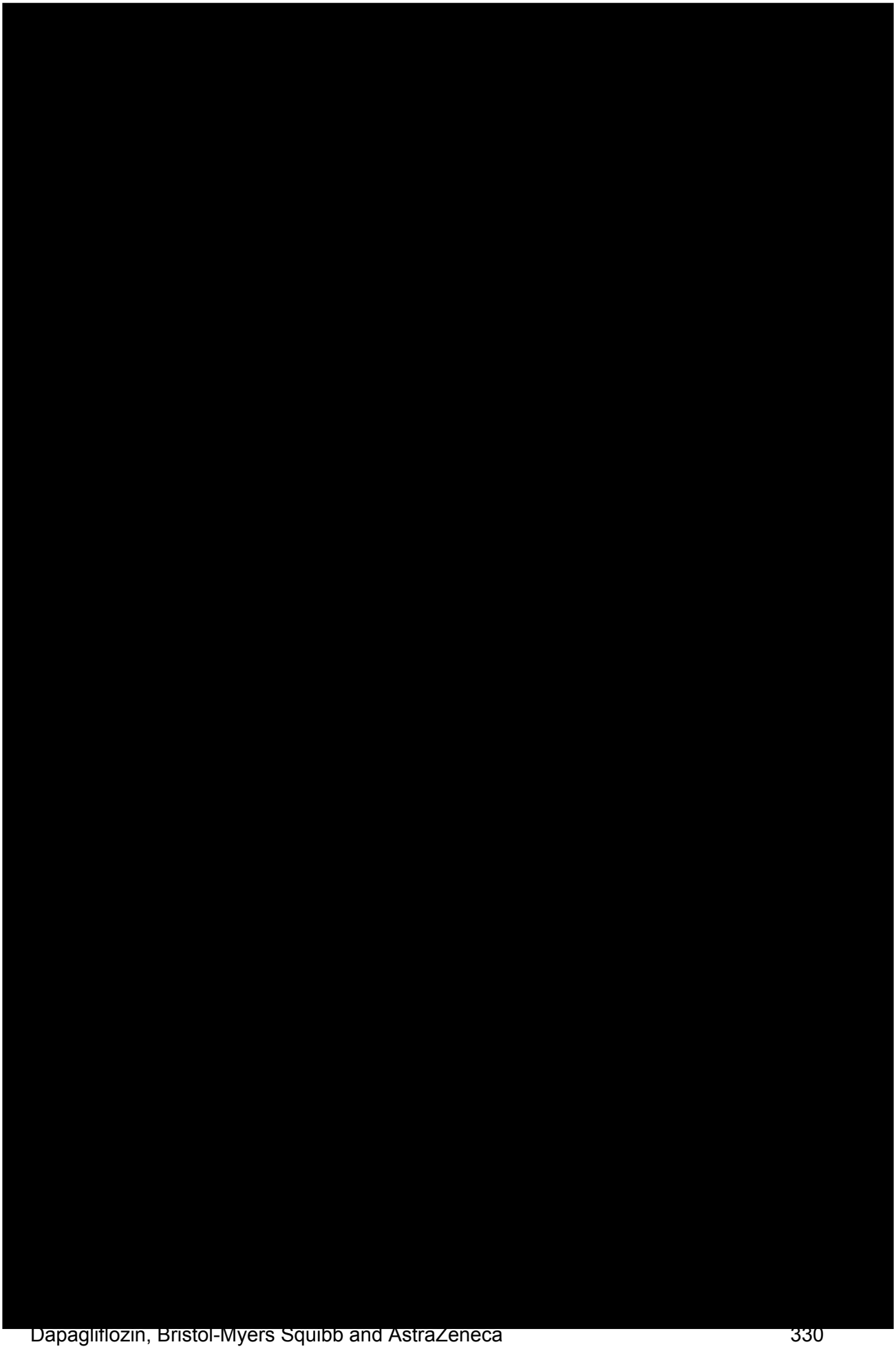

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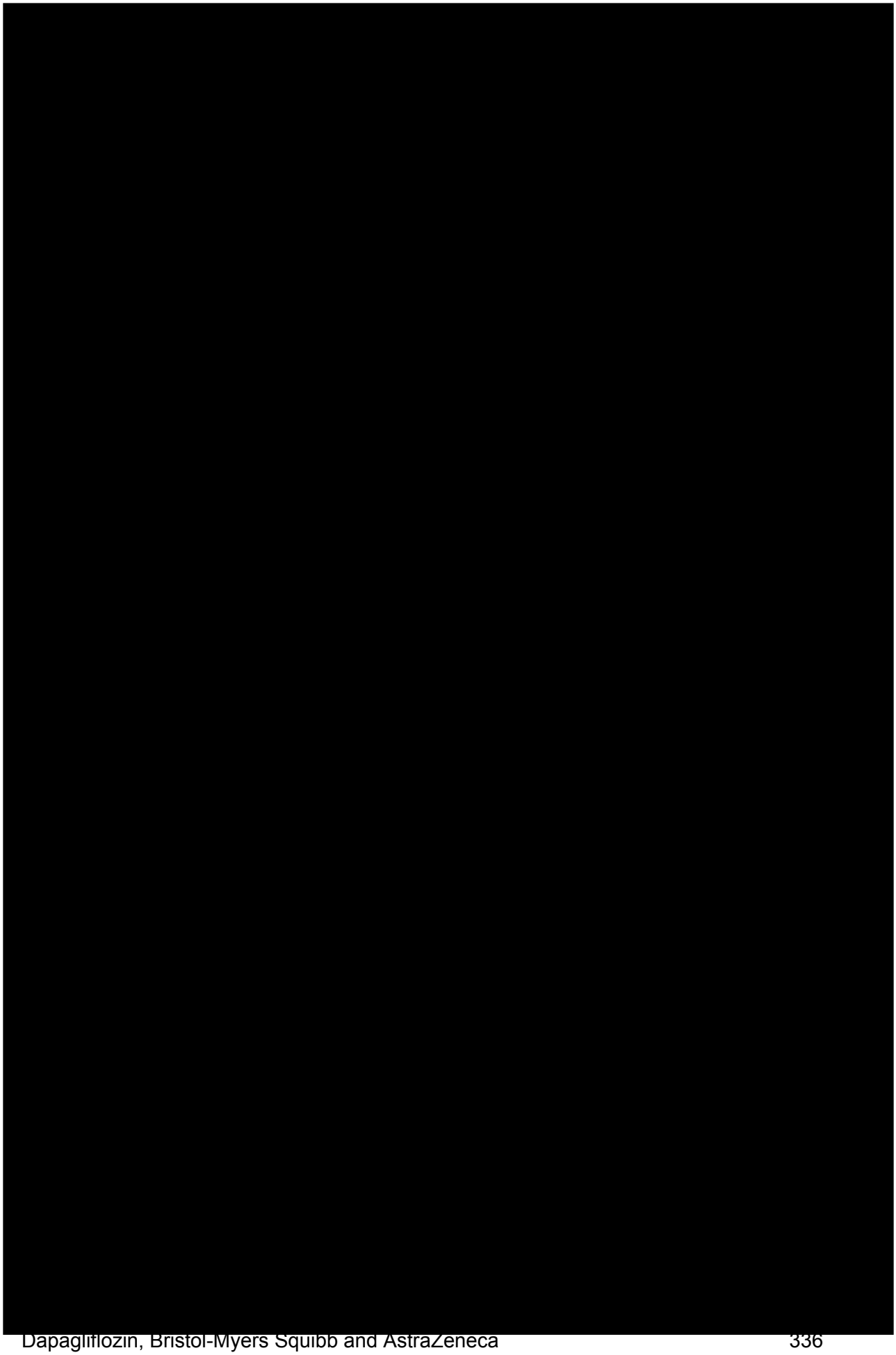

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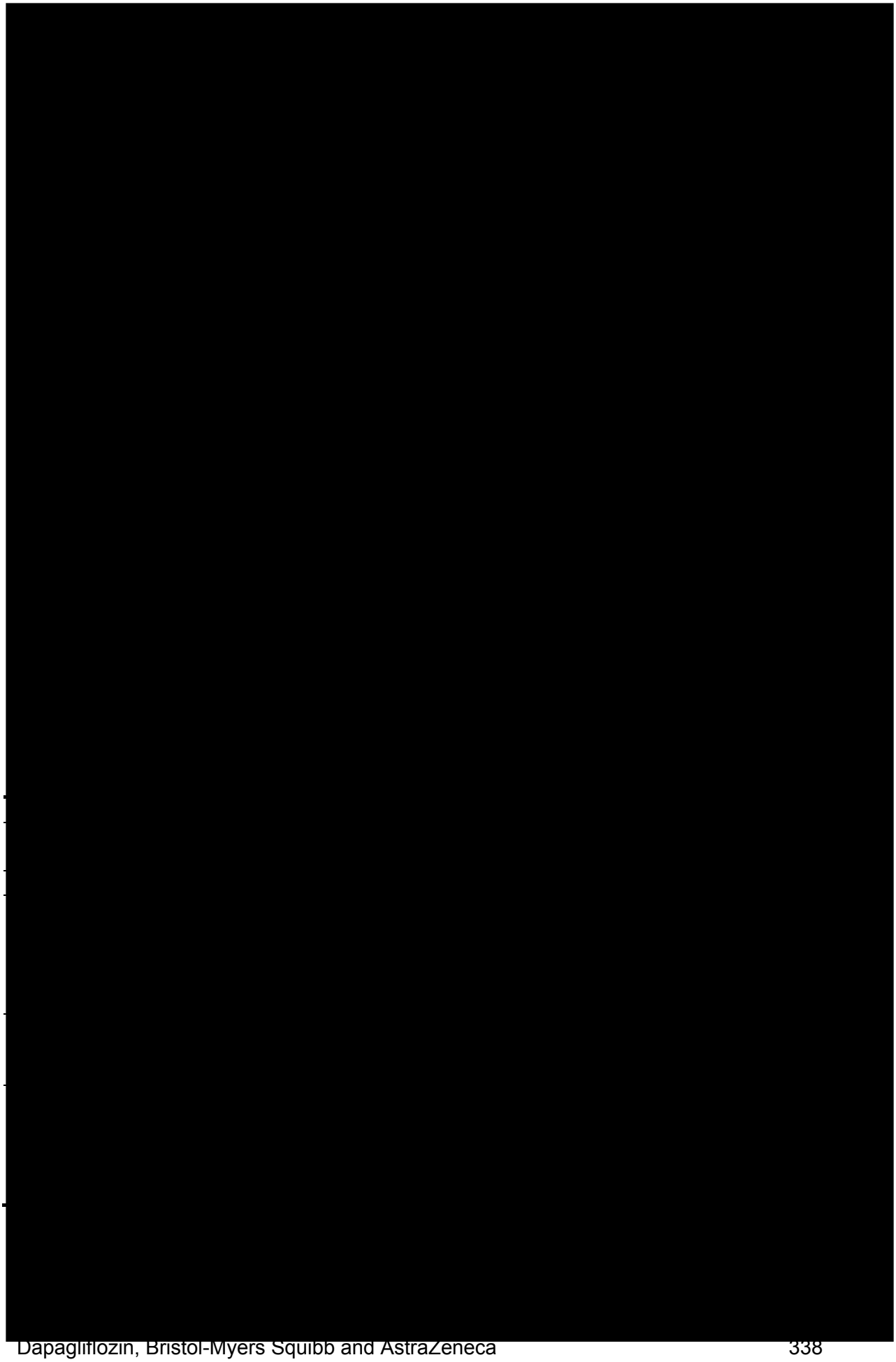

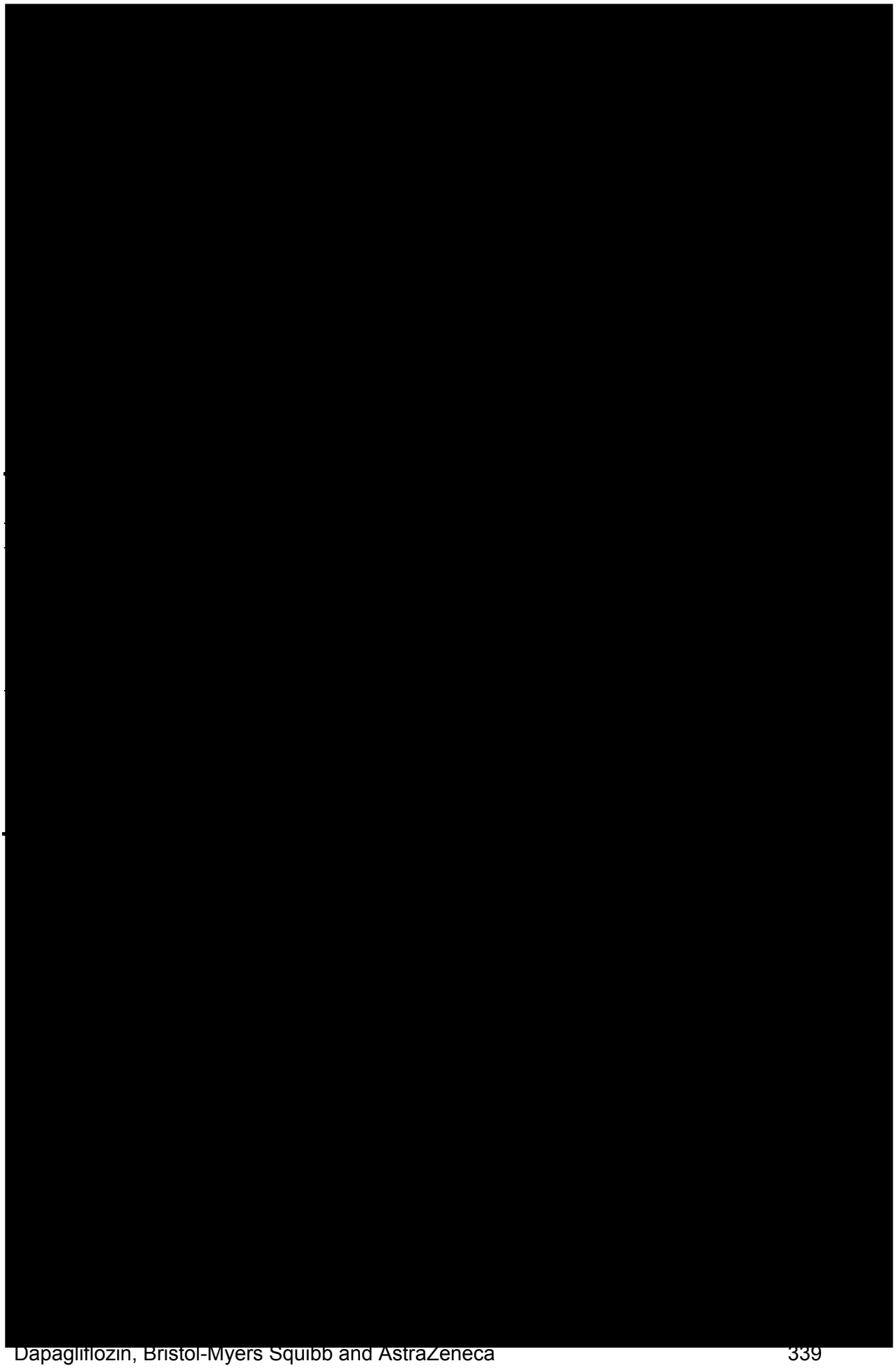

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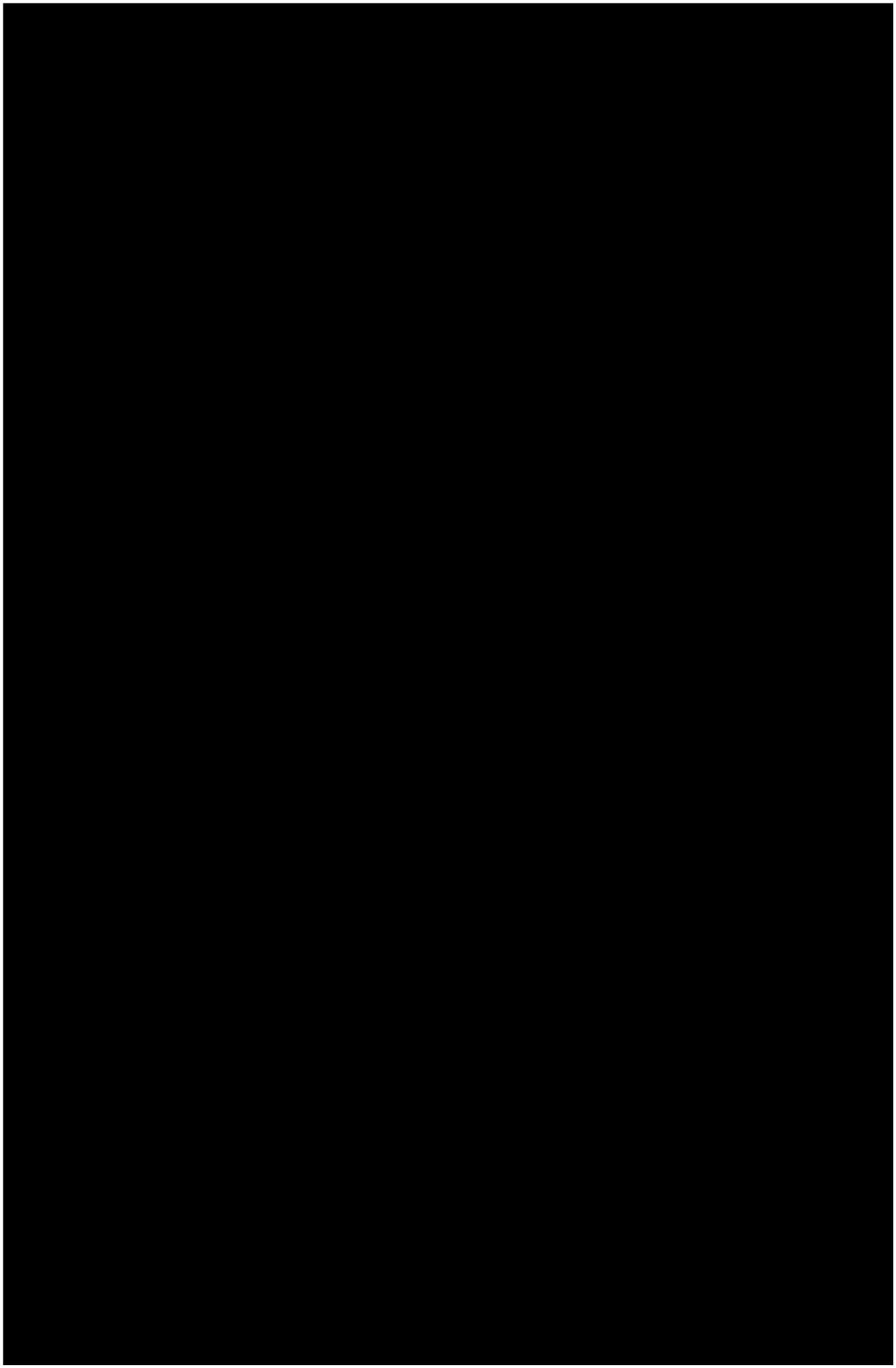

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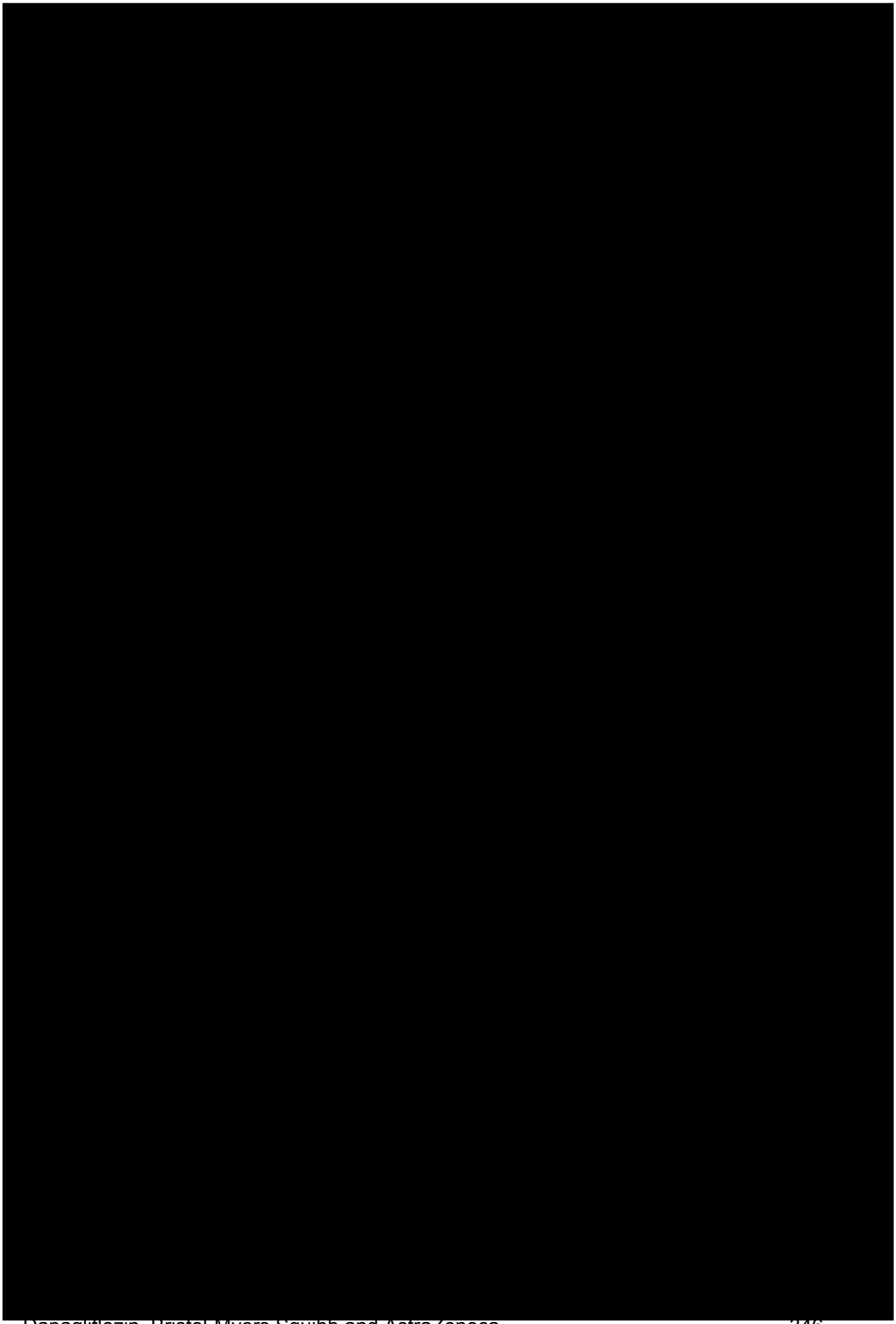

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9.2 Appendix 2: Search strategy for Section 5.1 (Identification of studies)

9.2.1 Databases searched

Using the Ovid® portal, the following databases were searched on May 11, 2011:

- Medline and Medline In-Process;
- EMBASE; and
- CENTRAL (Cochrane Central Register of Controlled Trials).

9.2.2 Search strategy

Below, the complete search strategies as executed within the various databases are presented.

9.2.2.1 Search strategy – EMBASE

Database: EMBASE <1980 to 2011 Week 17>

Search Strategy:

1 (dipeptidyl peptidase-4 inhibitor$ or dipeptidyl peptidase-IV inhibitor$).mp.
2 (dpp-iv inhibitor$ or dpp-4 inhibitor$).mp.
3 dipeptidyl-peptidase IV inhibitor/
4 sitagliptin/ or vildagliptin/ or saxagliptin/
5 (vildagliptin or sitagliptin or saxagliptin or linagliptin).mp.
6 dapagliflozin/
7 dapagliflozin.mp.
8 Glucagon-Like Peptide 1/
9 (Glucagon-Like Peptide 1 or GLP-1).mp.
10 exenatide/ or liraglutide/
11 (exenatide or liraglutide).mp.
12 Metformin$.mp.
13 metformin/
14 glibenclamide/
15 (glibenclamide or glyburide).mp.
16 gliclazide/
17 gliclazide.mp.
18 glimepiride/
19 glimepiride.mp.
20 glipizide/
21 glipizide.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui]
22 sulphonylurea derivative/
23 Thiazolidinediones/
24 pioglitazone/
25 pioglitazone.mp.
26 meglitinide/
27 nateglinide/
28 repaglinide/
29 (nateglinide or repaglinide).mp.
30 exp insulin derivative/
31 insulin$.mp.
32 or/1-31

33 exp drug combinations/
34 (drug therap$ or drug combination$).mp.
35 ((combination$ or oral or multiple) adj (therap$ or agent$ or drug$ or treatment$)).mp.
36 monotherap$.mp.
37 or/33-36
38 32 and 37
39 non insulin dependent diabetes mellitus/
40 (MODY or NIDDM or T2DM).mp.
41 (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ of non insulin?depend).mp.
42 ((typ$ 2 or typ$ II) adj diabet$).mp.
43 ((late or adult$ or matur$ or slow or stable$) adj diabet$).mp.
44 or/39-43
45 Randomized controlled trial/
46 controlled clinical trial/
47 randomized.ab.
48 placebo.ab.
49 randomly.ab.
50 trial.ti.
51 or/45-50
52 exp animals/ not humans.sh.
53 51 not 52
54 38 and 44 and 53
55 limit 54 to humans

9.2.2.2 Search strategy – Medline and Medline In-Process

Database: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) <1946 to May 11, 2011>

Search Strategy:

56 (dipeptidyl peptidase-4 inhibitor$ or dipeptidyl peptidase-IV inhibitor$).mp.
57 (dpp-iv inhibitor$ or dpp-4 inhibitor$).mp.
58 dipeptidyl-peptidase IV inhibitors/
59 (vildagliptin or sitagliptin or saxagliptin or linagliptin).mp.
60 dapagliflozin.mp.
61 Glucagon-Like Peptide 1/
62 (Glucagon-Like Peptide 1 or GLP-1).mp.
63 (exenatide or liraglutide).mp.
64 Metformin$.mp.
65 metformin/
66 glyburide/
67 (glibenclamide or glyburide).mp.
68 gliclazide/
69 gliclazide.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui]
70 glimepiride.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui]
71 glipizide/
72 glipizide.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui]
73 sulphonylurea compounds/ or sulphonylurea derivative/
74 Thiazolidinediones/
75 pioglitazone.mp.

76 (meglitinide$ or nateglinide$ or repaglinide$).mp.
77 exp insulin/
78 insulin$.mp.
79 or/56-78
80 exp drug combinations/
81 (drug therap$ or drug combination$).mp.
82 ((combination$ or oral or multiple) adj (therap$ or agent$ or drug$ or treatment$)).mp.
83 monotherap$.mp.
84 or/80-83
85 79 and 84
86 exp Diabetes Mellitus, Type 2/
87 (MODY or NIDDM or T2DM).mp.
88 (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ of non insulin?depend).mp.
89 ((typ$ 2 or typ$ II) adj diabet$).mp.
90 ((late or adult$ or matur$ or slow or stable$) adj diabet$).mp.
91 or/86-90
92 randomized controlled trial.pt.
93 controlled clinical trial.pt.
94 randomized.ab.
95 placebo.ab.
96 clinical trials as topic.sh.
97 randomly.ab.
98 trial.ti.
99 or/92-98
100 exp animals/ not humans.sh.
101 99 not 100
102 85 and 91 and 101
103 limit 102 to humans

104 55 or 103
105 remove duplicates from 104

9.2.2.3 Search strategy – Cochrane library

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <2nd Quarter 2011>

Search Strategy:
1 metformin/
2 metformin$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 (dipeptidyl peptidase-4 inhibitor$ or dipeptidyl peptidase-IV inhibitor$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 (dpp-iv inhibitor$ or dpp-4 inhibitor$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5 dipeptidyl-peptidase IV inhibitors/
6 (vildagliptin or sitagliptin or saxagliptin or linagliptin).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7 exp Glucagon-Like Peptide 1/
8 (Glucagon-Like Peptide 1 or GLP-1).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

9 (exenatide or liraglutide).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
10 dapagliflozin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
11 glyburide/
12 glibenclamide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
13 gliclazide/
14 gliclazide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
15 glimepiride.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
16 glipizide/
17 glipizide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
18 sulphonylurea compounds/ or sulphonylurea derivative/
19 exp insulin/
20 insulin$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
21 or/1-20
22 drug therapy, combination/
23 (drug therap$ or drug combination$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
24 ((combination$ or oral or multiple) adj (therap$ or agent$ or drug$ or treatment$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
25 monotherap$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
26 22 or 23 or 24 or 25
27 21 and 26
28 Diabetes Mellitus, Type 2/
29 (MODY or NIDDM or T2DM).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
30 (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ of non insulin?depend).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
31 ((typ$ 2 or typ$ II) adj diabet$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
32 ((late or adult$ or matur$ or slow or stable$) adj diabet$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
33 or/28-32
34 27 and 33
35 limit 34 to medline records
36 limit 34 to embase records
37 34 not (35 or 36)

9.2.3 Additional searches

Conference proceedings (2010) were searched for additional relevant records as described below.

- American College of Cardiology (ACC);

- All abstracts were published in Volume 55, Issue 10, Supplement 1 (March 2010) of the Journal of the American College of Cardiology,
- Used Science Direct search engine to search the issue for “diabetes” in the title, abstract, or keywords
- Returned 50 abstracts

- American Diabetes Association (ADA);
  - All abstracts were available through the organization’s website, http://professional.diabetes.org/Presentations_Details.aspx?typ=1&sr=adv&cng=116&meeting=116
  - In the Search box:
    - Selected Category > Pharmacologic Treatment of Diabetes or its Complications
    - Entered under Search Text: “Type 2” or “type II” or “T2DM”
    - Returned 222 abstracts

- American Heart Association (AHA);
  - All abstracts were published in Volume 122, Issue 21 Supplement (November 2010) of Circulation,
  - Also available at http://circ.ahajournals.org/content/vol122/21_MeetingAbstracts/
  - In the “Search this issue” box:
    - Entered under Search Text: “Type 2” or “type II” or “T2DM”
    - Returned 123 abstracts

- European Association for the Study of Diabetes (EASD);
  - All abstracts were published in Volume 53, Supplement 1 of Diabetologia,
  - Hand searched publication to identify relevant headings and hand searched within each heading:
    - OP 13: Incretin based therapies: new developments
    - OP 43: New oral agents
    - PS 73: DPP IV inhibitors
    - PS 74: GLP-1 analogues: clinical benefits

        - PS 75: Long acting GLP-1 agonists
        - PS 76: Incretin based therapies: metabolic effects
        - PS 77: GLP-1 analogues: safety and monitoring
        - PS 78: Incretins and insulin studies
        - PS 79: SGLT-2 inhibitors
        - PS 82: Conventional oral agents
        - The headings above included approximately 80 abstracts
- The Obesity Society
    - All abstracts were available through the organization's website (http://www.obesity.org),
    - Identified potentially relevant studies by searching for the following terms: "Type 2 diabetes", "type II diabetes", "T2DM", "diabetes mellitus"
    - Returned approximately 70 abstracts
- The International Diabetes Federation
    - No conference was held in 2010.

Using the search syntax described below, the following clinical trial registries were searched and cross-referenced with published articles. Manufacturers were contacted for data where published data could not be identified.

- Current Controlled Trials [ISRCTN] (www.controlled-trials.com);
    - Diabetes AND (dapagliflozin OR exenatide OR pioglitazone OR glyburide OR glimepiride OR glipizide OR gliclazide OR nateglinide OR repaglinide OR sitagliptin OR saxagliptin OR linagliptin)
    - Diabetes AND (metformin AND (dapagliflozin OR exenatide OR liraglutide OR pioglitazone OR glyburide OR glimepiride OR glipizide OR gliclazide OR nateglinide OR repaglinide OR sitagliptin OR vildagliptin OR saxagliptin OR linagliptin))
    - Diabetes AND (insulin AND (metformin OR dapagliflozin OR pioglitazone OR glyburide OR glimepiride OR glipizide OR gliclazide OR sitagliptin))
    - Returned 104 records
- ClinicalTrials.gov (http://clinicaltrials.gov);

- (NOT ("Recruiting" OR "Not yet recruiting" OR "Available")) [OVERALL-STATUS] AND "Interventional" [STUDY-TYPES] AND (diabetes AND ("type 2" OR "type II") AND NOT ("type 1" OR "type I")) [DISEASE] AND (metformin AND (dapagliflozin OR exenatide OR liraglutide OR pioglitazone OR glyburide OR glimepiride OR glipizide OR gliclazide OR nateglinide OR repaglinide OR sitagliptin OR vildagliptin OR saxagliptin OR linagliptin) OR insulin AND (metformin OR dapagliflozin OR pioglitazone OR glyburide OR glimepiride OR glipizide OR gliclazide OR sitagliptin)) [TREATMENT] AND ("Adult" OR "Senior") [AGE-GROUP]
- http://clinicaltrials.gov/ct2/results?recr=Closed&type=Intr&cond=diabetes+AND+%28+%22type+2%22+OR+%22type+II%22+%29+AND+NOT+%28+%22type+1%22+OR+%22type+I%22+%29&intr=metformin+AND+%28+dapagliflozin+OR+exenatide+OR+liraglutide+OR+pioglitazone+OR+glyburide+OR+glimepiride+OR+glipizide+OR+gliclazide+OR+nateglinide+OR+repaglinide+OR+sitagliptin+OR+vildagliptin+OR+saxagliptin+OR+linagliptin+%29+OR+insulin+AND+%28+metformin+OR+dapagliflozin+OR+pioglitazone+OR+glyburide+OR+glimepiride+OR+glipizide+OR+gliclazide+OR+sitagliptin+%29&age=12&show_xprt=Y
- Returned 318 records

- Clinical Study Results (www.clinicalstudyresults.org);
  - **Disease**> Diabetes, Type 2; Diabetes Mellitus, Type 2; Diabetes Mellitus, Non-Insulin-Dependent
  - **Generic name** > Exenatide injection; liraglutide; Pioglitazone; pioglitazone hydrochloride; pioglitazone, metformin; Glyburide and metformin HCL tablets; Glimepiride; Glipizide; glipizide and metformin HCl; Repaglinide; Repaglinide/metformin HCL tablets; Sitagliptin; sitagliptin phosphate; sitagliptin phosphate (+) metformin hydrochloride; Saxagliptin; Saxagliptin and Metformin HCL extended-release; Insulin aspart, Insulin detemir, Insulin glargine, Insulin glulisine
  - Returned 125 records
- International Clinical Trials Registry Platform [ICTRP] (www.who.int/ictrp)
  - **Title**: NOT type 1 NOT gestation*
  - **Condition**: diabetes
  - **Intervention**: metformin AND dapagliflozin OR metformin AND exenatide OR metformin AND liraglutide OR metformin AND pioglitazone OR metformin AND glyburide OR metformin AND glimepiride OR metformin

AND glipizide OR metformin AND gliclazide OR metformin AND nateglinide OR metformin AND repaglinide OR metformin AND sitagliptin OR metformin AND vildagliptin OR metformin AND saxagliptin OR metformin AND linagliptin

- Returned 185 records

Reference list of included RCTs and systematic reviews (in the three years prior to 2011) were hand searched.

Unpublished trials in the BMS/AZ dapagliflozin clinical trial program were searched by reviewing a list of all on-going and completed RCTs, provided by the manufacturer. The eligibility of each was evaluated according to the criteria in Section 5.2.1, based on published abstracts, records on ClinicalTrials.gov, and if necessary, the full clinical study report (CSR).

9.2.4 Data abstraction strategy.

Data were extracted into a customized Excel spreadsheet. The extraction sheet was pilot tested by the data extractors prior to data extraction. Data extraction was performed by one primary reviewer and a secondary reviewer independently reviewed the articles and confirmed each of the data elements. Discrepancies in the extracted data were resolved through consensus.

9.2.5 Inclusion and exclusion criteria

The order in which the inclusion/exclusion criteria were applied is provided in Table 102. For excluded abstracts, the first applicable reason was applied as the responsible reason.

Table 102. Exclusion criteria applied in systematic review of anti-diabetic agents used to manage T2DM

Exclusion Number	Description
1	Not a randomized clinical trial (also exclude pooled analyses of randomized clinical trials)
2	Study evaluates outcomes in animals only
3	Not evaluating people with T2DM
4	Intervention is not a specific antihyperglycaemic agent in one of the following drug classes: insulin, sulfonylureas, meglitinides, biguanides, TZDs, alpha-glucosidase inhibitors, GLP-1 analogues, DPP-4 inhibitors, dapagliflozin
5	Study duration <12 weeks
6	Includes subjects <18 years old
7	Contains no comparisons between arms with combinations of two or fewer comparators of interest. Exclude if it contains no useful comparisons between mono/double therapy arms or contains triple therapy without insulin
8	Study does not evaluate the target population, with inadequate glycaemic control at baseline on: Diet and exercise only (monotherapy)

Exclusion Number	Description
	Metformin monotherapy (metformin add-on) Insulin with or without other anti-diabetic agents (insulin add-on)
9	Not one of the comparators of interest (e.g. acarbose or a non-licensed agent)
10	Does not report baseline and follow-up data for at least one outcome of interest
11	Conference abstract not in 2010
12	Not published prior to May 2011
13	Enrolled population restricted to subgroup for which the effect size is not expected to generalize to the population of type 2 diabetics (e.g. renal impairment)
14	Within-class comparisons of included comparators (e.g. glipizide vs gliclazide)
15	Study contains only comparisons between monotherapy with metformin and another relevant comparator/placebo
16	Dosage and/or dosing schedule not approved
17	Available only in abstract form (unless from specified conferences in 2010)

The licensed dosing for agents used as an add-on to metformin treatment is provided in Table 103.

Table 103. Licensed dosing for agents used as add-on to metformin treatment

Class	Drug	US indication		EU indication	
		Dose (min)	Dose (max)	Dose (min)	Dose (max)
SGLT2 inhibitors	Dapagliflozin (anticipated dose)	10 mg od†	10 mg od†	10 mg od†	10 mg od†
GLP-1 analogues	Exenatide Liraglutide	5µg bd 1.2mg od	10µg bd 1.8mg od	5µg bd 0.6mg od	10µg bd 1.8mg od
Thiazolidinediones	Pioglitazone Pioglitazone/ metformin Pioglitazone/ metformin (extended release)	15mg od 15mg/500 mg od 15mg/ 1000mg od	45mg od 15mg/850mg bd‡ 30mg/ 1000mg od§	15mg od 15mg/ 850mg bd --	45mg od 15mg/ 850mg bd --
Sulfonylureas	Glyburide (Glibenclamide)	not stated	20mg daily	5mg od	15mg od
	Glyburide (micronized)	0.75mg daily	12mg daily	--	--
	Glyburide/metformin	2.5mg/ 500mg bd	20mg/ 2000mg daily	--	--
	Glimepiride	not stated	8 mg od	1mg od	6mg od
	Glipizide	--	--	5mg od	20mg od¶
		5mg od††	20mg od	--	--
	Glipizide/metformin	2.5mg/ 500mg bd	20mg/ 2000mg daily	--	--
	Gliclazide	--	--	40mg od	320mg‡‡
	Gliclazide (prolonged release)	--		30mg od	120mg od
Meglitinides	Nateglinide	60mg tds	120mg tds	60mg tds	180mg tds
	Repaglinide	0.5mg§§	16mg daily§§	0.5mg§§	16mg daily§§
	Repaglinide/metformin	1mg/500mg bd	10mg/2500mg daily¶¶	--	--
DPP-4 inhibitors	Sitagliptin	100mg od	100mg od	100mg od	100mg od

Class	Drug	US indication		EU indication	
		Dose (min)	Dose (max)	Dose (min)	Dose (max)
	Sitagliptin/metformin	50mg/500mg bd	50mg/ 1000mg bd	50mg/ 850mg bd	50mg/ 1000mg bd
	Vildagliptin	--	--	50mg bd	
	Vildagliptin/metformin	--	--	50mg/ 850mg bd	50mg/ 1000mg bd
	Saxagliptin	5mg od†††	5mg od	5mg od†††	5mg od
	Saxagliptin/metformin	5mg/500 mg or 2.5mg/ 1000mg	5mg/2000mg	--	--
	Linagliptin	unknown	Unknown	--	
Metformin	Metformin	--	2550 mg daily	500mg od	3000 mg od or divided
	Metformin prolonged/extended release	--	2000 mg daily	500mg od	2000 mg od or divided

Abbreviations: bd, Twice daily; DPP-4, Dipeptidyl peptidase-4 inhibitors; EU, European Union; GLP-1, Glucagon-like peptide-1 analogues; od, Once daily; SGLT2, Sodium-glucose cotransporter 2; tds, Thrice daily; US, United States of America; †, Anticipated dose for licensing; ‡, Based on metformin failure; May titrate dose up to 45mg/2550mg daily; §, May titrate up to 45mg/2000mg od; ¶, (above 15 mg to be divided doses); ††,(2.5mg if patient sensitive to hypoglycaemic agents); ‡‡, (Above 160 mg in divided doses); §§, Taken with meals; ¶¶, No more than 4mg/1000mg per meal; †††, 2.5mg permitted among subjects with renal impairment, but not considered in this analysis;

The licensed dosing for agents used as an add-on to insulin treatment is provided in Table 104.

Table 104. Licensed dosing for agents used as add-on to insulin treatment

Class	Drug	US indication		EU indication	
		Dose (min)	Dose (max)	Dose (min)	Dose (max)
SGLT2 inhibitors	Dapagliflozin	10 mg od†	10 mg od†	10 mg od†	10 mg od†
Thiazolidinediones	Pioglitazone	15mg od	45mg od	15mg od	45mg od
Sulfonylureas		5mg daily	20mg daily	--	--
	Glyburide (micronized)	3mg daily	12mg daily	--	--
	Glimepiride	8 mg od	8 mg od	1mg od	6mg od
	Glipizide	--	--	5mg od	20mg od‡
		5mg od§	20mg od		
	Gliclazide	--	--	--	--
	Gliclazide (prolonged release)	--	--	30mg od	120mg od
DPP-4 inhibitors	Sitagliptin	100mg od	100mg od	100mg od	100mg od
	Saxagliptin	5mg od¶	5mg od¶	5mg od¶	5mg od¶
Metformin	Metformin			500mg od	3000mg od or divided doses
	Metformin prolonged release	500mg od	2500mg od	500mg od	2500mg od

Abbreviations: DPP-4, Dipeptidyl peptidase-4 inhibitors; EU, European Union; od, Once daily; SGLT2, Sodium-glucose cotransporter 2; US, United States of America; †, Anticipated dose for licensing; ‡, (above 15 mg to be divided doses); §, (2.5mg if patient sensitive to hypoglycaemic agents), ¶, gained approval after execution of search strategy (2.5mg once daily for patients with moderate or severe renal impairment).

9.3 Appendix 3: Quality assessment of RCT(s)

9.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

The quality of the included RCTs was evaluated according to published criteria examining their internal and external validity (Sutton et al 1998; Sutton et al 1999; Juni et al 2001). Within Table 105 to Table 109, the results of the qualitative assessments of the included RCTs involving the interventional agent (dapagliflozin 10mg) are provided.

Table 105. Quality assessment of Study 14

Study 14‡		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	Randomisation schedule was computer-generated. Random assignment was performed using a central interactive voice response system (IVRS), and was stratified by site	Yes
Was the concealment of treatment allocation adequate?	The study was double blinded and treatment allocation was via the IVRS which randomly assigns patients with a unique kit number corresponding to numbers on the drug packaging	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	The demographic and baseline characteristics of study participants shows that the groups were similar at study outset	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators and sponsor personnel were blinded to treatment allocation	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No unexpected imbalances in drop-outs between randomised groups were reported	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There was no evidence suggesting that the authors measured more outcomes than they reported	No

Study 14‡		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Data were presented using a modified intention-to-treat approach (based on the definition of Abraha, 2010). The primary efficacy dataset consisted of all randomised subjects who received at least one dose of double-blind study medication and who had both a baseline and at least one post-baseline measurement. Last observation carried forward (LOCF) was used to account for occasional missing data Study authors further stated that the number of missing values represented only a small proportion of the patients randomised	Yes†

Abbreviations: IVRS, Interactive voice response system; LOCF, Last observation carried forward; †, Analysis included a modified intention-to-treat population, as defined by Abraha et al (Abraha, 2010); ‡, Published report and BMS/AZ data on file (clinical study report)

Table 106. Quality assessment of Study 12

Study 12†		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	The randomisation schedule was computer-generated. Randomisation was performed by means of unique randomisation codes and was done within balanced blocks and stratified by gender	Yes
Was the concealment of treatment allocation adequate?	The study was double blinded with the randomisation and treatment allocation scheme shielded from investigators, patients, and study monitors except for cases of medical emergencies	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	The demographic and baseline characteristics of study participants shows that the groups were similar at study outset	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators and sponsor personnel were blinded to treatment allocation	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No unexpected imbalances in drop-outs between randomised groups were reported	No

Study 12†		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There was no evidence suggesting that the authors measured more outcomes than they reported	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Data were presented using a modified intention-to-treat approach (based on the definition of Abraha, 2010). The full analysis dataset consisted of all randomised subjects who received at least one dose of double-blind study medication and who had both a baseline and at least one post-baseline measurement. Last observation carried forward (LOCF) was used to account for occasional missing data [redacted]	Yes‡

Abbreviations: LOCF, Last observation carried forward; †, Source: Published report and BMS/AZ data on file (clinical study report); ‡, Analysis included a modified intention-to-treat population, as defined by Abraha et al (Abraha, 2010)

Table 107. Quality assessment of Study 4

Study 4†		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	Randomisation was performed via an interactive web response system (IWRS), according to a computer generated randomisation scheme. Patients were randomised strictly sequentially as they become eligible for randomisation	Yes
Was the concealment of treatment allocation adequate?	The study was double blinded with the randomisation and treatment allocation scheme shielded from investigators, patients, and study monitors except for cases of medical emergencies	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	The demographic and baseline characteristics of study participants shows that the groups were similar at the study outset	Yes

Study 4†		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators and sponsor personnel were blinded to treatment allocation	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No unexpected imbalances in drop-outs between randomised groups were reported	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There was no evidence suggesting that the authors measured more outcomes than they reported	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Data were presented using a modified intention-to-treat approach (based on the definition of Abraha, 2010). The full analysis dataset consisted of all randomised subjects who received at least one dose of double-blind study medication and who had both a baseline and at least one post-baseline measurement. Last observation carried forward (LOCF) was used to account for occasional missing data [redacted]	Yes‡

Abbreviations: IWRS, Interactive web response system; LOCF, Last observation carried forward; †, Source: Published report and BMS/AZ data on file (clinical study report); ‡, Analysis included a modified intention-to-treat population, as defined by Abraha et al (Abraha, 2010)

Table 108. Quality assessment of Study 6

Study 6†		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	Randomisation schedule was computer-generated. Randomisation was done within balanced blocks and subjects were randomised sequentially as they are eligible for randomisation	Yes

Study 6†		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was the concealment of treatment allocation adequate?	The study was double blinded with the randomisation and treatment allocation scheme shielded from investigators, patients, and study monitors except for cases of medical emergencies	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	The demographic and baseline characteristics of study participants shows that the groups were similar at the study outset	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators and sponsor personnel were blinded to treatment allocation	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No unexpected imbalances in drop-outs between randomised groups were reported	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There was no evidence suggesting that the authors measured more outcomes than they reported	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Data were presented using a modified intention-to-treat approach (based on the definition of Abraha, 2010). The full analysis dataset consisted of all randomised subjects who received at least one dose of double-blind study medication and who had both a baseline and at least one post-baseline measurement. Last observation carried forward (LOCF) was used to account for occasional missing data 	Yes‡

Abbreviations: LOCF, Last observation carried forward; †, Source: Published abstract and BMS/AZ data on file (clinical study report); ‡, Analysis included a modified intention-to-treat population, as defined by Abraha et al (Abraha, 2010)

Table 109. Quality assessment of Study 9

Study 9†		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/NA)**
Was randomisation carried out appropriately?	Random assignment was performed by using a central interactive voice response system (IVRS), and was stratified by site	Yes
Was the concealment of treatment allocation adequate?	The study was double blinded with the randomisation and treatment allocation scheme shielded from investigators, patients, and sponsor personnel except for cases of medical emergencies	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	The demographic and baseline characteristics of study participants shows that the groups were similar at study outset	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigators and sponsor personnel were blinded to treatment allocation	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No unexpected imbalances in drop-outs between randomised groups were reported	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There was no evidence suggesting that the authors measured more outcomes than they reported	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Data were presented using a modified intention-to-treat approach (based on the definition of Abraha, 2010). The primary efficacy dataset consisted of all randomised subjects who received at least one dose of double-blind study medication	Yes‡

Abbreviations: IVRS, Interactive voice response system; LOCF, Last observation carried forward; †, Source: Published report and BMS/AZ data on file (clinical study report); ‡, Analysis included a modified intention-to-treat population, as defined by Abraha et al (Abraha, 2010)

9.4 Appendix 4: Search strategy for Section 5.7 (Indirect and mixed treatment comparisons)

9.4.1 Databases searched

Refer to Section 9.2.1.

9.4.2 Date on which the search was conducted

Refer to Section 9.2.1.

9.4.3 Date span of the search

Refer to Section 9.2.2.

9.4.4 Search strategy

Refer to Section 9.2.2.

9.4.5 Additional searches

Refer to Section 9.2.3.

9.4.6 The inclusion and exclusion criteria.

Refer to Section 9.2.5 and Section 5.7.2.2.

9.4.7 The data abstraction strategy.

Refer to Section 9.2.4.

9.5 Appendix 5: Quality assessment of comparator RCT(s) in Section 5.7

Please see Section 9.16, Appendix 16, Table 122 and Table 123

9.6 Appendix 6: Search strategy for Section 5.8 (Non-RCT evidence)

Non-RCT evidence was not considered based on pre-defined eligibility criteria used for the selection of studies.

9.6.1 Databases searched

Not applicable.

9.6.2 Date on which the search was conducted

Not applicable.

9.6.3 Date span of the search

Not applicable.

9.6.4 Search strategy

Not applicable.

9.6.5 Additional searches

Not applicable.

9.6.6 The inclusion and exclusion criteria.

Not applicable.

9.6.7 The data abstraction strategy.

Not applicable.

9.7 Appendix 7: Quality assessment of non-RCT(s) in Section 5.8

Not applicable.

9.8 Appendix 8: Search strategy for Section 5.9 (Adverse events)

9.8.1 Databases searched

Search strategy specific to adverse events were not used. Data on adverse events were collected from the studies meeting eligibility for inclusion in the review and involving the interventional agent (dapagliflozin 10 mg). Refer to Section 9.2.1 for additional details.

9.8.2 Date on which the search was conducted

Refer to Section 9.2.1.

9.8.3 Date span of the search

Refer to Section 9.2.2.

9.8.4 Search strategy

Refer to Section 9.2.2.

9.8.5 Additional searches

Refer to Section 9.2.3.

9.8.6 The inclusion and exclusion criteria.

Refer to Section 9.2.5.

9.8.7 The data abstraction strategy.

Refer to Section 9.2.4.

9.9 Appendix 9: Quality assessment of adverse event data in Section 5.9

Refer to Section 9.3.

9.10 Appendix 10: Search strategy for Section 6.1 (Cost-effectiveness studies)

9.10.1 Databases searched

A single comprehensive search of the literature was undertaken to cover the three non-clinical data requirements for the STA covering:

a) UK economic evaluations for the selected treatments for T2DM.

b) The measurement and valuation of health (i.e. utility studies) for T2DM.

c) UK resource utilisation studies (i.e. covering identification, measurement and valuation) for the selected treatments for T2DM.

The following electronic databases were searched:

- Ovid MEDLINE (1948 to Week 3, September 2011)
- Ovid MEDLINE In-Process & Other non-indexed citations (30 September 2011)
- Ovid EMBASE (1980 to Week 39, 2011)
- NHS Economic Evaluation Database (NHS EED),The Cochrane Library, Issue 4, October 2011
- Health Technology Assessment (HTA) database, Issue 4, October 2011, The Cochrane Library
- Cochrane Central Register of Controlled Trials (Central), Issue 4, October 2011, The Cochrane Library
- Cochrane Database of Systematic Reviews, Issue 10, October 2011, The Cochrane Library
- Database of Abstracts of Reviews of Effects (DARE), Issue 4, October 2011, The Cochrane Library
- BIOSIS Previews (1969-October 2011)
- Web of Science (1998-October 2011)

9.10.2 Date on which the search was conducted

The search was conducted during 1st – 5th October 2011.

9.10.3 Date span of the search

The date span is specified after each database searched under Section 9.10.1.

9.10.4 Search strategy

Search terms for electronic databases included a combination of index terms and free text words. Search strategies were limited to English-language papers and did not include methodological filters that would limit results to specific publication types or study designs.

The search strategy for each database is provided below

Ovid MEDLINE(R) 1948 to September Week 3 2011

#	Searches	Results
1	(dapagliflozin$ or liraglutide$ or metformin$ or gliclazide$ or glibenclamide$ or glipizide$ or chloropropamide$ or tolbutamide$ or glimepiride$ or pioglitazone$ or sitagliptin$ or vildagliptin$ or saxagliptin$ or thiazolidinedione$).tw.	21107
2	*Thiazolidinediones/ or *Insulin/ or *Sulfonylurea Compounds/ or *Metformin/ or *Glucagon-Like Peptide 1/ or *Glipizide/	84562
3	(glucagon-Like Peptide 1 or GLP-1 or dipeptidyl peptidase 4 or DPP-4 or sodium glucose-cotransporter 2 or SGLT-2).tw.	4625
4	exp Diabetes Mellitus, Type 2/	68900
5	((typ$ 2 or typ$ II or typ$2 or typ$II) adj2 diabet$).tw.	77835
6	(non insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$ or NIDDM).tw.	13708
7	or/1-3	98739
8	or/4-6	109232
9	7 and 8	19652
10	exp Economics/ or exp "Costs and Cost Analysis"/ or exp "Cost of Illness"/ or exp Cost-Benefit Analysis/ or exp Health Care Costs/	445573
11	exp "Quality of Life"/ or exp Quality-Adjusted Life Years/ or exp "Value of Life"/ or exp Health Status/ or exp health status indicators/	319468
12	exp "fees and charges"/ or exp budgets/	33895
13	(pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw.	358581
14	(decision adj2 model).tw.	2911
15	exp Health Resources/ or exp Resource Allocation/	31198
16	(resource utilization or health utilit$ or utility score$ or utility measure$ or utility estimation$ or utility data or cost utility analys$ or cost-utility analys$ or person trade off or person trade-off or PTO or time trade-off or time trade off or WTO or standard gamble or SG or EuroQol 5D or EQ-5D or EQ 5D or EQ5D).tw.	12275
17	or/10-16	987669
18	9 and 17	1094
19	limit 18 to (english language and humans)	953

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations September 30, 2011

#	Searches	Results
1	(dapagliflozin$ or liraglutide$ or metformin$ or gliclazide$ or glibenclamide$ or glipizide$ or chloropropamide$ or tolbutamide$ or glimepiride$ or pioglitazone$ or sitagliptin$ or vildagliptin$ or saxagliptin$ or thiazolidinedione$).tw.	1095
2	(glucagon-Like Peptide 1 or GLP-1 or dipeptidyl peptidase 4 or DPP-4 or sodium glucose-cotransporter 2 or SGLT-2).tw.	355
3	((typ$ 2 or typ$ II or typ$2 or typ$II) adj2 diabet$).tw.	4795
4	(non insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$ or NIDDM).tw.	159
5	(pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw.	24281
6	(decision adj2 model).tw.	148
7	(resource utilization or health utilit$ or utility score$ or utility measure$ or utility estimation$ or utility data or cost utility analys$ or cost-utility analys$ or person trade off or person trade-off or PTO or time trade-off or time trade off or WTO or standard gamble or SG or EuroQol 5D or EQ-5D or EQ 5D or EQ5D).tw.	850
8	(1 or 2) and (3 or 4)	548
9	or/5-7	24922
10	8 and 9	26

Ovid EMBASE(R) 1980 to 2011 Week 39

#	Searches	Results
1	(dapagliflozin$ or liraglutide$ or metformin$ or gliclazide$ or glibenclamide$ or glipizide$ or chloropropamide$ or tolbutamide$ or glimepiride$ or pioglitazone$ or sitagliptin$ or vildagliptin$ or saxagliptin$ or thiazolidinedione$).tw.	27234
2	*2,4 thiazolidinedione derivative/ or *insulin/ or *sulphonylurea/ or *metformin/ or *glucagon like peptide/ or *glipizide/	95382
3	(glucagon-Like Peptide 1 or GLP-1 or dipeptidyl peptidase 4 or DPP-4 or sodium glucose-cotransporter 2 or SGLT-2).tw.	6225
4	exp non insulin dependent diabetes mellitus/	97521
5	((typ$ 2 or typ$ II or typ$2 or typ$II) adj2 diabet$).tw.	103082
6	(non insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$ or NIDDM).tw.	15861
7	or/1-3	118343
8	or/4-6	147026
9	7 and 8	25336
10	(pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$).tw.	444108
11	(decision adj2 model).tw.	3661
12	exp resource allocation/ or exp health care planning/	78442
13	(resource utilization or health utilit$ or utility score$ or utility measure$ or utility estimation$ or utility data or cost utility analys$ or cost-utility analys$ or person trade off or person trade-off or PTO or time trade-off or time trade off or WTO or standard gamble or SG or EuroQol 5D or EQ-5D or EQ 5D or EQ5D).tw.	16164
14	exp health economics/ or exp "health care cost"/ or exp "cost effectiveness analysis"/ or exp "drug cost"/ or exp "cost control"/ or exp "hospital cost"/ or exp "cost utility analysis"/ or exp "cost benefit analysis"/ or exp "cost of illness"/	506864
15	*"quality of life"/ or *quality adjusted life year/or exp health status/	130441
16	or/10-15	965292
17	9 and 16	1652
18	limit 17 to (english language and human and embase)	1195

The Cochrane Library (Issue 10, October 2011)

The Cochrane library is composed of several databases that are searched simultaneously, but the results were exported separately.

ID	Search	Hits
#1	dapagliflozin* or liraglutide* or metformin* or gliclazide* or glibenclamide* or glipizide* or chloropropamide* or tolbutamide* or glimepiride* or pioglitazone* or sitagliptin* or vildagliptin* or saxagliptin* or thiazolidinedione* or insulin* or sulphonylurea* or glucagon*	18667
#2	MeSH descriptor **Diabetes Mellitus, Type 2**, this term only	6629
#3	(#1 AND #2)	3958
#4	MeSH descriptor **Costs and Cost Analysis** explode all trees	16891
#5	pharmacoeconomic* or pharmaco-economic* or cost* or economic* or quality of life or resource utilization or health utilit* or utility score* or utility measure* or utility estimation* or utility data or cost utility analys* or cost-utility analys* or person trade off or person trade-off or PTO or time trade-off or time trade off or WTO or standard gamble or SG or EuroQol 5D or EQ-5D or EQ 5D or EQ5D	68462
#6	(#4 OR #5)	68469
#7	(#3 AND #6)	425 (Cochrane reviews:36; DARE: 36; CENTRAL: 219; HTA: 9; NHS EED:125)

BIOSIS Previews® (1969-October 2011)

Search History

Set	Results	
# 1	**262**	Title=((diabetes type 2)) AND Title=((cost* or economic* or resource use)) Databases=BIOSIS Previews Timespan=All Years Lemmatization=On

---

Web of Science (1998-October 2011)

Search History

Set	Results	
# 1	**634**	(TI=(diabetes type 2) AND TI=(cost* or economic* or resource use)) AND Language=(English) AND Document Types=(Article OR Abstract of Published Item OR Meeting Abstract OR Meeting Summary OR Meeting-Abstract OR Proceedings Paper OR Review) Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH Timespan=All Years Lemmatization=On

9.10.5 Additional searches

In addition, the following sources were used to search for relevant studies:

- Published systematic reviews for T2DM. In particular, the following source was used for economic evaluations: *Tucker, D. M. D. and A. J. Palmer (2011): "The cost-effectiveness of interventions in diabetes: A review of published economic evaluations in the UK setting, with an eye on the future." Primary Care Diabetes **5**(1): 9-17.*

- Recent HTA and Evidence Review Group (ERG) reports (i.e. within the last three years) produced for NICE technology appraisals of T2DM drugs, and recent NICE clinical guidelines in T2DM (that cover dual therapy and/or add-on to insulin therapy). The following reports were assessed for relevant studies:

    - Waugh, N., E. Cummins, et al. (2010). "Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. [Review]." Health Technology Assessment **14**(36): 1-248. [This publication supported the development of NICE Clinical Guideline 87, 2009].

- Cummins C, Royle P, Shyangdan D, Waugh N. Liraglutide for the treatment of type 2 diabetes: a single technology appraisal. Aberdeen HTA Group, 2009. [This report supported NICE STA:, Liraglutide for the treatment of type 2 diabetes mellitus, No. 203, 2010].

- Waugh N, Cummins E, Shyangdan D, et al. Long-acting exenatide in the management of type 2 diabetes. A single technology appraisal. Warwick Evidence, August 2011 [This report supported NICE STA:, Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes, No. 248, 2012].

A review of manufacturer submissions to NICE was not covered by the systematic search, hence only any economic evaluations developed by a NICE assessment group or NICE Guidelines Development Group.

9.10.6 The inclusion and exclusion criteria.

The review considered all types of full economic evaluation (cost-utility, cost-effectiveness, cost-benefit, cost-minimisation) conducted in a UK setting.

The patient populations and drug treatments included in the review have been specified in section 6.1

In addition, only original economic evaluations with full methodological details available were included. Hence, the types of studies excluded were:

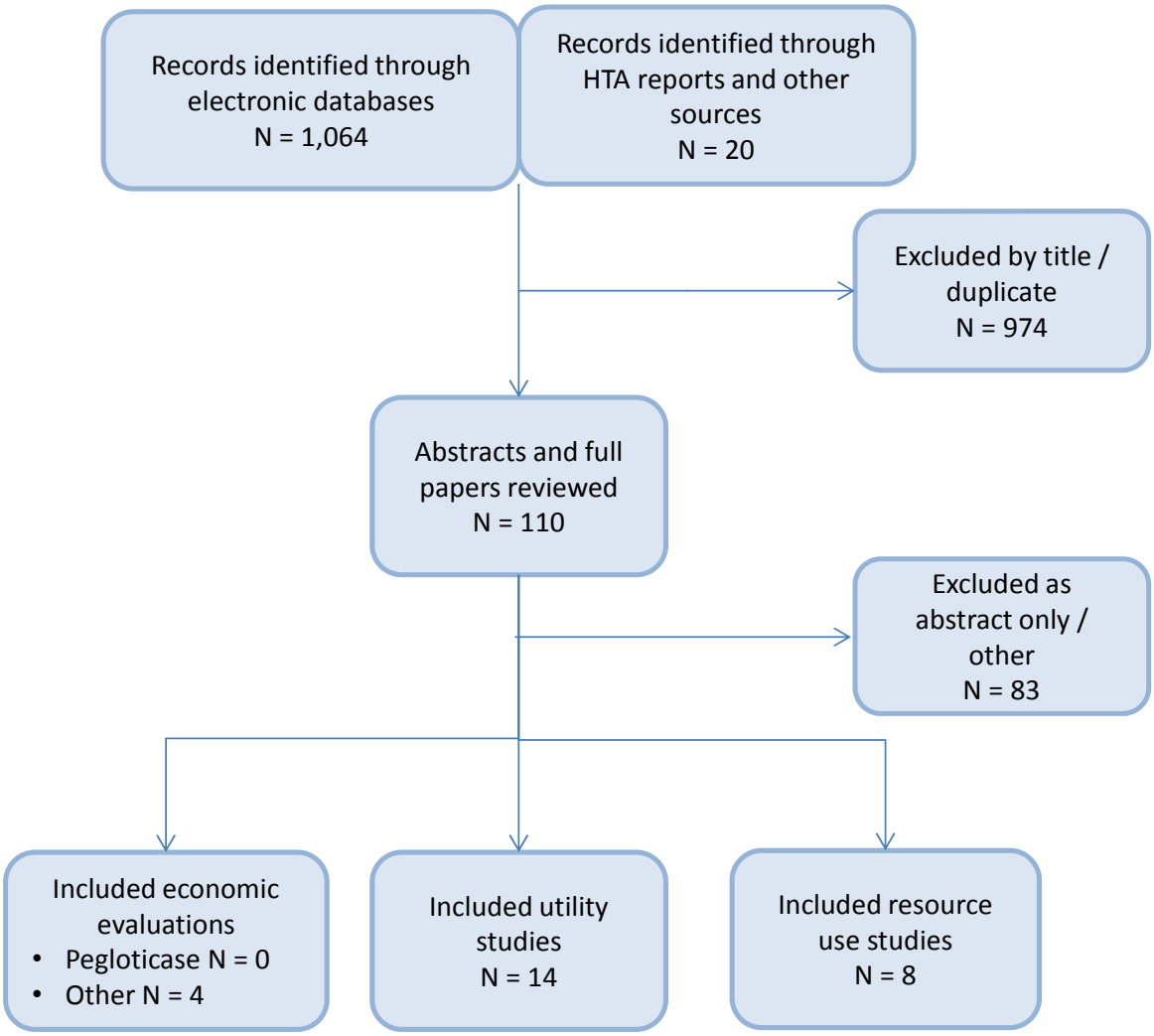
- Editorials, opinions, reviews (other than systematic reviews)
- Non-English language studies
- Reports where insufficient methodological details provided, and papers published as abstracts only.

9.10.7 The data abstraction strategy.

In total the electronic search strategy identified 1,064 hits for the comprehensive review covering economic evaluations, utility, and resource use studies in T2DM, and 20 from the the review of HTA submissions, and reference lists in other publications. The relevance of each citation identified from the databases was first based on a review of the title and abstract for each of the search hits (performed by one reviewer, then checked by a second reviewer), and a full paper review for selected paper. The review only covered full papers hence studies available as abstracts only were excluded.

Figure 42 presents the flow diagram for the single comprehensive search. In terms of the final economic evaluations selected there were no studies identified for dapagliflozin, 4 economic evaluations for other T2DM OADs used as dual therapy with metformin/background therapy, and zero studies for OADs as an add-on to insulin.

Figure 42. Flow diagram for identified published studies



9.11 Appendix 11: Quality assessment of cost-effectiveness studies

Table 110. Quality assessment of cost-effectiveness studies reviewed in section 6.1.2

Study question	Grade (yes/no/not clear/NA)	Comments
Study design		
1. Was the research question stated?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	
2. Was the economic importance of the research question stated?	Davies: **Y** Schwarz: **Y** Tilden: **No** Valentine: **Y**	Tilden: economic importance of diabetes treatment is not mentioned.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	
5. Were the alternatives being compared clearly described?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	
6. Was the form of economic evaluation stated?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	Schwarz: A CUA was performed, but not explicitly mentioned in text. Valentine: A CUA was performed but described as CEA
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Davies: **NC** Schwarz: **NC** Tilden: **Y** Valentine: **NC**	Davies: not explicitly justified in text but clear from disease topic. Schwarz: not explicitly justified in text but clear from disease topic. Valentine: not explicitly justified in text but clear from disease topic.
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	

Study question	Grade (yes/no/not clear/NA)	Comments
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Davies: **N** Schwarz: **N** Tilden: **N** Valentine: **Y**	Davies: results from the clinical trials are not given. Schwarz: results from the clinical trials are not given. Tilden: results from the clinical trials are not given.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Davies: **NA** Schwarz: **NA** Tilden: **NA** Valentine: **NA**	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Davies: **Y** Schwarz: **No** Tilden: **Y** Valentine: **Y**	Schwarz: CUA is performed, but not outcomes are not stated.
12. Were the methods used to value health states and other benefits stated?	Davies: **No** Schwarz: **No** Tilden: **No** Valentine: **No**	Davies: utility values are described in supplementary table S2
13. Were the details of the subjects from whom valuations were obtained given?	Davies: **No** Schwarz: **No** Tilden: **No** Valentine: **Y**	
14. Were productivity changes (if included) reported separately?	Davies: **NA** Schwarz: **NA** Tilden: **NA** Valentine: **NA**	
15. Was the relevance of productivity changes to the study question discussed?	Davies: **NA** Schwarz: **NA** Tilden: **NA** Valentine: **NA**	

Study question	Grade (yes/no/not clear/NA)	Comments
16. Were quantities of resources reported separately from their unit cost?	Davies: **No** Schwarz: **No** Tilden: **No** Valentine: **Y**	Davies: unit costs are reported, resource use is not reported. Schwarz: unit costs are reported, resource use is not reported. Tilden: unit costs are not reported, resource use is reported.
17. Were the methods for the estimation of quantities and unit costs described?	Davies: **Y** Schwarz: **NC** Tilden: **No** Valentine: **Y**	Davies: in supplementary table S1 Schwarz: "country-specific costs" are said to be used, but not sourced. Tilden: only drug costs are described, not non-drug costs.
18. Were currency and price data recorded?	Davies: **Y** Schwarz: **No** Tilden: **Y** Valentine: **Y**	
19. Were details of price adjustments for inflation or currency conversion given?	Davies: **Y** Schwarz: **No** Tilden: **Y** Valentine: **Y**	Schwarz: "country-specific costs" are said to be used, but not sourced.
20. Were details of any model used given?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	Davies: life-time horizon Schwarz: life-time horizon Tilden: life-time horizon Valentine: life-time and within-trial horizon
23. Was the discount rate stated?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	

Study question	Grade (yes/no/not clear/NA)	Comments
24. Was the choice of rate justified?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	All studies: standard UK rates (3.5% for costs and effects)
25. Was an explanation given if cost or benefits were not discounted?	Davies: **NA** Schwarz: **NA** Tilden: **NA** Valentine: **NA**	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Davies: **Y** Schwarz: **No** Tilden: **Y** Valentine: **No**	
27. Was the approach to sensitivity analysis described?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	Davies: Univariate and PSA were done. Schwarz: Univariate SA was done. Tilden: **U**nivariate and scenario SA were done. Valentine: Univariate SA was done.
28. Was the choice of variables for sensitivity analysis justified?	Davies: **Y** Schwarz: **No** Tilden: **Y** Valentine: **No**	Tilden: rationales for factors in SA are given in Table VI
29. Were the ranges over which the parameters were varied stated?	Davies: **Y** Schwarz: **No** Tilden: **Y** Valentine: **Y**	Davies: given in supplementary tables S1 and S2
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	
31. Was an incremental analysis reported?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	

Study question	Grade (yes/no/not clear/NA)	Comments
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Davies: **No** Schwarz: **No** Tilden: **No** Valentine: **No**	All studies: only aggregated results
33. Was the answer to the study question given?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	
34. Did conclusions follow from the data reported?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	
35. Were conclusions accompanied by the appropriate caveats?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	
36. Were generalisability issues addressed?	Davies: **Y** Schwarz: **Y** Tilden: **Y** Valentine: **Y**	

9.12 Appendix 12: Search strategy for Section 6.4 (Measurement and valuation of health effects)

9.12.1 Databases searched

A single search was performed which covered economic evaluations, health measurement and valuation, and resource utilisation for T2DM treatments as dual or add-on to insulin therapy. Hence, the measurement and valuation of health effects search was covered by the specific databases listed in Section 9.10.1.

9.12.2 Date on which the search was conducted

The search was conducted during 1st – 5th October 2011.

9.12.3 Date span of the search

See Section 9.10.1.

9.12.4 Search strategy

See Section 9.10.1

9.12.5 Additional searches

In addition to the electronic searches, the reference list of the identified full economic evaluations were searched for relevant utility data (see Table 54, as well as recent HTA and Evidence Review Group [ERG] reports [i.e. within the last three years] produced for NICE technology appraisals of T2DM drugs, and recent NICE clinical guidelines in T2DM that cover dual therapy and/or add-on to insulin therapy) (see Section 9.10.5. A review of manufacturer submissions to NICE was not covered by the systematic search, hence only any relevant utility estimates reported by the NICE assessment group or NICE Guidelines Development Group were included (if original estimates).

9.12.6 The inclusion and exclusion criteria.

See Section 9.10.6.

9.12.7 The data abstraction strategy.

In total the electronic search strategy identified 1,064 hits for the comprehensive review covering economic evaluations, utility, and resource use studies in T2DM, and 20 from the review of HTA submissions, and reference lists in other publications. The relevance of each citation identified from the databases was first based on a review of the title and abstract for each of the search hits (performed by one reviewer, then checked by a second reviewer), and a full paper review for selected paper. The review only covered full papers hence studies available as abstracts only were excluded.

Figure 42 presents the flow diagram for the single comprehensive search. There were 14 utility studies considered eligible for full review.

9.13 Appendix 13: Search strategy for Section 6.5 (Resource identification, measurement and valuation)

9.13.1 Databases searched

A single search was performed which covered economic evaluations, health measurement and valuation, and resource utilisation for T2DM treatments as dual or add-on to insulin therapy. Hence, the resource utilisation search was covered by the specific databases listed in Section 9.10.1.

9.13.2 Date on which the search was conducted

The search was conducted during 1st – 5th October 2011.

9.13.3 Date span of the search

See Section 9.10.1.

9.13.4 Search strategy

See Section 9.10.1

9.13.5 Additional searches

In addition to the electronic searches, the reference list of the identified full economic evaluations were searched for relevant utility data (Table 54), as well as recent HTA and Evidence Review Group (ERG) reports (i.e. within the last three years) produced for NICE technology appraisals of T2DM drugs, and recent NICE clinical guidelines in T2DM (that cover dual therapy and/or add-on to insulin therapy) (see Section 9.10.5). A review of manufacturer submissions to NICE was not covered by the systematic search, hence only any relevant resource use/cost estimates reported by the NICE assessment group or NICE Guidelines Development Group were included (if original estimates).

9.13.6 The inclusion and exclusion criteria.

See Section 9.10.6.

9.13.7 The data abstraction strategy.

In total the electronic search strategy identified 1,064 hits for the comprehensive review covering economic evaluations, utility, and resource use studies in T2DM, and 20 from the the review of HTA submissions, and reference lists in other publications. The relevance of each citation identified from the databases was first based on a review of the title and abstract for each of the search hits (performed by one reviewer, then checked by a second reviewer), and a full paper review for selected paper. The review only covered full papers hence studies available as abstracts only were excluded.

Figure 42 presents the flow diagram for the single comprehensive search. There were 8 resource use/cost studies considered eligible for full review.

9.14 Appendix 14: Random effects NMA: technical details

This appendix presents the technical details of a random-effects NMA, which is the *a priori* choice of model to be used in the analysis. The fixed effect NMA uses similar conventions; however, does not involve a parameter for between studies variance.

Different Types of Network Meta-Analyses

We now state the two different types of NMA analyses we envision performing for the data in this project; these are listed below and presented in detail in later sections. For ease of reference, we state only the distributional assumptions governing the data, rather than the full likelihood of the data.

- Random-Effects NMA for Binary Outcomes
- Random-Effects NMA for Continuous Outcomes

Details of the Bayesian Network Meta-Analysis

A Bayesian approach differs from the classical frequentist approach since it considers that all unknown parameters in an analysis (be them nuisance or of primary interest) are random variables rather than fixed, but unknown, quantities. For this reason, this approach requires that prior distributions for these parameters be defined initially. These prior distributions express the information available about these parameters before seeing the data. Once the data become available, their likelihood can be derived under appropriate distributional assumptions, with the likelihood expressing the information about the parameters that is contained in the data. Combining the prior information on the parameters with the information provided by the data, yields posterior information on these parameters in the form of marginal posterior distributions. These distributions, which can be derived theoretically or via simulations, will be used as a basis for making posterior inference on each parameter. In particular, posterior summaries can be provided for each parameter (e.g., mean of posterior distribution), as well as posterior credible intervals. For instance, for a given parameter, a 95% posterior credible interval has the convenient interpretation that there is a 95% probability that the parameter falls within it. Specification of the prior distributions is important in a Bayesian approach, since it influences the posterior inference. Usually, no prior information is available. In this case we need to specify priors that will not influence the marginal posterior distributions of the parameters and thus “let the data speak for themselves”. Such distributions are frequently called non-informative or vague prior distributions.

A Bayesian approach to NMA involves the following elements (Ades et al 2006):

a) The *data* supplied by each arm of the RCT included in the NMA;

b) The *likelihood of the data*, derived using the distributional assumptions underlying the data. For binary outcome data, we will work with a binomial likelihood, whereas for continuous outcome data, we will work with a normal likelihood;

c) The *basic parameters* and unrelated *nuisance parameters*, as well as a *functional parameter*.

d) A *consistency relation*, which connects all or some of the basic parameters to the functional parameter.

e) A *model* that expresses the relationship between the basic/nuisance parameters and the data.

f) *Prior distributions* for the basic/nuisance parameters.

The following explains briefly how these components work together.

The *basic parameters* and *nuisance parameters* will be given prior distributions and will be updated by the information in the likelihood. The *functional parameters* are related to the basic parameters through linear relationships. These *basic parameters* typically quantify the effects of the treatments in the network relative to a "baseline" treatment but, if necessary, can also describe the between-study variability. The *nuisance parameters* are deemed as such because they are not of primary interest; they usually capture trial-specific treatment effects. The *functional parameters* quantify the relative effects of the various pairs of treatments in the network, with the exception of those pairs that include the "baseline" treatment.

The *model* will be a random-effects regression model, reflecting the *a priori* assumptions imposed on the nature of the relative treatment effects. For binary outcome data, we will work with logistic regression models. In contrast, for continuous outcome data, we will work with linear regression models.

The *prior distributions* for the baseline and nuisance parameters will be chosen such that they are non-informative.

The marginal *posterior distributions* of the parameters involved in the analysis will be derived using MCMC simulations.

Random-Effects NMA for Binary Outcomes

In a random-effects NMA for binary outcome data, we will assume that the data come from a binomial likelihood. We will then model the log odds of the outcome on a given treatment in a specified trial via a random-effects logistic regression model. The analysis will assume that the relative effects of treatment B versus A are random and come from a common distribution. A similar assumption applies for C versus A. Further, the spread of this distribution will be assumed to be the same across the two treatment comparisons (B versus A, and C versus A) and will be quantified by a parameter referred to as the between-study variance. The basic parameters for the analysis will be the relative treatment effects of B versus A and C versus A, along with the between-study variance. The study-specific log-odds of the outcome on the "baseline" treatment for a given pairwise treatment comparison will be treated as unrelated nuisance parameters. Prior distributions will be placed on the basic and nuisance parameters. The functional

parameter capturing the relative effect of C versus B will be derived from the basic parameters as explained previously. Details are provided below

a) Data: $\left(r_{jk}, n_{jk}\right)$, *where*

r_{jk} = *number of outcomes on treatment* k *in trial* j

n_{jk} = number of patients on treatment k in trial j

b) Likelihood: $r_{jk} \sim \text{Binomial}\left(p_{jk}, n_{jk}\right)$, where

p_{jk} = probability of the outcome on treatment k in trial j

c) Basic Parameters:

d_{Ak} = mean log-odds ratio of the outcome for treatment k

relative to the "baseline" treatment A, where $k = \text{B,C}$

τ^2 = between-study variance

Nuisance Parameters:

μ_{jA} = trial-specific log-odds of the outcome for the "baseline" treatment A,

where $j = 1,...,J$

Functional Parameter:

d_{BC} = mean log-odds ratio of the outcome for treatment C relative to treatment B

d) Consistency Relation:

$$d_{BC} = d_{AC} - d_{AB}$$

e) Random-Effects Logistic Regression Model:

$$\text{logit}\left(p_{jk}\right) = \begin{cases} \mu_{jA}, & k = \text{A} \\ \mu_{jA} + \delta_{jAk}, & k = \text{B, C} \end{cases}$$

$$\delta_{jAk} \sim \text{Normal}\left(d_{Ak}, \tau^2\right)$$

where

δ_{jAk} = trial-specific log-odds ratio of the outcome for treatment k relative

to the "baseline" treatment A, assumed random across trials, with

$k = \text{B}$ for $j = 1,...,J_1$ and $k = \text{C}$ for $j = J_1 + 1,...,J$

f) Priors on Basic Parameters:

$$d_{Ak} \sim \text{Normal}(0, 10{,}000), \qquad k = B, C$$

$$\tau^2 \sim Uniform(0, U)$$

where U is a specified constant

Priors on Unrelated Nuisance Parameters:

$$\mu_{jA} \sim \text{Normal}(0, 10{,}000), \qquad j = 1, \ldots, J$$

Random-Effects NMA for Continuous Outcomes

In a random-effects NMA for continuous outcome data, we will assume that the data come from a normal likelihood. We will then model the mean of the outcome on a given treatment in a specified trial via a random-effects linear regression model. The relative effect of B versus A will be assumed to be random and to come from a common distribution. Similarly for the relative effect of C versus A. Further, the spread of the two distributions will be assumed to be the same across the two treatment comparisons (B versus A and C versus A) and will be quantified by a parameter referred to as the between-study variance. The basic parameters for this analysis will be the relative treatment effects of B versus A and C versus A, along with the between-study variance. The study-specific mean value of the outcome on the "baseline" treatment A will be treated as unrelated nuisance parameters. Prior distributions will be placed on the basic and nuisance parameters. The functional parameter capturing the relative effect of C versus B will be derived from the basic parameters as explained previously. Details follow.

a) Data: $\left(y_{j,k}, \text{SE}_{jk}^2\right)$

where y is the continuous outcome for treatment k in trial y, and SE is its standard error

b) Likelihood: $y_{j,k} \sim \text{Normal}\left(\theta_{jk}, \text{SE}_{jk}^2\right)$

c) Basic Parameters:

d_{Ak} = mean difference in the mean values of the outcome for

treatment k relative to the "baseline" treatment A

τ^2 = between-study variance

Nuisance Parameters:

μ_{jA} = study-specific mean value of the outcome for the "baseline" treatment A

Functional Parameter:

d_{BC} = mean difference in the mean values of the outcome for

treatment C relative to treatment B

d) Consistency Relation:

$$d_{BC} = d_{AC} - d_{AB}$$

e) Random-Effects Linear Regression Model:

$$\theta_{jk} = \begin{cases} \mu_{jA}, & k = \text{A} \\ \mu_{jA} + \delta_{jAk}, & k = \text{B, C} \end{cases}$$

$$\delta_{jAk} \sim \text{Normal}\left(d_{Ak}, \tau^2\right), \qquad j=1,2,...,\text{N}, \quad k = \text{B,C}$$

where

δ_{jAk} = trial-specific difference in the mean values of the outcome for

treatment k relative to the “baseline” treatment A, random across trials

f) Priors on basic parameters:

$$d_{Ak} \sim \text{Normal}(0, 1000^2), \qquad k = B, C$$

$$\tau^2 \sim Uniform(0, U)$$

where U is a pre-specified constant, chosen to reflect the scale of the continuous measurements

Priors on unrelated nuisance parameters:

$$\mu_{jA} \sim \text{Normal}(0, 10{,}000), \qquad j = 1, \ldots, J$$

9.15 Appendix 15: WinBUGS code

9.15.1 Continuous outcomes; fixed effect model

```
model{

#prior on treatment effect betas
beta[1]<-0


#prior on tx effect mean
for (qq in 2:nTx){
                    beta[qq]~dnorm(0,1.0E-6)
}

#define prior on intercept

      for(ss in 1:nStudies){
          alpha[ss] ~ dnorm(0,1.0E-6)
                    }


             #fit data
       for(ii in 1:nObs )              {

                                predMean[ii] <-  alpha[study[ii]] + beta[tx[ii]] - beta[baseTx[ii]]

              var[ii] <- 1/pow(se[ii],2)
               mn[ii] ~ dnorm(predMean[ii], var[ii])


                    }

}
```

9.15.2 Continuous outcomes; random effects model

```
model{


#prior on random tx effect variance
        reSD~dunif(0,2)
        reTau <- 2/pow(reSD,2)

        #prior on treatment effect betas
        beta[1]<-0

        #prior on tx effect mean
        for (qq in 2:nTx){
                beta[qq]~dnorm(0,1.0E-6)
        }


        #define prior on intercept
          for(ss in 1:nStudies){
            alpha[ss] ~ dnorm(0,1.0E-6)
                        for (tt in 1:nTx){
                                re[ss,tt] ~dnorm(0,reTau)
                        }
                }


            #fit data
      for(ii in 1:nObs )            {

        predMean[ii] <- alpha[study[ii]] + beta[tx[ii]] - beta[baseTx[ii]] + re[study[ii],tx[ii]] -
re[study[ii],baseTx[ii]]

             var[ii] <- 1/pow(se[ii],2)
              mn[ii] ~ dnorm(predMean[ii], var[ii])



                }
}
```

9.15.3 Continuous outcomes; fixed effect model; with covariate

```
model{


        #prior on treatment effect betas
        beta[1]<-0


        #prior on tx effect mean
        for (qq in 2:nTx){
                beta[qq]~dnorm(0,1.0E-6)
        }


        #define prior on intercept
      #random baseline effect
          for(ss in 1:nStudies){
           alpha[ss] ~ dnorm(0,1.0E-6)
                  }

        #prior on covariate
        delta ~ dnorm(0,1.0E-6)
        covData_bar <- mean(covData[]) #centres covariate


           #fit data
      for(ii in 1:nObs )              {

                              predMean[ii] <-  alpha[study[ii]] + beta[tx[ii]] - beta[baseTx[ii]] +
delta*(covData[ii] - covData_bar)*(1-equals(tx[ii],1))

                    var[ii] <- 1/pow(se[ii],2)
                     mn[ii] ~ dnorm(predMean[ii], var[ii])




                     }
}
```

9.15.4 Continuous outcomes; random effects model; with covariate

```
model{


#prior on random tx effect variance
        reSD~dunif(0,2)
        reTau <- 2/pow(reSD,2)

        #prior on treatment effect betas
        beta[1]<-0


        #prior on tx effect mean
        for (qq in 2:nTx){
                beta[qq]~dnorm(0,1.0E-6)
        }



        #define prior on intercept
          for(ss in 1:nStudies){
            alpha[ss] ~ dnorm(0,1.0E-6)
                        for (tt in 1:nTx){
                                re[ss,tt] ~dnorm(0,reTau)
                        }
                }

        # prior on covariate
        delta ~ dnorm(0, 1.0E-6)
        covData_bar <- mean(covData[,1]) # centres covariate



          #fit data
      for(ii in 1:nObs )            {

     predMean[ii] <- alpha[study[ii]] + beta[tx[ii]] - beta[baseTx[ii]] + re[study[ii],tx[ii]] -
re[study[ii],baseTx[ii]] + delta*(covData[ii,1] - covData_bar)*(1 - equals(tx[ii],1))

                var[ii] <- 1/pow(se[ii],2)
                  mn[ii] ~ dnorm(predMean[ii], var[ii])


                }
}
```

9.15.5 Binary outcome; fixed effect model

```
model{

        #prior on treatment effect betas
        beta[1]<-0
        or[1] <- exp(0)


        #prior on tx effect mean
        for (qq in 2:nTx){
                beta[qq]~dnorm(0,1.0E-3)
                or[qq] <- exp(beta[qq])
        }

        #define prior on intercept
          for(ss in 1:nStudies){
        alpha[ss] ~ dnorm(0,1.0E-3)
                }



          #fit data
      for(ii in 1:nObs )            {

                        x[ii] <- alpha[study[ii]] + beta[tx[ii]] - beta[baseTx[ii]]

                        #logit link for probability of response control and treatment arms
                 logit(prob[ii]) <- x[ii]

          #binomial link between number of responses and probability of response from
treatment arm
          r[ii] ~ dbin(prob[ii], n[ii])


                }
}
```

9.15.6 Binary outcome; random effects model

```
model{


        #prior on random tx effect variance
        reSD~dunif(0,2)
        reTau <- 2/pow(reSD,2)

        #prior on treatment effect betas
        beta[1]<-0
        or[1] <- exp(0)


        #prior on tx effect mean
        for (qq in 2:nTx){
                beta[qq]~dnorm(0,1.0E-3)
                or[qq] <- exp(beta[qq])
        }

        #define prior on intercept
          for(ss in 1:nStudies){
        alpha[ss] ~ dnorm(0,1.0E-3)
                        for (tt in 1:nTx){
                                re[ss,tt] ~dnorm(0,reTau)
                        }
                }



          #fit data
      for(ii in 1:nObs )            {

                        x[ii] <- alpha[study[ii]] + beta[tx[ii]]-beta[baseTx[ii]] + re[study[ii],tx[ii]] -
re[study[ii],baseTx[ii]]


                        #logit link for probability of response control and treatment arms
                 logit(prob[ii]) <- x[ii]

          #binomial link between number of responses and probability of response from
treatment arm
          r[ii] ~ dbin(prob[ii], n[ii])


                }
}
```

9.16 Appendix 16: Detailed summaries of RCTs

Table 111. Summary of randomised clinical trials involving patients with T2DM poorly controlled on metformin monotherapy

Author, Year	Study setting	Duration (weeks)	Lead in phase	Sample size; N	Intervention(s)	Comparator	Primary outcome
18 to 30 weeks (non-SU)							
Study 14	International	24	2-week single-blind lead-in	546	• Dapagliflozin (10mg)	• Placebo	∆ HbA1c
Study 12	Europe	24	2-week single-blind lead-in	182	• Dapagliflozin (10mg)	• Placebo	∆ weight
Scott, 2008	International	18	Yes; duration not reported	186	• Sitagliptin (100mg)	• Placebo	∆ HbA1c
Charbonnel, 2006	International	24	2-week single-blind lead-in	701	• Sitagliptin (100mg)	• Placebo	∆ HbA1c
DeFronzo, 2009	International	24	2-week placebo lead-in period	743	• Saxagliptin (5mg)	• Placebo	∆ HbA1c
Bosi, 2007	International	24		544	• Vildagliptin (100mg)	• Placebo	∆ HbA1c
Taskinen, 2011	International	24	2-week open-label lead-in	701	• Linagliptin (5mg)	• Placebo	∆ HbA1c
Bergenstal, 2010	N/R	24		N/R	• Sitagliptin (100mg)	• Placebo	∆ HbA1c
Raz, 2008	International	30	2-week open-label lead-in	190	• Sitagliptin (100mg)	• Placebo	∆ HbA1c
Bolli, 2008	International	24		576	• Vildagliptin (100mg)	• Pioglitazone (30mg)	∆ HbA1c
Bergenstal, 2010	International	26		331	• Sitagliptin (100mg)	• Pioglitazone (45mg)	∆ HbA1c
DeFronzo, 2005	US	30	4-week single-blind lead-in with subcutaneous injection of placebo bid	336	• Exenatide (10µg) • Exenatide (20µg)	• Placebo	∆ HbA1c
Nauck, 2009	International	26		849	• Liraglutide (1.2mg) • Liraglutide (1.8mg) • Glimepiride (4mg)	• Placebo	∆ HbA1c
Pratley, 2010	N/R	26		665	• Liraglutide (1.2mg) • Liraglutide (1.8mg)	• Sitagliptin (100mg)	∆ HbA1c

Author, Year	Study setting	Duration (weeks)	Lead in phase	Sample size; N	Intervention(s)	Comparator	Primary outcome
Kaku, 2009	Japan	28		169	• Pioglitazone (30mg)	• Placebo	∆ HbA1c
18 to 30 weeks (with SU; eligible only for meta-analysis of systolic blood pressure)							
Ristic, 2006	International	24		262	• Nateglinide (180-540mg)	• Gliclazide (80-240mg)	∆ HbA1c
Marre, 2002	International	24	4-week single-blind nateglinide placebo lead-in	467	• Nateglinide (180mg) • Nateglinide (360mg)	• Placebo	∆ HbA1c
Arechavaleta, 2011	International	30		1035	• Sitagliptin (100mg)	• Glimepiride (1-6mg)	∆ HbA1c
Charpentier, 2001	France	20		222	• Glimepiride (1-6mg)	• Placebo	∆ HbA1c
Papathanassiou, 2009	Greece	26		28	• Pioglitazone (30mg)	• Glimepiride (4mg)	Flow-mediated dilation in brachial artery
Umpierrez, 2006	US	26		210	• Pioglitazone (30-45mg)	• Glimepiride (2-8mg)	∆ HbA1c
Moses, 1999	Australia	17-21		54	• Repaglinide (3-12mg)	• Placebo	∆ HbA1c
> 30 weeks							
Nauck, 2010	International	52	2-week open-label lead-in	816	• Dapagliflozin (10mg)	• Glipizide (5-20mg)	∆ HbA1c
Matthews, 2005	International	52		632 (630 treated)	• Pioglitazone (30-45mg)	• Gliclazide (160-320mg)	∆ HbA1c
Nauck, 2007	International	52	2-week open-label lead-in	1172	• Sitagliptin (100mg)	• Glipizide (5-20mg)	∆ HbA1c
Goke, 2010	International	52	2-week open-label lead-in	858	• Saxagliptin (5mg)	• Glipizide (5-20mg)	∆ HbA1c
Filozof, 2010	International	52		1007	• Vildagliptin (100mg)	• Gliclazide (80-320mg)	∆ HbA1c
Salvadeo, 2010	N/R	52		130	• Exenatide (20µg)	• Glimepiride (6mg)	Unclear
Derosa, 2010	Italy	52		128	• Exenatide (20µg)	• Glibenclamide	Unclear

Author, Year	Study setting	Duration (weeks)	Lead in phase	Sample size; N	Intervention(s)	Comparator	Primary outcome
						(15mg)	
Matthews, 2010	International	104		3118	• Vildagliptin (100mg)	• Glimepiride (2-6mg)	Δ HbA1c†

Abbreviations: N, Number; N/R, Not reported; SU, Sulphonylurea; US, United States; †Assumed from text but not explicit; †The study was originally planned to last for up to five years and had a primary endpoint of risk of failure of glycaemic control defined as HbA1c > 8%. Due to a higher-than-expected discontinuation rate and fewer patients reaching the target endpoint, the study purpose was modified to measure a primary endpoint of change in HbA1c at 104 weeks.

Table 112. Summary of randomised clinical trials involving patients with T2DM poorly controlled on insulin therapy

Author, Year	Study setting	Duration (weeks)	Sample size; N†	Intervention(s)	Comparator	Primary outcome
16 to 32 weeks; Requiring maintenance of stable insulin dose						
Vilsboll, 2010	International	24	641	Sitagliptin 100 mg	Placebo	Δ HbA1c
Barnett, 2012	International	24	455	Saxagliptin 5mg	Placebo	Δ HbA1c
Rosenstock, 2002	US	16	375	Pioglitazone 30mg	Placebo	Δ HbA1c
Study 6	International	24	387	Dapagliflozin 10 mg	Placebo	Δ HbA1c
16 to 32 weeks; Not included in meta-analysis due to lack of requirement for stable insulin dose						
Asnani, 2006	US	17.2	16	Pioglitazone 30mg	Placebo	Endothelial function
Mattoo, 2005	International	25.8	289	Pioglitazone 30mg	Placebo	Δ HbA1c
Zib, 2007	US	25.8	32	Pioglitazone 30mg	No placebo	Cardiac and hepatic TG contents

Abbreviations: HbA1c, Glycosylated haemoglobin; N, Number; TG, Triglyceride; US, United States; †, Sample size, N refers to the total sample size from the relevant arms (as identified under the '*intervention(s)'* and '*comparator'* headers of table)

Table 113. Summary of inclusion criteria in randomised clinical trials involving patients with T2DM poorly controlled on metformin monotherapy

Author, Year	HbA1c inclusion range (%)	BMI inclusion range (kg/m^2)	Age inclusion range (years)	FPG inclusion range (mmol/L)	Minimum Diabetes Duration (years)
18 to 30 weeks (non-SU)					
Study 14	7 to 10	< 45	18 to 77	N/R	N/R
Study 12	6.5 to 8.5	> 25	30/55 - 75†	< 13.2	3 ‡
Scott, 2008	7 to 11	N/R	18 to 75	N/R	2.3‡
Charbonnel, 2006	7 to 10	N/R	18 to 78	< 13.2	N/R
DeFronzo, 2009	7 to 10	< 40	18 to 77	N/R	N/R
Bosi, 2007	7.5 to 11	22 to 45	18 to 78	< 15.0	3‡
Taskinen, 2011	7.0 to 10.0§	< 40	18 to 80	N/R	3‡
Bergenstal, 2010	7 to 10	25¶ to 45	18 to 75	N/R	N/R
Raz, 2008	8 to 11	20 to 43	18 to 78	7.2 to 15.6	N/R
Bolli, 2008	7.5 to 11	22 to 45	18 to 77	< 15.0	N/R
Bergenstal, 2010	7.1 to 11	25 to 45	> 18	< 15.5	2‡
DeFronzo, 2005	7.1 to 11	27 to 45	19 to 78	< 13.3	3‡
Nauck, 2009	7 to 10.0/11.0††	< 40	18 to 80	N/R	3‡
Pratley, 2010	7.5 to 10	< 45	18 to 80	N/R	N/R
Kaku, 2009	6.5 to 10	N/R	> 20	N/R	N/R
18 to 30 weeks (with SU; eligible only for meta-analysis of systolic blood pressure)					
Ristic, 2006	6.8 to 9	20 to 35	N/R	N/R	6
Marre, 2002	6.8 to 11	20 to 35	> 30	< 270	6
Arechavaleta, 2011	6.5 to 9	N/R	> 18	110 to 240	3‡
Charpentier, 2001	N/R	< 40‡‡	35 to 70	141 to 250	<1
Papathanassiou, 2009	> 6.5	N/R	N/R	N/R	6
Umpierrez, 2006	7.5 to 10	> 24	18 to 79	126 to 235	6
Moses, 1999	> 7.1	> 21	40 to 75	N/R	6
> 30 weeks					

Author, Year	HbA1c inclusion range (%)	BMI inclusion range (kg/m^2)	Age inclusion range (years)	FPG inclusion range (mmol/L)	Minimum Diabetes Duration (years)
Nauck, 2010	6.5 to 10	N/R	> 18	< 15.0	2‡
Matthews, 2005	7.5 to 11	N/R	35 to 75	N/R	3‡
Nauck, 2007	6.5 to 10	N/R	18 to 78	< 15.0	N/R
Goke, 2010	6.5 to 10	N/R	> 18	N/R	2‡
Filozof, 2010	7.5 to 11	N/R	18 to 78	N/R	1‡
Salvadeo, 2010	> 8	N/R	N/R	N/R	N/R
Derosa, 2010	> 8	25 to 30	> 18	N/R	N/R
Matthews, 2010	6.5 to 8.5	22 to 45	18 to 73	N/R	3

Abbreviations: N/R, Not reported; SU, Sulphonylureas. † The lower bound age was 30 years for males and 55 years for females; ‡ Minimum diabetes duration was inferred from inclusion criteria for minimum duration of prior anti-diabetic therapy ; § HbA1c range measured after washout period; ¶ Lower bound BMI was 23 kg/m^2 for Asians; †† patients previously treated with OAD combination therapy: 7.0-10.0%; patients previously treated with OAD monotherapy: 7.0-11.0%; ‡‡ There was a lower bound BMI of 23.0 kg/m2 for newly-diagnosed (<1 yr) females and 25.0 kg/m2 for newly-diagnosed males.

Table 114. Summary of inclusion criteria in randomised clinical trials involving patients with T2DM poorly controlled on insulin therapy

Author, Year	HbA1c inclusion range (%)	BMI inclusion range (kg/m^2)	Age inclusion range (years)	FPG inclusion range (mmol/L)	Minimum diabetes duration (years)
16 to 32 weeks; Requiring maintenance of stable insulin dose					
Vilsboll, 2010	7.5 to 11	20 to 43	> 21	> 7.2	N/R
Barnett, 2012	7.5 to 11	≤ 45	18 to 78	N/R	N/R
Rosenstock, 2002	> 8	N/R	30 to 75	N/R	N/R
Wilding, 2010	7.5 to 10.5	< 45	18 to 80	N/R	N/R
16 to 32 weeks; Not included in meta-analysis due to lack of requirement for stable insulin dose					
Asnani, 2006	> 7.5	N/R	18 to 75	N/R	N/R
Mattoo, 2005	> 7.5†	N/R	> 30	N/R	N/R
Zib, 2007	> 7.5	N/R	> 18	N/R	N/R

Abbreviations: BMI, Body mass index; FPG, Fasting plasma glucose; HbA1c, Glycosylated haemoglobin; N/R, Not reported; †, HbA1c was >7.5 at screening, but was 7.0 after insulin intensification period;

Table 115. Summary of exclusion criteria in randomised clinical trials involving patients with T2DM poorly controlled on metformin monotherapy

Author, Year	Key exclusion criteria
18 to 30 weeks (non-SU)	
Study 14	See summary of dapagliflozin trials
Study 12	See summary of dapagliflozin trials
Scott, 2008	T1D; contraindications for use of TZDs or metformin, impaired renal function, ALT or AST levels more than twofold the ULN or a FPG value >15 mmol/l prior to randomization
Charbonnel, 2006	T1D; insulin use within 8 weeks of screening; renal function impairment inconsistent with metformin use; FPG or fasting finger-stick glucose >14.4 mmol/l at randomization
DeFronzo, 2009	Symptoms of poorly controlled diabetes; history of diabetic ketoacidosis or hyperosmolar nonketotic coma; use of any other AHA (8 weeks before) or insulin (1 year before); CV event within 6 months before study entry or NYHA stage III/IV CHF and/or known left ventricular ejection fraction ≤40%; chronic or repeated intermittent corticosteroid treatment; history of alcohol or drug abuse within the previous year; treatment with potent systemic cytochrome P450 3A4 inhibitors or inducers; active liver disease and/or clinically significant abnormalities on screening tests of hepatic, renal, endocrine, metabolic, or hematologic function, or assessment of an immunocompromised state; women who were pregnant or breastfeeding were also excluded.
Bosi, 2007	History of T1D; acute metabolic diabetes complications within the past 6 months; CHF requiring pharmacologic treatment; MI, unstable angina, or coronary artery bypass surgery within the previous 6 months; liver disease; renal disease or renal dysfunction.
Taskinen, 2011	Treatment with rosiglitazone, pioglitazone, a GLP-1 analogue, insulin or anti-obesity drug within 3 months; change in dosage of TH treatment within 6 weeks or treatment with systemic steroids at the date of informed consent; impaired hepatic function; renal failure or renal impairment or had suffered MI, stroke or TIA within 6 months of giving informed consent; history of acute or chronic metabolic acidosis, unstable or acute CHF, hereditary galactose intolerance or dehydration; participation in another trial of an investigational drug within the previous 2 months.
Bergenstal, 2010	History of T1D or acute metabolic diabetic complications in previous 6 months; evidence of clinically significant diabetic complications; clinically symptomatic GI disease; MI, coronary artery bypass surgery, post-transplantation cardiomyopathy or stroke within previous 6 months; known hemoglobinopathy or chronic anemia.
Raz, 2008	T1D; patients who were pregnant or breast-feeding
Bolli, 2008	History of T1D, acute metabolic diabetic complications, MI, unstable angina or coronary artery bypass surgery within the previous 6 months; CHF (NYHA classes I–IV) or liver disease; ALT or AST >2.5 times the ULN, direct bilirubin >1.3 times the ULN, serum creatinine levels >132 µmol/l (males) or >125 µmol/l (females), clinically significant abnormal TSH or FTG >7.9 mmol/l.
Bergenstal, 2010	Hepatic disease or an ALT or AST value >3 times the ULN, renal disease, CV disease, including significant edema, CHF, or NYHA Class III or IV cardiac status, gastroparesis, clinically significant malignant disease (with the exception of basal and squamous cell carcinoma of the skin) within 5 years, macular edema, evidence of known or suspected chronic infections; abuses drugs or alcohol or has a history of abuse; FTG concentration ≥600 mg/dL; previously exposed to exenatide LAR; donated blood

Author, Year	Key exclusion criteria
	within 60 days; major surgery or a blood transfusion within 2 months; currently being treated, or is expected to require or undergo treatment with any of the following treatment-excluded medications: any AHA within 30 days, insulin within 2 weeks or for more than 1 week within 3 months, systemic corticosteroids; or potent, inhaled, or intrapulmonary steroids known to have a high rate of systemic absorption, drugs interacting with the CYP2C8 enzyme system; received any investigational drug within 1 month (or five halflives of investigational drug, whichever is greater); known allergies or hypersensitivity to any component of study treatment; previously experienced a clinically significant adverse event related to TZD or DPP-4 inhibitor use.
DeFronzo, 2005	Use of SUs, meglitinides, TZDs, AG inhibitors, exogenous insulin therapy, weight loss drugs, corticosteroids, drugs known to affect GI motility, transplantation medications, or any investigational drug; evidence of clinically significant comorbid conditions for 3 months up to screening
Nauck, 2009	Insulin use during previous 3 months (except short-term treatment)
Pratley, 2010	Recurrent major hypoglycaemia or hypoglycaemic unawareness; contraindication to trial drugs; impaired renal or hepatic function; clinically significant CV disease; cancer.
Kaku, 2009	T1D; impaired hepatic function, renal insufficiency, serious heart disease, cerebrovascular disease, and patients with other conditions that could potentially require hospitalization; a history of lactic acidosis/ketoacidosis/diabetic coma (or precoma within the preceding 26 weeks), or with a history of drug dependency; concurrent use of other drugs which might affect glycaemic control
18 to 30 weeks (with SU; eligible only for meta-analysis of systolic blood pressure)	
Ristic, 2006	N/R
Marre, 2002	Significant diabetic complications; significant changes in body weight (>5%) during run-in period; significant or unstable cardiac abnormalities; liver function abnormalities; treatment with antidiabetic agents other than metformin three months before study start.
Arechavaleta, 2011	History of T1D, use of any AHA besides metformin within 12 weeks of screening; renal function impairment prohibiting use of metformin.
Charpentier, 2001	Any evidence or history of spontaneous weight loss or ketonuria associated with glycosuria for newly-diagnosed (<1 yr) patients; secondary or T1D, any severe chronic disease, BMI >40.0 kg/m^2, history of major CV event in the last 6 months, allergy to SUs, or drug or alcohol abuse; concurrent treatment with any AHA other than metformin chlorhydrate, or with miconazole, systemic corticosteroids or any other investigational treatment in the 4 weeks before entry to the study was prohibited
Papathanassiou, 2009	History of coronary artery, cerebrovascular, or peripheral vascular disease, chronic heart failure, liver or renal disease, anemia, thyroid dysfunction; new onset of any medications within previous 8 weeks
Umpierrez, 2006	Treatment with insulin, TZDs, or SUs within 3 months prior to study enrollment; history of substance abuse, severe hypoglycaemia, acute metabolic complications, or clinically significant abnormal baseline laboratory values
Moses, 1999	Clinically significant elevation in either serum creatinine or liver transaminases; vitamin B12 <150 pmol/l (associated with hemoglobin <130 g/l in men or <119 g/l in women); anemia; previous insulin treatment; unawareness of hypoglycaemia; cardiac problems; uncontrolled hypertension; alcohol or drug abuse; a history of lactic acidosis; known contraindications to metformin, and an intention to become pregnant

Author, Year	Key exclusion criteria
> 30 weeks	
Study 4	See summary of dapagliflozin trials
Matthews, 2005	T1D; ketoacidosis, MI, transient ischaemic attacks or stroke in the previous 6 months; symptomatic heart failure; acute malabsorption or chronic pancreatitis; familial polyposis coli; malignant disease in the previous 10 years or substance abuse, pregnant or breastfeeding women
Nauck, 2007	History of T1D; insulin use within 8 weeks of screening; renal function impairment inconsistent with the use of metformin; other treatments for hyperglycaemia during the study.
Goke, 2010	T1D; history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; insulin therapy within 1 year of enrolment; treatment with a TZD within 12 weeks prior to enrolment; treatment with systemic glucocorticoids other than replacement therapy; previous DPP-4 inhibitor treatment; donation of blood, plasma or platelets within the 3 months prior to enrolment; CHF defined as NYHA class III or IV and/or known left ventricular ejection fraction ≤40%; significant CV history within past 6 months, valvular disease or repair, unstable angina pectoris, transient ischaemic attack or cerebrovascular accident; history of haemoglobinopathies; significant alcohol or drug abuse within the year prior to enrolment; treatment with HIV/antiviral drugs or cytochrome P450 3A4 (CYP450 3A4) inducers; serum creatinine ≥1.5 mg/dl for men or ≥1.4 mg/dl for women; active liver disease and/or significant abnormal liver function or any clinically significant laboratory abnormality upon screening.
Filozof, 2010	History of T1D, diabetes as a result of pancreatic injury or secondary forms of diabetes; acute metabolic diabetic complications within the past 6 months; serious cardiac conditions or clinically significant renal or liver disease; ALT or AST > 2 times the ULN, total bilirubin > 2 times the ULN, positive hepatitis B surface antigen and/or hepatitis C antibody, serum creatinine ≥132 µmol/l in male patients and ≥123 µmol/l in female patients, or a history of abnormal creatinine clearance, clinically significant TSH values at screening, or FTG > 7.9 mmol/l at screening.
Salvadeo, 2010	N/R
Derosa, 2010	History of ketoacidosis, unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy, impaired hepatic function, impaired renal function, or severe anemia; serious CV disease or cerebrovascular conditions ≤6 months before study enrollment; women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions.
Matthews, 2010	History of T1D or secondary forms of diabetes; acute metabolic diabetic complications in the past 6 months, acute infections that might affect blood glucose control in the 4 weeks prior to visit 1; serious cardiac conditions or clinically significant liver or renal disease; any of the following laboratory abnormalities at screening: ALT or AST >3 times the ULN, direct bilirubin >1.3 times ULN, serum creatinine levels ≥132 mmol/l in men or ≥123 mmol/l in women, clinically significant TSH at screening; or FTG >7.9 mmol/l

Abbreviations: AG, Alpha-glucosidase; AHA, Antihyperglycaemic Agent; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CHF, Congestive heart failure; CV, Cardiovascular; DPP-4, Dipeptidyl peptidase 4; FPG, Fasting plasma glucose; FTG, Fasting triglycerides; GI, Gastrointestinal; HIV, Human immunodeficiency virus; LAR, Long acting release; MI, Myocardial infarction; NYHA, New York Heart Association; SGLT2, Sodium-glucose transporter-2; SU, Sulphonylurea; T1D, Type 1 Diabetes; T2DM, Type 2 diabetes mellitus; TH, Thyroid hormone; TIA, Transient ischemic attack; TSH, Thyroid stimulating hormone; TZD, Thiazolidinediones; ULN, Upper limit of normal.

Table 116. Summary of exclusion criteria in randomised clinical trials involving patients with T2DM poorly controlled on insulin therapy

Author, Year	Key exclusion criteria
16 to 32 weeks; Requiring maintenance of stable insulin dose	
Vilsboll, 2010	Patients with T1D, FPG <7.2 mmol/L, unstable cardiac disease, significant renal impairment, ALT or AST > 2 times the ULN, elevated TG's, or treatment with AHA's (except metformin) or exenatide within 8–12 weeks of study entry.
Barnett, 2012	Patients were excluded if they had symptoms of poorly controlled diabetes, including but not limited to marked polyuria and polydipsia with >10% weight loss during the 3 months prior to screening, or a history of diabetic ketoacidosis or hyperosmolar nonketotic coma. Other major exclusion criteria included a major cardiovascular event within 6 months before screening; New York Heart Association class III/ IV congestive heart failure and/or known left ventricular ejection fraction <40%; serum creatinine ≥132.6 µmol/L) for men and ≥123.8 µmol/L) for women or calculated serum creatinine clearance (Cockcroft–Gault equation) <60 mL/min; history of unstable renal disease or hemoglobinopathies; alcohol or drug abuse within the year prior to screening; unstable, major psychiatric disorders; active liver disease; or clinically significant abnormalities on screening tests for hepatic or renal function, free T4, or anemia. Patients also were excluded if they received any antihyperglycaemic therapy, other than insulin and metformin, for more than 3 consecutive days or 7 non-consecutive days during the 8 weeks before screening or were treated with potent systemic cytochrome P450 3A4 inducers. In addition, those who were immunocompromised or had chronic or repeated intermittent corticosteroid use were ineligible.
Rosenstock, 2002	History of ketoacidosis, unstable of rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; impaired hepatic function (AST, ALT, total bilirubin, or alkaline phosphatase >2.5 times ULN); impaired kidney function (serum creatinine >1.8 mg/dL [159 µmol/l]); anaemia; or unstable or symptomatic cardiovascular or cerebrovascular conditions (e.g. NYHA class III or IV cardiac status, congestive heart failure, stroke, transient ischaemic attacks, or MI within 6 months before enrollment)
Study 6	See summary of dapagliflozin Study 6.
16 to 32 weeks; Not included in meta-analysis due to lack of requirement for stable insulin dose	
Mattoo, 2005	T1D, clinical signs or symptoms of any chronic systemic condition or signs or symptoms of drug or alcohol abuse. Previous TZD use, systemic glucocorticoid therapy, nicotinic acid at a dose >500 rag/d, or therapy for a malignancy other than basal cell or squamous cell skin cancer were excluded. Women who were breastfeeding or pregnant were excluded, as were women of childbearing potential not actively practicing birth control.
Asnani, 2006	Active liver disease, pregnant or breast-feeding women, history or recent myocardial infarction within the last 6 months or recent major surgery within the last 6 months
Zib, 2007	Previously used TZDs; reported to have more than two alcoholic drinks a day; had CHF classed as NYHA class III or IV, kidney failure requiring dialysis, liver transaminases over three times the ULN; were unwilling to practice safe contraception, severe claustrophobia, metallic implants within the body, and a weight or a body shape that would preclude positioning in the MRI system. None of the patients studied had a history of hepatitis B and G, and none were on medications for HIV.

Abbreviations: AHA, Antihyperglycaemic Agent; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CHF, Congestive heart failure; COPD, Chronic obstructive pulmonary disease; CV, Cardiovascular; FPG, Fasting plasma glucose; HIV, Human immunodeficiency virus; MRI, Magnetic resonance imaging; NYHA, New York Heart Association; SU, Sulphonylurea; T1D, Type 1 Diabetes; TG, Triglyceride; TZD, Thiazolidinediones; ULN, Upper limit of normal

Table 117. Summary of characteristics of included randomised clinical trials involving patients with T2DM poorly controlled on metformin monotherapy

Author, Year	Treatment arm	Mean age; years (SD)	% Male	Ethnicity/Race		Mean duration of diabetes (years)
				% White/ Caucasian (excluding Hispanic)	% Non-White or non-Caucasian	
18 to 30 weeks (non-SU)						
Study 14	Dapagliflozin 10 mg + metformin	52.7 (9.9)	57	N/R	N/R	6.1 (5.4)
	Placebo + metformin	53.7 (10.3)	55	N/R	N/R	5.8 (5.1)
Study 12	Dapagliflozin + metformin	60.6 (8.16)	55	100	0	6.03 (4.534)
	Placebo + metformin	60.8 (6.82)	56	100	0	5.52 (5.266)
Scott, 2008	Sitagliptin + metformin	55.2 (9.8)	55	61	39	4.9 (3.5)
	Placebo + metformin	55.3 (9.3)	59	61	39	5.4 (3.7)
Charbonnel, 2006	Sitagliptin + metformin	54.4 (10.4)	56	63	37	6.0 (5.0)
	Metformin + placebo	54.7 (9.7)	59	67	33	6.6 (5.5)
DeFronzo, 2009	Saxagliptin 5 mg + metformin	54.7 (9.6)	54	83	17	6.4 (4.7)
	Placebo + metformin	54.8 (10.2)	54	84	16	6.7 (5.6)
Bosi, 2007	Vildagliptin + metformin	53.9 (9.5)	62	74	26	5.8 (4.7)
	Placebo + metformin	54.5 (10.3)	53	73	27	6.2 (5.3)
Taskinen, 2011	Linagliptin + metformin	56.5 (10.1)	53	75	25	>5§
	Placebo + metformin	56.6 (10.9)	57	79	21	>5§
Bergenstal, 2010	Sitagliptin + metformin	56†	N/R	N/R	N/R	N/R
	Placebo + metformin	56†	N/R	N/R	N/R	N/R
Raz, 2008	Sitagliptin + metformin	53.6 (9.5)	51	42	58	8.4 (6.5)
	Placebo + metformin	56.1 (9.5)	41	47	53	7.3 (5.3)
Bolli, 2008	Vildagliptin + metformin	56.3 (9.3)	62	82	18	6.4 (4.9)
	Pioglitazone + metformin	57.0 (9.7)	64	82	18	6.4 (5.2)
Bergenstal, 2010	Sitagliptin + metformin	52 (11)	52	30	70	5 (4)

Author, Year	Treatment arm	Mean age; years (SD)	% Male	Ethnicity/Race		Mean duration of diabetes (years)
				% White/ Caucasian (excluding Hispanic)	% Non-White or non-Caucasian	
	Pioglitazone + metformin	53 (10)	48	39	61	6 (5)
DeFronzo, 2005	5-µg exenatide BID	53(11)	52	77	23	6.2(5.9)
	10-µg exenatide BID	52(11)	60	80	20	4.9(4.7)
	Placebo	54(9)	59	73	27	6.6(6.1)
Nauck, 2009	Liraglutide 1.2 mg + metformin	57 (9)	54	88	13	7 (5)
	Liraglutide 1.8 mg + metformin	57 (9)	59	88	11	8 (5)
	Glimepiride + metformin	57 (9)	57	89	12	8 (5)
	Placebo + metformin	56 (9)	60	88	13	8 (6)
Pratley, 2010	Liraglutide 1.2 mg + metformin	55.9 (9.6)	52	82	18	6.0 (4.5)
	Liraglutide 1.8 mg + metformin	55.0 (9.1)	52	87	13	6.4 (5.4)
	Sitagliptin + metformin	55.0 (9.0)	55	91	10	6.3 (5.4)
Kaku, 2009	Pioglitazone + metformin	52 (8.6)	66	0	100‡	4.5 (3.7)
	Placebo + metformin	53 (7.5)	57	0	100‡	5.6 (5.0)
18 to 30 weeks (with SU; eligible only for meta-analysis of systolic blood pressure)						
Ristic, 2006	Nateglinide + metformin	62.0 (11.0)	54	99	2	7.16 (6.30)
	Gliclazide + metformin	61.6 (10.1)	50	96	4	6.70 (5.55)
Marre, 2002	Nateglinide 60 mg + metformin	57.9 (9.9)	61	90	10	7.2 (6.4)
	Nateglinide 120 mg + metformin	57.3 (10.5)	61	91	9	6.8 (5.5)
	Placebo + metformin	56.4 (10.3)	55	91	9	6.5 (6.5)
Arechavaleta, 2011	Glimepiride + metformin	56.2 (10.1)	54	57	43	6.7 (4.8)
	Sitagliptin + metformin	56.3 (9.7)	55	58	42	6.8 (4.6)
Charpentier, 2001	Glimepiride + metformin	56.8	59	N/R	N/R	5.6
	Metformin + placebo	56.7	60	N/R	N/R	7.0
Papathanassiou, 2009	Glimepiride + metformin	63.6 (7.3)	21	N/R	N/R	5.3 (6.5)

Author, Year	Treatment arm	Mean age; years (SD)	% Male	Ethnicity/Race		Mean duration of diabetes (years)
				% White/ Caucasian (excluding Hispanic)	% Non-White or non-Caucasian	
	Pioglitazone + metformin	62.8 (7.2)	21	N/R	N/R	5.3 (3.6)
Umpierrez, 2006	Glimepiride + metformin	51.6 (11.8)	55	79	21	4.9 (3.8)
	Pioglitazone + metformin	55.7 (9.7)	52	79	22	5.9 (6.1)
Moses, 1999	Repaglinide + metformin	57.2 (8.3)	67	96	4	5.9 (2.9)
	Placebo + metformin	57.8 (9.5)	63	85	15	8.0 (6.2)
> 30 weeks						
Study 4	Dapagliflozin + metformin	58.1 (9.37)	55	82	18	6.08 (4.61)
	Glipizide + metformin	58.6 (9.80)	55	81	20	6.55 (5.90)
Matthews, 2005	Gliclazide + metformin	57 (9.0)	49	100	0	5.5 (5.1)
	Pioglitazone + metformin	56 (9.2)	51	99	1	5.8 (5.1)
Nauck, 2007	Glipizide + metformin	56.6 (9.8)	61	74	26	6.2 (5.4)
	Sitagliptin + metformin	56.8 (9.3)	57	74	27	6.5 (6.1)
Goke, 2010	Glipizide + metformin	57.6 (10.37)	54	84	16	5.4 (4.7)
	Saxagliptin + metformin	57.5 (10.26)	50	82	18	5.5 (4.5)
Filozof, 2010	Gliclazide + metformin	59.7 (10.2)	52	78	21	6.8 (5.3)
	Vildagliptin + metformin	59.2 (9.9)	52	79	21	6.4 (5.1)
Salvadeo, 2010	Exenatide + metformin	N/R	N/R	N/R	N/R	N/R
	Glimepiride + metformin	N/R	N/R	N/R	N/R	N/R
Derosa, 2010	Exenatide	57 (8)	48	100	0	N/R
	Glibenclamide	56 (7)	51	100	0	N/R
Matthews, 2010	Glimepiride + metformin	57.5 (9.19)	54	86	14	5.7 (5.0)
	Vildagliptin + metformin	57.5 (9.07)	53	87	13	5.7 (5.2)

Abbreviations: BID, twice daily; N/R, Not reported; SD, Standard deviation; SU, Sulphonylurea; †Value for overall study population; ‡ 100% of patients were Japanese; § Did not report mean duration of diabetes, but reported that 56% (linagliptin arm) and 53% (placebo arm) of patients had had diabetes for over 5 years

Table 118. Summary of characteristics of included randomised clinical trials involving patients with T2DM poorly controlled on insulin therapy

Author, Year	Treatment arm	Agent, Dose	Mean age; years (SD)	% male	Race (%)				Mean duration of diabetes (years) (SD)
					White	African American	Asian	Others	
16 to 32 weeks; Requiring maintenance of stable insulin dose									
Vilsboll, 2010	DPP-4	Sitagliptin 100mg	58.3 (9.1)	48.8	71	6	17	6	13 (7)
	Placebo	Placebo	57.2 (9.3)	53.0	69	7	19	5	12 (6)
Barnett, 2012	DPP-4	Saxagliptin 5mg	57.2 (9.4)	39.5	78.0	4.3	13.2	4.6	11.8 (6.9)
	Placebo	Placebo	57.3 (9.3)	45.0	78.1	6.0	12.6	3.3	12.2 (7.4)
Rosenstock, 2002	TZD	Pioglitazone 30 mg	57.5 (9.9)	50.5	73.4	N/R	N/R	26.6	N/R
	Placebo	Placebo	56.7 (9.4)	45.5	71.1	N/R	N/R	28.9	N/R
Study 6	Dapa	Dapagliflozin 10mg	59.3 (8.75)	44.8	94.8	2.6	1.5	1	14.15 (7.3)
	Placebo	Placebo	58.8 (8.61)	49.2	96.4	3.1	0	0.5	13.5 (7.3)
16 to 32 weeks; Not included in meta-analysis due to lack of requirement for stable insulin dose									
Asnani, 2006	TZD	Pioglitazone 30mg	59 (6)	N/R	N/R	N/R	N/R	N/R	17
	Placebo	Placebo	57 (5)	N/R	N/R	N/R	N/R	N/R	11
Mattoo, 2005	TZD	Pioglitazone 30mg	58.8 (7.4)	43.7	96.5	N/R	N/R	3.5	13.6 (6.8)
	Placebo	Placebo	58.9 (6.9)	42.9	96.6	N/R	N/R	3.4	13.4 (6.1)
Zib, 2007	TZD	Pioglitazone 30mg	51 (9)	43.8	25	43.8	N/R	31.2	5.6 (4.1)
	Placebo	No placebo	47 (11)	50.0	43.8	31.2	N/R	25	6.6 (5.2)

Abbreviations: Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4; N/R, Not reported; SD, Standard deviation; TZD, Thiazolidinediones

Table 119. Summary of baseline clinical characteristics of included randomised clinical trials involving patients with T2DM poorly controlled on metformin monotherapy

Study author and year	Treatment arm	Baseline HbA1c, % (SD)	Baseline Weight, kg (SD)	Baseline BMI, kg/m^2 (SD)	Baseline FPG, mmol/L (SD)	Baseline Cholesterol, mmol/L (SD)	Baseline LDL, mmol/L (SD)	Baseline HDL, mmol/L (SD)	Baseline Triglycerides, mmol/L (SD)	Baseline SBP, mmHg (SD)
18 to 30 weeks (non-SU)										
Study 14	Dapagliflozin 10 mg + metformin	7.92 (0.82)	N/R	31.2 (5.1)	8.66 (2.15)	4.8 (1)	2.7 (0.9)	1.1 (0.3)	2.2 (1.6)	126.0 (15.9)
	Placebo + metformin	8.11 (0.96)	N/R	31.8 (5.3)	9.19 (2.57)	4.7 (1.2)	2.6 (0.9)	1.1 (0.2)	2 (1.2)	127.7 (14.6)
Study 12	Dapagliflozin + metformin	7.19 [redacted]	92.1 (14.1)	32.06 (3.9)	8.21 (1.37)	N/R	N/R	N/R	N/R	135.9 (N/R)
	Placebo + metformin	7.16 [redacted]	90.9 (13.7)	31.7 (3.9)	8.3 (1.39)	N/R	N/R	N/R	N/R	133.3 (N/R)
Scott, 2008	Sitagliptin + metformin	7.75 (0.99)	83.1 (17.1)	30.3 (4.7)	8.74 (1.74)	4.53 (0.93)	2.47 (0.8)	1.14 (0.3)	2.01 (0.91)	N/R
	Placebo + metformin	7.68 (0.88)	84.6 (16.5)	30.0 (4.5)	8.88 (2.08)	4.48 (0.89)	2.48 (0.8)	1.13 (0.27)	1.93 (0.83)	N/R
Charbonnel, 2006	Sitagliptin + metformin	7.96 (0.81)	86.7 (17.8)	30.9 (5.3)	9.4 (2.3)	4.57 (0.92)	2.53 (0.79)	1.17 (0.28)	1.97 (1.13)	N/R
	Metformin + placebo	8.03 (0.82)	89.6 (17.5)	31.5 (4.9)	9.6 (2.3)	4.68 (0.98)	2.62 (0.81)	1.15 (0.28)	2.1 (1.44)	N/R
DeFronzo, 2009	Saxagliptin 5 mg + metformin	8.1 (0.8)	87.3 (17.0)	31.2 (4.7)	9.99 (2.61)	N/R	N/R	N/R	N/R	129.0 (15.4)
	Placebo + metformin	8.1 (0.9)	87.1 (17.8)	31.6 (4.8)	9.66 (2.44)	N/R	N/R	N/R	N/R	128.8 (14.3)
Bosi, 2007	Vildagliptin + metformin	8.4 (1.0)	95.3 (20.4)	32.9 (5.0)	9.9 (2.6)	N/R	N/R	N/R	N/R	N/R
	Placebo + metformin	8.3 (0.9)	94.8 (24.5)	33.2 (6.1)	10.1 (2.4)	N/R	N/R	N/R	N/R	N/R
Taskinen, 2011	Linagliptin + metformin	8.09 (0.86)	82.2 (17.2)	29.85 (4.84)	9.4 (2.4)	N/R	N/R	N/R	N/R	N/R
	Placebo + metformin	8.02 (0.88)	83.3 (16.6)	30.05 (5.01)	9.2 (2.3)	N/R	N/R	N/R	N/R	N/R
Bergenstal, 2010	Sitagliptin + metformin	7.94	92.48	32†	N/R	N/R	N/R	N/R	N/R	N/R
	Placebo + metformin	8.03	91.09	32†	N/R	N/R	N/R	N/R	N/R	N/R
Raz, 2008	Sitagliptin + metformin	9.3 (0.9)	81.5 (16.8)	30.1 (4.4)	11.2 (2.6)	N/R	N/R	N/R	N/R	N/R

Study author and year	Treatment arm	Baseline HbA1c, % (SD)	Baseline Weight, kg (SD)	Baseline BMI, kg/m^2 (SD)	Baseline FPG, mmol/L (SD)	Baseline Cholesterol, mmol/L (SD)	Baseline LDL, mmol/L (SD)	Baseline HDL, mmol/L (SD)	Baseline Triglycerides, mmol/L (SD)	Baseline SBP, mmHg (SD)
	Placebo + metformin	9.1 (0.8)	81.2 (19.4)	30.4 (5.3)	11 (2.4)	N/R	N/R	N/R	N/R	N/R
Bolli, 2008	Vildagliptin + metformin	8.4 (1.0)	91.8 (18.5)	32.2 (5.6)	10.9 (2.6)	4.8 (1.72)	2.6 (1.72)	1.2 (0)	2.4 (1.72)	N/R
	Pioglitazone + metformin	8.4 (0.9)	91.2 (16.9)	32.1 (5.1)	11 (2.7)	5 (1.68)	2.7 (1.68)	1.2 (0)	2.5 (1.68)	N/R
Bergenstal, 2010	Sitagliptin + metformin	8.5 (1.2)	87 (20)	32 (5)	9.1 (2.5)	4.6 (1.1)	2.7 (0.9)	1.1 (0.3)	1.9 (1.3)	126 (14)
	Pioglitazone + metformin	8.5 (1.1)	88 (20)	32 (6)	9.1 (2.4)	4.9 (1.1)	2.9 (1)	1.1 (0.3)	2.2 (1.3)	127 (14)
DeFronzo, 2005	5-µg exenatide BID	8.3(1.1)	100(22)	34(6)	9.77 (2.39)	N/R	N/R	N/R	N/R	N/R
	10-µg exenatide BID	8.2(1.0)	101(20)	34(6)	9.32 (2.55)	N/R	N/R	N/R	N/R	N/R
	Placebo	8.2(1.0)	100(19)	34(6)	9.44 (2.22)	N/R	N/R	N/R	N/R	N/R
Nauck, 2009	Liraglutide 1.2 mg + metformin	8.3 (1.0)	N/R	31.1 (4.8)	9.9 (2.3)	N/R	N/R	N/R	N/R	132 (14)
	Liraglutide 1.8 mg + metformin	8.4 (1.0)	N/R	30.9 (4.6)	10.1 (2.3)	N/R	N/R	N/R	N/R	131 (14)
	Glimepiride + metformin	8.4 (1.0)	N/R	31.2 (4.6)	10 (2.6)	N/R	N/R	N/R	N/R	132 (16)
	Placebo + metformin	8.4 (1.1)	N/R	31.6 (4.4)	10 (2.3)	N/R	N/R	N/R	N/R	135 (16)
Pratley, 2010	Liraglutide 1.2 mg + metformin	8.4 (0.8)	93.7 (18.4)	32.6 (5.2)	10.1 (2.4)	N/R	N/R	N/R	N/R	131.2 (14.4)
	Liraglutide 1.8 mg + metformin	8.4 (0.7)	94.6 (18.1)	33.1 (5.1)	9.9 (2.4)	N/R	N/R	N/R	N/R	133.4 (14.5)
	Sitagliptin + metformin	8.5 (0.7)	93.1 (18.9)	32.6 (5.4)	10 (2)	N/R	N/R	N/R	N/R	132.1 (14.8)
Kaku, 2009	Pioglitazone + metformin	7.58 (1.0)	N/R	25.6 (4.2)	8.8 (1.96)	5.15 (0.78)	3.23 (0.8)	1.33 (0.31)	1.81 (1.11)	N/R
	Placebo + metformin	7.55 (0.9)	N/R	25.4 (3.6)	8.83 (1.7)	5.29 (0.86)	3.25 (0.79)	1.44 (0.36)	1.76 (1.32)	N/R
18 to 30 weeks (with SU; eligible only for meta-analysis of systolic blood pressure)										
Ristic, 2006	Nateglinide + metformin	7.67 (0.59)	N/R	28.5 (3.5)	8.95 (1.49)	N/R	N/R	N/R	N/R	N/R

Study author and year	Treatment arm	Baseline HbA1c, % (SD)	Baseline Weight, kg (SD)	Baseline BMI, kg/m^2 (SD)	Baseline FPG, mmol/L (SD)	Baseline Cholesterol, mmol/L (SD)	Baseline LDL, mmol/L (SD)	Baseline HDL, mmol/L (SD)	Baseline Triglycerides, mmol/L (SD)	Baseline SBP, mmHg (SD)
	Gliclazide + metformin	7.60 (0.58)	N/R	29.5 (3.6)	8.73 (1.48)	N/R	N/R	N/R	N/R	N/R
Marre, 2002	Nateglinide 60 mg + metformin	7.99	84.8 (13.7)	29.4 (3.7)	9.8 (2.49)	5.5 (1.25)	3.4 (1.25)	1.2 (0)	2.2 (1.25)	N/R
	Nateglinide 120 mg + metformin	8.18	85.2 (13.9)	29.3 (3.5)	9.9 (2.53)	5.4 (1.26)	3.2 (1.26)	1.2 (0)	2.1 (1.26)	N/R
	Placebo + metformin	8.25	84.9 (14.8)	29.6 (3.9)	10.1 (2.46)	5.4 (1.23)	3.3 (1.23)	1.2 (0)	2.1 (1.23)	N/R
Arechavaleta, 2011	Glimepiride + metformin	7.5 (0.8)	82.0 (16.7)	30.2 (4.4)	8.1 (1.9)	N/R	N/R	N/R	N/R	N/R
	Sitagliptin + metformin	7.5 (0.7)	80.6 (15.2)	29.7 (4.5)	8 (1.8)	N/R	N/R	N/R	N/R	N/R
Charpentier, 2001	Glimepiride + metformin	6.4 (1.1)	81.2	29.5	10.4 (1.8)	5.44 (0.99)	N/R	1.19 (0.31)	1.91 (1.24)	140 (12)
	Metformin + placebo	6.8 (1.2)	82.2	29.2	10.6 (1.8)	5.5 (1.04)	N/R	1.19 (0.35)	1.93 (1.34)	142 (11)
Papathanassiou, 2009	Glimepiride + metformin	7.4 (0.8)	81.4 (15.3)	31.9 (5.5)	8.2 (1.4)	5.4 (1)	3 (1)	1.5 (0.3)	2 (1.4)	152.4 (16.6)
	Pioglitazone + metformin	7.7 (0.7)	85.9 (18.7)	33.9 (7.0)	8.7 (2.5)	5.8 (1)	3.7 (0.9)	1.3 (0.3)	1.7 (0.5)	149.5 (14.3)
Umpierrez, 2006	Glimepiride + metformin	8.40 (0.72)	N/R	34.54 (6.68)	10.01 (2.15)	5.06 (1.07)	2.93 (0.99)	1.13 (0.33)	1.05 (0.64)	N/R
	Pioglitazone + metformin	8.31 (0.77)	N/R	33.81 (6.62)	10.22 (2.34)	5 (1.01)	2.81 (0.82)	1.11 (0.26)	1.27 (1.15)	N/R
Moses, 1999	Repaglinide + metformin	8.3 (0.9)	N/R	33.2 (5.6)	10.22 (2.28)	5.97 (1.49)	3.36 (0.85)	1.07 (0.2)	2.77 (2.13)	N/R
	Placebo + metformin	8.6 (1.1)	N/R	31.8 (6.0)	10.8 (3.03)	5.89 (1.11)	3.48 (0.84)	1.07 (0.16)	2.91 (1.64)	N/R
> 30 weeks										
Study 4	Dapagliflozin + metformin	7.69 (0.86)	[redacted]	31.71 (5.10)	9 (2.1)	4.82 (1.08)	2.78 (0.91)	1.17 (0.3)	1.95 (1.12)	132.8 (14.89)
	Glipizide + metformin	7.74 (0.89)	[redacted]	31.23 (5.05)	9.1 (2.31)	4.64 (1.02)	2.55 (0.83)	1.21 (0.32)	1.93 (1.28)	133.8 (14.69)
Matthews, 2005	Gliclazide + metformin	8.53 (0.89)	92.7 (17.4)	32.6 (5.8)	11.3 (2.6)	5.58 (1.15)	3.28 (0.93)	1.09 (0.23)	2.78 (1.89)	N/R

Study author and year	Treatment arm	Baseline HbA1c, % (SD)	Baseline Weight, kg (SD)	Baseline BMI, kg/m^2 (SD)	Baseline FPG, mmol/L (SD)	Baseline Cholesterol, mmol/L (SD)	Baseline LDL, mmol/L (SD)	Baseline HDL, mmol/L (SD)	Baseline Triglycerides, mmol/L (SD)	Baseline SBP, mmHg (SD)
	Pioglitazone + metformin	8.71 (1.00)	91.8 (16.2)	32.6 (5.0)	11.8 (3.1)	5.64 (1.14)	3.34 (0.98)	1.1 (0.25)	2.9 (1.94)	N/R
Nauck, 2007	Glipizide + metformin	7.6 (0.9)	89.7 (17.5)	31.3 (5.2)	9.1 (2.3)	N/R	N/R	N/R	N/R	N/R
	Sitagliptin + metformin	7.7 (0.9)	89.5 (17.4)	31.2 (5.0)	9.2 (2.3)	N/R	N/R	N/R	N/R	N/R
Goke, 2010	Glipizide + metformin	7.7 (0.9)	88.6 (19.64)	31.3 (6.17)	8.94 (2.18)	N/R	N/R	N/R	N/R	N/R
	Saxagliptin + metformin	7.7 (0.9)	88.7 (18.61)	31.5 (5.70)	9.05 (2.29)	N/R	N/R	N/R	N/R	N/R
Filozof, 2010	Gliclazide + metformin	8.5 (1.0)	84.2 (17.9)	30.8 (5.0)	10.6 (2.8)	N/R	N/R	N/R	N/R	N/R
	Vildagliptin + metformin	8.5 (1.0)	85.7 (16.6)	31.2 (5.0)	10.8 (2.8)	N/R	N/R	N/R	N/R	N/R
Salvadeo, 2010	Exenatide + metformin	N/R	N/R	28.4 (1.3)	N/R	N/R	N/R	N/R	N/R	N/R
	Glimepiride + metformin	N/R	N/R	28.5 (1.4)	N/R	N/R	N/R	N/R	N/R	N/R
Derosa, 2010	Exenatide	8.8 (0.7)	82.0 (8.3)	28.7 (1.5)	7.99 (0.89)	N/R	N/R	N/R	N/R	N/R
	Glibenclamide	8.9 (0.8)	82.4 (9.1)	28.5 (1.4)	8.16 (1)	N/R	N/R	N/R	N/R	N/R
Matthews, 2010	Glimepiride + metformin	7.3 (0.7)	88.9 (17.8)	31.7 (5.3)	9.2 (2.2)	N/R	N/R	N/R	N/R	N/R
	Vildagliptin + metformin	7.3 (0.7)	89.5 (18.1)	31.9 (5.3)	9.2 (2.3)	N/R	N/R	N/R	N/R	N/R

Abbreviations: BMI, Body mass index; FPG, Fasting plasma glucose; HbA1c, Glycosylated haemoglobin; HDL, High density lipoprotein; LDL, Low density lipoprotein; N/R, Not reported; SBP, Systolic blood pressure; SD, Standard deviation; SU, Sulphonylurea; †Value for overall study population.

Table 120. Summary of baseline clinical characteristics of included randomised clinical trials involving patients with T2DM poorly controlled on insulin therapy

Author, Year	Treatment arm	Baseline HbA1c, % (SD)	Baseline Weight, kg (SD)	Baseline BMI, kg/m^2 (SD)	Baseline FPG, mmol/L (SD)	Baseline Cholesterol, mmol/L (SD)	Baseline LDL, mmol/L (SD)	Baseline HDL, mmol/L (SD)	Baseline Triglycerides, mmol/L (SD)	Baseline SBP, mmHg (SD)
16 to 32 weeks; Requiring maintenance of stable insulin dose										
Vilsboll, 2010	Sitagliptin + insulin ± metformin	8.7 (0.9)	86.5 (18.6)	31 (5)	9.75 (2.87)	N/R	N/R	N/R	N/R	N/R
	Placebo + insulin ± metformin	8.6 (0.9)	87.3 (17.9)	31 (5)	9.92 (3.31)	N/R	N/R	N/R	N/R	N/R
Barnett, 2012	Saxagliptin 5mg + insulin	8.7 (0.9)	87.7 (18.6)	32.6 (5.7)	9.63 (3.02)	N/R	N/R	N/R	N/R	132.2 (14.1)
	Placebo + insulin	8.6 (0.9)	86.2 (16.6)	31.8 (4.8)	9.61 (3.09)	N/R	N/R	N/R	N/R	129.1 (12.0)
Rosenstock, 2002	Pioglitazone 30 mg	9.84 (1.4)	98.7 (17.7)	34.3 (6.2)	229.3 (70.6)	207.32 (48.4)	121.7 (42.5)	42.7 (12.9)	262.3 (239.9)	N/R
	Placebo + insulin	9.75 (1.4)	95.4 (17.0)	33.2 (5.2)	220.5 (71.4)	214.03 (49.0)	131 (42.4)	42.7 (13.1)	242.5 (243.4)	N/R
Study 6	Dapagliflozin 10mg + insulin ± OAD	8.57 (0.82)	94.5 (16.8)	33.41 (5.061)	9.61 (3.05)	[redacted]	[redacted]	[redacted]	[redacted]	140.6(16.7)‡
	Placebo + insulin ± OAD	8.47 (0.77)	94.5 (19.8)	33.14 (5.862)	9.47 (3.17)	[redacted]	[redacted]	[redacted]	[redacted]	136.1(17.17)‡
16 to 32 weeks; Not included in meta-analysis due to lack of requirement for stable insulin dose										
Asnani, 2006	Pioglitazone + insulin	10.0 (2.3)	N/R	N/R	N/R	N/R	N/R	N/R	N/R	135 (13)
	Placebo + insulin	8.7 (2.3)	N/R	N/R	N/R	N/R	N/R	N/R	N/R	145 (9)
Mattoo, 2005	Pioglitazone 30 mg + insulin	8.85 (1.3)	N/R	32.5 (4.8)	11.36 (4.63)	5.31 (1.2)	3.2 (1.08)	1.23 (3.58)	1.99 (2.26)	137.3 (15.5)
	Placebo + insulin	8.79 (1.2)	N/R	31.8 (5.0)	11.27 (4.51)	5.04 (1.1)	3.18 (0.97)	1.24 (3.64)	1.58 (2.18)	137.4 (15.8)

Author, Year	Treatment arm	Baseline HbA1c, % (SD)	Baseline Weight, kg (SD)	Baseline BMI, kg/m^2 (SD)	Baseline FPG, mmol/L (SD)	Baseline Cholesterol, mmol/L (SD)	Baseline LDL, mmol/L (SD)	Baseline HDL, mmol/L (SD)	Baseline Triglycerides, mmol/L (SD)	Baseline SBP, mmHg (SD)
Zib, 2007	Pioglitazone + insulin	11.0 (2.8)	88.03 (23.45)	32 (8)	N/R	5.28 (0.83) ¶	3.39 (0.78) ¶	1.17 (0.23) ¶	1.54 (0.75) ¶	132 (20)
	Insulin alone (no placebo)	10.6 (1.4)	90.79 (23.28)	33 (7)	N/R	4.48 (0.73) ¶	2.67 (0.7) ¶	1.17 (0.41) ¶	1.62 (0.79) ¶	131 (30)

Abbreviations: BMI, Body mass index; FPG, Fasting plasma glucose; HbA1c, Glycosylated haemoglobin; HDL, High density lipoprotein; LDL, Low density lipoprotein; N/R, Not reported; OAD, Oral antidiabetic drug; SBP, Systolic blood pressure; SD, Standard deviation. ‡Seated; ¶ Extractors assumed that authors incorrectly reported as g/L instead of mg/dL (based on order of magnitude). A query to authors was made but no response was received.

Table 121. Summary of insulin regimens used in randomised clinical trials of patients with T2DM inadequately controlled on insulin therapy

Author, Year	Intervention	Insulin (IU/day) [Δ= change from baseline]	Stable insulin	Criteria for Insulin titration (U = up-titration; D = down-titration)	Insulin type	Concomitant anti-diabetic agents
16 to 32 weeks; Requiring maintenance of stable insulin dose						
Vilsboll, 2010†	Sitagliptin 100 mg; Placebo	Baseline: ~45 Sitagliptin Δ: 0 Placebo Δ +1.6	Y	D: hypoglycaemia or risk of hypoglycaemia	~27% on premixed insulin	Sitagliptin: 71% metformin Placebo: 73% metformin
Barnett, 2012‡	Saxagliptin 5mg; Placebo	Baseline: ~54 Saxagliptin Δ: +1.7 Placebo Δ: +5.0	Y	U: Patients with FPG >13.3 mmol/L at weeks 4 or 6; >12.2 mmol/L at week 8 or > 11.1 mmol/L at weeks 12, 16 or 20 were rescued D: At discretion of investigator.	54-62% with any premixed insulin; 38-46% with no pre-mixed.	Saxagliptin: 69% on metformin; Placebo: 70% on metformin †††
Rosenstock, 2002§	Pioglitazone 30mg; Placebo	Baseline: ~72 Pioglitazone Δ: -8.1 Placebo Δ:-0.6	Y	D: hypoglycaemia (FPG ≤5.55 mmol/L on two occasions or symptoms of hypoglycaemia not explained by other conditions). Maximum permitted decrease was 10%. of current daily dose‡‡‡	≥30 units/day for ≥4 months, stable dose ≥30 days; 88% were monotherapy	8% metformin, 2% glyburide, 2% glipizide (these groups may overlap)
Wilding, 2010¶	Dapagliflozin 10 mg; Placebo	Baseline: ~76 Dapagliflozin Δ -1.2 Placebo Δ +5.1	Y	U: FPG > 13.3 mmol/L or > 12.2 mmol/L¶¶ D: hypoglycaemia.	~20% basal; ~80% sliding scale insulin (~48% with both)	Dapagliflozin: 43% metformin; Dapagliflozin: 7.7% metformin ± other OAMs Placebo: 40% metformin;

Author, Year	Intervention	Insulin (IU/day) [Δ= change from baseline]	Stable insulin	Criteria for Insulin titration (U = up-titration; D = down-titration)	Insulin type	Concomitant anti-diabetic agents
						Placebo: 9.8% metformin ± other OAMs
16 to 32 weeks; Not included in meta-analysis due to lack of requirement for stable insulin dose						
Asnani, 2006††	Pioglitazone 30mg; Placebo	N/R	N/R	N/R	N/R	Not reported; but continued taking existing OAD, if any
Mattoo, 2005‡‡	Pioglitazone 30mg; Placebo	N/R	N	D/U: self-monitored blood glucose levels	N/R	0% (OAMs discontinued)
Zib, 2007§§	Pioglitazone 30mg; Placebo	N/R	N	D/U: self-monitored blood glucose levels	N/R	0% (OAMs discontinued)

Abbreviations: D, Down-titration; FPG, Fasting plasma glucose; N, No; N/R, Not reported; OAD, Oral anti-diabetic drug; OAMs, Oral anti-hyperglycaemic medications; U, Up-titration; Y, Yes. Δ, Change from baseline; †, During lead-in period, existing regimen was continued for 2 weeks; ‡, Lead in consisted of four week single-blind placebo dietary and exercise period where patients had to maintain baseline therapy and mean total daily insulin dose required to differ by <20% from the mean total daily dose at screening; §, After two weeks into the lead in period, patients received single-blind stable insulin + placebo (lasting 1 week for patients on insulin monotherapy, and 4 weeks for those with OAM); ¶, No lead-in phase; however, between enrollment and randomization (2 weeks), mean daily insulin dose must have been > 30 IU and daily insulin doses were not permitted to vary more than 10% of the calculated mean on more than one occasion; ††, No lead-in period; ‡‡, 2-stage lead-in: *Stage 1*: continue with existing medications for 2 weeks, *Stage 2*: All OAMs stopped and insulin monotherapy optimized for 3 months, and patients achieving glycaemic control in stage 2 were not randomised; §§, Two week lead-in to optimize insulin; ¶¶, Weeks 1 to 12: 13.3 mmol/L; weeks 16 to 24: 12.2 mmol/L; †††, Capped at 75% and stratified based on metformin use at enrollment; ‡‡‡, The reduced dose then remained fixed unless new occurrences of hypoglycaemia warranted further 10% reduction

Table 122. Risk of bias in included randomised clinical trials involving patients with T2DM poorly controlled on metformin monotherapy

Author, Year	Patients Blinded	Clinicians blinded	Adequate generation of randomization sequence	Adequate concealment of randomization	Adequate reporting of patient baseline characteristics	Groups in terms of prognostic factors?	Adequate reporting of study design
18 to 30 weeks (non-SU)							
Study 14	Y	Y	Y	Y	Y	Y	Y
Study 12	Y	Y	N/R	N/R	Y	Y	Y
Scott, 2008	Y	Y	N/R	N/R	Y	Y	Y
Charbonnel, 2006	Y	Y	N/R	N/R	Y	Y	N††
DeFronzo, 2009	Y	Y	N/R	Y	Y	Y	N††
Bosi, 2007	Y	Y	N/R	N/R	Y	Y	N††

Author, Year	Patients Blinded	Clinicians blinded	Adequate generation of randomization sequence	Adequate concealment of randomization	Adequate reporting of patient baseline characteristics	Groups in terms of prognostic factors?	Adequate reporting of study design
Taskinen, 2011	Y	Y	N/R	N/R	Y	Y	Y
Bergenstal, 2010	Y	Y	N/R	N/R	N†	N§	N††
Raz, 2008	Y	Y	Y	N/R	Y	Y	Y
Bolli, 2008	Y	Y	Y	Y	Y	Y	N††
Bergenstal, 2010	Y	Y	Y	Y	Y	Y	Y
DeFronzo, 2005	Y	Y	Y	Y	Y	Y	Y
Nauck, 2009	Y	Y	Y	Y	Y	Y	N‡‡
Pratley, 2010	N	N	Y	Y	Y	Y	Y
Kaku, 2009	Y	Y	N/R	N/R	Y	N¶	Y
18 to 30 weeks (with SU; eligible only for meta-analysis of systolic blood pressure)							
Ristic, 2006	Y	Y	Y	Y	N¶¶	Y	N
Marre, 2002	Y	Y	Y	Y	Y	Y	Y
Arechavaleta, 2011	Y	Y	Y	Y	Y	Y	Y
Charpentier, 2001	Y	Y	Y	Y	Y	Y	Y
Papathanassiou, 2009	N	N	N§§	N/R	Y	Y	Y
Umpierrez, 2006	N	N	N/R	N/R	Y	N†††	Y
Moses, 1999	Y	Y	N/R	N/R	Y	Y	N
> 30 weeks							
Study 4	Y	Y	N/R	N/R	Y	Y	Y
Matthews, 2005	Y	Y	Y	Y	Y	Y	Y
Nauck, 2007	Y	Y	N/R	N/R	Y	Y	Y
Goke, 2010	Y	Y	Y	Y	Y	Y	Y
Filozof, 2010	Y	Y	N/R	N/R	Y	Y	Y
Salvadeo, 2010	N/R	N/R	N/R	N/R	N‡‡‡	N§	N††
Derosa, 2010	Y	N	Y	Y	N‡	Y	Y

Author, Year	Patients Blinded	Clinicians blinded	Adequate generation of randomization sequence	Adequate concealment of randomization	Adequate reporting of patient baseline characteristics	Groups in terms of prognostic factors?	Adequate reporting of study design
Matthews, 2010	Y	Y	N/R	N/R	Y	Y	N††

Abbreviations: N, No; N/R, Not reported; SU, Sulphonylurea; Y, Yes. †Did not report sex distribution of patient population; ‡Did not report duration of diabetes at baseline; §Inadequate reporting of patient baseline characteristics; ¶Duration of diabetes was longer in the metformin monotherapy group (p=0.04); ††Did not adequately report use of prior and/or concomitant anti-diabetic therapies; ‡‡Unclear whether concomitant medications were discontinued at lead-in period; §§ Patients were randomized based on the order of presentation in the outpatient clinic; ¶¶Did not report presence/absence of comorbid conditions; †††Mean age of pioglitazone group was significantly greater; ‡‡‡Did not report baseline patient characteristics

Table 123. Risk of bias in included randomised clinical trials involving patients with T2DM poorly controlled on insulin therapy

Author, Year	Patient Blinded	Clinicians blinded	Adequate generation of randomization sequence	Adequate concealment of randomization	Adequate reporting of patient baseline characteristics	Groups similar in terms of prognostic factors?	Adequate reporting of study design
16 to 32 weeks; Requiring maintenance of stable insulin dose							
Vilsboll, 2010	Y	Y	Y	N/R	Y	Y	Y
Barnett, 2012	Y	Y	Y	Y	Y	Y	Y
Rosenstock, 2002	Y	Y	N/R	N/R	N†	N†	Y
Study 6	Y	Y	N/R	Y	Y	Y	Y
16 to 32 weeks; Not included in meta-analysis due to lack of requirement for stable insulin dose							
Asnani, 2006	Y	Y	Y	N/R	N‡	N†	Y
Mattoo, 2005	Y	Y	Y	Y	Y	Y	Y
Zib, 2007	N§	N§	N/R	N/R	N	N¶	Y

Abbreviations: N, No; N/R, Not reported; Y, Yes; †, Inadequate reporting of patient baseline characteristics, but among the reported information, the groups were similar; ‡, Inadequate reporting of patient baseline characteristics; §, Open-label study; ¶, patient baseline characteristics for both treatment groups were comparable , except for LDL and total cholesterol levels that were higher in the pioglitazone plus insulin group

Table 124. Glycosylated haemoglobin data extracted from randomised clinical trials of anti-diabetic agents used in adults with T2DM, inadequately controlled on metformin monotherapy

Author	Year	Duration	Comparator	Agent, Dose	N	BL mean (%)	BL SD (%)	Delta mean (%)	Delta SE (%)
18 to 30 weeks									
Study 14	2010	24	Dapa	Dapagliflozin 10mg	132	7.92	0.82	-0.84	0.07
Study 14	2010	24	Placebo	Placebo	134	8.11	0.96	-0.3	0.07
Study 12	2010	24	Dapa	Dapagliflozin 10mg	88	7.19	0.44	-0.39	0.0485
Study 12	2010	24	Placebo	Placebo	91	7.16	0.53	-0.1	0.0477
Kaku	2009	28	TZD	Pioglitazone 30mg	83	7.58	1	-0.67	0.08781
Kaku	2009	28	Placebo	Placebo	86	7.55	0.9	0.25	0.09921
Charbonnel	2006	24	DPP-4	Sitagliptin 100mg	453	7.96	0.81	-0.67	0.05
Charbonnel	2006	24	Placebo	Placebo	224	8.03	0.82	-0.02	0.06
DeFronzo	2009	24	DPP-4	Saxagliptin 5mg	186	8.1	0.8	-0.69	0.07
DeFronzo	2009	24	Placebo	Placebo	175	8.1	0.9	0.13	0.07
Raz	2008	30	DPP-4	Sitagliptin 100mg	95	9.3	0.9	-1	0.2
Raz	2008	30	Placebo	Placebo	92	9.1	0.8	0	0.2
Bosi	2007	24	DPP-4	Vildagliptin 100mg	143	8.4	1	-0.9	0.1
Bosi	2007	24	Placebo	Placebo	130	8.3	0.9	0.2	0.1
Taskinen	2011	24	DPP-4	Linagliptin 5mg	513	8.09	0.86	-0.49	0.04
Taskinen	2011	24	Placebo	Placebo	175	8.02	0.88	0.15	0.06
Scott	2008	18	DPP-4	Sitagliptin 100mg	91	7.75	0.99	-0.73	0.07
Scott	2008	18	Placebo	Placebo	88	7.68	0.88	-0.22	0.07
Bergenstal	2010	24	DPP-4	Sitagliptin 100mg	177	7.94	N/A	-0.889	0.057
Bergenstal	2010	24	Placebo	Placebo	90	8.03	N/A	-0.1	0.079
DeFronzo	2005	30	GLP-1	Exenatide 10ug	110	8.3	1.1	-0.4	0.1
DeFronzo	2005	30	GLP-1	Exenatide 20ug	113	8.2	1	-0.8	0.1
DeFronzo	2005	30	Placebo	Placebo	113	8.2	1	0.1	0.1

Author	Year	Duration	Comparator	Agent, Dose	N	BL mean (%)	BL SD (%)	Delta mean (%)	Delta SE (%)
Bolli	2008	24	DPP-4	Vildagliptin 100mg	264	8.4	1	-0.88	0.05
Bolli	2008	24	TZD	Pioglitazone 30mg	246	8.4	0.9	-0.98	0.06
Bergenstal	2010	26	DPP-4	Sitagliptin 100mg	166	8.5	1.2	-0.9	0.1
Bergenstal	2010	26	TZD	Pioglitazone 45mg	165	8.5	1.1	-1.2	0.1
Pratley	2010	26	GLP-1	Liraglutide 1.2mg	221	8.4	0.8	-1.24	0.07
Pratley	2010	26	GLP-1	Liraglutide 1.8mg	218	8.4	0.7	-1.5	0.07
Pratley	2010	26	DPP-4	Sitagliptin 100mg	219	8.5	0.7	-0.9	0.07
Nauck	2009	26	GLP-1	Liraglutide 1.2mg	240	8.3	1	-0.97	0.1
Nauck	2009	26	GLP-1	Liraglutide 1.8mg	242	8.4	1	-1	0.1
Nauck	2009	26	Placebo	Placebo	121	8.4	1.1	0.09	0.1
52 weeks									
Study 4	2010	52	Dapa	Dapagliflozin 10mg	400	7.69	0.86	-0.52	0.04
Study 4	2010	52	SU	Glipizide 5-20mg	401	7.74	0.89	-0.52	0.04
Matthews	2005	52	SU	Gliclazide 160-320mg	313	8.53	0.89	-1.01	0.03
Matthews	2005	52	TZD	Pioglitazone 30-45 mg	317	8.71	1	-0.99	0.05
Matthews	2010	52	SU	Glimepiride 2-6mg	1072	7.3	0.65	-0.53	0.02
Matthews	2010	52	DPP-4	Vildagliptin 100mg	1118	7.31	0.64	-0.44	0.02
Nauck	2007	52	SU	Glipizide 5-20mg	559	7.6	0.9	-0.56	0.05
Nauck	2007	52	DPP-4	Sitagliptin 100mg	576	7.7	0.9	-0.51	0.04
Goke	2010	52	SU	Glipizide 5-20mg	423	7.7	0.9	-0.66	0.039
Goke	2010	52	DPP-4	Saxagliptin 5mg	423	7.7	0.9	-0.57	0.039
Filozof	2010	52	SU	Gliclazide 80-320mg	393	8.5	1	-0.85	0.06
Filozof	2010	52	DPP-4	Vildagliptin 100mg	386	8.5	1	-0.81	0.06
Salvadeo†	2010	52	GLP-1	Exenatide 20ug	65	8.8	N/A	-1.2	0.06
Salvadeo†	2010	52	SU	Glimepiride 6mg	65	7.757	N/A	-1.4	0.05
Derosa†	2010	52	GLP-1	Exenatide 20ug	63	8.8	0.7	-1.5	0.0959

Author	Year	Duration	Comparator	Agent, Dose	N	BL mean (%)	BL SD (%)	Delta mean (%)	Delta SE (%)
Derosa†	2010	52	SU	Glibenclamide 15mg	65	8.9	0.8	-1.8	0.1023

Abbreviations: BL, Baseline; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4; GLP-1, Glucagon-like peptide-1; N, Number; N/A, Not applicable; SD, Standard deviation; SE, Standard error; SU, Sulphonylurea; TZD, Thiazolidinediones. †Included, but results are not presented in base case NMA

Table 125. Glycosylated haemoglobin data extracted from randomised clinical trials of anti-diabetic agents used in adults with T2DM, inadequately controlled on insulin with or without other oral anti-diabetic agents

Author	Year	Duration	Comparator	N	Baseline Mean (%)	Baseline SD (%)	Delta mean (%)	Delta SE (%)
16 to 32 weeks; Requiring maintenance of stable insulin dose								
Vilsboll	2010	24	DPP-4	305	8.70	0.90	-0.60	0.10
Vilsboll	2010	24	Placebo	312	8.60	0.90	0.00	0.10
Barnett	2012	24	DPP-4	300	8.7	0.90	-0.73	0.054
Barnett	2012	24	Placebo	149	8.6	0.86	-0.32	0.074
Rosenstock	2002	16	TZD	185	9.84	1.36	-1.26	0.08
Rosenstock	2002	16	Placebo	177	9.75	1.33	-0.26	0.08
Study 6	2010	24	Dapagliflozin	192	8.58	0.82	[redacted]	[redacted]
Study 6	2010	24	Placebo	188	8.46	0.76	[redacted]	[redacted]
16 to 32 weeks; Not included in meta-analysis due to lack of requirement for stable insulin dose								
Asnani	2006	17.2	TZD	8	10.00	2.30	-1.60	1.08
Asnani	2006	17.2	Placebo	8	8.70	2.30	-0.10	0.95
Mattoo	2005	25.8	TZD	138	8.85	1.29	-0.69	0.09
Mattoo	2005	25.8	Placebo	144	8.79	1.20	-0.14	0.08
Zib	2007	25.8	TZD	16	11.00	2.80	-4.00	0.72
Zib	2007	25.8	Placebo	16	10.60	1.40	-3.46	0.52

Abbreviations: DPP-4, Dipeptidyl peptidase-4 inhibitors; N, Number; SD, Standard deviation; SE, Standard error; TZD, Thiazolidinediones; † values differ from those reported in Section 5.5.3.4, as these are unpublished values which were available in advance of the publication and were used in the NMA

Table 126. Data estimates of weight change from baseline extracted from randomised clinical trials of anti-diabetic agents used in adults with T2DM, inadequately controlled on metformin monotherapy

Author	Year	Duration	Comparator	Agent, Dose	N	Baseline mean (kg)	Baseline SD (kg)	Delta mean (kg)	Delta SE (kg)
24 weeks									
Study 14	2010	24	Dapa	Dapagliflozin 10mg	133	N/R	N/R	-2.9	0.3
Study 14	2010	24	Placebo	Placebo	136	N/R	N/R	-0.9	0.3
Study 12	2010	24	Dapa	Dapagliflozin 10mg	89	92.06	14.128	-2.96	0.2766
Study 12	2010	24	Placebo	Placebo	91	90.91	13.716	-0.88	0.2746
Kaku	2009	28	TZD	Pioglitazone 15-30mg	83	N/R	N/R	1.68	0.2401†
Kaku	2009	28	Placebo	Placebo	86	N/R	N/R	-0.47	0.2959†
Raz	2008	30	DPP-4	Sitagliptin 100mg	96	81.5	16.8	-0.5	0.2784†
Raz	2008	30	Placebo	Placebo	94	81.2	19.4	-0.5	0.2959†
Bosi	2007	24	DPP-4	Vildagliptin 100mg	143	95.3	17.94	0.2	0.3
Bosi	2007	24	Placebo	Placebo	130	94.8	20.52	-1	0.3
Taskinen	2011	24	DPP-4	Linagliptin 5mg	513	82.2	17.2	-0.4	0.2784†
Taskinen	2011	24	Placebo	Placebo	175	83.3	16.6	-0.5	0.2959†
Scott	2008	18	DPP-4	Sitagliptin 100mg	94	83.1	17.1	-0.4	0.2
Scott	2008	18	Placebo	Placebo	91	84.6	16.5	-0.8	0.2
Bergenstal	2010	24	DPP-4	Sitagliptin 100mg	177	92.48	N/R	-0.091	0.204
Bergenstal	2010	24	Placebo	Placebo	90	91.09	N/R	-0.488	0.392
DeFronzo‡	2009	24	DPP-4	Saxagliptin 5mg	191	87.3	17	-0.87	0.23
DeFronzo‡	2009	24	Placebo	Placebo	177	87.1	17.8	-0.92	0.22
DeFronzo	2005	30	GLP-1	Exenatide 10ug	110	100	22	-1.6	0.4
DeFronzo	2005	30	GLP-1	Exenatide 20ug	113	101	20	-2.8	0.5
DeFronzo	2005	30	Placebo	Placebo	113	100	19	-0.3	0.3
Bolli	2008	24	DPP-4	Vildagliptin 100mg	264	91.8	18.5	0.3	0.2
Bolli	2008	24	TZD	Pioglitazone 30mg	246	91.2	16.9	1.9	0.2

Author	Year	Duration	Comparator	Agent, Dose	N	Baseline mean (kg)	Baseline SD (kg)	Delta mean (kg)	Delta SE (kg)
Bergenstal	2010	26	DPP-4	Sitagliptin 100mg	166	87	20	-0.8	0.4
Bergenstal	2010	26	TZD	Pioglitazone 45mg	165	88	20	2.8	0.3
Pratley	2010	26	GLP-1	Liraglutide 1.2mg	221	93.7	18.4	-2.86	0.28
Pratley	2010	26	GLP-1	Liraglutide 1.8mg	218	94.6	18.1	-3.38	0.28
Pratley	2010	26	DPP-4	Sitagliptin 100mg	219	93.1	18.9	-0.96	0.28
Nauck	2009	26	GLP-1	Liraglutide 1.2mg	240	N/R	N/R	-2.6	0.2
Nauck	2009	26	GLP-1	Liraglutide 1.8mg	242	N/R	N/R	-2.8	0.2
Nauck	2009	26	Placebo	Placebo	121	N/R	N/R	-1.5	0.3
52 weeks									
Study 4	2010	52	Dapa	Dapagliflozin 10mg	400	88.44	16.323	-3.22	0.18
Study 4	2010	52	SU	Glipizide 5-20mg	401	87.6	16.97	1.44	0.18
Matthews	2010	52	SU	Glimepiride 2-6mg	1072	88.62	17.8	1.56	0.12
Matthews	2010	52	DPP-4	Vildagliptin 100mg	1118	89.01	18.1	-0.23	0.11
Nauck	2007	52	SU	Glipizide 5-20mg	584	89.7	17.5	1.1	0.3
Nauck	2007	52	DPP-4	Sitagliptin 100mg	588	89.5	17.4	-1.5	0.3
Goke	2010	52	SU	Glipizide 5-20mg	426	88.6	19.64	1.1	0.17‡
Goke	2010	52	DPP-4	Saxagliptin 5mg	424	88.7	18.61	-1.1	0.17‡
Filozof	2010	52	SU	Gliclazide 80-320mg	393	84.2	17.9	1.36	0.1634†
Filozof	2010	52	DPP-4	Vildagliptin 100mg	386	85.7	16.6	0.08	0.1605†
Derosa§	2010	52	GLP-1	Exenatide 20ug	63	82	8.3	-8	1.16633†
Derosa§	2010	52	SU	Glibenclamide 15mg	65	82.4	9.1	4.3	1.78993†

Abbreviations: Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; N, Number; N/R, Not reported; SD, Standard deviation; SE, Standard error; SU, Sulphonylureas; TZD, Thiazolidinediones. †Data was imputed; ‡Unpublished from clinical study report; § Included, but results are not presented in base case NMA

Table 127. Weight data extracted from randomised clinical trials of anti-diabetic agents used in adults with T2DM, inadequately controlled on insulin with or without oral anti-diabetic agents

Author	Year	Duration	Comparator	N	Baseline mean (kg)	Baseline SD (kg)	Delta mean (kg)	Delta SE (kg)
16 to 32 weeks; Requiring maintenance of stable insulin dose								
Vilsboll	2010	24	DPP-4	322	86.5	18.60	0.10	0.20
Vilsboll	2010	24	Placebo	319	87.3	17.90	0.10	0.20
Barnett	2012	24	DPP-4	303	87.7	18.57	0.39	0.151
Barnett	2012	24	Placebo	151	86.2	16.54	0.18	0.209
Rosenstock	2002	16	TZD	188	98.70	17.70	3.70	N/R
Rosenstock	2002	16	Placebo	187	95.40	17.00	-0.04	N/R
Study 6	2010	24	Dapa	192	94.63	16.83	-1.67	0.1814
Study 6	2010	24	Placebo	188	94.21	19.49	0.02	0.1833
16 to 32 weeks; Not included in meta-analysis due to lack of requirement for stable insulin dose								
Mattoo	2005	25.8	TZD	142	N/R	N/R	4.05	0.34
Mattoo	2005	25.8	Placebo	147	N/R	N/R	0.20	0.24
Zib	2007	25.8	TZD	16	88.03	23.45	7.16	1.37
Zib	2007	25.8	Placebo	16	90.79	23.28	6.07	1.25

Abbreviations: Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; N, Number; N/R, Not reported; SD, Standard deviation; SE, Standard error; TZD, Thiazolidinediones. †Data imputed.

Table 128. Systolic blood pressure data extracted from randomised clinical trials of anti-diabetic agents used in adults with T2DM, inadequately controlled on metformin monotherapy

Author	Year	Duration	Comparator	N	BL mean (mmHg)	BL SD (mmHg)	Delta mean (mmHg)	Delta SE (mmHg)
18 to 30 weeks								
Study 14	2010	24	Dapa	122	126	15.9	-5.1	1.3
Study 14	2010	24	Placebo	119	127.7	14.6	-0.2	1.2
Study 12	2010	24	Dapa	88	135.9	13.92	-2.7	1.088
Study 12	2010	24	Placebo	91	133.3	13.66	0.1	1.071
Papathanassiou	2009	26	SU	14	152.4	16.6	-11.08	5.340
Papathanassiou	2009	26	TZD	14	149.5	14.3	-8.67	5.067

Author	Year	Duration	Comparator	N	BL mean (mmHg)	BL SD (mmHg)	Delta mean (mmHg)	Delta SE (mmHg)
Charpentier	2001	20	SU	147	140	12	-0.14	1.089
Charpentier	2001	20	Placebo	75	142	11	-0.65	1.411
Bergenstal	2010	26	DPP-4	166	126	14	0.22	0.93
Bergenstal	2010	26	TZD	165	127	14	-1.58	0.94
Pratley	2010	26	GLP-1	221	131.2	14.4	-0.55	0.89
Pratley	2010	26	GLP-1	218	133.4	14.5	-0.72	0.89
Pratley	2010	26	DPP-4	219	132.1	14.8	-0.94	0.89
Nauck	2009	26	GLP-1	240	132	14	-2.8	0.599†
Nauck	2009	26	GLP-1	242	131	14	-2.3	0.599†
Nauck	2009	26	SU	242	132	16	0.4	0.892†
Nauck	2009	26	Placebo	121	135	16	-1.8	1.125†
DeFronzo‡	2009	24	DPP-4	141	129	15.4	-3.8	1.4
DeFronzo‡	2009	24	Placebo	105	128.8	14.3	-3.7	1.3
52 weeks								
Study 4	2010	52	Dapa	399	132.8	14.89	-4.3	0.59†
Study 4	2010	52	SU	396	133.8	14.69	0.8	0.59†
Goke‡	2010	52	SU	293	N/R	N/R	-1.2	0.63
Goke‡	2010	52	DPP-4	293	N/R	N/R	-4.1	0.82

Abbreviations; BL, Baseline; Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; N, Number; N/R, Not reported, SD, Standard deviation; SE, Standard error; SU, Sulphonylureas; TZD, Thiazolidinediones. †Data imputed; ‡Unpublished.

Table 129. Systolic blood pressure data extracted from randomised clinical trials of anti-diabetic agents used in adults with T2DM, inadequately controlled on insulin with or without other oral anti-diabetic agents

Author	Year	Duration	Comparator	N	Baseline mean (mmHg)	Baseline SD (mmHg)	Delta mean (mmHg)	Delta SE (mmHg)
16 to 32 weeks; Requiring maintenance of stable insulin dose								
Barnett	2012	24	DPP-4	304	132.2	14.1	-1.4	0.92

Barnett	2012	24	Placebo	151	129.1	12.0	-0.9	1.29
Study 6	2010	24	Dapa	192	140.6	16.7	-6.9	0.912
Study 6	2010	24	Placebo	186	136.1	17.17	-3.9	0.927
16 to 32 weeks; Not included in meta-analysis due to lack of requirement for stable insulin dose								
Zib	2007	25.8	TZD	16	132	20.00	1.00	6.56
Zib	2007	25.8	Placebo	16	131	30.00	3.00	10.43

Abbreviations: Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; N, Number; SD, Standard deviation; SE, Standard error; TZD, Thiazolidinediones.

Table 130. Hypoglycaemia data extracted from randomised clinical trials of anti-diabetic agents used in adults with T2DM, inadequately controlled on metformin monotherapy

Author	Year	Duration	Agent, dose	Comparator	% with hypoglycaemia	n	N	Definition
24 weeks								
Study 14	2010	24	Dapagliflozin 10mg	Dapa	3.7	5	135	**Any/Minor**: not defined; including Major: 3rd party, glucose <3 mmol/l, glucose/glucagon (0 cases)
Study 14	2010	24	Placebo	Placebo	2.9	4	137	**Any/Minor**: not defined; including Major: 3rd party, glucose <3 mmol/l, glucose/glucagon (0 cases)
Study 12	2010	24	Dapagliflozin 10mg	Dapa	2.2	2	91	**Any/Minor**: symptomatic/asymptomatic with or without glucose <3.5 mmol/l that is not major; including Major: 3rd party, glucose <3 mmol/l, glucose/glucagon (0 cases)
Study 12	2010	24	Placebo	Placebo	3.3	3	91	**Any/Minor**: symptomatic/asymptomatic with or without glucose <3.5 mmol/l that is not major; including Major: 3rd party, glucose <3 mmol/l, glucose/glucagon (0 cases)
Kaku	2009	28	Pioglitazone 15-30mg	TZD	1.2	1	83	Not defined
Kaku	2009	28	Placebo	Placebo	0.0	0	86	Not defined
Charbonnel	2006	24	Sitagliptin 100mg	DPP-4	1.3	6	464	Not defined
Charbonnel	2006	24	Placebo	Placebo	2.1	5	237	Not defined
DeFronzo	2009	24	Saxagliptin 5mg	DPP-4	5.2	10	191	**Any/Minor**: symptomatic without confirmation, symptomatic with confirmation (glucose <50 mg/dl). Includes Major (0 cases reported).
DeFronzo	2009	24	Placebo	Placebo	5.0	9	179	**Any/Minor:** symptomatic without confirmation, symptomatic with confirmation (glucose <50 mg/dl). Includes Major (0 cases reported).

Author	Year	Duration	Agent, dose	Comparator	% with hypoglycaemia	n	N	Definition
Raz	2008	30	Sitagliptin 100mg	DPP-4	1.0	1	96	Not defined
Raz	2008	30	Placebo	Placebo	0.0	0	94	Not defined
Bosi	2007	24	Vildagliptin 100mg	DPP-4	0.6	1	183	**Any/Minor**: symptomatic with confirmation (glucose <3.1 mmol/L). Includes Major (0 cases reported).
Bosi	2007	24	Placebo	Placebo	0.6	1	181	**Any/Minor**: symptomatic with confirmation (glucose <3.1 mmol/L). Includes Major (0 cases reported).
Taskinen	2011	24	Linagliptin 5mg	DPP-4	0.6	3	523	**Any/Minor:** asymptomatic/symptomatic with confirmation (glucose <3 mmol/L). Includes major (0 cases reported)
Taskinen	2011	24	Placebo	Placebo	2.8	5	177	**Any/Minor**: asymptomatic/symptomatic with confirmation (glucose <3 mmol/L). Includes major (0 cases reported)
Scott	2008	18	Sitagliptin 100mg	DPP-4	1.1	1	94	**Any/Minor**: symptomatic with confirmation (glucose <3.1 mmol/l); Major: 3rd party, glucose <3.1 mmol/l (0 cases)
Scott	2008	18	Placebo	Placebo	2.2	2	91	**Any/Minor**: symptomatic with confirmation (glucose <3.1 mmol/l); Major: 3rd party, glucose <3.1 mmol/l (0 cases)
DeFronzo	2005	30	Exenatide 10ug	GLP-1	4.6	5	110	**Any/Minor:** symptomatic without confirmation, symptomatic with confirmation (glucose <3.3 mmol/l); Major: 3rd party, glucose/glucagon (0 cases)
DeFronzo	2005	30	Exenatide 20ug	GLP-1	5.3	6	113	**Any/Minor**: symptomatic without confirmation, symptomatic with confirmation (glucose <3.3 mmol/l); Major: 3rd party, glucose/glucagon (0 cases)
DeFronzo	2005	30	Placebo	Placebo	5.3	6	113	**Any/Minor:** symptomatic without confirmation, symptomatic with confirmation (glucose <3.3 mmol/l);

Author	Year	Duration	Agent, dose	Comparator	% with hypoglycaemia	n	N	Definition
								Major: 3rd party, glucose/glucagon (0 cases)
Bolli	2008	24	Vildagliptin 100mg	DPP-4	0.3	1	295	**Any/Minor**: symptomatic with confirmation (glucose <3.1 mmol/l); includes Major: 3rd party (0 cases)
Bolli	2008	24	Pioglitazone 30mg	TZD	0.0	0	280	**Any/Minor**: symptomatic with confirmation (glucose <3.1 mmol/l); includes Major: 3rd party (0 cases)
Bergenstal	2010	26	Sitagliptin 100mg	DPP-4	3.0	5	166	**Any/Minor**: symptomatic with confirmation (glucose <3 mmol/l); Major: 3rd party, glucose<3 mmol/l, glucose/glucagon (0 cases)
Bergenstal	2010	26	Pioglitazone 45mg	TZD	0.6	1	165	**Any/Minor**: symptomatic with confirmation (glucose <3 mmol/l); Major: 3rd party, glucose <3 mmol/l, glucose/glucagon (0 cases)
Pratley	2010	26	Liraglutide 1.2mg	GLP-1	5.9	13	225	**Any**: symptomatic with confirmation (glucose <3.1 mmol/l) and self-treated; including Major: 3rd party, irrespectively of glucose (1 case)
Pratley	2010	26	Liraglutide 1.8mg	GLP-1	5.1	11	221	**Any/Minor**: symptomatic with confirmation (glucose <3.1 mmol/l) and self-treated; Major: 3rd party, irrespectively of glucose (0 cases)
Pratley	2010	26	Sitagliptin 100mg	DPP-4	4.6	10	219	**Any/Minor**: symptomatic with confirmation (glucose <3.1 mmol/l) and self-treated; Major: 3rd party, irrespectively of glucose (0 cases)
52 weeks								
Study 4	2010	52	Dapagliflozin 10mg	Dapa	1.7	14	406	**Any**: symptomatic/asymptomatic with or without glucose <3.5mmol/l, including major.
Study 4	2010	52	Glipizide 5-20mg	SU	36.0	162	408	**Any**: symptomatic/asymptomatic with or without glucose <3.5mmol/l, including major.
Matthews	2005	52	Gliclazide	SU	11.2	35	313	**Any/Minor**: symptomatic without

Author	Year	Duration	Agent, dose	Comparator	% with hypoglycaemia	n	N	Definition
			160-320mg					confirmation; includes major events (0 cases).
Matthews	2005	52	Pioglitazone 30-45 mg	TZD	1.3	4	317	**Any/Minor**: symptomatic without confirmation; includes major events (0 cases).
Matthews	2010	52	Glimepiride 2-6mg	SU	16.2	224	1383	**Any**: symptomatic with confirmation (glucose <3.1 mmol/l); includes major events (10 cases)
Matthews	2010	52	Vildagliptin 100mg	DPP-4	1.7	23	1389	**Any/Minor**: symptomatic with confirmation (glucose <3.1 mmol/l); includes major events (0 cases).
Nauck	2007	52	Glipizide 5-20mg	SU	32.0	187	584	**Any**: symptomatic without confirmation, symptomatic with confirmation (glucose <70 mg/dl reported but not used to define hypo); includes Major (3rd party; 7-15 cases)
Nauck	2007	52	Sitagliptin 100mg	DPP-4	5.0	29	588	**Any**: symptomatic without confirmation, symptomatic with confirmation (glucose <70 mg/dl reported but not used to define hypo); includes Major (3rd party; 1-2 cases)
Goke	2010	52	Glipizide 5-20mg	SU	36.3	156	430	**Any**: symptomatic without confirmation, symptomatic/asymptomatic with confirmation (glucose<2.8 mmol/l); includes Major (3rd party; 7-11 cases)
Goke	2010	52	Saxagliptin 5mg	DPP-4	3.0	13	428	**Any/Minor**: symptomatic without confirmation, symptomatic/asymptomatic with confirmation (glucose <2.8 mmol/l); includes Major (3rd party; 0 cases)

Abbreviations: Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; GLP-1, Glucagon-like peptide-1 analogues; n, numerator number; N, Denominator number; SU, Sulphonylureas; TZD, Thiazolidinediones.

Table 131. Hypoglycaemia data extracted from randomised clinical trials of anti-diabetic agents used in adults with T2DM, inadequately controlled on insulin therapy with or without other oral anti-diabetic agents

Author	Year	Duration	Comparator	Agent, dose	% with hypoglycaemia	n	N	Definition
16 to 32 weeks; Requiring maintenance of stable insulin dose								
Vilsboll	2010	24	DPP-4	Sitagliptin 100mg	15.5	50	322	**Any**: symptomatic without confirmation. Includes Major (2 cases reported).
Vilsboll	2010	24	Placebo	Placebo	7.8	25	319	**Any**: symptomatic without confirmation. Includes Major (1 case reported).
Barnett	2012	24	DPP-4	Saxagliptin 5mg	18.4	56	304	**Any**: symptomatic/asymptomatic with or without confirmation. Includes Major (3 cases reported). Excludes data after uptitration.
Barnett	2012	24	Placebo	Placebo	19.9	30	151	**Any**: symptomatic/asymptomatic with or without confirmation. Includes Major (2 cases reported). Excludes data after uptitration.
Rosenstock	2002	16	TZD	Pioglitazone 30mg	15	29	188	**Any**: symptomatic , no requirement for confirmation. Includes Major (0 cases reported). Use of rescue data not reported ¶
Rosenstock	2002	16	Placebo	Placebo	5	9	187	**Any**: symptomatic , no requirement for confirmation. Includes Major (0 cases reported). Use of rescue data not reported ¶
Study 6	2010	24	Dapa	Dapagliflozin 10mg	42.3‡	83	196	**Any:** symptomatic/asymptomatic with or without glucose <3.5mmol/l, and major (1 case reported).
Study 6	2010	24	Placebo	Placebo	35.0§	69	197	**Any:** symptomatic/asymptomatic with or without glucose <3.5mmol/l, and major (1 case reported).
16 to 32 weeks; Not included in meta-analysis due to lack of requirement for stable insulin dose								
Mattoo	2005	25.8	TZD	Pioglitazone 30mg	63.4	90	142	**Any**†: symptomatic, with or without confirmation (glucose <2.8mmol/l). Unclear if includes Major.
Mattoo	2005	25.8	Placebo	Placebo	51.0	75	147	**Any**†: symptomatic, with or without confirmation (glucose <2.8mmol/l). Unclear if includes Major.

Abbreviations: Dapa, Dapagliflozin; DPP-4, Dipeptidyl peptidase-4 inhibitors; N, Number; TZD, Thiazolidinediones. †Unclear whether author was reporting episodes or patients with > 1 episode; ‡Excludes data after insulin up-titration: 44.9 % if safety analysis set; §Excludes data after insulin up-titration: 42.13 % if safety analysis set; ¶, Note: patients withdrew from study due to poor glycaemic control – assume hypoglycaemia events occurring post-withdrawal are not included, and is equivalent to excluding data after insulin up-titration

9.17 Appendix 17: Systematic review of antidiabetic agents (metformin add-on)

Please refer to separate document.

Systematic review of anti-diabetic agents in type 2 diabetes mellitus: metformin add-on therapy. Updated search results to 2012 – Oxford Outcomes

9.18 Appendix 18: Systematic review of antidiabetic agents (insulin add-on)

Please refer to separate document.

Systematic review of anti-diabetic agents in type 2 diabetes mellitus: insulin add-on therapy. Updated search results to 2012 – Oxford Outcomes

9.19 Appendix 19: Model validation

Please see separate documents:

Validation of the Dapagliflozin Cost Effectiveness Model (DCEM) version 2.0 – McEwan P

Validation of cost effectiveness of dapagliflozin using the IMS core diabetes model – Palmer J

10 Related procedures for evidence submission

10.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the

agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

10.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).